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RESEARCH**

APPLICATION NUMBER:

203108Orig1s000

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

| | |
|--|---------------------------------------|
| APPLICATION: NDA 203108 | CODE NAME: Striverdi Respiimat |
| APPLICANT/SPONSOR: Boehringer-Ingelheim | USAN NAME: olodaterol |
| MEDICAL OFFICER: Robert Lim, MD | |
| TEAM LEADER: Anthony Durmowicz, MD | CATEGORY: LABA |
| DUE DATE: 7/15/14 | ROUTE: Oral inhalation |

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| Document Date | CDER Stamp Date | Submission | Comments |
|----------------------|------------------------|-------------------|------------------|
| 6/2/14 | 6/2/14 | Sd-38 | NDA resubmission |

RELATED APPLICATIONS

| Document Date | Application Type | Comments |
|----------------------|-------------------------|------------------------------|
| 5/14/12 | New NDA | Complete response on 3/14/13 |

REVIEW SUMMARY:

Boehringer-Ingelheim has resubmitted their NDA for olodaterol inhalation solution following a Complete Response (CR) action taken on 3/14/13. The CR action was taken as manufacturing and testing facilities associated with the drug substance and drug product did not receive an acceptable GMP recommendation from the Office of Compliance. This precluded approval in the initial review cycle, despite adequate clinical data to support the safety and efficacy of olodaterol for its proposed indication, the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease at a dose of 5mcg once daily. A Complete Response action was taken during the initial review cycle as manufacturing and testing facilities associated with the drug substance and drug product did not receive an acceptable GMP recommendation from the Office of Compliance, which precluded approval. This was despite adequate clinical data to support the safety and efficacy of olodaterol inhalation solution and a Pulmonary Allergy Drug Advisory Committee meeting where the vote was 15 to 1 supporting approval. In this resubmission, the sponsor has included a safety update summarizing safety data from two 12-week trials. The additional safety information contained in the safety update does not alter the risk/benefit assessment of olodaterol. The manufacturing issues have been resolved. The recommended regulatory action for this NDA resubmission is for Approval pending agreement on labeling.

OUTSTANDING ISSUES:

none

RECOMMENDED REGULATORY ACTION

| | | |
|---|------------------------|----------------------|
| IND/NEW STUDIES: <input type="checkbox"/> | SAFE TO PROCEED | CLINICAL HOLD |
| NDA/SUPPLEMENTS: <input type="checkbox"/> | FILEABLE | NOT FILEABLE |
| <input checked="" type="checkbox"/> | APPROVAL | APPROVABLE |
| OTHER ACTION: <input type="checkbox"/> NOT APPROVABLE | | |

1. Executive Summary

The recommended regulatory action for this NDA resubmission is Approval for the long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema at a dose of 5mcg once daily. A Complete Response action was taken during the initial review cycle as manufacturing and testing facilities associated with the drug substance and drug product did not receive an acceptable GMP recommendation from the Office of Compliance, which precluded approval. This was despite adequate clinical data to support the safety and efficacy of Olodaterol inhalation solution and a Pulmonary Allergy Drug Advisory Committee meeting where the vote was 15 to 1 supporting approval. In this resubmission, the sponsor has included a safety update summarizing safety data from two 12-week trials. The additional safety information contained in the safety update does not alter the risk/benefit assessment of olodaterol. The manufacturing issues have been resolved.

2. Background

Boehringer-Ingelheim has resubmitted their NDA for olodaterol inhalation solution (Olo) following a Complete Response (CR) action taken on 3/14/13. The CR action was taken as manufacturing and testing facilities associated with the drug substance and drug product did not receive an acceptable GMP recommendation from the Office of Compliance. This precluded approval in the initial review cycle, despite adequate clinical data to support the safety and efficacy of Olo for its proposed indication. This application was also discussed a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting held on 1/29/13. The PADAC vote 15 to 1 favoring approval. As there was adequate clinical evidence of safety/efficacy and given the PADAC discussion, despite the manufacturing issues, labeling negotiations were conducted and were near completion at the time of the CR action. The label included in the CR letter represented the Division final edits on the document and incorporated input from labeling consultants.

Support for efficacy and safety was derived primarily from the four parallel group 48-week COPD trials, two of which were conducted primarily in the United States (US) and two of which were conducted primarily in Europe (EU). These trials included a total of 3104 patients, 1759 of which were exposed to Olo (mean exposure approximately 300 days). These trials shared the same spirometric co-primary endpoints of forced expiratory volume in 1 second (FEV1) AUC (0-3 hours) response and trough FEV1 response. The difference for Olo 5mcg from placebo for FEV1 AUC (0-3 hours) response in trials 1222.11, 1222.12, 1222.13, and 1222.14 were 0.164, 0.134, 0.151, and 0.129L (all p-values <0.0001), respectively. For trough FEV1 response, the differences from placebo were 0.084 (p=0.0002), 0.033 (p>0.05), 0.078 (p=0.0002), and 0.053L (p=0.006), respectively. No safety signals were identified based on analysis of the four 48-week trials. For in depth discussion

of the safety and efficacy of olodaterol refer to the clinical review by Dr. Robert Lim, dated January 17, 2013.

The development program was also discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting held on 1/29/13. The PADAC also felt that the data supported approval for the proposed indication.

Since the Complete Response action, BI has addressed the manufacturing issues identified in the initial review cycle (see CMC review). They have also completed two 12-week bronchodilator trials (1222.51 and 1222.52). Included in the resubmission are the pooled and individual safety analyses of these trials and a proposed label which incorporates the revisions included in the CR letter for the original NDA submission. Note that the exposure in trials 1222.51 and 1222.52 was less than that in the four 48-week trials used as primary support for safety. Additional efficacy data were not included in this submission.

3. Safety Update

The two trials included in the safety update (1222.51 and 1222.52) were replicate 12-week randomized, double-blind, placebo controlled trials in patients with moderate to severe COPD. The trials included two treatment arms which were as follows:

- 1) Olo 5mcg via Respimat device co-administered with tiotropium Handihaler (THH). Referred to as T+O.
- 2) Placebo via Respimat co-administered with THH. Referred to as T+PBO.

The trial consisted of a screening (2-weeks), treatment (12-weeks), and follow-up period (3-weeks). The co-primary endpoints were FEV1 AUC (0-3 hours) and trough FEV1 response at week 12 of treatment. Safety monitoring included physical exam, adverse events, ECG, pregnancy testing, and clinical labs.

In these trials, a total of 1134 and 1133 patients were included in the T+PBO and T+O treatment arms, respectively. Mean exposure in both groups was approximately 84 days. Demographic and baseline data were similar between treatment groups and were typical for a COPD trial. The majority of patients were male (52%), white (91%), GOLD stage II (59%) with a mean age of 64 years and mean FEV1 of 46% predicted.

There were 11 deaths in these trials, 3 (0.3%) in the T+PBO treatment arm and 8 (0.7%) in the T+O treatment arm. The causes of death were typical for a COPD trial. The most common cause of death was in the cardiac disorder system organ class (SOC). Based on SOC and PT, there were small numerical differences when comparing treatment groups. However, the differences were small and the events were relatively rare. Causes of death are summarized in Table 1.

Table 1. Pooled analysis of trial 1222.51 and 1222.52. Causes of death by SOC and PT

| SOC/PT | T+PBO n (%) | T+O n (%) | Total n (%) |
|--|----------------|--------------|----------------|
| Number of patients | 1134 (100.0) | 1133 (100.0) | 2267 (100.0) |
| Total with adverse events leading to death | 3 (0.3) | 8 (0.7) | 11 (0.5) |
| Nervous system disorders | 1(0.1) | 1 (0.1) | 2 (0.1) |
| Convulsion | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Hemorrhagic cerebral infarction | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Cardiac disorders | 1 (0.1) | 3 (0.3) | 4 (0.2) |
| Cardiac arrest | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Myocardial infarction | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Myocardial ischemia | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Vascular disorders | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Arteriosclerosis | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Respiratory, thoracic and mediastinal disorders | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Chronic obstructive pulmonary disease | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Acute respiratory failure | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| General disorders and administration site conditions | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Death | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Sudden death | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Injury, poisoning and procedural complications | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Toxicity to various agents (cocaine) | 0 (0.0) | 1 (0.1) | 1 (0.0) |

Source: Safety update; table 2.1.4:1; pg33

Serious adverse events (SAE) occurred in 117 (5.7%) patients and were more common in the T+O group [n=64 (5.6%)] compared to T+PBO group [n=53 (4.7%)]. The types of SAEs were typical for a COPD trial. SAEs occurred most commonly in the respiratory, thoracic, and mediastinal system organ class (SOC). SAEs in the cardiac disorder and vascular disorder SOCs were numerically more common in the T+O group compared to T+PBO groups. While there were some differences between treatment groups, they were generally small and the overall numbers were small.

Table 2. Pooled analysis of trial 1222.51 and 1222.52. Serious adverse events that occurred in ≥2 patients

| SOC/PT | T+PBO n (%) | T+O n (%) | Total n (%) |
|------------------------------------|----------------|--------------|----------------|
| Number of patients | 1134 (100.0) | 1133 (100.0) | 2267 (100.0) |
| Total with serious adverse events | 53 (4.7) | 64 (5.6) | 117 (5.2) |
| Infections and infestations | 8 (0.7) | 10 (0.9) | 18 (0.8) |
| Pneumonia | 5 (0.4) | 3 (0.3) | 8 (0.4) |
| Cellulitis | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Gastroenteritis | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Metabolism and nutrition disorders | 1 (0.1) | 1 (0.1) | 2 (0.1) |

| | | | |
|---|----------|----------|----------|
| Dehydration | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Psychiatric disorders | 2 (0.2) | 1 (0.1) | 3 (0.1) |
| Anxiety | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Cardiac disorders | 8 (0.7) | 13 (1.1) | 21 (0.9) |
| Cardiac failure congestive | 3 (0.3) | 4 (0.4) | 7 (0.3) |
| Atrial fibrillation | 0 (0.0) | 3 (0.3) | 3 (0.1) |
| Acute myocardial infarction | 2 (0.2) | 1 (0.1) | 3 (0.1) |
| Atrial flutter | 2 (0.2) | 0 (0.0) | 2 (0.1) |
| Myocardial infarction | 1 (0.1) | 2 (0.2) | 3 (0.1) |
| Vascular disorders | 2 (0.2) | 7 (0.6) | 9 (0.4) |
| Aortic aneurysm | 1 (0.1) | 2 (0.2) | 3 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 23 (2.0) | 19 (1.7) | 42 (1.9) |
| Chronic obstructive pulmonary disease | 20 (1.8) | 18 (1.6) | 38 (1.7) |
| Acute respiratory failure | 0 (0.0) | 5 (0.4) | 5 (0.2) |
| Pulmonary hypertension | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Respiratory failure | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Gastrointestinal disorders | 5 (0.4) | 7 (0.6) | 12 (0.5) |
| Gastritis | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Intestinal obstruction | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Esophagitis | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Renal and urinary disorders | 3 (0.3) | 3 (0.3) | 6 (0.3) |
| Nephrolithiasis | 2 (0.2) | 0 (0.0) | 2 (0.1) |
| Renal failure acute | 1 (0.1) | 2 (0.2) | 3 (0.1) |
| General disorders and administration site | 3 (0.3) | 4 (0.4) | 7 (0.3) |
| Chest-pain | 2 (0.2) | 3 (0.3) | 5 (0.2) |

Source: Safety update; table 2.1.5:1; pg39

Common adverse events ($\geq 2\%$ by treatment) were typical of what would be expected in a COPD trial. Approximately 43% of patients reported AEs. Overall, these were balanced between treatment groups. The most common AE by preferred term was COPD (10.7%), followed by dry mouth (2.7%). These are summarized in Table 3.

Table 3. Pooled analysis of trial 1222.51 and 1222.52. Common adverse events that occurred in $\geq 2\%$ patients/treatment

| | T+PBO | T+O | Total |
|---|--------------|--------------|--------------|
| SOC/PT | n (%) | n (%) | n (%) |
| Number of patients | 1134 (100.0) | 1133 (100.0) | 2267 (100.0) |
| Total with adverse events | 489 (43.1) | 484 (42.7) | 973 (42.9) |
| Respiratory, thoracic and mediastinal disorders | 207 (18.3) | 192 (16.9) | 399 (17.6) |
| Chronic obstructive pulmonary disease | 116 (10.2) | 126 (11.1) | 242 (10.7) |
| Cough | 28 (2.5) | 17 (1.5) | 45 (2.0) |
| Gastrointestinal disorders | 92 (8.1) | 89 (7.9) | 181(8.0) |
| Dry mouth | 29 (2.6) | 32 (2.8) | 61 (2.7) |

Source: Safety update; table 2.1.2:1; pg31

Overall, the types of adverse events reported in the pooled analysis were typical of what would be expected in this patient population. While there were some numerical

differences in terms of deaths and SAEs, the differences and overall numbers were small. Additionally, the exposure to Olo in these trials was considerably smaller compared to the safety database included in the original NDA submission where no safety signals were identified. As such, safety data from these trials do not alter the risk/benefit assessment of Olo.

4. Labeling

Labeling negotiations are currently ongoing. In the resubmission, the Applicant's proposed label incorporated the major revisions included in the label that was attached to the CR action letter. Labeling consults were obtained and recommendations were incorporated into the most recent label sent to the Applicant on 7/8/14. Note that not all DMPP recommendations regarding the instructions for use (IFU) were incorporated. This was to maintain consistency with labeling for another approved product (Combivent Respimat) which uses the same device (Respimat), has a similar IFU, and for which there have been no issues with label comprehension and device use.

5. Recommended Regulatory Action: Approval pending agreement on labeling

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/s/

ROBERT H LIM
07/10/2014

ANTHONY G DURMOWICZ
07/11/2014

Summary Basis for Regulatory Action

| | |
|---|--|
| Date | March 14, 2013 |
| From | Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II |
| Subject | Summary Review |
| NDA/BLA # | 203108 |
| Supp # | |
| Applicant Name | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Proprietary / Established (USAN) Names | Striverdi Respimat (Olodaterol) |
| Dosage Forms / Strength | Inhalation Spray 2.5 mcg per actuation/two actuations once-daily |
| Proposed Indication(s) | Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. |
| Action: | <i>Complete Response</i> |

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding olodaterol and the reader should review the action package for more detail. Olodaterol's mode of action is through stimulation of the beta-2 adrenergic receptor. Olodaterol has a long duration of action and therefore belongs to the class of drugs known as long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used to provide bronchodilation in patients with COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol and indacaterol. Some of the aforementioned LABAs are marketed as single ingredient products and others are marketed as combination products with inhaled corticosteroids. Salmeterol, formoterol and arformoterol are dosed twice-daily and indacaterol is dosed once-daily, the same interval being proposed for olodaterol. Other drug classes besides beta-2 adrenergic agonists (including short-acting) used to treat the symptoms of COPD include anticholinergic agents, combinations of LABAs and corticosteroids, combinations of LABAs and anticholinergics, phosphodiesterase-4 (PDE4) inhibitors and methylxanthines.

As discussed by Dr. Chowdhury, inhaled beta-2 adrenergic agonists have a safety concern of severe asthma exacerbation, sometimes leading to death, in patients treating the symptoms of asthma.¹ However, this type of signal has never been shown with use of inhaled beta-2 agonists in patients with COPD. In the past, inhaled beta-2 adrenergic agonist agents were developed for both asthma and COPD indications, but recently the trend has been for sponsors to develop these types of agents only for COPD indications. This is probably, at least partially, due to sponsor's concerns that the safety signal existing in those using these agents

¹ A Higher dose of inhaled formoterol was not approved because of more severe asthma exacerbations compared to lower doses.

for asthma may lead to more peril in seeking approval for this indication. However, past experience in these develop programs has informed us that the dose and dosing interval are the same in either disease. Traditionally in the past, dose-ranging trials were performed in subjects with asthma due to their greater airway sensitivity response to adrenergic activation which is necessary to establish separation of dose responses. Once a dose was determined in those with asthma, that dose was carried forward into COPD trials. As such it is important to perform at least some dose-selection trials in subjects with asthma.²

The NDA for olodaterol demonstrated efficacy with safety expected for a LABA, when used as a bronchodilator in patients with COPD. The efficacy and safety demonstrated seems in line with other agents that are currently marketed. The sponsor is also seeking unique claims for increased exercise tolerance. DPARP has concluded and recommends that the sponsor has not provided evidence of efficacy that would support increased exercise tolerance claims. DPARP does recommend that the sponsor has provided enough evidence to support approval for the indication listed above (typical COPD indication) but is recommending that this application receive a complete response at present because there is a withhold recommendation from compliance in relation to general GMP inspection at the main manufacturing site. While this may not reflect any specific findings for this product, it may represent a failure of the Quality System for the site which will receive a warning letter for inadequate GMPs by the Office of Compliance.

I agree with the recommendations of DPARP. I will discuss my reasoning and conclusions below.

Efficacy

The sponsor submitted many trials in subjects with COPD. Unique to this application was the sponsor's desire to have a claim of improvement in exercise endurance in patients with COPD. I will discuss these trials (1222.37 and 1222.38) separately.

Below is a table from Dr. Chowdhury's review summarizing the efficacy results for the COPD trials.

Table 1. 48-week COPD studies; ΔFEV_1 trough and $\Delta\text{FEV}_1 \text{ AUC}_{0-3 \text{ hr}}$ at week 12 (co-primary efficacy end point)

| Study | Treatment | N | Trough FEV_1 Response Mean Change (95% CI) | $\text{FEV}_1 \text{ AUC}_{0-3 \text{ hr}}$ Response Mean Change (95% CI) |
|---------|------------------|-----|--|--|
| 1222.11 | Placebo | 188 | - 0.032 | 0.002 |
| | Olo 5 mcg QD | 192 | 0.052 0.084 (0.040, 0.129) | 0.167 0.164 (0.120, 0.209) |
| | Olo 10 mcg QD | 192 | 0.048 0.080 (0.037, 0.124) | 0.157 0.155 (0.111, 0.199) |

² Dose-ranging was performed in both asthma and COPD populations for this application and the agency agreed with the doses selected and carried forth in clinical trials. Dose-ranging trials included the same nominal dose given twice daily compared to once daily.

| Study | Treatment | N | Trough FEV ₁ Response | | FEV ₁ AUC _{0-3 hr} Response | |
|---------|---------------|-----|----------------------------------|-----------------------|---|----------------------|
| | | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| 1222.12 | Placebo | 197 | 0.005 | | 0.021 | |
| | Olo 5 mcg QD | 196 | 0.038 | 0.033 (-0.013, 0.080) | 0.155 | 0.134 (0.090, 0.177) |
| | Olo 10 mcg QD | 201 | 0.049 | 0.045 (-0.001, 0.090) | 0.151 | 0.130 (0.087, 0.172) |
| | | | | | | |
| 1222.13 | Placebo | 187 | - | 0.027 | - | 0.003 |
| | Olo 5 mcg QD | 208 | 0.056 | 0.083 (0.043, 0.123) | 0.176 | 0.178 (0.137, 0.219) |
| | Olo 10 mcg QD | 207 | 0.048 | 0.075 (0.035, 0.114) | 0.167 | 0.170 (0.129, 0.211) |
| | For 12 mcg BD | 200 | 0.033 | 0.059 (0.019, 0.100) | 0.182 | 0.185 (0.144, 0.226) |
| | | | | | | |
| 1222.14 | Placebo | 212 | - | 0.041 | - | 0.008 |
| | Olo 5 mcg QD | 220 | 0.018 | 0.059 (0.022, 0.095) | 0.138 | 0.145 (0.108, 0.182) |
| | Olo 10 mcg QD | 219 | 0.052 | 0.093 (0.057, 0.130) | 0.167 | 0.175 (0.138, 0.212) |
| | For 12 mcg BD | 217 | 0.024 | 0.065 (0.028, 0.101) | 0.163 | 0.170 (0.133, 0.208) |
| | | | | | | |

The mean treatment effect across trials for trough FEV₁ was 65mL. As the other reviewers note, this is somewhat less than was demonstrated for other agents, but is most likely due to the allowance for continued COPD background treatments (except LABAs). The response demonstrated for olodaterol is similar to that of formoterol. Olodaterol doses of 5 and 10 mcg were both effective and had similar responses.

Exercise endurance:

The sponsor proposes to include exercise endurance benefit based on the results of exercise testing. This would be a novel claim for COPD that has not been presented to, or considered by, the agency previously. Below from Dr. Chowdhury's review are the results of two trials.

Table 2. 6-week COPD studies; Exercise endurance time in seconds and inspiratory capacity in liters at week 6

| Study | Treatment | Endurance Time (sec) | | Inspiratory Capacity (L) | |
|---------|---------------|----------------------|---------------------|--------------------------|----------------------|
| | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| 1222.37 | Placebo | 369.8 | | 1.887 | |
| | Olo 5 mcg QD | 421.6 | 1.14 (1.065, 1.221) | 2.067 | 0.180 (0.107, 0.252) |
| | Olo 10 mcg QD | 420.7 | 1.14 (1.062, 1.219) | 2.024 | 0.137 (0.064, 0.210) |
| 1222.38 | Placebo | 354.3 | | 2.158 | |
| | Olo 5 mcg QD | 396.3 | 1.12 (1.043, 1.199) | 2.236 | 0.078 (0.010, 0.146) |

| Study | Treatment | Endurance Time (sec) | | Inspiratory Capacity (L) | |
|-------|---------------|----------------------|---------------------|--------------------------|----------------------|
| | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| | Olo 10 mcg QD | 391.5 | 1.10 (1.030, 1.184) | 2.330 | 0.172 (0.105, 0.240) |

This table demonstrates that those subjects receiving olodaterol did on average have longer exercise times. However, the increases in exercise time was 40-50 seconds (12-14%) above the average baseline (354 seconds to 370 seconds). Presently, there is not a recognized minimal clinically important difference (MCID) for exercise testing. There also has not been any correlation demonstrated defining the magnitude of increase in exercise tolerance that corresponds to improvement in activities of daily living. For these trials, exercise testing was performed 2 hours post-dose, corresponding to peak bronchodilator effect and there wasn't any evaluation for persistence of effect or evaluation at timepoints greater than six weeks.

Finally, the mechanism of action of olodaterol is the same as other beta-agonists used in COPD and one might predict the other agents to have the same effect. It does seem that the sponsor is proposing a new, novel claim, without developing the supporting evidence of what should be expected as the criteria to support such an indication or with any idea if this is something novel for their product that really warrants identification in labeling. Also, the effect of olodaterol in this regard is probably not unique compared to other LABAs, which may be seen as efforts to find a marketing tool instead of a unique benefit worthy of differentiation. In any event, I do not feel they have demonstrated a unique and clinically important difference worthy of labeling.

Safety

The major safety concern with LABAs, at least in those with asthma, is severe asthma exacerbations and asthma-related deaths. These effects appear dose-related, making dose selection for efficacy to afford the optimal risk for benefit the primary consideration. While these risks have not been demonstrated in those with COPD it still would seem to be reasonable not to market an unnecessarily high dose. As such, and because there did not seem to be separation between the 5 and 10 mcg doses, the sponsor's proposal to pursue the 5 mcg dose is appropriate.

There balanced events between olodaterol and placebo for deaths and SAEs. There was a small imbalance in neoplasm. But this was based on limited events making any conclusions impossible.³

³ 9 (1.0%), 14 (1.6%), 19 (2.2%) and 8 (1.7%) in placebo, olodaterol 5 mcg, olodaterol 10 mcg and formoterol respectively. The rate per 100 patient years is 1.94, 2.89, 4.24, and 2.84 in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 2, 3, 6, and 4 malignant lung neoplasms in placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. Approximately half of the total malignant lung neoplasms, including 2 of the small cell lung carcinomas, were diagnosed within 5 months of beginning of randomized treatment.

Overall the safety profile is similar to other drugs of the same class and acceptable for marketing.

Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on January 29, 2013. The committee voted 15-yes, 1-no and 1 abstain that there was substantial evidence of efficacy, and also voted 15-yes, 1-no and 1 abstain that the safety of olodaterol was appropriate. The committee voted 15-yes, 1-no and 1 abstain that olodaterol should be approved for marketing.

Regarding a non-voting question requesting the discussion of the evidence to support an exercise endurance claim, most panel members noted that more information was needed to understand optimal exercise trial design for COPD and clinically important exercise improvement and endpoints.

Conclusions and Recommendations

The benefit and risk assessment is appropriate to allow marketing of olodaterol inhalation spray at 5 mcg once daily for long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema. The sponsor will need to respond to the GMP issues that resulted in a withhold recommendation. Until that time I recommend a Complete Response action.

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/s/

CURTIS J ROSEBRAUGH

03/14/2013

SUMMARY REVIEW OF REGULATORY ACTION

Date: March 13, 2013

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 203108

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Date of Submission: May 14, 2012

PDUFA Goal Date: March 14, 2013

Proprietary Name: Striverdi Respimat

Established Name: Olodaterol

Dosage form: Inhalation Spray

Strength: 2.5 mcg olodaterol per actuation

Proposed Indications: Chronic Obstructive Pulmonary Disease

Action: Complete Response

1. Introduction

Boehringer Ingelheim (BI) submitted this 505(b)(1) new drug application for use of Striverdi Respimat (olodaterol inhalation spray) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is 5 mcg of olodaterol (two actuations of 2.5 mcg per actuation) once-daily, recommended to be taken at the same time each day. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines.

Olodaterol is a new molecular entity that belongs to the class called beta-2 adrenergic agonists. Due to its longer duration of action, olodaterol belongs to the subclass called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol, and indacaterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. Salmeterol, formoterol,

and arformoterol are dosed twice-daily, and indacaterol is dosed once-daily. Olodaterol is proposed to be dosed once daily.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.^{1, 2, 3, 4} More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.⁵ This has been discussed at various FDA Advisory Committee meetings,⁶ has led to publications expressing concerns on safety,^{7, 8, 9} and establishment of a safe use strategy outlined by the FDA.¹⁰ To further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.¹¹ The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.¹² Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including olodaterol, which is proposed to be marketed for COPD. Most of the U.S. marketed beta-adrenergic agonists carry both asthma and COPD indications, and the dose and dosing frequency in both indications are the same.

¹ Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. *J Allergy* 1948; 19:129-140.

² Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproterenol in spontaneous and induced asthma. *N Eng J Med* 1949; 240:45-51.

³ Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. *Thorax* 1991; 46:105-111.

⁴ Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. *N Eng J Med* 1992; 326:501-506.

⁵ US Product Labels of salmeterol and formoterol containing products.

⁶ Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.

⁷ Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. *New Eng J Med* 2005; 353:2637-2639.

⁸ Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. *New Eng J Med* 2009; 360:1952-1955.

⁹ Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *New Eng J Med* 2009; 360:1671-1672.

¹⁰ Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *New Eng J Med* 2010; 362:1169-1171.

¹¹ Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *New Eng J Med* 2011; 364:2473-2475.

¹² Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. *Chest* 2003; 124:70-74.

The indication claims of short-acting beta-adrenergic agonists, such as albuterol (Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, ProAir HFA Inhalation Aerosol, Proventil Inhalation solution) are for general bronchodilation (“treatment or prevention of bronchospasm with reversible obstructive airway disease”). The albuterol product labels do not mention a specific disease, such as asthma or COPD, in the indication section. Clinical studies supporting approval of these products were conducted in patients with asthma. Nevertheless, albuterol is used in patients with asthma and COPD. The indication claims of LABAs, such as salmeterol (Serevent Diskus, Serevent Inhalation Aerosol) and formoterol (Foradil Aerolizer) are also for general bronchodilation, but the product labels mention asthma and COPD as specific diseases in the indication section. Clinical trials supporting the dose and dosing frequency for these two long-acting beta agonists were also conducted in patients with asthma, and the same bronchodilatory dose was carried forward to studies in COPD. The regulatory precedence of performing dose ranging and dose regimen studies for bronchodilators in asthma patients has been established in order to demonstrate a large separation between doses, because the range of response is greatest in a bronchoresponsive population, such as patients with asthma. A COPD population, with some degree of fixed obstruction, has a smaller response range to a bronchodilator. The regulatory precedence of performing dose ranging and dose regimen studies in patients with asthma were followed in the development of indacaterol, a LABA that was approved¹³ for marketing in the United States in 2011 as a bronchodilator in patients with COPD.

The Agency and BI had milestone meetings typical of development of a new molecular entity and of a first-cycle NDA submission. In the End of Phase 2 meeting, the Agency agreed with BI that the 5 and 10 mcg doses were reasonable to carry forward into definitive COPD phases. The Agency advised BI to conduct studies to establish the dosing interval. In a subsequent meeting, the Agency recommended evaluating dose and dose regimen in patients with asthma. BI conducted these studies that are included in this NDA submission.

3. Chemistry, Manufacturing, and Controls

The product Striverdi Respimat Inhalation Spray is composed of a Striverdi Respimat cartridge and a Striverdi Respimat inhaler. The Striverdi Respimat cartridge is a 4.5 mL plastic container (crimped into an aluminum cylinder) that contains a sterile aqueous solution of olodaterol in the excipients benzalkonium chloride ((b)(4)), edetate disodium ((b)(4)), water for injection, and citric acid ((b)(4)).

Striverdi Respimat Inhalation Spray is supplied in a carton containing one Striverdi Respimat cartridge and one Striverdi Respimat inhaler. Prior to first use, the patient or care provider places the Striverdi Respimat cartridge into the Striverdi Respimat inhaler and primes the unit. To actuate the product, the patient turns the bottom of the inhaler 180°, which will cause a small volume of the formulation to be metered into a chamber and compress a spring. The patient then presses a trigger, which will release the spring to provide mechanical energy that propels the formulation through a nozzle with two outlets

¹³ Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. The risks and benefits of indacaterol – The FDA review. N Eng J Med 2011; 365:2247-2249.

that form two jets of solution. The two jets converge on each other and create an aerosol cloud that emits gently from the mouthpiece of the product. The assembled Striverdi Respimat Inhalation Spray is designed to deliver 60 metered actuations. The product has a dose indicator that is visible on the clear base. After the 60 metered actuations are delivered, a locking mechanism is engaged and no more drug can be dispensed. The Striverdi Inhalation Spray should be discarded after the locking mechanism is engaged or 3 months after first use, whichever comes first.

BI submitted adequate stability data to support an expiry of 36 months for the drug product that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and an in-use period of 3 months after the cartridge is assembled with the Respimat Inhaler.

The steps needed to use the product and the internal mechanisms of the product are rather complex. The Respimat device is relatively new to the United States market, with one BI product, Combivent Respimat (ipratropium bromide and albuterol) Inhalation Spray, approved for marketing in October 2011. During review of another Respimat Inhaler product of BI that contained tiotropium (Spiriva Respimat), a consultation with CDRH was obtained because of the complexity of the product. [REDACTED] ^{(b) (4)}

[REDACTED] BI has performed adequate specific patient handling studies with the Respimat device. In two phase 3 studies conducted for Combivent Respimat and in two phase 3 studies conducted for Spiriva Respimat, patient handling of the device was assessed and representative devices used in clinical studies were tested for *in vitro* performance characteristics. These assessments did not suggest any problems with patient handling, performance, and robustness of the Respimat device. The only issue identified was that some older patients or patients with hand joint problems may need assistance with initial assembly of the cartridge and the Respimat Inhaler.

The drug substance and drug product including the Respimat device are manufactured at a Boehringer Ingelheim facility in Ingelheim am Rhein, Germany. Manufacturing and testing facilities associated with the drug substance and drug product do not have an acceptable GMP recommendation from Office of Compliance, which will preclude approval of this application in this review cycle. All DMFs associated with this application were also found to be acceptable.

4. Nonclinical Pharmacology and Toxicology

BI submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Pivotal inhalation toxicity studies were conducted in rats for up to 26 weeks and in dogs for up to 52 weeks. The target organs of toxicity (with organ-specific findings in parentheses) in rats were skeletal muscle (hypertrophy and single cell necrosis); heart (increased heart rate, congestion, and ventricular scar formation); trachea (squamous cell metaplasia); pancreas (lobular hypertrophy); and female reproductive

tract (increased incidence of ovarian cysts). Target organs of toxicity in dogs (with organ-specific findings in parentheses) were the cardiovascular system (increased heart rates, ventricular premature beats, and fibrosis of the left ventricle of the heart); kidney (mononuclear infiltration); liver (glycogen deposition and hemorrhage); and trachea (epithelial atrophy, infiltration, and mineralization). Many of these findings in rats and dogs (cardiovascular, liver, skeletal muscle, and female rodent reproductive tract) are known class effects of beta-agonist drugs. There were adequate margins of safety for the expected human exposure for findings of concern. Studies addressing genotoxicity, reproductive toxicity, and carcinogenicity were also performed. Olodaterol was negative for genotoxicity in a complete battery of genetic toxicology assays. A reproductive toxicity study in rats did not reveal adverse effects on male and female fertility or reproductive performance. Embryo-fetal development studies in rats and rabbits showed teratogenic effects at the high dose only in rabbit. The pregnancy category was determined to be C, which is the same category for many other beta-2 adrenergic agonists. Carcinogenicity was assessed in a 2 year study in CD-1 mice, and in a 2-year study in Wistar Han rats. These studies showed increased incidences of uterine leiomyomas and malignant leiomyosarcomas in mice and ovarian leiomyomas in rats. These tumors have been observed with other beta-adrenergic agonists. The relevance of these findings to humans is unknown.

5. Clinical Pharmacology and Biopharmaceutics

BI submitted results from a comprehensive clinical pharmacology program. The program addressed the key pharmacokinetic issues, including *in vitro* studies to assess protein binding and metabolism, pharmacokinetics after single and multiple doses, *in vitro* and *in vivo* metabolism, effect of hepatic and renal impairment, QTc prolongation effect, and drug-drug interaction. Clinical pharmacology studies included inhalation, oral, and IV administration to fully characterize the pharmacokinetics of olodaterol. Inhaled olodaterol has approximately 30% bioavailability resulting from pulmonary absorption; oral bioavailability is very low (<1%). Elimination is through both the biliary and renal routes; in a mass balance study, 53% of drug-related radioactivity was recovered in the feces and 38% was excreted in the urine. Following inhalation of a single dose of olodaterol, C_{max} values were generally reached within 10 to 20 minutes post-dose, with an elimination half-life of approximately 45 hours. Pharmacokinetics were linear, and steady state was reached after 8 days. Olodaterol is a substrate for the efflux pump P-gp. It is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety mainly by CYP2C9 followed by conjugation. A renal impairment study showed that olodaterol levels were increased by approximately 40% in subjects with severe renal impairment. Olodaterol exposure was comparable between normal and mild to moderate hepatic impairment patients. Population pharmacokinetic studies showed approximately 2-fold higher systemic exposure in Japanese patients compared to Caucasians. Dose-dependent QTcF prolongation was observed in the QTc prolongation study. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 3.4 (7.1) ms, 5.9 (9.6) ms, 7.4 (10.9) ms and 8.5 (12.4) ms following doses of 10, 20, 30 and 50 mcg, respectively. The QT IRT team

determined that the study did not demonstrate a significant effect of olodaterol on the QTcF.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant clinical studies with olodaterol

| ID [Year*] | Study Characteristics - Patient age, mean (range) - Patient characteristics - Study design, objective - Study duration | Treatment groups † | N ‡ | Efficacy variables § | Countries or Region (% US patients) |
|---|--|---|----------------------------|---|-------------------------------------|
| <i>Dose-ranging and dose-regimen studies in asthma patients</i> | | | | | |
| 1222.4 [2006] | - 29 (19-53) yrs - Asthma - Crossover, dose ranging - Single dose | Olo 2 mcg Olo 5 mcg Olo 10 mcg Olo 20 mcg Placebo | 31 | 1 ^o : PC 20 FEV ₁ at 24 hr 2 ^o : PC 20 FEV ₁ at 0.5, 4, 8, 8, and 32 hr | Canada (0% US) |
| 1222.6 [2008] | - 45 (18-91) yrs - Asthma - Parallel arm, dose ranging - 4 weeks | Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD Placebo | 61 60 60 61 54 | 1 ^o : ΔFEV ₁ trough at wk 4 2 ^o : PEFR at wk 4 | USA, Canada, Europe (21% US) |
| 1222.27 [2011] | - 45 (18-70) yrs - Asthma - Crossover, dose ranging - 4 weeks | Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD For 12 mcg BID Placebo | 198 | 1 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 4 2 ^o : ΔFEV ₁ trough, ΔFEV ₁ AUC _{0-12 hr} , and ΔFEV ₁ AUC _{12-24 hr} at wk 4 | Europe (0% US) |
| 1222.29 [2011] | - 44 (19-69) yrs - Asthma - Crossover, dose regimen - 3 weeks | Olo 2.5 mcg BID Olo 5 mcg QD Olo 5 mcg BID Olo 10 mcg QD Placebo | 206 | 1 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 3 2 ^o : ΔFEV ₁ AUC _{0-12 hr} , and ΔFEV ₁ AUC _{12-24 hr} at wk 3 | USA, Europe (31% US) |
| <i>Dose-ranging and dose-regimen studies in COPD patients</i> | | | | | |
| 1222.3 [2006] | - 65 (45-86) yrs - COPD - Crossover, dose ranging - Single dose | Olo 2 mcg Olo 5 mcg Olo 10 mcg Olo 20 mcg Placebo | 36 | 1 ^o : ΔFEV ₁ trough at 24 hr 2 ^o : ΔFEV ₁ AUC _{0-3 hr} , ΔFEV ₁ AUC _{0-12 hr} , ΔFEV ₁ AUC _{0-24 hr} , ΔFEV ₁ AUC _{12-24 hr} at 24 hr | Netherlands (0% US) |
| 1222.5 [2008] | - 63 (40-86) yrs - COPD - Parallel arm, dose ranging - 4 weeks | Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD Placebo | 81 80 86 79 79 | 1 ^o : ΔFEV ₁ trough at wk 4 2 ^o : ΔFEV ₁ trough, ΔFEV ₁ AUC _{0-3 hr} , at wk 1 and wk 2 | USA, Canada, Europe (51% US) |

| ID [Year*] | Study Characteristics - Patient age, mean (range) - Patient characteristics - Study design, objective - Study duration | Treatment groups † | N ‡ | Efficacy variables § | Countries or Region (% US patients) |
|--|--|---|--------------------------|--|--|
| 1222.26 [2009] | - 66 (42-78) yrs - COPD - Crossover, dose regimen - 3 weeks | Olo 2 mcg BID Olo 5 mcg QD Olo 5 mcg BID Olo 10 mcg QD | 47 | 1 ^o : ΔFEV ₁ AUC _{0-12 hr} and ΔFEV ₁ AUC _{12-24 hr} at wk 3 2 ^o : ΔFEV ₁ trough, and ΔFEV ₁ AUC _{0-24 hr} at wk 3 | Europe (0% US) |
| Pivotal COPD studies: 48-week spirometry | | | | | |
| 1222.11 Trial 1 [2010] | - 65 (40-87) yrs - COPD - Parallel arm - 48 weeks | Olo 5 mcg QD Olo 10 mcg QD Placebo | 208 207 209 | 1 ^o : ΔFEV ₁ trough at wk 12 ΔFEV ₁ AUC _{0-3 hr} at wk 12 2 ^o : Moderate exacerbation ΔFEV ₁ AUC _{0-12 hr} at wk 12 | USA, Asia, Australia & N Zealand (~41% US) |
| 1222.12 Trial 2 [2010] | - 65 (40-84) yrs - COPD - Parallel arm - 48 weeks | Olo 5 mcg QD Olo 10 mcg QD Placebo | 209 217 216 | 1 ^o : ΔFEV ₁ trough at wk 12 ΔFEV ₁ AUC _{0-3 hr} at wk 12 2 ^o : Moderate exacerbation ΔFEV ₁ AUC _{0-12 hr} at wk 12 | USA, Asia, Europe (~53% US) |
| 1222.13 Trial 3 [2010] | - 64 (40-89) yrs - COPD - Parallel arm - 48 weeks | Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo | 227 225 227 225 | 1 ^o : ΔFEV ₁ trough at wk 24 ΔFEV ₁ AUC _{0-3 hr} at wk 24 Mahler TDI focal score 2 ^o : Moderate exacerbation SGRQ at wk 24 | Europe, Asia, Africa (0% US) |
| 1222.14 Trial 4 [2010] | - 64 (40-88) yrs - COPD - Parallel arm - 48 weeks | Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo | 232 234 233 235 | 1 ^o : ΔFEV ₁ trough at wk 24 ΔFEV ₁ AUC _{0-3 hr} at wk 24 Mahler TDI focal score 2 ^o : Moderate exacerbation SGRQ at wk 24 | Europe, Asia, Africa (0% US) |
| Profiling studies in COPD patients: 6-week spirometry profile | | | | | |
| 1222.24 Trial 5 [2010] | - 62 (43-86) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo | 99 | 1 ^o : ΔFEV ₁ AUC _{0-12 hr} at wk 6 ΔFEV ₁ AUC _{12-24 hr} at wk 6 2 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 6 | USA (100% US) |
| 1222.25 Trial 6 [2010] | - 64 (45-82) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo | 100 | 1 ^o : ΔFEV ₁ AUC _{0-12 hr} at wk 6 ΔFEV ₁ AUC _{12-24 hr} at wk 6 2 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 6 | USA (100% US) |
| 1222.39 Trial 7 [2010] | - 62 (44-79) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD Tio 18 mcg QD Placebo | 108 | 1 ^o : ΔFEV ₁ AUC _{0-12 hr} at wk 6 ΔFEV ₁ AUC _{12-24 hr} at wk 6 2 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 6 | Europe (0% US) |
| 1222.40 Trial 8 [2011] | - 63 (45-79) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD Tio 18 mcg QD Placebo | 122 | 1 ^o : ΔFEV ₁ AUC _{0-12 hr} at wk 6 ΔFEV ₁ AUC _{12-24 hr} at wk 6 2 ^o : ΔFEV ₁ AUC _{0-24 hr} at wk 6 | Europe (0% US) |
| Profiling studies in COPD patients: 6-week exercise endurance | | | | | |
| 1222.37 Trial 9 [2011] | - 61 (41-74) yrs - COPD - Crossover, Exercise - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD Placebo | 151 | 1 ^o : Endurance time at wk 6 2 ^o : Breathing discomfort intensity at isotime FRC and IC at isotime | Europe, Canada, Australia (0% US) |
| 1222.38 Trial 10 [2011] | - 61 (41-75) yrs - COPD - Crossover, Exercise - 6 weeks | Olo 5 mcg QD Olo 10 mcg QD Placebo | 151 | 1 ^o : Endurance time at wk 6 2 ^o : Intensity of breathing discomfort at isotime FRC and IC at isotime | Europe, Canada (0% US) |

* Study ID shown (top to bottom) as BI's study number, as referenced in the proposed olodaterol product label, and [year study subject enrollment ended]

† Olo = Olodaterol inhalation spray; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder);

‡ Number randomized and received at least one dose

| ID [Year*] | Study Characteristics - Patient age, mean (range) - Patient characteristics - Study design, objective - Study duration | Treatment groups † | N ‡ | Efficacy variables § | Countries or Region (% US patients) |
|--|--|-----------------------|-----|----------------------|--|
| § Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal 48 week studies and profiling 6 week studies were mixed model for repeated measure (MMRM). | | | | | |

b. Design and conduct of the studies

Dose ranging (1222.4, 1222.6, and 1222.27) and dose regimen (1222.29) studies in patients with asthma:

Study 1222.4 was a crossover, single dose, dose-ranging trial in patients with intermittent asthma. Patients were randomized to receive a sequence of single doses of various doses of olodaterol and placebo (Table 1). Following administration of study medication patients received a series of methacholine challenges. The primary endpoint was the provocative concentration of methacholine required to cause a 20% fall in FEV1 from baseline [$\text{Log}_2(\text{PC}20 \text{ FEV}1)$] at 24 hours following treatment. This is not an acceptable method of dose-ranging study; therefore, this study will not be discussed further in this review.

Study 1222.6 was a parallel arm, multiple dose, dose-ranging study in patients with asthma ($\text{FEV}1 \geq 60\%$ and $< 90\%$ predicted). Study 1222.27 was a crossover, multiple dose, dose-ranging study in patients with asthma who were on ICS and were still symptomatic. Study 1222.29 was a crossover, multiple dose, dose-regimen study in patients with moderate to severe persistent asthma. Various treatment arms and primary and secondary efficacy variables for the studies are shown in Table 1.

Dose ranging (1222.3, and 1222.5) and dose regimen (1222.26) studies in patients with COPD:

Study 1222.3 was a crossover, single dose, dose-ranging study in patients with COPD. For inclusion in the trial, patients were required to have an $\text{FEV}1 \leq 60\%$ predicted and demonstrate airway reversibility following albuterol administration ($\geq 12\%$ improvement). Study 1222.5 was a parallel arm, multiple-dose, dose-ranging study in patients with COPD. Patients were required to have an $\text{FEV}1 \geq 30\%$ and $< 80\%$ predicted. Study 1222.26 was a crossover, multiple-dose, dose regimen study in patients with moderate to severe stable COPD. Various treatment arms and primary and secondary efficacy variables for the studies are shown in Table 1.

Pivotal 48-week studies in patients with COPD (1222.11, 1222.12, 1222.13, and 1222.14):

Studies 1222.11 and 1222.12 were identical in design. These were parallel group studies conducted in patients with COPD with $\text{FEV}1$ of $< 80\%$ predicted, $\text{FEV}1/\text{FVC}$ ratio of $< 70\%$ predicted, and with at least a 10 pack year smoking history. Patients with asthma were excluded. These studies allowed standard of care background therapy with short-

acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics (including tiotropium), and methylxanthines in all treatment groups. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and Holter monitoring in a subset of patients.

Studies 1222.13 and 1222.14 were also identical in design. The studies were similar in design to 1222.11 and 1222.12 except for the addition of an active comparator arm of formoterol and inclusion of additional endpoints related to dyspnea and quality of life. These studies also allowed standard of care background therapy. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Spirometry profiling 6-week studies in patients with COPD (1222.24, 1222.25, 1222.39, and 1222.40):

Studies 1222.24 and 1222.25 were identical studies conducted to characterize the 24-hour FEV time profile of olodaterol. These were cross-over studies conducted in patients with COPD with $\text{FEV}_1 \leq 80\%$ predicted. The studies included formoterol as an active comparator. Studies 1222.39 and 1222.40 were similar to studies 1222.24 and 1222.25 except that they included tiotropium as active comparator. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. In studies 1222.24 and 1222.25, patients were permitted to continue long-acting muscarinic antagonists (LAMAs); however, LABAs were prohibited. In studies 1222.39 and 1222.40, both LABAs and LAMAs were prohibited.

Exercise endurance 6-week studies in patients with COPD (1222.37 and 1222.38):

Studies 1222.37 and 1222.38 were identical in design conducted to assess exercise endurance response of olodaterol. These were crossover studies conducted in patients with moderate to severe COPD with an exercise endurance time of at least 25 minutes at baseline. Patients were allowed to take ICS, methylxanthines, and short acting anticholinergics during the trial. However, LABAs and tiotropium were not permitted. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Endurance time was assessed by constant rate cycle ergometry to symptom limitation at 75% maximal work capacity. Isotime was defined as the endurance time of constant work rate exercise of shortest duration at 75% maximal work capacity. Intensity of breathing discomfort as measured by the Borg Scale at isotime.

c. Efficacy findings and conclusions

The clinical program showed that olodaterol 5 mcg and 10 mcg once-daily doses (two actuations of 2.5 mcg per actuation) provided a statistically significant bronchodilatory effect compared to placebo in patients with COPD, with replicate findings for both doses.

There were no statistically significant differences between the olodaterol 5 mcg and 10 mcg doses. The olodaterol 5 mcg and 10 mcg once-daily doses also demonstrated a statistically significant difference in exercise endurance measures compared to placebo in patients with COPD; however, the effect sizes were small and the effect was only assessed at peak bronchodilatory effect time point and at 6 weeks. The submitted data support approval of BI's proposed dose of olodaterol 5 mcg once-daily as a bronchodilator treatment in patients with COPD, but do not support an exercise endurance claim for olodaterol.

Dose ranging and dose regimen:

As discussed in section 2 above, selection of appropriate dose and dosing regimen is an important consideration for development of LABAs, and these studies need to be conducted in patients with asthma in addition to COPD because the bronchodilator response is greater in bronchoresponsive patients, such as patients with asthma who can show larger separation between doses. BI conducted adequate exploration of dose ranges and dose regimens in patients with asthma and COPD (Table 1). In dose ranging studies conducted, olodaterol doses from 2 mcg to 20 mcg were explored, both in patients with asthma and COPD. In these studies olodaterol 5 mcg and 10 mcg doses produced adequate bronchodilator response, the 20 mcg dose did not appear to produce further benefit, and the 2 mcg dose appeared to be suboptimal (results from two representative studies are shown in Figure 1). In dose regimen studies olodaterol 5 mcg and 10 mcg once daily doses were compared to similar total daily nominal doses given twice daily, both in patients with asthma and in COPD. In the asthma study, a small numerical benefit of twice daily dose over once daily dose was seen, but the benefit was small and seen in the second half of the 24-hour dosing interval, which was not sufficient to favor a twice daily dosing for olodaterol (data not shown in this review). The COPD study did not show benefit of twice daily dose over once daily dose (Figure 2). These data support once daily dosing regimen for olodaterol. Based on these studies, and with Agency concurrence, BI selected olodaterol 5 mcg and 10 mcg once daily doses for further evaluation in confirmatory COPD studies. Inclusion of two doses in confirmatory COPD studies provides additional dose response information for both efficacy and safety and further informs dose selection.

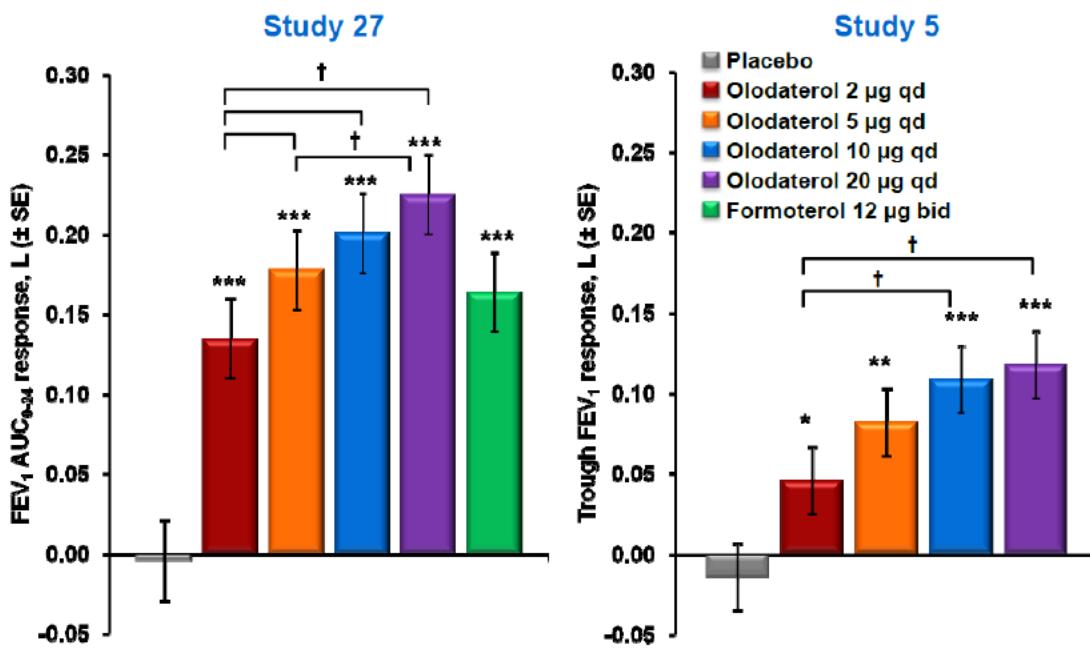


Figure 1. Dose ranging studies in asthma (1222.27) and COPD (1222.5); mean (SE) $\Delta\text{FEV}_1 \text{AUC}_{0-24 \text{ hr}}$ response at week 4 (Source: BI presentation at PADAC held on January 29, 2013).

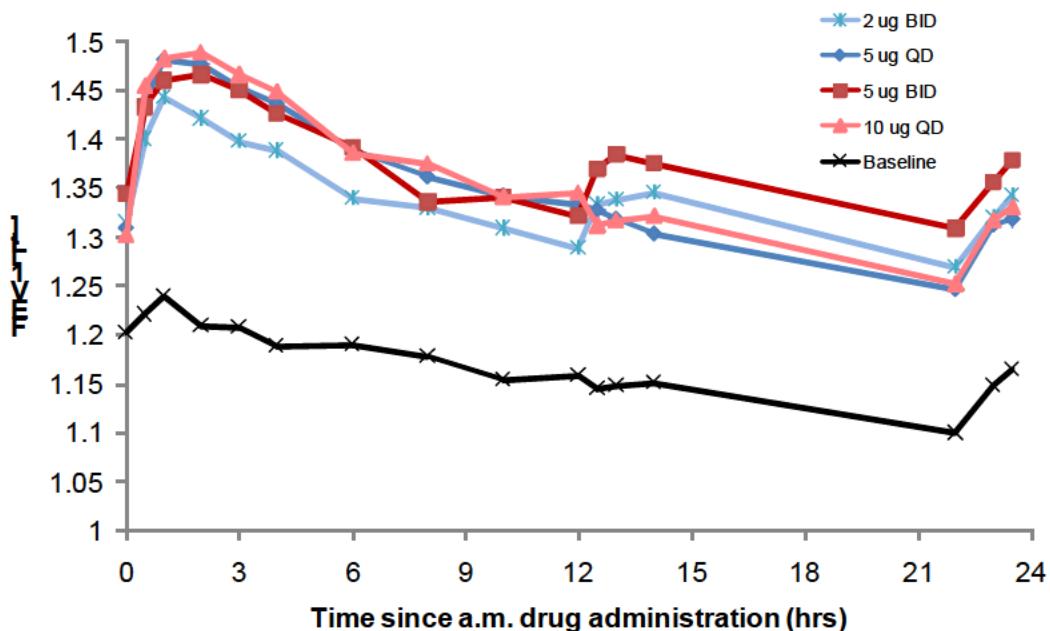


Figure 2. COPD dose regimen study 1222.26; FEV1 time profile for 24 hour after olodaterol administered QD (5 mcg and 10 mcg) and BID (2 mcg and 5 mcg). Horizontal axis is time since olodaterol administration in hours and vertical axis is FEV1 in liters.

Bronchodilator effects:

The results for the primary efficacy variables for the 48-week COPD studies are shown in Table 2. For ease of comparison, data from week 12 are shown for all studies, although the primary efficacy endpoints for studies 1222.13 and 1222.14 were at week 24. The results show that olodaterol 5 mcg once daily and 10 mcg once daily doses were statistically significantly superior to placebo for the primary endpoints with the exception of study 1222.12 in which the 5 mcg olodaterol group was not significant for trough FEV₁. Results at weeks 24 and 48 were generally comparable to results at week 12. Comparison of the two doses of olodaterol shows that the 5 mcg and 10 mcg were generally similar (Table 2, Figure 3). Olodaterol had a fairly rapid onset of bronchodilator effect after first dose, and the bronchodilator effect was sustained over 12 weeks, with a numerical trend of a blunted peak effect at week 12 that may be due to tachyphylaxis often seen with beta-agonists (Figure 4). In Figure 4 the box on the top panel shows the onset of effect after first dose, and the box on the bottom panel shows shift of baseline after 12 weeks of treatment that possibly reflects the bronchodilator effect from the previous dose. The 6-week studies, which profiled FEV₁ over 24 hours, showed a bronchodilator effect of olodaterol over the 24-hour dosing interval, and responses were comparable with two active comparators (Figure 5). Based on these data, along with dose ranging data, BI proposed a 5 mcg once daily dose for marketing approval, which is reasonable.

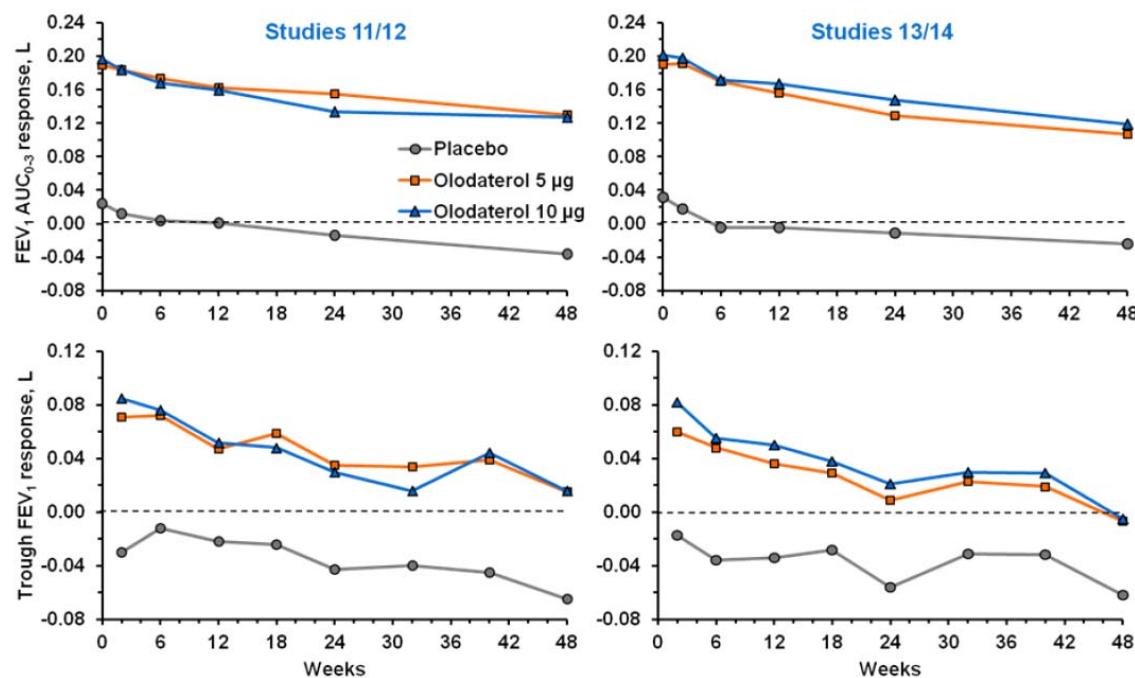
The observed effect size for olodaterol across studies appeared to be smaller than that observed in previous registration trials for other LABAs for COPD. The mean treatment effect across trials for trough FEV₁ was 65 mL. For FEV₁ AUC_{0-3 hr} the mean treatment effect across trials was 155mL. The smaller treatment effects were possibly due to the olodaterol study design that allowed for patients to continue COPD background treatments, except for LABAs, which was not the case in previous COPD development programs. In studies where formoterol was included as an active comparator, the treatment effect of olodaterol was generally comparable to the observed treatment effect of formoterol (Table 2, Figure 5).

Olodaterol 5 mcg demonstrated a bronchodilatory treatment effect at 5 minutes after the first dose with a mean increase in FEV₁ compared to placebo of 110 mL (range 100 to 120 mL).

Table 2. 48-week COPD studies; Δ FEV₁ trough and Δ FEV₁ AUC_{0-3 hr} at week 12 (co-primary efficacy end point)

| Study | Treatment | N | Trough FEV ₁ Response | | FEV ₁ AUC _{0-3 hr} Response | |
|---------|---------------|-----|----------------------------------|----------------------|---|----------------------|
| | | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| 1222.11 | Placebo | 188 | -0.032 | | 0.002 | |
| | Olo 5 mcg QD | 192 | 0.052 | 0.084 (0.040, 0.129) | 0.167 | 0.164 (0.120, 0.209) |
| | Olo 10 mcg QD | 192 | 0.048 | 0.080 (0.037, 0.124) | 0.157 | 0.155 (0.111, 0.199) |

| Study | Treatment | N | Trough FEV ₁ Response | | FEV ₁ AUC _{0-3 hr} Response | |
|---------|---------------|-----|----------------------------------|-----------------------|---|----------------------|
| | | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| 1222.12 | Placebo | 197 | 0.005 | | 0.021 | |
| | Olo 5 mcg QD | 196 | 0.038 | 0.033 (-0.013, 0.080) | 0.155 | 0.134 (0.090, 0.177) |
| | Olo 10 mcg QD | 201 | 0.049 | 0.045 (-0.001, 0.090) | 0.151 | 0.130 (0.087, 0.172) |
| 1222.13 | Placebo | 187 | -0.027 | | -0.003 | |
| | Olo 5 mcg QD | 208 | 0.056 | 0.083 (0.043, 0.123) | 0.176 | 0.178 (0.137, 0.219) |
| | Olo 10 mcg QD | 207 | 0.048 | 0.075 (0.035, 0.114) | 0.167 | 0.170 (0.129, 0.211) |
| | For 12 mcg BD | 200 | 0.033 | 0.059 (0.019, 0.100) | 0.182 | 0.185 (0.144, 0.226) |
| 1222.14 | Placebo | 212 | -0.041 | | -0.008 | |
| | Olo 5 mcg QD | 220 | 0.018 | 0.059 (0.022, 0.095) | 0.138 | 0.145 (0.108, 0.182) |
| | Olo 10 mcg QD | 219 | 0.052 | 0.093 (0.057, 0.130) | 0.167 | 0.175 (0.138, 0.212) |
| | For 12 mcg BD | 217 | 0.024 | 0.065 (0.028, 0.101) | 0.163 | 0.170 (0.133, 0.208) |



Common baseline mean (SE): Studies 11/12: 1.145 (0.014); Studies 13/14: 1.208 (0.011). Analysis with imputation (FAS).

Figure 3. Mean FEV1 AUC₀₋₃ and trough FEV₁ response over 48 weeks in COPD studies 1222.11 and 1222.12 (Source: BI presentation at PADAC held on January 29, 2013).

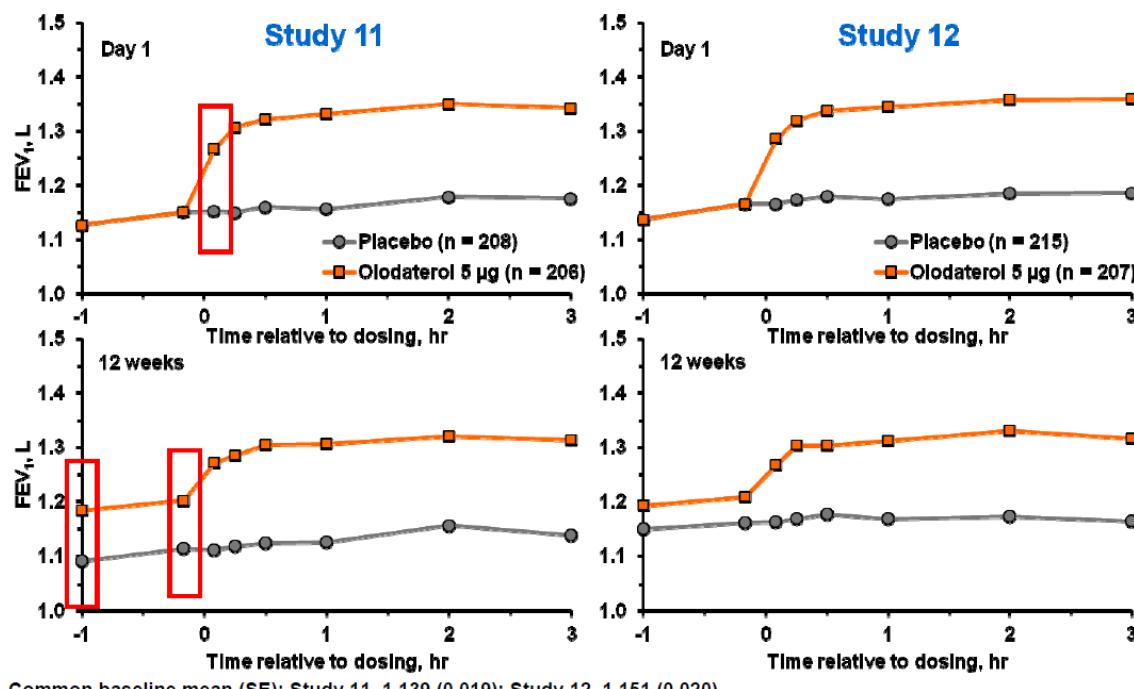


Figure 4. Adjusted mean FEV₁ response after dosing on treatment day 1 and after 12 weeks in COPD studies 1222.11 and 1222.12 (Source: BI presentation at PADAC held on January 29, 2013).

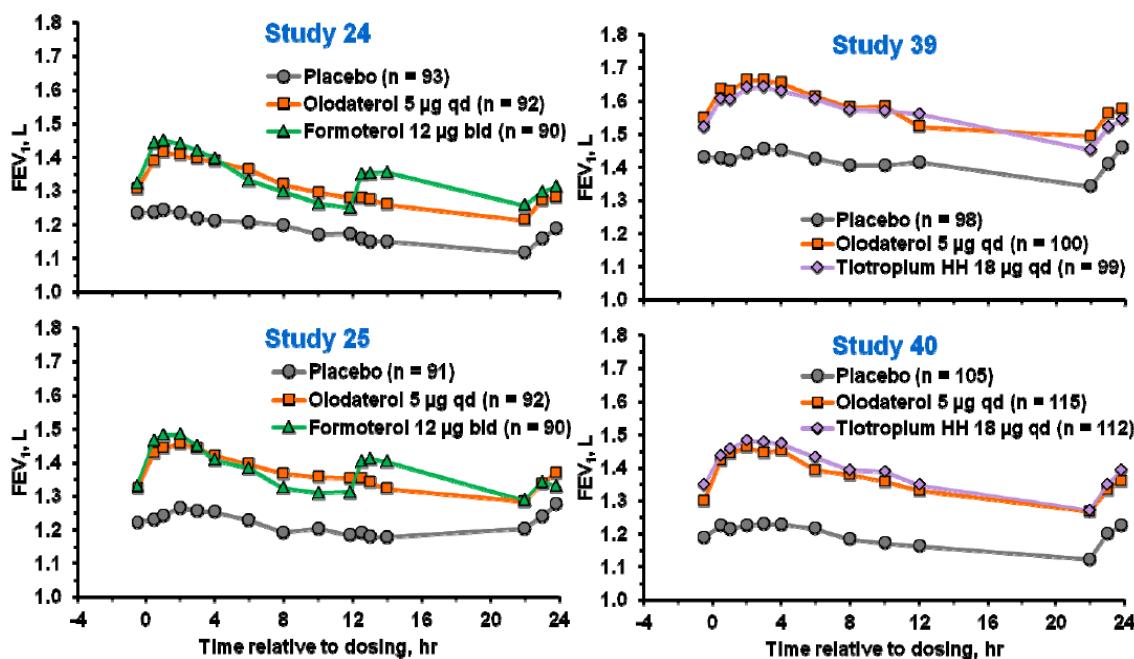


Figure 5. Adjusted mean FEV₁ response over 24 hours after 6 weeks of treatment in COPD studies 1222.24, 1222.25, 1222.39, and 1222.40 (Source: BI presentation at PADAC held on January 29, 2013).

SGRQ:

BI initially proposed to include SGRQ claims in the proposed label based on results from studies 1222.13 and 1222.14, but later in the review cycle submitted a revised label removing SGRQ claims. In one of the two studies, a statistically significant difference of 3.15 in mean total SGRQ scores was observed between olodaterol 5 mcg and placebo, which is below the threshold of the minimally important difference (MID) of -4 units or more for the SGRQ total score. The MCID of -4 for SGRQ has support in the literature.^{14, 15}

Exercise endurance:

BI proposes to include exercise endurance claims in the proposed label based on results of improvement in exercise endurance time, and reduced lung hyperinflation (decreased in functional residual capacity or FRC) resulting in increased inspiratory capacity (IC) from two 6-week studies (Table 1). Results of the two studies show statistically significant differences between olodaterol and placebo for these measures (Table 3); however, clinical interpretation of statistical significance is not straightforward for variety of reasons. First, the minimal clinically important difference (MCID) for exercise endurance in drug trials in patients with COPD is unknown. Clinical studies evaluating effects of pulmonary rehabilitation suggest that the MCID may be around a 101-153 second improvement from baseline (34%)^{16,17}. However, these results are not universally accepted or validated, and it is unclear if the results in pulmonary rehabilitation would also pertain to drug trials. For inspiratory capacity, the MCID is likewise unknown. Second, the relationship between a magnitude of effect demonstrated in the olodaterol studies to any activity of daily living that relates to exercise in COPD patients is not known. Third, exercise testing was performed approximately 2 hours post-dose, which correspond to the time at which the bronchodilator effect of olodaterol has reached its peak. It is not known if the benefit with olodaterol would persist later in the dosing period. Fourth, studies lasting for 6 weeks are not adequate to show sustainability of effect. For comparison, studies to show bronchodilator efficacy are at least 12 weeks in duration, and studies to show exacerbation efficacy are 6 to 12 months in duration. Finally, no other bronchodilator drugs approved for COPD in the United States has an exercise endurance claim, and these products potentially could show similar numerical changes if studied. The pharmacological effect of olodaterol is likely to be similar to other beta-agonists.

¹⁴ Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19:398-404.

¹⁵ Jones PW. St. George's Respiratory Questionnaire: MCID. J of COPD 2005; 2:75-79.

¹⁶ Lavoie L, Bourbeau J, Bernard S, et al. Assessing the impact of pulmonary rehabilitation on functional status in COPD. Thorax. 2008 Feb;63(2):115-21.

¹⁷ Puente-Maestu L, Villar F, et al. Clinical relevance of constant power exercise duration changes in COPD. Eur Respir J. 2009 Aug;34(2):340-5.

The proposed wordings for inclusion of an exercise claim in the Clinical Trials section of olodaterol product label are not supported by the submitted data. To support such labeling claim, reasonable expectation would be that olodaterol treatment demonstrates a benefit in some exercise related activity of daily living in COPD patients, or a benefit in exercise endurance test based measures with effect sizes that cross accepted MCIDs. In either scenario, the benefit will need to be demonstrated at various relevant time points of the day after dosing, and over at least 6 months of treatment. Lack of accepted MCIDs for exercise endurance test based measures makes studies challenging. Development of MCIDs for such measure will likely need linking the measures to some exercise related activity of daily living in COPD patients.

Table 3. 6-week COPD studies; Exercise endurance time in seconds and inspiratory capacity in liters at week 6

| Study | Treatment | Endurance Time (sec) | | Inspiratory Capacity (L) | |
|---------|---------------|----------------------|---------------------|--------------------------|----------------------|
| | | Mean | Change (95% CI) | Mean | Change (95% CI) |
| 1222.37 | Placebo | 369.8 | | 1.887 | |
| | Olo 5 mcg QD | 421.6 | 1.14 (1.065, 1.221) | 2.067 | 0.180 (0.107, 0.252) |
| | Olo 10 mcg QD | 420.7 | 1.14 (1.062, 1.219) | 2.024 | 0.137 (0.064, 0.210) |
| 1222.38 | Placebo | 354.3 | | 2.158 | |
| | Olo 5 mcg QD | 396.3 | 1.12 (1.043, 1.199) | 2.236 | 0.078 (0.010, 0.146) |
| | Olo 10 mcg QD | 391.5 | 1.10 (1.030, 1.184) | 2.330 | 0.172 (0.105, 0.240) |

8. Safety

a. Safety database

The safety assessment of olodaterol is based primarily on studies shown in Table 1. A total of 3353 patients with COPD and a total of 731 patients with asthma were exposed to olodaterol in various studies. Of the COPD patients, 3142 were exposed to olodaterol 5 mcg or 10 mcg in parallel group or cross-over studies. The 48-week parallel group studies included a total of 3104 patients, of whom 1759 patients were exposed to olodaterol 5 mcg or 10 mcg. The safety database for olodaterol was reasonable. Given that the 5 mcg dose is proposed for marketing, the 10 mcg dose provides important supporting safety data.

b. Safety findings and conclusion

The submitted data support safety of olodaterol for use as a maintenance bronchodilator treatment of airflow obstruction in patients with COPD at a dose of 5 mcg once daily.

A major safety concern with LABAs is linked to selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators, including olodaterol, which is proposed to be marketed for COPD. Marketing an unnecessary and unreasonably high dose has safety concerns. BI conducted adequate dose ranging and dose regimen studies and selected 5 mcg and 10 mcg once daily doses for pivotal confirmatory studies. Of the two doses, BI is proposing

to market the lower 5 mcg dose because there was no separation between the two doses. This is a very reasonable strategy from a safety perspective. Safety data from the asthma program, though limited, did not show a signal of severe asthma exacerbation. The safety findings noted in the COPD program were not concerning and typical of beta-agonist bronchodilators.

BI conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs¹⁸), adverse events (AEs), and also specific analyses of Major Adverse Cardiac Events (MACE) endpoints and respiratory adverse events. All deaths and SAEs were adjudicated by independent committees. BI also collected vital status information out to 337 + 14 days (50 weeks) for patients who discontinued from the studies. Overall, vital status data are available for 98% of all patients randomized in the 48-week trials. Safety data from the 48-week studies were most informative.

A total of 53 on-treatment deaths were reported in the 48-week studies. These were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure, and pneumonia, which are expected causes of death in older COPD patients. A total of 499 patients with SAEs (fatal and non-fatal) were reported in the 48-week studies. There were also balanced among the treatment causes, and the events were typical and expected in COPD patients. The number of deaths and SAEs in other studies was also balanced and did not raise any concerns.

There was a small imbalance in the olodaterol 10 mcg group compared to placebo for neoplasms, primarily lung-related malignancies. Overall, there were 9 (1.0%), 14 (1.6%), 19 (2.2%), and 8 (1.7%) neoplasms in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. The rate per 100 patient years is 1.94, 2.89, 4.24, and 2.84 in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 2, 3, 6, and 4 malignant lung neoplasms in placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. Approximately half of the total malignant lung neoplasms, including 2 of the small cell lung carcinomas, were diagnosed within 5 months of beginning of randomized treatment. Given the small number of neoplasms, short lead-time to the diagnosis of neoplasms, and lack of similar findings in animal carcinogenicity studies, it is not likely that this is a safety signal.

Cardiovascular adverse events are a specific safety event of interest for beta-adrenergic agonist drugs because of their known pharmacologic effects. An adjudicated analysis of MACE did not reveal any concerns. Fatal MACE events occurred in 8 (0.9%), 3 (0.3%), 3 (0.3%), and 6 (1.3%) of patients in the placebo, olodaterol 5 mcg, olodaterol 10 mcg,

¹⁸ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

and formoterol groups, respectively. Likewise, nonfatal MACE events were generally balanced.

Other safety assessments, such as ECGs, Holter monitoring and a thorough QT study, did not show any cardiac safety signals. Analysis of common adverse events and laboratory parameters and common adverse events also did not show any specific findings of concern.

c. REMS/RiskMAP

BI submitted a REMS for olodaterol consisting of a Medication Guide and a communication plan regarding LABA safety of asthma related death. The communication plans included a Health Care Professional Letter, information posted on a website, and notification of professional societies.

Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. The information regarding LABA safety and asthma-related death has been widely distributed to health care providers with demonstrated uptake of the information into clinical practice; the communication plan REMS requirements for other LABAs are currently being removed. Thus, while a Medication Guide is required to communicate the potential risks of olodaterol, a Medication Guide as part of REMS is not necessary.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on January 29, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indication, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for olodaterol 5 mcg once daily for its proposed indication. In general, the panel members concluded that there were sufficient data to support the efficacy of olodaterol for the proposed indication. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy (15 yes, 1 no, and 1 abstain), and also voted favorably on the safety of olodaterol (15 yes, 1 no, and 1 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval (15 yes, 1 no, and 1 abstain). Overall, members felt that BI had conducted a rigorous, well-designed program that was strengthened by the inclusion of usual care background therapy. The only safety issue of concern was the occurrence of 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. Members noted that while this may have been a random occurrence, appropriate post-marketing surveillance is warranted.

The committee was asked to discuss the finding of the exercise endurance studies. There was no voting question on exercise endurance because this was not an indication that BI was seeking and for complexity of the data discussed in section 7 above. The committee

observed that exercise tolerance is an important endpoint for patients, and many members expressed support for inclusion of exercise endpoints in pharmaceutical trials in COPD. However, members noted that more information is needed to understand the optimal design of exercise trials for COPD and MCID of exercise endpoints. Several members recommended that FDA hold a scientific meeting to discuss exercise. With regard to the BI studies, members requested additional data at later time-points after administration of the drug as well as longer duration trials. One member also wanted to see correlation of exercise endpoints with symptoms and activities of daily living.

10. Pediatric

BI is requesting a claim for olodaterol for COPD only and is not requesting a claim for asthma. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required that relate to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited three clinic sites that enrolled patients in the pivotal 48-week studies and the BI site. The clinical review team recommended the clinic sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had significant financial interest in BI. The number of subjects enrolled in the investigator site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP (formerly known as DDMAC), DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

BI initially submitted [REDACTED] ^{(b) (4)} as the proposed proprietary name. The DMEPA rejected this proposed name because [REDACTED] ^{(b) (4)} BI subsequently submitted Striverdi Respimat as the proposed proprietary name, which was accepted by the DMEPA.

b. Physician Labeling

BI submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Clinical Trials section related to exercise endurance was not allowed due to reasons discussed in section 7 above. Asthma-related safety warnings are described in the label, including in a Boxed Warning, which are present in all LABAs. The Division and BI have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Olodaterol will carry an asthma-related safety warning that will be part of the Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

BI has submitted adequate data to support approval of Striverdi Respimat (olodaterol inhalation spray) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, at a dose of 5 mcg once daily. Manufacturing and testing facilities associated with the drug substance and drug product do not have an acceptable GMP recommendation from Office of Compliance, which will preclude approval of this application in this review cycle. The recommended regulatory action on this application is Complete Response.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of olodaterol inhalation spray at a dose of 5 mcg once daily for long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema.

A major safety concern with olodaterol is linked to selection of appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators. BI conducted a comprehensive program, including dose ranging through pivotal confirmatory studies, to select the 5 mcg once daily dose. The submitted safety data do not show safety findings of unique concerns with olodaterol. From an efficacy standpoint, the clinical program showed that olodaterol at 5 mcg once-daily dose provided statistically significant replicate bronchodilator effect with effect. Although the observed effect size for olodaterol across studies appeared to be somewhat lower than

that observed in previous registration trials for other LABAs for COPD, the effect sizes were comparable to other marketed bronchodilators when they were compared in the olodaterol program where the background therapy across treatment groups were similar.

c. Post-marketing Risk Management Activities

Olodaterol will carry an asthma-related safety warning that will be part of the Medication Guide. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY

03/13/2013

CLINICAL REVIEW

| | |
|------------------------|--|
| Application Type | NDA |
| Application Number(s) | 203,108 |
| Priority or Standard | Standard |
| Submit Date(s) | 5/14/2012 |
| Received Date(s) | 5/14/2012 |
| PDUFA Goal Date | 3/14/2013 |
| Division / Office | DPARP/ODEII |
| Reviewer Name(s) | Robert H. Lim, MD |
| Review Completion Date | 1/17/2013 |
| Established Name | Olodaterol |
| (Proposed) Trade Name | Striverdi |
| Therapeutic Class | Long acting beta-agonist |
| Applicant | Boehringer-Ingelheim |
| Formulation(s) | oral inhalation |
| Dosing Regimen | 5mcg daily |
| Indication(s) | For the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema |
| Intended Population(s) | Adult |

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At the time of this review, the recommended regulatory action, from a clinical prospective, is Approval of olodaterol inhalational solution (Olo) 5mcg (2 actuations of 2.5mcg/actuation) once daily (qD) 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. Note that an Pulmonary Allergy Drug Advisory Committee (PADAC) is scheduled for 1/29/13 to discuss the safety and efficacy of this product. Based on the discussion, the recommended regulatory action may be subject to change.

1.2 Risk Benefit Assessment

The core development program to support olodaterol 5mcg qD consisted of 3 dose-ranging trials in COPD patients (1222.3, 1222.5, 1222.26), 4 dose ranging trials in asthma patients (1222.4, 1222.6, 1222.27, and 1222.29), 4 forty-eight week efficacy and safety trials (1222.11, 1222.12, 1222.13, 1222.14), 2 six week treatment period crossover exercise endurance trials (1222.37, 1222.38), and 4 six week treatment period crossover 24 hour spirometry trials (1222.24, 1222.25, 1222.39, 1222.40).

Support for efficacy is derived primarily from the four parallel group 48-week COPD trials, two of which were conducted primarily in the United States (US) and two of which were conducted primarily in Europe (EU). These trials shared the same spirometric co-primary endpoints of forced expiratory volume in 1 second (FEV1) AUC (0-3 hours) response and trough FEV1. The two US trials (1222.11 and 1222.12) were 3-arm trials which assessed the co-primary endpoints after 12 weeks of treatment. The two EU trials (1222.13 and 1222.14) were 4-arm trials including the active comparator formoterol and assessed the co-primary endpoints after 24 weeks. Trials 1222.13 and 1222.14 also included a third non-spirometric co-primary endpoint of Mahler Transitional Dyspnea Index (TDI) score assessed at 24 weeks and the key secondary endpoint of the Saint George's Respiratory Questionnaire (SGRQ).

Bronchodilator effects

In three (1222.11, 1222.13, and 1222.14) of the four 48 week COPD trials, olodaterol 5mcg demonstrated significant improvements in both spirometric co-primary endpoints. For trial 1222.12, results were only statistically significant for FEV1 AUC (0-3 hours) response, but not trough FEV1 response when using the protocol-specified analysis. The difference from placebo for FEV1 AUC (0-3 hours) response in trials 1222.11, 1222.12, 1222.13, and 1222.14 were 0.164, 0.134, 0.151, and 0.129L (all p-values

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<0.0001), respectively. For trough FEV₁ response, the differences from placebo were 0.084 (p=0.0002), 0.033 (p>0.05), 0.078 (p=0.0002), and 0.053L (p=0.006), respectively. Based on these results, the effect size was relatively modest with respect to trough FEV₁. However, this may have been in part related to concomitant medications, as patients were allowed to continue on all maintenance COPD medications, except for LABAs. In these trials approximately 20-25% of patients were on tiotropium as background therapy. When the sponsor performed a stratified analysis based on baseline tiotropium usage, the difference between strata was not statistically significant. In the 6-week trials 1222.39 and 1222.40 in which LAMAs were prohibited as background therapy, the treatment effect of olodaterol 5mcg on trough FEV₁ after 6 weeks of treatment was higher at 0.133 and 0.134L, respectively (p<0.0001). It should also be noted that in trials 1222.13 and 1222.14 the treatment effect of olodaterol 5mcg was similar to the active comparator fomoterol.

Efficacy was further supported by the spirometric secondary endpoints in these trials. These secondary endpoints included FEV₁ AUC (0-3 hours) response at days 1, 43, 85, 169, and 337; and trough FEV₁ response at days 15, 43, 85, 169, and 337. At all time points and across all the 48 week trials, olodaterol 5mcg demonstrated a statistically significant improvement compared to placebo. The magnitude of the treatment effect at these time points was similar to that of the co-primary endpoints. It is of note that secondary endpoint analyses were not corrected for multiple comparisons. In distinction to the spirometric endpoints, olodaterol 5mcg had no statistically significant effect on Mahler TDI scores. With regard to SGRQ, while there were statistically significant differences between olodaterol 5mcg and placebo, the differences were consistently less than the minimal clinically important difference (MCID) of 4.

The 4 six week crossover trials (1222.24, 1222.25, 1222.39 and 1222.40) were also supportive of a bronchodilatory effect. These trials were meant to characterize the 24-hour FEV₁ time profile of olodaterol. In all trials, statistically significant improvements were demonstrated for both co-primary endpoints [FEV₁ AUC(0-12 hours) and FEV₁ AUC(12-24hours)] for the olodaterol 5mcg dose compared to placebo. The difference from placebo for FEV₁ AUC (0-12 hours) response in trials 1222.24, 1222.25, 1222.39, and 1222.40 were 0.148, 0.172, 0.185, 0.197L (all p-values <0.0001), respectively. For FEV₁ AUC(12-24 hours) response, the differences from placebo were 0.109, 0.118, 0.131, 0.153L (p<0.0001), respectively. However, whether or not this data is applicable to later time points (i.e. 12 and 24 weeks) and appropriate for inclusion in the label is questionable. In the 48-week COPD trials, in the majority of trials, the treatment effect was numerically greater at 6 weeks versus 12 or 24 weeks. As such, the results from these 6 week treatment period cross-over trials may not accurately reflect the 24-hour spirometry at later time points.

Overall, based on the totality of the data, olodaterol 5mcg appears to have a clinically significant effect on bronchodilation. Although the magnitude of the treatment effect is somewhat modest in the 48-week trials, this may be related to the baseline COPD

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medications allowed in those trials. Whether or not the treatment effect in the setting of other baseline medications is sufficient to warrant a bronchodilator claim for olodaterol will be a topic of discussion at the January 29, 2013 PADAC meeting. The outcome of the discussion may affect the clinical recommendation.

Effects on exercise tolerance

To support their labeling claims for increased exercise tolerance, increased inspiratory capacity (IC) at rest and at end exercise, and reduced lung hyperinflation based on decreased functional residual capacity (FRC), the sponsor submitted the results from trials 1222.37 and 1222.38. These were 6-week treatment period cross-over trials with a primary endpoint of exercise endurance time (ET) during constant workrate cycle ergometry (CWRCE) at 75% maximal workload after 6 weeks of treatment. Maximal workload was determined using incremental cycle ergometry performed prior to receiving any trial medication. Key secondary endpoints included IC and intensity of breathing discomfort at isotime. Isotime was defined as ET during of the shortest during. CWRCE was performed 2 hours after trial medication was administered.

ET after 6 weeks of olodaterol 5mcg was statistically significantly greater than after 6 weeks of placebo. The treatment difference was 12-14% or 40-50 seconds across the two trials [baseline 374-414 seconds (geometric mean)]. ICs were also increased at isotime and at rest (trough and 1 hour post-dose) after receiving olodaterol 5mcg compared to placebo. Statistically significant differences for breathing discomfort as measured by the Borg Category Ratio Scale (BCRS) were only reported in trial 1222.37 and not 1222.38. This lack of replication implies that olodaterol does not improve breathing discomfort. For FRC, while it was statistically significantly decreased 1 hour post dose when comparing olodaterol 5mcg to placebo, this was not the case for the trough value. These data imply that the olodaterol 5mcg effect on FRC was not durable over the dosing interval. The clinical significance of the effect of olodaterol 5mcg on exercise tolerance and lung hyperinflation will be a topic for discussion at the PADAC meeting. The outcome of this discussion may affect how this product is ultimately labeled.

Safety

The safety information for olodaterol 5mcg comes primarily from the 48-week COPD trials. In the 48-week trials, 876 patients were exposed to olodaterol 5mcg and 883 to olodaterol 10mcg for a total of 1,759 exposed patients. An additional 1594 COPD patients were exposed to olodaterol in shorter-term trials, for a total of 3353 COPD patients exposed for any duration during the olodaterol program. Of these patients, 1014 patients were exposed to olodaterol for \geq 48 weeks (\geq 337 days). Five-hundred-twelve (512) asthmatic patients were also exposed to oldodaterol during the development program.

There were a total of 53 on-treatment deaths in the 48-week trials. These were relatively evenly split between treatment groups (placebo=1.5%, Olo 5mcg=1.5%, Olo

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10mcg=1.9%, and formoterol=2.2%). Based on adjudicated data, the most frequent cause of death was COPD exacerbation as expected in this patient population.

Serious adverse events (SAEs) were also evenly balanced among treatment groups, with 16.4% of placebo patients, 15.8% of olodaterol 5mcg patients, 16.6% of olodaterol 10mcg patients, and 15.0% of formoterol patients experiencing an SAE in the 48 week trials. As expected in this patient population, the most common serious adverse events (SAE) were COPD exacerbation (5.8%), pneumonia (1.8%), all fractures (0.5%), and atrial fibrillation (0.5%). COPD exacerbations were evenly distributed across treatment groups. However, pneumonias were more common in the high-dose olodaterol (Olo) groups (Olo 5mcg=1.6%, Olo 10mcg=2.5%) compared to placebo (1.5%). The same was true of atrial fibrillation (placebo=0.3%, Olo 5mcg=0.6%, Olo 10mcg=0.6%).

The most common adverse [by preferred terms (PT)] leading to discontinuation were COPD exacerbation (2.2%), dyspnea (0.4%), pneumonia (0.3%), and atrial fibrillation (0.3%). There were not significant imbalances between groups. The most commonly reported treatment emergent adverse events (TEAEs) were COPD exacerbation (28.3%), nasopharyngitis (9.8%), upper respiratory infection (7.5%), dyspnea (3.9%), and bronchitis (3.8%). Of these, only nasopharyngitis was more commonly reported in both olodaterol groups compared to placebo. It should also be noted that there was a marked differential discontinuation in the placebo groups compared to olodaterol groups. Approximately 23% of placebo patients discontinued the 48-week trials early compared to 15-16% in the olodaterol groups. The most common reasons for discontinuation were adverse events (AEs) and lack of efficacy.

An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances. The sponsor's MACE analysis was also complemented by a cardiovascular assessment based on Standard MedDRA Queries (SMQs). Only in 2 SMQs were imbalances noted when comparing both olodaterol groups to placebo. Adverse events in the SMQ Cardiac arrhythmias sub- SMQ ventricular tachyarrhythmias occurred in 9 (1%), 17 (1.9%), and 12 (1.4%) in placebo, olodaterol 5mcg and olodaterol 10mcg, respectively. It should be noted that AEs in this SMQ occurred most frequently in the formoterol group [9 (2%)]. AEs in the SMQ Cardiac failure (narrow) occurred in 5 (0.6%), 11 (1.3%), and 7 (0.8%) in placebo, olodaterol 5mcg and olodaterol 10mcg, respectively. The noted imbalances were low in frequency, but consistent with the known potential cardiac effects of LABAs.

An adjudicated analysis of events leading to death, hospitalization, and intubation was also performed in the all COPD patients from the phase 2/3 trials, as well as all the asthma patients from the asthma dose-ranging trials. In the asthma population, there were no asthma-related deaths, hospitalizations, or intubations. There was single respiratory related event (pneumonia), which occurred in a patient who had received olodaterol 10mcg. The analysis of the COPD dataset did not reveal any significant imbalances nor any new safety signals.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical review does not recommend a Risk Evaluation and Mitigation strategy (REMS) for olodaterol inhalation solution.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical review recommends no postmarketing requirements or commitments

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product, olodaterol inhalation spray, is an aqueous solution of olodaterol hydrochloride delivered via the Respimat device. The aqueous solution contains (b) (4) olodaterol drug substance (b) (4) as the hydrochloride salt and is contained in a plastic container in an aluminum cartridge. This cartridge is packaged with the Respimat device, which delivers 60 actuations (2.5mcg of olodaterol/actuation) after priming. The proposed dosing for treatment of COPD is 5mcg (2 actuations) once daily. Figure 1 depicts the Respimat inhaler with the cartridge inserted.

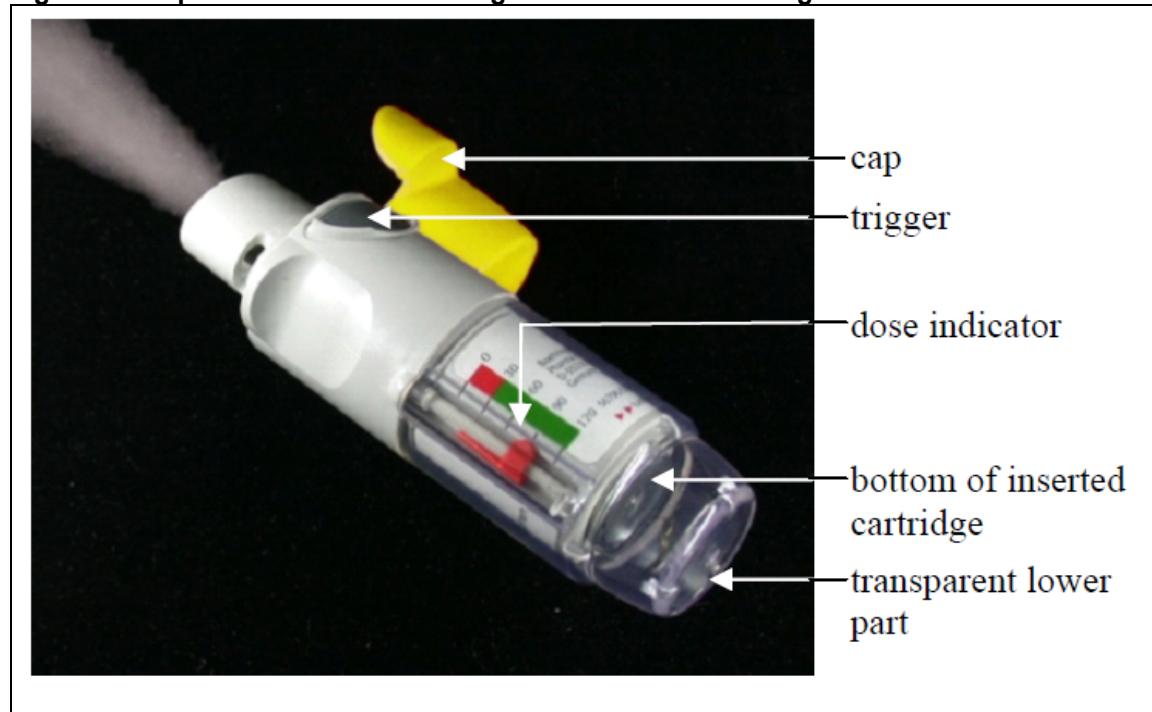
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Figure 1. Respimat device with cartridge inserted and aerosol generated



source: Quality Overall Summary; Figure 3; pp26

The first time a patient uses the drug product, he removes the transparent base on the Respimat device and inserts the cartridge containing the formulation. The clear base is replaced and the patient turns the base until a 'click' is heard, then primes the device by spraying until a mist is observed and then another 3 times into the air. To administer a dose, the yellow cap is then opened and the patient seals his lips around the mouthpiece. During inhalation, the patient presses the trigger button while continuing to inhale.

The Respimat device and cartridge is approved in the United States for use with the Combivent Respimat (albuterol/ipratropium) drug product (NDA 21-747; October 7, 2011) and in Europe for use with the Spiriva Respimat (tiotropium) drug product.

2.2 Tables of Currently Available Treatments for Proposed Indications

All currently available pharmaceutical treatments for the maintenance treatment of airflow obstruction in COPD are listed in Table 1. There are currently five long-acting beta-agonists (LABAs) approved for the treatment of airflow obstruction in COPD. Of these, only one is approved for once daily dosing (indacaterol maleate, 75mcg). None carry a labeling claim for increased exercise tolerance or decreased hyperinflation. Other classes of products approved for COPD include anticholinergic agents, inhaled corticosteroids/LABA combination products, xanthines, and phosphodiesterase

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inhibitors. Short-acting beta-agonists are approved for bronchodilation, but not specifically COPD.

Table 1. Other available COPD treatments

| Class | | Generic Name | Brand Name |
|--|-----------------------|------------------------|--|
| Beta ₂ -adrenergic agonists | Short-acting (SABA)* | Albuterol sulfate | Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA |
| | | Levalbuterol tartrate | Xopenex HFA |
| | | Pirbuterol | Maxair autoinhaler |
| | | Terbutaline sulfate | |
| | Long-acting (LABA) | Salmeterol | Serevent Diskus |
| | | Formoterol | Foradil Aerolizer |
| | | Arformoterol | Brovana |
| | | Formoterol Solution | Perforomist |
| | | Indacaterol maleate | Arcapta Neohaler |
| Anti-cholinergics | Short-acting | Ipratropium bromide | Atrovent HFA |
| | Long-acting | Tiotropium bromide | Spiriva Handihaler |
| | | Aclidinium bromide | Tudorza Pressair |
| Combination | SABA/anti-cholinergic | Albuterol/Ipratropium | Combivent |
| | | Albuterol/Ipratropium | Combivent respimat |
| | Corticosteroid/LABA | Fluticasone/Salmeterol | Advair Diskus |
| Xanthines | Theophylline | Budesonide/Formoterol | Symbicort |
| | | Theophylline | Multiple |
| Phosphodiesterase Inhibitors | PDE4 Inhibitor | Roflumilast | Daliresp |

* products with a general bronchodilator claim, not COPD specific

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, olodaterol, is a new chemical entity that is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Inhaled beta-2 adrenergic agonists have been associated with an increased risk of severe exacerbations and asthma-related deaths in patients with asthma. Given the longer duration of action, this is of particular concern with LABAs. This risk was first highlighted by the 1996 Salmeterol Multicenter Asthma Research Trial (SMART). SMART was a randomized, double-blind trial that enrolled patients with asthma not currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). In January 2003,

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after a total of approximately 30,000 patients had been enrolled, this trial was prematurely terminated due to a planned interim analysis suggesting that salmeterol may be associated with an increased risk of severe asthma exacerbations including death.

Due to findings of SMART, as well as findings in smaller safety studies conducted with another LABA, formoterol, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting (PADAC). Based on this meeting and a follow up PADAC meeting on December 10, 2008, the existing product labels have been revised and now include a Boxed Warning and a Medication Guide for all marketed LABA products. In addition, the paradigm for asthma treatment with LABAs has now changed, contraindicating the use of a LABA without a concomitant asthma controller medication, such as an inhaled corticosteroid (ICS).

Because it is unclear if addition of an inhaled corticosteroid mitigates the risk of LABAs in asthma, sponsors of LABA products indicated for asthma are being required to perform large safety trials to evaluate serious asthma outcomes in patients receiving concomitant ICS and LABA. The design of these trials was discussed at a PADAC meeting held March 10-11, 2010.

While no such safety signal has been observed in COPD patients, dose-related class effects of beta-agonists, especially those affecting the cardiac and central nervous systems, can be deleterious to older patients with COPD, many of whom have increased cerebral and cardiovascular risk factors. As such, FDA recommends that all sponsors of LABA products explore dose ranging as thoroughly as possible, taking into account both safety and efficacy issues.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to submission of this NDA, this product was developed under IND 76,362. Major regulatory milestones are summarized below:

1/26/07: IND submission

7/17/08: End-of-phase 2 (EOP2) meeting. The major clinical points of discussion were as follows:

- Agreement that the 5mcg and 10mcg doses were reasonable to carry forward, with the caveat that the optimum dosing interval had not been established.
- Agreement that the co-primary endpoints of FEV1 AUC (0-3 hours) and trough FEV1 at 12 weeks were reasonable to assess bronchodilator efficacy in phase 3.
- The phase 3 trials (1222.11 and 1222.12) should include a subset of patients with 24-hour serial spirometry to support the time profile of olodaterol.
 - 8/19/08 the sponsor submitted an amended protocol:

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- The sponsor included additional timepoints for post-dose serial spirometry for a subset of 240 patients in trials 1222.11 and 1222.12 (out to 12 hours post-dose).
- The Agency agreed that this would allow for adequate description of FEV1 time profile.
- Statement that 24-hour serial spirometry data from 6-week trials would only be supportive if the treatment effect was similar at 6-weeks compared to 12-weeks [FEV1 AUC (0-3 hours) and trough FEV1].
- Recommendation that the sponsor add COPD exacerbations as an additional secondary endpoint to phase 3 trials.

12/22/09: Advice request. Sponsor submitted data to support once-daily dosing. The major points of discussion were as follows:

- Data in addition to the COPD dose posology trial were required to support a once-daily dosing regimen.
- Recommendation that the sponsor determine optimum dose and dose regimen in asthmatics prior to proceeding to with COPD development program.

7/19/11: Pre-NDA meeting request (meeting canceled). The agency's major points of were as follows:

- Agreement with the format of summary of clinical efficacy and summary of clinical safety.
- The sponsor should perform sub-group analysis based on reversibility, treatment by sub-group interaction analysis, and major adverse cardiac event (MACE) analysis.
- Submit all narratives for SAEs for phase 3 trials.
- Include safety analyses for those patients with a cardiac history.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. A DSI audit was requested and completed for 4 sites. Sites were selected based on a combination of financial disclosures, total patients randomized, percent of patients with AE, SAEs, and MACE events.

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| Contact information | Trial/Site# | Number of Patients |
|---|--------------|--------------------|
| Dr. De Salvo Centro Medico de la Dra. De Salvo Capital Federal, Buenos Aires Cabildo 1548, 1A C1426ABP, Argentina | 1222.13/2401 | 128 enrolled |
| Dr. Dunn Clinical Research of West Florida, Inc. 2147 North East Coachman Road Clearwater, FL 33765 | 1222.12/1207 | 61 enrolled |
| Dr. Snell Mountain View Clinical Research 405 Memorial Drive, Extension Greer, SC 29651 | 1222.11/1119 | 20 enrolled |
| Dr. Kaelin Lowcountry Lung & Critical Care 9150 Medcom Street, Suite B Charleston, SC 29406 | 1222.11/1112 | 37 enrolled |

DSI review of these sites did not demonstrate any findings which bring into question data integrity. Only minor violations were reported. Note that at the De Salvo site, there were several errors in randomization. FDA biostatistics reanalyzed the efficacy data from trial 1222.13, removing the De Salvo site. Removal did not affect statistical significance.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report.

3.3 Financial Disclosures

The Applicant has submitted a statement certifying that no debarred individuals were used in the conduct of the trials included in this NDA. From the pivotal 48 week trials only one investigator ([REDACTED] ^{(b) (6)} trial 1222.13, site [REDACTED] ^{(b) (6)}) had interests that required financial disclosure. This was category 2 (significant payments >\$25,000) and was for grant funding and attendance for 3 meetings. His site randomized [REDACTED] ^{(b) (6)} patients. Given the size of the phase 3 program, it is unlikely that his site would have significantly skewed results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review is Approval. Details of the CMC review can be found in Dr. Craig Bertha's review. The proposed product, olodaterol inhalation spray, is an aqueous solution of olodaterol hydrochloride delivered via the Respimat device. The aqueous solution contains [REDACTED] ^{(b) (4)} olodaterol drug substance ^{(b) (4)} as the hydrochloride salt) and is contained in a plastic container in an aluminum cartridge. This cartridge is packaged with the Respimat device, which delivers 60 actuations (2.5mcg of olodaterol/actuation) after priming. The proposed dosing for treatment of COPD is 5mcg (2 actuations) once daily.

The first time a patient uses the drug product, he removes the transparent base on the Respimat device and inserts the cartridge containing the formulation. Once inserted the cartridge cannot be removed. The clear base is replaced and the patient turns the base until a 'click' is heard, then primes the device by spraying until a mist is observed and then another 3 times into the air. To administer a dose, the yellow cap is then opened and the patient seals his lips around the mouthpiece. During inhalation, the patient presses the trigger button while continuing to inhale.

The device also has an integrated dose-counter. After delivering 60 actuations, the device locks to prevent further dosing. The to-be-marketed device was used in all the phase 2 and 3 trials. The Respimat device and cartridge is approved in the United States for use with the Combivent Respimat (albuterol/ipratropium) drug product (NDA 21-747; October 7, 2011) and in Europe for use with the Spiriva Respimat (tiotropium) drug product.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the Pharmacology/Toxicology review is Approval. Details of the Pharmacology/Toxicology review can be found in Dr. Carol Lopez-Rivera's review.

A complete nonclinical safety program for olodaterol was submitted with this NDA and is considered adequate to support the safety of the proposed clinical dose of 5 µg/day.

Repeat-dose toxicity studies were conducted with olodaterol in three species: mouse, rat, and dog. The target organs of toxicity identified in all species were the heart

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(chronotropic effect that led to histopathology findings of fibrosis/fibroplasia over the long term) and liver. In rodents, the female reproductive tract (rat and mouse uterine leiomyomas) and skeletal muscle (rat) were identified. In dogs, the kidney was identified. In addition, in the respiratory tract; the nasal cavity, the larynx, and the trachea were affected by olodaterol. All these are common target organs of toxicity of β -adrenergic agonists. There are no apparent differences between the effects observed with olodaterol compared to other approved LABAs. A NOAEL for systemic toxicities was identified in the rat and the dog and provide adequate exposure margins compared to the exposure at the proposed clinical dose

Based on the sponsor's analysis of the genotoxicity studies, olodaterol is not genotoxic. Carcinogenicity studies did not demonstrate carcinogenic potential for olodaterol at relevant doses. However, as with other beta-2 AR agonists, exposure to olodaterol was related to rodent uterine leiomyomas. These findings were noted at >20x the human exposure. Lung and mediastinal neoplasms were not seen in any of the carcinogenicity studies.

Rat studies demonstrated no effect on fertility. At very high doses olodaterol was teratogenic in rabbits and rats; however, given the safety margins (>1000 fold), these findings are not likely of clinical relevance.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The recommendation from the Clinical Pharmacology (CP) review is Approval. Details of the CP review can be found in Dr. Ping Ji's review. Olodaterol promotes bronchodilation by binding to beta-2 adrenergic receptors in the lungs, predominantly in smooth muscle. Although it can bind at beta-1 and beta-3 adrenergic receptors, it does so at much lower affinity, theoretically decreasing off-target effects.

4.4.2 Pharmacodynamics

BI submitted a comprehensive Clinical Pharmacology program. Results from these trials demonstrated that there were dose and exposure dependent increases in plasma cyclic AMP levels in healthy volunteers. Decreases in serum potassium concentrations were also noted at doses >10mcg in healthy females and 20mcg in healthy males. While decreases were noted, they were generally modest and transient. This is consistent with the data from the Phase 2 and 3 trials in COPD and asthma patients (section 5.3). A thorough QT trial (1222.8) was also performed. The results demonstrated that there was a dose dependent increase in QTcF. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 3.4ms (7.1), 5.9ms (9.6), 7.4ms (10.9) and 8.5ms (12.4) following doses of 10, 20, 30 and 50 mcg, respectively. With regard to effects on blood pressure, no clear association was

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demonstrated with inhaled olodaterol. However, in trials using intravenous olodaterol (1222.7), dose dependent decreases in diastolic blood pressure and increases in systolic blood pressure were noted.

4.4.3 Pharmacokinetics

The sponsor also performed multiple trials which included PK endpoints. Results from these trials demonstrated that at doses below 5mcg inhaled, olodaterol was not detectable in the plasma. At the 5mcg inhaled dose, plasma levels were only quantifiable in a limited number of patients. At doses of 10mcg inhaled and greater, plasma levels were quantifiable in the majority of patients. Maximal plasma concentrations were usually observed within 10-20 minutes of inhalation and declined thereafter. The terminal half-life (inhaled) was approximately 45 hours.

Pharmacokinetics were linear, and steady state was reached after 8 days. Inhaled bioavailability was approximately 30%. This was in contrast to an oral bioavailability of <1%. In trials using radiolabelled olodaterol, over 90% of olodaterol was excreted within 6 days of IV administration, and 5 days of oral administration. Elimination was primarily via biliary and renal routes. When delivered IV, 38% was recovered in the urine and 53% in the feces. For the oral route, 9% was recovered in the urine and 84% in the feces.

Olodaterol is metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety mainly by CYP2C9 followed by conjugation. There are 6 identified metabolites. Of these, one (SOM 1522) demonstrates pharmacologic activity at the beta2-receptor with a similar affinity as olodaterol. However, SOM 1522 is a minor metabolite and not detectable in plasma following chronic inhalation at the proposed dose. A renal impairment study showed that olodaterol levels were increased by approximately 40% in subjects with severe renal impairment. Olodaterol exposure was comparable between normal and mild to moderate hepatic impairment patients.

5 Sources of Clinical Data

5.1 Tables of studies/clinical trials

The sources of clinical data used in this review are summarized in Table 2.

Table 2. Sources of clinical data

| Study | Objective | Design | Population | Olodaterol Dose | Treatment Duration | Primary endpoint |
|----------------------------|----------------|---------------|----------------------------------|--|--------------------|------------------|
| Phase 2 –COPD Dose Ranging | | | | | | |
| 1222.3 | Dose range, PK | R, DB, PC, CO | COPD patients ≥40 years old N=36 | Olo 2 mcg x1 Olo 5 mcg x1 Olo 10 mcg x1 Olo 20 mcg x1 | Single dose | Trough FEV1 |

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| | | | | | | |
|--|---------------------------------|-------------------------|-------------------------------------|---|-------------|---|
| | | | | Pbo x 1 | | |
| 1222.5 | Dose range | R, DB, PC, MC | COPD patients ≥40 years N=405 | Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Pbo | 4-weeks | Trough FEV1 |
| 1222.26 | Dosing frequency | R, DB, PC, CO | COPD patients ≥40 years N=47 | Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2 mcg BID Pbo | 3-weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| Phase 2-Asthma Dose Ranging | | | | | | |
| 1222.4 | Dose range | R,DB,PC CO | Asthma ≥18 years N=31 | Olo 2 mcg x1 Olo 5 mcg x1 Olo 10 mcg x1 Olo 20 mcg x1 Pbo x 1 | Single dose | PC20 |
| 1222.6 | Dose range | R, DB, PC, MC | Asthma ≥18 years N=296 | Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Pbo | 4-weeks | Trough FEV1 |
| 1222.27 | Dose range | R, DB, PC, AC, CO | Asthma 18-70 years N=198 | Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Foradil 12 mcg BID Pbo | 4-weeks | FEV1 AUC ₍₀₋₂₄₎ |
| 1222.29 | Dosing frequency | R, DB, PC, CO | Asthma 18-70 years N=180 | Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2.5 mcg BID Pbo | 3-weeks | FEV1 AUC ₍₀₋₂₄₎ |
| Phase 3- 48 week Pivotal Trials | | | | | | |
| 1222.11 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=624 | Olo 5 mcg qD Olo 10 mcg qD | 48-weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 85 |
| 1222.12 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=642 | Olo 5 mcg qD Olo 10 mcg qD | 48-weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 85 |
| 1222.13 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=904 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID | 48-weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 169 |
| 1222.14 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=934 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID | 48-weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 169 |
| Phase 3- Six week Trials | | | | | | |
| 1222.24 | 24 hour FEV1 time profile | R, DB, PC, AC, CO | COPD ≥40 years N=99 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |

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| | | | | | | |
|---------|---------------------------|-------------------|-------------------------------|--|---------|---|
| 1222.25 | 24 hour FEV1 time profile | R, DB, PC, AC, CO | COPD ≥ 40 years N=100 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.39 | 24 hour FEV1 time profile | R, DB, PC, AC, CO | COPD ≥ 40 years N=108 | Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.40 | 24 hour FEV1 time profile | R, DB, PC, AC, CO | COPD ≥ 40 years N=122 | Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.37 | Exercise endurance | R, DB, PC, CO | COPD ≥ 40 years N=151 | Olo 5 mcg qD Olo 10 mcg qD Pbo | 6 weeks | Endurance time IC FRC |
| 1222.38 | Exercise endurance | R, DB, PC, CO | COPD ≥ 40 years N=151 | Olo 5 mcg qD Olo 10 mcg qD Pbo | 6 weeks | Endurance time IC FRC |

Olo=olodaterol, Tio=tiotropium, R=randomized, DB=double-blind, PC=placebo controlled, AC=active controlled, CO=cross-over, MC=multicenter, PK=pharmacokinetics, FEV1=force expiratory volume in 1 second, IC=inspiratory capacity, FRC=functional residual capacity, AUC=area under the curve, qD= once daily, BID=twice daily, Pbo=placebo, PC20=provocative concentration of methacholine required to cause a 20% fall in FEV1 from baseline.

5.2 Review Strategy

The clinical review focuses on the pivotal phase 3 forty-eight week trials (1222.11, 1222.12, 1222.13, and 1222.14) and the exercise endurance trials (1222.37 and 1222.38). The 6 week treatment period cross-over phase 3 trials (1222.25, 1222.26, 1222.39, and 1222.40) are also reviewed; however, they are considered to be supportive in nature. The protocols listed in Table 2 are discussed individually in section 5.3 Discussion of Individual Studies/Clinical Trial. The efficacy results of the phase 3 trials are summarized in section 5.3. The combined safety of the 48 week COPD trials will be presented in section 7 Review of Safety. Safety data from 6 week treatment period cross-over trials (1222.24, 1222.25, 1222.37, 1222.38, 1222.39, 1222.40) were reviewed but are not presented in section 7, as these trials had short treatment periods (6 weeks), were cross-over in design, and had varying washout periods. Safety data from the asthma dose ranging trials were also reviewed, but are also not included in section 7, as these trials varied in design and length of treatment. Safety data from these trials were consistent with data from the 48-week COPD trials and did not identify any new safety signals.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 1222.3 (COPD)

Administrative Information

- **Study title:** Randomized, Double-Blind, Placebo-Controlled, 5-Way Cross-Over Study to Assess the Efficacy and Safety of a Single Dose of Orally Inhaled Olodaterol (2 mcg, 5 mcg, 10 mcg, 20 mcg) in COPD Patients Followed by Open-Label Olodaterol (40 mcg)
- **Study dates:** 12/15/2005-11/26/2006
- **Study sites:** one site in the Netherlands
- **Study report date:** 8/13/2007

Objectives/Rationale

- To investigate the efficacy, safety, and exploratory PK of single doses of olodaterol in patients with COPD
- To investigate the PK, safety, and tolerability of a single dose of olodaterol 40mcg (open-label extension)

Study Design and Conduct

Overview

This was a randomized, double-blind placebo controlled, 5-way cross-over trial with an open label extension in 36 patients with COPD. Following screening at visit 1, patients began a 1-2 week run-in period. After the run-in period, eligible patients were randomized to receive placebo and 4 doses of olodaterol (2, 5, 10, and 20mcg) in a random sequence. After each dose, PFTs were conducted over a 24 hour time period (-10 minutes, 30 minutes, 1, 2, 3, 4, 6, 8, 10, 12, 14, 22, 23, and 24 hours). PK measurements were also performed. Between doses, there was a 14 day washout period. Olodaterol was administered on visit 2, 3, 4, 5, and 6. Patients participating in the open label extension received an additional single dose of 40mcg followed by PFTs and PK measurements. The assessment schedule is summarized in Table 3.

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Table 3. Trial 1222.3. Assessment schedule

| Trial Periods | Screening | Treatment | | | | | Follow-up ⁷ |
|---|--------------|----------------|----------------------|----------------------|----------------------|----------------------|------------------------|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Week | -2 | - | 2 | 4 | 6 | 8 | 11 |
| Day | V2 -7 to -14 | 1 | V2 + 14 ¹ | V3 + 14 ¹ | V4 + 14 ¹ | V5 + 14 ¹ | V6 + 21 |
| Informed consent ² | X | | | | | | |
| Demographics | X | | | | | | |
| Medical History | X | | | | | | |
| Smoking status | X | | | | | | |
| COPD background characteristics | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Physical examination | X | | | | | X ^{3,7} | |
| Full laboratory tests (fasting) | X | | | | | X ^{3,7} | |
| serum pregnancy test ⁴ | X | | | | | | |
| urine pregnancy test ⁴ | | X | X | X | X | X | X |
| Theophylline level ⁵ | X | | | | | | |
| Respimat® training | X | | | | | | |
| Randomisation | | X | | | | | |
| Administer test medication | | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ⁶ | |
| 12-lead ECG | X | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ^{6,7} | |
| Abbreviated laboratory test | | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ⁶ | |
| Pharmacokinetics | | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ⁶ | |
| Vital signs (seated) | X | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X |
| Medication washout compliance assessment | X | X | X | X | X | X | |
| Pulmonary function tests (FEV ₁ , FVC) | X | X ⁶ | X ⁶ | X ⁶ | X ⁶ | X ⁶ | |
| Adverse events | X | X | X | X | X | X | X |
| Concomitant therapy | X | X | X | X | X | X | X |
| Drug accountability | | X | X | X | X | X | |
| Termination of Trial medication | | | | | | X ⁷ | |
| Conclusion of subject participation | | | | | | | X ⁷ |

1) A minimum of at least 14 days is required between doses; 2) Prior to participation in the trial (and prior to any medication washout / restrictions); 3) To be performed after completion of the 24-h lung function profile. If findings, repeat at Visit 7;
 4) Urine pregnancy test required for all women of child-bearing potential at each test-day before drug inhalation / serum pregnancy tests at Visits 1 and 6; 5) Theophylline levels only on patients taking theophylline; 6) See timing of procedures on page 8; 7) To be completed whenever trial participation ends.

Source: Trial 1222.3 CSR, pp 627

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The timing of safety, PK, and PFT monitoring at visits 2-6 are summarized in Table 4.

Table 4. Trial 1222.3. Timing of procedures on visits 2-6

| | Time (relative to dosing) | | | | | | | | | | | | | | | | | |
|---|---------------------------|---|-----|-----|-----|----|----|----|-----|----|----|------|------|------|------|------|------|--|
| | -10' | 0 | 10' | 20' | 30' | 1h | 2h | 3h | 4h | 6h | 8h | 10 h | 12 h | 14 h | 22 h | 23 h | 24 h | |
| Administer trial medication | | X | | | | | | | | | | | | | | | | |
| 12-lead ECG | X | | X | | | X | X | | | | X | | | | | | X | |
| PK plasma sampling ² | X | | X | X | | X | X | | X | | | | | | | | | |
| Abbreviated laboratory testing ³ | X | | | X | | X | X | | X | | | | | | | | | |
| Vital signs | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Pulmonary function test (PFT) | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| PK urine sampling ^{2,4} | ← → | | ← | | | | | → | ← → | ← | | | | | | | → | |

¹ The timing of assessments is related to start of pulmonary function test. If applicable, ECG recording or blood sampling should start earlier. The 10 min assessments should start with blood sampling, followed by ECG recording.

² The time point zero for PK blood and urine sampling is defined as the end of drug inhalation.

³ Will include potassium and calcium.

⁴ Pre-dose and, 0 - 4 h, 4 - 8 h and 8 - 24 h post-dosing.

Source: Trial 1222.3 CSR; pp628

Study Population:

This study included 36 adult COPD patients. Patients were randomized using a central, computerized randomization system (Interactive Voice Response System, IVRS)

Key Inclusion Criteria

1. Male or female ≥40 years in age
2. Current or ex-smokers with a >10 year pack history
3. A diagnosis of COPD with an FEV1 ≤60% predicted and an FEV1/FVC ratio ≤70% at baseline visit PFTs taken at visit 1 and 2.
4. At visit 1 all patients must have airway reversibility based a >12% increase in FEV1 following salbutamol treatment

Key Exclusion Criteria

1. Patient with significant disease other than COPD.
2. Clinically relevant abnormal baseline lab values
3. All patients with SGOT >80, SGPT>80, bilirubin >2, or creatinine >2
4. History within past 5 years of myocardial infarction.
5. Patients with unstable or life threatening cardiac arrhythmias or arrhythmias requiring intervention.
6. A diagnosis of paroxysmal tachycardia
7. Baseline prolongation of QT/QTc interval.

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8. Patients with a history of asthma, allergic rhinitis or total blood eosinophil count of $\geq 600/\text{mL}$.
9. Patients who have completed a pulmonary rehabilitation program in the 6 weeks prior to the visit 1.
10. Women of childbearing potential not using a highly effective method of birth control ($<1\%$ failure rate).
11. Patients on restricted medications
12. Patients using oral steroids at unstable doses (<6 weeks at a stable dose)
13. Patients with and respiratory infection or COPD infection in the 6 weeks prior to visit 1 or during the run-in period between visits 1 and 2.
14. Patients who use regularly use daytime oxygen for more than one hour per day.
15. Patients on beta-blocker medication.

Reviewer Comment:

The trial design and inclusion/exclusion criteria are appropriate. Although not all COPD patients have reversible airway obstruction, inclusion of only reversible COPD patients is acceptable in a dose ranging trial, though this would potentially be problematic in phase 3 pivotal trials. The patient population was appropriate and typical for a COPD dose ranging trial.

Treatments

Treatment Groups

Olodaterol 2mcg once (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once (2 actuations of 5mcg/actuation)

Olodaterol 20mcg once (2 actuations of 10mcg/actuation)

Olodaterol 40mcg once (4 actuations of 10mcg/actuation)

Placebo

Concomitant Medications/Prohibited Medications:

All medications used by the patients for the 3 months prior to visit 1 and through the trial were recorded in the case report form.

The following medications were allowed provided that the doses were stable for >6 weeks prior to visit 1 and throughout the trial period.

- oral steroids
- inhaled corticosteroids
 - patients on inhaled corticosteroids (ICS)/long acting beta-agonists (LABA) were switched to ICS alone 48 hours prior to visit 1, and were not permitted during treatment and washout periods (visits 2-6).
- LABAs
 - 48 hour washout period required prior to PFTs
- Mucolytics agents not containing bronchodilators

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- Short-acting beta-adrenergic or anticholinergic agents; however, washout prior to PFTs were required.
- Cromolyn, nedocromil, antihistamines, antileukotriene and leukotriene receptor antagonists are permitted if used for conditions other than asthma and allergic disease.

The following medications were not allowed for at least one month prior to visit 1 and throughout the trial period:

- All other investigational drugs
- Oral beta-adrenergics
- Theophylline preparations except for temporary use during exacerbations
- The long-acting anticholinergic tiotropium
- Beta-blocker medications. Note: cardio-selective beta-blocker eye medications for treatment of non-narrow angle glaucoma are allowed.

The following medications were not allowed during the trial period:

- Fixed combination ICS/LABA therapies
- LABA therapies as mono-product were allowed during the run-in period (between Visits 1 and 2) and during the washout periods in between the five pulmonary function test-days. However, there was a 48-hour washout of these long-acting beta-adrenergics prior to the five pulmonary function test-days (Visits 2, 3, 4, 5 and 6).

Efficacy Parameters

Primary Efficacy Endpoint

- FEV1 24 hours after inhalation of a single dose of olodaterol

Secondary Efficacy Endpoint

- FEV1 AUC (0-3 hours), FEV1 AUC (0-12 hours), FEV1 AUC (0-24 hours) and FEV1 AUC(12-24 hours)
- Peak FEV1 and Peak FVC within 3 hours of dosing
 - Peak values defined as maximum value within 3 hours of dosing.
 - Response values were defined as change test day baseline (PFTs 10 minutes prior to dosing)
- Time to peak bronchodilator response and onset of response
 - Bronchodilator response was considered to have been achieved when response was >12% from baseline
- Individual FEV1 and FVC at each measured time point
- Rescue medication use

Other Endpoints

- AUC of plasma concentration-time curve of olodaterol over the time interval from 0 to time of last quantifiable data point

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- AUC of plasma concentration-time curve of olodaterol over the time interval from 0 to 4 hours
- Maximum measure plasma concentration
- Time from dosing to maximum concentration

Compliance Parameters

All medication was given under the supervision of the investigating physician during clinic visits.

Safety Parameters

Monitoring for safety included the following assessments.

- AEs and SAEs
- Vital signs and ECG at all visits
- Physical exam and clinical labs at visit 1 and 6
 - Labs will include a complete blood count, chemistry panel, and urinalysis
- Pregnancy testing

Ethics

An institutional review board (IRB) reviewed and approved this study protocol. No changes were made without the IRB's approval. The study was performed in accordance with the Declaration of Helsinki and ICH Good Clinical Practices.

Reviewer comment:

The primary endpoint and secondary endpoints were appropriate and typical for COPD dose ranging trials. Positive findings for these endpoints in this single dose trial would be supportive of performing further multiple dose ranging trials. The safety monitoring parameters were also appropriate.

Statistical Plan

Sample Size

The proposed sample size of 30 patients per dose provides a 90% power to detect a difference of 100mL with a standard deviation of 150mL.

Analysis populations

The sponsor pre-specified four analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and any post-dosing efficacy data. The per-protocol (PP) population consisted of the patients who did not have significant protocol violations (i.e. violations that could affect efficacy results). The safety population was made up of all treated patients. The PK set consisted of all data obtained from the subset of patients who participated in the PK sub-study.

Efficacy Analysis

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The primary variable to be analyzed was FEV1 24 hours after dosing in the FAS population. The variable was analyzed using ANCOVA. To account for type 1 error analysis was performed in an ordered fashion starting with a comparison of Olo 20mcg to placebo. If Olo 20mcg demonstrated a statistically significantly greater FEV1 than placebo (one-tailed p-value 0.025), then the next lower dose was compared to placebo.

The secondary efficacy variables were analyzed using ANCOVA in a manner similar to the primary efficacy variable.

Results:

Protocol Changes:

Following completion of the 5-way cross over portion of this trial, preliminary analysis of the PK data revealed that single doses of up to 20mcg of olodaterol resulted in only very low serum concentrations. Therefore, the extension portion of the trial was added, during which the 18 patients who participated in the PK substudy received a single dose of 40mcg open-label olodaterol followed by measurement of PK parameters.

There were also changes to the planned statistical analysis. The PP population was amended to state that a relevant protocol deviation would only exclude patient data for the relevant treatment period(s). Additionally, the PP population would only be defined if there were a greater than 10% difference compared to the FAS. Also, if the bronchodilator response, defined as an increase in FEV1 of 12%, did not occur within 3 hours of dosing, then the time to onset would be defined at 3 hours 1 minute.

Protocol Violations

There were no protocol violations in the 40mcg extension portion of this trial. In the main portion of this trial, there were a total of 12 patients with important protocol deviations (IPV). These occurred more frequently during the placebo and Olo 2mcg treatment periods [7 (19.4%) and 5 (13.9%), respectively] compared to the 5, 10, and 20mcg treatment periods [3 (8.3%), 3 (8.3%), and 2 (5.6%), respectively]. The most common violations were missing primary endpoint data and baseline variability of the FEV1. These results are summarized in Table 5.

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Table 5. Trial 1222.3. Important protocol violations

| | Placebo N (%) | 2 µg N (%) | 5 µg N (%) | 10 µg N (%) | 20 µg N (%) | Total N (%) |
|--|------------------|---------------|---------------|----------------|----------------|----------------|
| Entered/randomised | 36 (100.0) | 36 (100.0) | 36 (100.0) | 36 (100.0) | 36 (100.0) | 36 (100.0) |
| Treated | 35 (97.2) | 35 (97.2) | 35 (97.2) | 34 (94.4) | 35 (97.2) | 36 (100.0) |
| Important protocol violations | 7 (19.4) | 5 (13.9) | 3 (8.3) | 3 (8.3) | 2 (5.6) | 12 (33.3) |
| Improper medication washout | 0 (0.0) | 0 (0.0) | 1 (2.8) | 0 (0.0) | 0 (0.0) | 1 (2.8) |
| Missing primary endpoint data | 3 (8.3) | 4 (11.1) | 0 (0.0) | 1 (2.8) | 1 (2.8) | 6 (16.7) |
| Baseline variability of FEV ₁ | 4 (11.1) | 2 (5.6) | 2 (5.6) | 2 (5.6) | 1 (2.8) | 6 (16.7) |

As this was crossover trial, the number of patients in each treatment does not add up to the total. Patients may have also had more than one important protocol violation

Source: Trial 1222.3 CSR, table 10.2:1, pp67

Reviewer comment:

It is unlikely that the protocol changes would have significantly affected data interpretation. With regard to the protocol violations, they were more frequent during the placebo and Olo 2mcg treatment periods. While this could potentially affect data interpretation, as there were multiple further dose ranging trials, these violations are unlikely to have significantly affected the overall dose ranging program and dose conclusions.

Patient Disposition

A total of 37 patients enrolled in the main portion of trial. Of these 36 were randomized, all were treated. Two patients did not complete all treatment periods due to adverse events. For the 40mcg single dose extension, 15 patients were enrolled and 14 patients were treated. Patient disposition is summarized in Table 6.

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Table 6. Trial 1222.3. Patient disposition

| | Oladaterol Dose | | | | | |
|-------------------------------|-----------------|------|------|-------|-------|----------------|
| | Placebo | 2mcg | 5mcg | 10mcg | 20mcg | 40mcg |
| Entered/randomized | 36 | 36 | 36 | 36 | 36 | Not defined |
| Safety set | 35 | 35 | 35 | 34 | 35 | Not defined |
| Full analysis set (FAS) | 35 | 35 | 35 | 34 | 35 | Not defined |
| Per protocol set (PPS) | 28 | 30 | 32 | 31 | 33 | Not defined |
| Exclusions | | | | | | |
| Not treated | 1 | 1 | 1 | 2 | 1 | Not applicable |
| Important protocol deviations | 7 | 5 | 3 | 3 | 2 | Not applicable |

Source: Trial 1222.3 CSR, table 11.1:1, pp70

Demographics/Baseline characteristics

Of the 36 patients in this trial, most were caucasian males over 50 years in age. The majority were ex-smokers with an average 36.85 pack year history. The mean time since COPD diagnosis was 9.39 years. After bronchodilation, the mean FEV1 was 45.13% predicted and mean reversibility was 21.15%. These data are summarized in Table 7.

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Table 7. Trial 1222.3. Demographics and baseline characteristics

| Variable | Total (N=36) |
|--------------------------|---------------|
| Sex | |
| Male | 25 (69.4) |
| Female | 11 (30.6) |
| Age | |
| Mean (SD) | 65.0 (9.8) |
| Median | 64.5 |
| Range | 45-86 |
| Race | |
| White | 34 (94.4) |
| Black | 0 (0.0) |
| Asian | 2 (5.6) |
| BMI | |
| Mean (SD) | 23.99 (4.20) |
| Median | 23.70 |
| Range | 15.4-34.7 |
| Smoking History | |
| Never smoked | 0 (0.0) |
| Ex-smoker | 22 (61.1) |
| Smoker | 14 (38.9) |
| Smoking History | |
| Mean (SD) | 36.85 (15.96) |
| Median | 32.50 |
| Range | 15-87.5 |
| COPD diagnosis Duration | |
| Mean (SD) | 9.39 (6.59) |
| Median | 6.88 |
| Range | 0.5-24 |
| FEV1 (%predicted) | |
| Pre-bronchodilator (SD) | 37.44 (10.79) |
| Post-bronchodilator (SD) | 45.13 (12.47) |
| %change in FEV1 (SD) | 21.15 (7.96) |

Source: Trial 1222.3 CSR; tables 11.2.1:1, 11.2.2:1, 11.2.4:1;pp71, 72, 74

Reviewer Comment:

Aside from having reversible airway obstruction, the patient population is fairly representative of the COPD population as a whole.

Compliance

All patients were compliant as all study medication was given under direct supervision.

Efficacy

Primary Endpoints:

This trial's primary endpoint was FEV1 24 hours after dosing. Analysis was performed on the FAS. Mean FEV1 for all olodaterol treatment periods was statistically significantly greater than placebo. Additionally, there appeared to be a dose response, although the

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difference between 10 mcg and 20 mcg at 24 hours was minimal. These results are summarized in Table 8.

Table 8. Trial 1222.3. Primary endpoint: FEV1 24 hours after dosing with olodaterol

| Treatment | FEV1 [L] Mean (SE) | Difference from placebo | | |
|-----------|-----------------------|-------------------------|---------|----------------|
| | | Mean (SE) | p-value | 95% CI |
| Placebo | 0.916 (0.014) | — | — | — |
| Olo 2mcg | 0.986 (0.014) | 0.070 (0.020) | 0.0005 | (0.031, 0.109) |
| Olo 5mcg | 1.015 (0.014) | 0.099 (0.020) | <0.0001 | (0.060, 0.138) |
| Olo 10mcg | 1.029 (0.014) | 0.113 (0.020) | <0.0001 | (0.074, 0.152) |
| Olo 20mcg | 1.035 (0.014) | 0.119 (0.020) | <0.0001 | (0.080, 0.158) |

Source: Trial 1222.3 CSR; Table 11.4.1.1:1; pp76

Secondary Endpoints:

This trial's secondary efficacy variables included FEV1 AUC at various time intervals, peak FEV1 response, time to peak FEV1 response, and rescue medication use. FEV1 AUCs at all time intervals for all olodaterol treatment periods were greater than for placebo. These differences were statistically significant. There was also a clear dose response. This is summarized in Table 9. For the remaining spirometric related secondary endpoints, the results were similar. With regard to rescue medication use on the day of olodaterol administration, more patients during the placebo and Olo 2mcg treatment period require rescue compared to the Olo 5, 10 and 20mcg treatment periods. These differences were not statistically assessed.

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Table 9. Trial 1222.3. Secondary endpoint: FEV1 AUC (0-3 hours), (0-12 hours), (0-24 hours), and (12-24 hours)

| Interval | Treatment | FEV AUC [interval] (SE) | Difference from Placebo (SE) |
|-------------------|-----------|-------------------------|------------------------------|
| AUC (0-3 hours) | Placebo | 0.997 (0.011) | |
| | Olo 2mcg | 1.105 (0.011) | 0.108 (0.016) |
| | Olo 5mcg | 1.152 (0.011) | 0.155 (0.016) |
| | Olo 10mcg | 1.158 (0.011) | 0.161 (0.016) |
| | Olo 20mcg | 1.189 (0.011) | 0.192 (0.016) |
| AUC (0-12 hours) | Placebo | 0.954 (0.012) | |
| | Olo 2mcg | 1.053 (0.011) | 0.099 (0.016) |
| | Olo 5mcg | 1.093 (0.011) | 0.139 (0.016) |
| | Olo 10mcg | 1.108 (0.012) | 0.153 (0.016) |
| | Olo 20mcg | 1.138 (0.011) | 0.184 (0.016) |
| AUC (0-24 hours) | Placebo | 0.923 (0.011) | |
| | Olo 2mcg | 1.009 (0.011) | 0.087 (0.015) |
| | Olo 5mcg | 1.040 (0.011) | 0.118 (0.015) |
| | Olo 10mcg | 1.061 (0.011) | 0.138 (0.015) |
| | Olo 20mcg | 1.085 (0.011) | 0.162 (0.015) |
| AUC (12-24 hours) | Placebo | 0.891 (0.012) | |
| | Olo 2mcg | 0.965 (0.012) | 0.074 (0.017) |
| | Olo 5mcg | 0.987 (0.012) | 0.096 (0.017) |
| | Olo 10mcg | 1.014 (0.012) | 0.122 (0.017) |
| | Olo 20mcg | 1.032 (0.012) | 0.141 (0.017) |

Source: Trial 1222.3 CSR; Table 11.4.1.2.1:1; pp78

FEV1 for each individual time point was consistent with the previously summarized spirometric endpoints. This data is represented graphically in Figure 2.

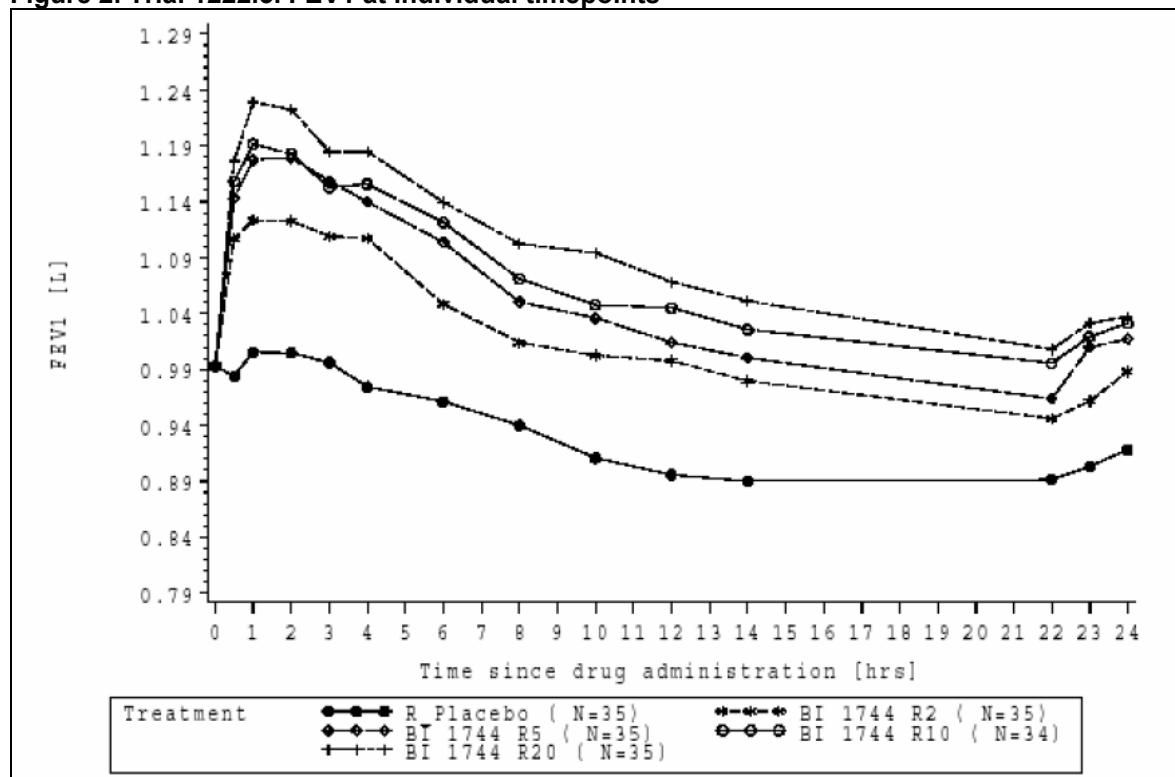
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Figure 2. Trial 1222.3. FEV1 at individual timepoints



BI1774 R10=Olo 10mcg, BI1744 R5=Olo 5mcg, BI1744 R2=Olo 2mcg, BI1744 R20=Olo 20mcg
Source: Trial 1222.3 CSR; Figure 11.4.2.4:1; pp81

During all olodaterol treatment periods, peak FEV1 within the 1st 3 hours post-dose was statistically significantly greater compared to placebo. The same was also true for peak FVC within 3 hours post-dosing.

Reviewer Comment:

Based on the primary endpoint, all doses of olodaterol have significant bronchodilatory action compared to placebo. There is also a clear dose response. The secondary endpoints are consistent with this conclusion. It should also be noted that as olodaterol doses were increased, the incremental benefits decreased. In general, it appears that the greatest incremental benefit occurred between the 2mcg and 5mcg doses.

Other Endpoints:

In addition to efficacy endpoints, this trial also assessed the PK characteristics of a single dose of olodaterol. Initially PK data was only collected for the 2, 5, 10, and 20 mcg doses; however, due to low serum concentrations following dosing an additional 40 mcg dosing period was added. Following a single dose of Olo 2mcg, serum olodaterol could only be detected in 5 of the 18 participants. The levels detected were marginally greater than the lower limit of detection. For the 5mcg group, 9 of 18 patients had detectable levels of olodaterol for 20 minutes following dosing. In the 20 and 40mcg

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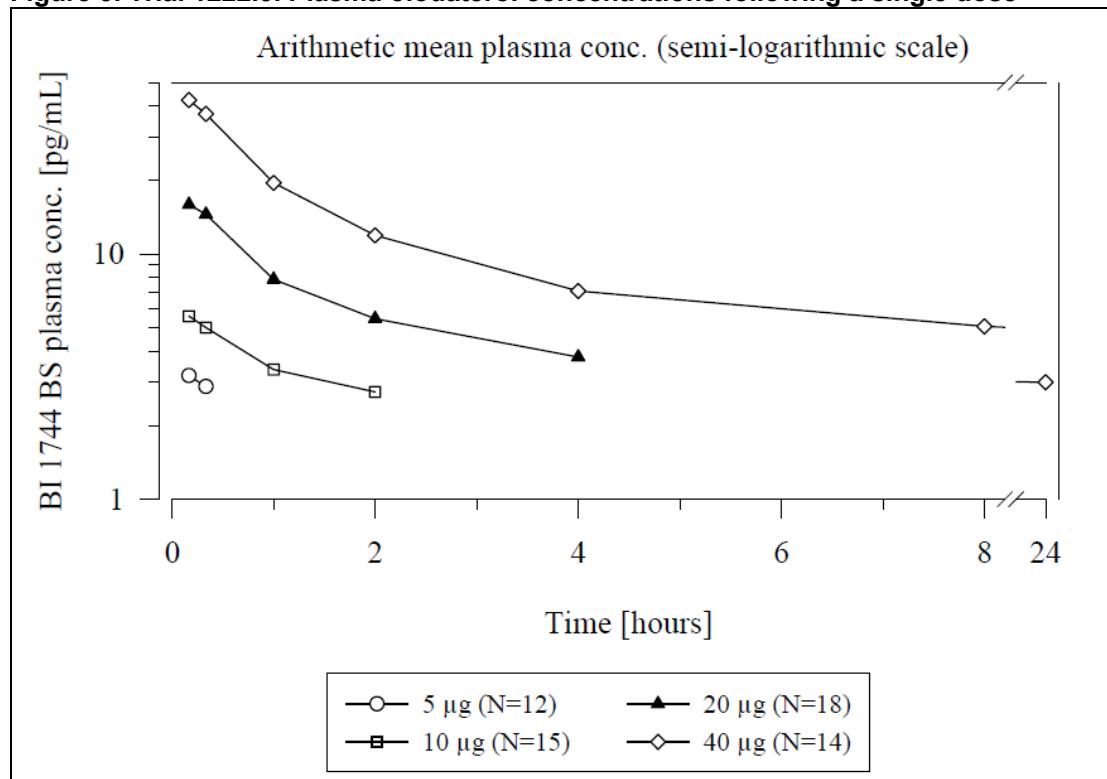
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dose groups, plasma concentrations were detectable up to 4 and 24 hours, respectively in most patients. These results are graphically summarized in Figure 3.

Figure 3. Trial 1222.3. Plasma olodaterol concentrations following a single dose



BI 1744 BS=olodaterol

Source: Trial 1222.3 CSR; Figure 11.5.1.1:1; pp85

Reviewer Comment:

Serum levels appear to be dose proportional, and at the 5mcg qD dose proposed by the sponsor, serum levels are likely to be undetectable by 1 hour post-dose.

Safety

Exposure

Safety analysis was performed on all randomized patients who received at least one dose of study medication. A total of 36 patients were included in the safety data set. All but 2 patients received all olodaterol doses in the main portion of the trial. These patients were withdrawn from the trial due to COPD exacerbations.

Deaths/SAEs

There were no deaths. Four patients reported SAEs, which were recorded as hemoptysis, perineal abscess, and COPD x2. The episode of hemoptysis occurred 6 days after the patient receive the last dose in his treatment sequence (placebo).

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Adverse Events (AE)

Adverse events that occurred during a treatment period or within 14 days after the treatment period were assigned to that treatment period. The most commonly reported AEs by system organ class (SOC) were in the respiratory, thoracic, and mediastinal, and infections and infestations. No AEs demonstrated a dose response. AEs that occurred in more than 3 patients are summarized in Table 10.

Table 10. Trial 1222.3. Adverse Events Reported in at Least 3 Patients

| System organ class and preferred term | Placebo ¹ N (%) | 2 µg ¹ N (%) | 5 µg ¹ N (%) | 10 µg ¹ N (%) | 20 µg ¹ N (%) | 40 µg ² N (%) |
|---|-------------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Number of patients | 35 (100.0) | 35 (100.0) | 35 (100.0) | 34 (100.0) | 35 (100.0) | 14 (100.0) |
| Respiratory, thoracic and mediastinal disorders | 4 (11.4) | 0 (0.0) | 4 (11.4) | 2 (5.9) | 3 (8.6) | 0 (0.0) |
| COPD exacerbation | 1 (2.9) | 0 (0.0) | 3 (8.6) | 1 (2.9) | 2 (5.7) | 0 (0.0) |
| Infections and infestations | 3 (8.6) | 2 (5.7) | 1 (2.9) | 4 (11.8) | 2 (5.7) | 1 (7.1) |
| Nasopharyngitis | 3 (8.6) | 0 (0.0) | 1 (2.9) | 1 (2.9) | 1 (2.9) | 0 (0.0) |
| Respiratory tract infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (5.9) | 1 (2.9) | 1 (7.1) |
| Nervous system disorders | 1 (2.9) | 2 (5.7) | 1 (2.9) | 1 (2.9) | 1 (2.9) | 0 (0.0) |
| Headache | 1 (2.9) | 2 (5.7) | 0 (0.0) | 1 (2.9) | 1 (2.9) | 0 (0.0) |

Patients may be counted in more than one treatment group.

1. Safety set

2. Extension set (a subset of patients in the safety set)

Source: Trial 1222.3 CSR; Table 12.2.2.1; pp99

Labs

In general hematologic and chemistry lab values were stable from baseline to end of treatment. Three patients had lab abnormalities that were identified as AEs. One was for an elevated bilirubin level, one for elevated blood glucose level, and one for decreased hemoglobin.

Vital signs

The number of patients with changes in blood pressure was comparable between olodaterol treatment periods and placebo treatment periods. There were also no differences in pulse rates. New or worsening of ECG changes were not noted.

Reviewer Comment:

This was a small trial with very limited exposure, as such it is difficult to make any safety conclusions/comments based on this trial alone. With that in mind, there did not appear to any significant imbalances with regard to AEs when comparing Olodaterol to placebo.

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Overall Comments on Trial 1222.3:

The results of this trial imply that olodaterol has a bronchodilatory effect in COPD patients with reversible obstruction. This effect demonstrates a dose response. The safety data, while minimal, also did not demonstrate any significant imbalances.

5.3.2 Trial 1222.5 (COPD)

Administrative Information

- **Study title:** Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial to Assess Efficacy and Safety of 4-weeks of Orally Inhaled Olodaterol (5mcg, 10mcg, and 20 mcg) in COPD Patients
- **Study dates:** 3/12/07-1/14/08
- **Study sites:** USA (24 sites), Canada (10 sites), Germany (7 sites), Netherlands (4 sites)
- **Study report date:** 3/26/09

Objectives/Rationale

- To determine the optimum dose of olodaterol inhalation solution delivered by the Respimat once daily for 4-weeks in patients with COPD

Study Design and Conduct

Overview

This was a randomized, double-blind placebo controlled, parallel group trial in 405 patients with COPD. Following an initial screening period, patients entered a 2 week baseline period. Following the baseline period, eligible patients were randomized to receive one of four doses of olodaterol (2, 5, 10, or 20mcg) once daily for 4 weeks. Following completion of 4 weeks of therapy, patients were followed for an additional 30 days.

Patients were seen in clinic at -2 to -4 weeks (visit 1), week 0, 1, 2, 4, and 8 (visits 2, 3, 4, 5, and 6, respectively). Prior to visit 1, informed consent was obtained and patients' washout of restricted medications began. After medication washout, at visit 1, eligible patients began the 2 week baseline period. During this period baseline PEFR and rescue medication use was recorded. Patients were who not sufficiently compliant or had unstable disease during the baseline period were not randomized to treatment with olodaterol at visit 2 (week 0). During the treatment phase (visits 2-5), patients continued to measure daily PEFR and rescue medication use. During visits 2-4, serial spirometry was performed prior to dosing and up to 3 hours after dosing. At visit 5, serial spirometry was performed up to 6 hours after dosing. Trial assessment schedule is summarized in Table 11.

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Table 11. Trial 1222.5. Assessment schedule

| Trial Periods | Screening | Treatment | | | | Follow-up |
|---|----------------|----------------|-------|--------|------------------|----------------|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 |
| Week | -2 to -4 | - | 1 | 2 | 4 | 8 |
| Day | -14 to -28 | 1 | 8 + 2 | 15 + 2 | 29 + 2 | V5 + 30 |
| Informed consent ¹ | X | | | | | |
| Demographics | X | | | | | |
| Medical history | X | | | | | |
| Review in-/exclusion criteria | X | X | | | | |
| Physical examination | X | | | | X ² | |
| Laboratory test | X ³ | X ⁴ | X | X | X ^{2,3} | |
| Pregnancy test ⁵ | X | X | X | X | X | X ⁶ |
| Respirat [®] training | X | | | | | |
| Randomisation | | X | | | | |
| Medication washout compliance assessment | X | X | X | X | X | |
| Pulmonary Function Testing | X | X | X | X | X | X |
| Reversibility Testing | X | | | | | |
| Administer trial medication ⁷ | | X | X | X | X | |
| 12-lead ECG | X | X | X | X | X ² | X ⁶ |
| Issue AM2+ / e-Diary | X | X | X | X | X | |
| Dispense trial drug | | X | X | X | | |
| Dispense rescue medication | X | X | X | X | X | |
| Pharmacokinetics | | X | X | X | X | |
| Compliance check | | | X | X | X | |
| Vital signs (seated) | X | X | X | X | X | X ⁶ |
| Collect and review e-Diary | | X | X | X | X | X |
| COPD symptom scores | | X | X | X | X | X |
| Global evaluation | | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X ⁶ |
| Concomitant therapy | X | X | X | X | X | X ⁶ |
| Drug accountability | | X | X | X | X | |
| Trial medication termination | | | | | X | |
| Conclude patient participation | | | | | | X ⁶ |

¹ All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions

² If findings, repeat at follow-up (Visit 6)

³ Fasting for at least 8 hours

⁴ Up to 2 additional blood samples at Visit 2 required for genotype analysis (β 2-receptor polymorphisms)

⁵ To be completed on all women of childbearing potential. A serum β HCG will be performed at Visit 1. A urine pregnancy test will be performed prior to trial medication administration at Visits 2-5, and at follow-up (Visit 6).

⁶ To be completed whenever trial participation ends (including discontinued patients)

⁷ At Visit 2, trial drug administered between 7:00-10:00 a.m. At Visits 3-5, trial drug administered within \pm 30 minutes of the time of trial drug administration at Visit 2 AND between 7:00-10:00 a.m.

Source: Trial 1222.5 Protocol; 'Flow Chart,' pp8

Study Population

This study included 405 COPD patients. Patients were randomized using a validated system which uses a pseudo-random number generator.

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Key Inclusion Criteria

1. Male or female ≥ 40 years in age
2. Current or ex-smokers with $a > 10$ year pack history
3. A diagnosis of COPD with an FEV1 $\geq 30\%$ and $< 80\%$ predicted with an FEV1/FVC ratio $\leq 70\%$ at visit 1
4. At visit 1 all patients must have airway reversibility based a $> 12\%$ increase in FEV1 following salbutamol treatment

Key Exclusion Criteria

1. Patient with significant disease other than COPD.
2. Clinical relevant abnormal baseline lab values
3. All patients with SGOT > 80 IU/L, SGPT > 80 IU/L, bilirubin > 17 umol/L, or creatinine > 110 umol/L (male) or 95 umol/L will be excluded.
4. Patients with a history of myocardial infarction within 1 year of the screening visit., a diagnosis of clinical relevant cardiac arrhythmia, active tuberculosis, clinically evident bronchiectasis, or life threatening pulmonary obstruction.
5. Patients who have undergone thoracotomy with pulmonary resection.
6. Patients being treated with medication that prolong QT/QTc interval, oral beta-adrenergics, beta-blockers, or oral steroids at unstable doses (< 6 weeks on a stable dose or at doses > 10 mg of prednisone per day or 20 mg every other day).
7. A diagnosis of paroxysmal tachycardia or hyperthyrosis
8. Baseline prolongation of QT/QTc interval.
9. Patients with a history of asthma, allergic rhinitis or total blood eosinophil count of ≥ 600 /mL.
10. A history fo additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalemia, family history of long QT).
11. Patients who have completed a pulmonary rehabilitation program in the 6 weeks prior to the visit 1.
12. Women of childbearing potential not using a highly effective method of birth control ($< 1\%$ failure rate).

Reviewer Comment:

The trial design is typical of a COPD dose ranging trial for a LABA, and specifically targets patients with beta-agonist reversibility at baseline. The inclusion/exclusion criteria are reasonable. This population is similar to populations used in other COPD LABA dose ranging trials.

Treatments

Treatment Groups

Olodaterol 2mcg once daily (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Olodaterol 20mcg once daily (2 actuations of 10mcg/actuation)

Placebo

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Concomitant Medications/Prohibited Medications:

All medications taken by the patients were recorded in the CRF. During the treatment period, patients were allowed to be on salbutamol (albuterol) PRN. One temporary increase or addition of steroids or theophylline was also allowed for exacerbation. PFT's were not performed within 7 days of the last dose. The use of antibiotics was not restricted. If antibiotics were needed for a respiratory infection, PFTs were postponed until at least 2 days after the last dose, but prior to 7 days. Patients on ICS/LABA combination therapies were switched to ICS alone 48 hours prior to visit 1. Anti-leukotrienes were only allowed if they were prescribed for conditions other than asthma. The prohibited and allowed medications are summarized in Table 12.

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Table 12. Trial 1222.5. Allowed and prohibited medications

| Drug-Class | Sub-class | Prior to Trial | Trial Period | | |
|---|---|----------------|-----------------|------------------|------------------|
| | | | Baseline Period | Treatment Period | Follow-up Period |
| Corticosteroids | Inhaled corticosteroids ¹ | permitted | permitted | permitted | permitted |
| | Oral corticosteroids ¹ [≤ 10 mg prednisone per day or ≤ 20 mg prednisone every other day (or equivalent)] | permitted | permitted | permitted | permitted |
| Beta-adrenergics / Beta-blockers | Inhaled short-acting beta-adrenergics | permitted | rescue | rescue | rescue |
| | Inhaled long-acting beta-adrenergics ² | permitted | permitted | study medication | permitted |
| | Oral beta-adrenergics | not permitted | not permitted | not permitted | not permitted |
| | Beta blockers | not permitted | not permitted | not permitted | not permitted |
| Anticholinergics | Short-acting anticholinergics (inhalation aerosol and nasal spray) | permitted | permitted | permitted | permitted |
| | Long-acting anticholinergics ³ | not permitted | not permitted | not permitted | not permitted |
| Miscellaneous | Other investigational drugs ⁴ | not permitted | not permitted | not permitted | not permitted |
| | Oral cromolyn sodium / nedocromil sodium | not permitted | not permitted | not permitted | not permitted |
| | Antihistamines, antileukotrienes ⁶ | not permitted | not permitted | not permitted | not permitted |
| | Methylxanthines ⁵ | not permitted | not permitted | not permitted | not permitted |
| | Mucolytics ¹ | permitted | permitted | permitted | permitted |

¹if stabilized for 6 weeks prior to visit 1

²at least a 48 hour washout of LABA prior to visit 1 and visit 2

³at least a 4 week washout period prior to visit 1

⁴washout of at least one month or 6-half lives (whichever is greater)

⁵at least 24 hour washout of short-acting theophylline preparations prior to visit 1

at least a 48 hour washout of long-acting theophylline preparations prior to visit 1

⁶may be used if not prescribed for asthma

Source: Trial 1222.5 Protocol, section 4.2.2; pp48

Reviewer Comment:

The medication restrictions are reasonable. It is also reasonable to allow for single use of oral steroids or theophylline in the setting of an exacerbation, as PFTs were not to be performed until at least 7 days after the last dose.

Efficacy Parameters

Primary Endpoint

The primary efficacy variable was trough FEV1 response after 4 weeks of treatment. Trough FEV1 was defined as the average of the -1 hour and -10 minute FEV1. Trough

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FEV1 response was defined as the change from baseline in FEV1. Baseline was determined at visit 2

Secondary Endpoints

The secondary endpoints will include the following parameters:

- 1) Trough FEV1 response after 1 and 2 weeks of treatment
- 2) Trough FVC response after 1, 2, and 4 weeks of treatment
- 3) FEV1, FVC AUC (0-3 hours) and peak(0-3) response after the 1st dose and after 1 and 2 weeks of treatment
- 4) FEV1, FVC AUC(0-6) and peak(0-6) response after 4 weeks of treatment
- 5) FEV1, FVC (unsupervised) AUC(0-6) and AUC(6-12) response [L] after 4 weeks of treatment
- 6) FEV1, FVC (unsupervised) AUC (0-3 hours) and AUC(3-12) response [L] after the first dose and after 1 and 2 weeks of treatment
- 7) Individual FEV1 and FVC (supervised) measurements [L] at each time point
- 8) Individual FEV1 and FVC (unsupervised) measurements [L] at each time point
- 9) Weekly mean pre-dose morning and evening PEFR (peak expiratory flow rate) [L/min]
- 10) Weekly mean number of occasions of rescue therapy used per day (PRN salbutamol (albuterol))
- 11) COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest)
- 12) Physician's Global Evaluation

Note that for the secondary endpoints 'response' was defined as in the primary endpoint (i.e. change from baseline).

Unsupervised spirometry for the secondary endpoints was performed at home on a Viasys AM2+ device between post-dose hours 6-12. The Viasys device was also be used to measure twice daily PEFR. These values were recorded in the eDiary, as was rescue medication use.

The severity of COPD symptoms was recorded in the eCRF at each visit. Severity was scored from 0 to 3 (none, mild, moderate, or severe). Assessments were made by the investigator.

At each visit, the physician also performed a global assessment prior to spirometry. The score was graded from poor to excellent based on the need for concomitant medications, number and severity of exacerbations since the last visit, severity of cough, ability to exercise, amount of wheezing, and other clinically relevant observations. It was scored 1-2 for poor, 3-4 for fair, 5-6 for good, and 7-8 for excellent. This was recorded in the eCRF.

Safety Assessments:

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Monitored safety parameters included the following and were assessed as per Table 11.

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs
- Physical examinations
- Clinical laboratory evaluations
 - Labs will include a complete blood count, chemistry panel, and urinalysis
- Vital signs (blood pressure and pulse rate)
- ECG (at -30 minutes, 10 minutes, and 3 hours post-dose)
- Pregnancy testing

Pharmacokinetic Assessments

Blood and urine were also sampled to calculate the following parameters

- Maximum serum concentration and time to maximum concentration
- AUC of serum plasma concentrations from time 0 to the last quantifiable data point
- Amount and fraction excreted in urine from time 0 to 3 hours.

Serum concentrations were only reported if ≥1/3 of patients in the dose group had detectable levels.

Compliance Assessments

Compliance was based on entries in patient eDiaries. Each time a patient took study medication, they made an entry.

Reviewer Comments:

The primary endpoint is typical for LABA dose ranging trials. Positive results for the primary endpoint would be supportive of a bronchodilator effect. With regard to the secondary endpoints, the Physician Global Assessment and COPD symptoms score may be of limited value given its subjective nature. Additionally, the use of non-supervised at home PFTs is of questionable value, as it is unclear how reliable those results would be. Other secondary endpoints would generally be supportive of a bronchodilatory effect for olodaterol. The safety, PK, and compliance assessments are also reasonable. However, ideally the sponsor would have used additional measures of compliance such as medication weight/returned medication.

Ethics:

This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

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Based on an assumed standard deviation in trough FEV1 of 0.229 liters, a sample size of 80 patients per group should be able to detect a difference of 120mL compared to placebo with a 5% level of significance with 90% power.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and at least one adequate measurement following at least 5 days of randomized treatment for at least one endpoint. The per protocol (PP) data set that consisted of all FAS minus patients with important protocol deviations. The safety population was made up of all treated patients.

Missing Data

For missing spirometry data, values were estimated using other recorded values for that day. If the value was missing due to rescue medication use, then the least favorable value from that day was used. Estimations were made by linear interpolation of the adjacent data, or by last observed carried forward if no subsequent data were available. However if a single pre-dose measurement was missing, the other pre-dose measurement was used. If both were missing, pre-dose data from the prior visit was used.

Efficacy Analysis

The primary variable was FEV1 response after 4 weeks of treatment. The variable was analyzed using ANCOVA. To account for type 1 error analysis was performed in an ordered fashion starting with a comparison of Olo 20mcg to placebo. If the Olo 20mcg dose demonstrated a significantly greater trough FEV1 response than placebo (one-tailed p-value 0.025), then the next lower dose was compared to placebo.

The secondary efficacy variables will be analyzed using ANCOVA in a manner similar to the primary efficacy variable. For the FEV1 and FVC at individual time points, the adjusted means were illustrated graphically to show the time-response profile.

Safety Analysis

The safety analysis was descriptive. All events were coded with the MedDRA 9.1 dictionary. All events with an onset after the first dose of study medication up to 12 days after the last dose were assigned to the treatment period. Other AEs were assigned to the follow-up period or screening period as appropriate. Laboratory values were assigned in a similar manner. Results were summarized by treatment group

Results:

Protocol Amendments:

After the initial submission of this protocol, there were 3 amendments. In the first, submitted on 12/15/2006, BI adding wording stating that genetic investigations would be limited to the effect of genetic variations on respiratory diseases. The 2nd amendment was submitted 5/7/2007. This amendment added an additional lab draw for potassium

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(1 hour post dose). This amendment also added serum creatinine phosphokinase (CPK) to the standard lab draw, clarified data to be included in the eDiary, and prohibited use of antihistamines and antileukotrienes unless prescribed for a condition other than asthma. The 3rd amendment was submitted on 8/17/2007. This amendment modified the normal limits of bilirubin and creatinine to be in line with the central lab.

Protocol Violations

The majority of protocol violations were related to compliance data (missing compliance data or compliance outside range). Compliance issues were the most common cause of protocol violations. They occurred in the placebo, Olo 2mcg, Olo 5mcg, Olo 10mcg, and Olo 20mcg with incidences of 16.9%, 12.4%, 21.3%, 11.6%, and 24.1%, respectively. Otherwise, the numbers were similar generally similar across groups.

Reviewer Comment:

It is unlikely that the protocol amendments would have impacted trial results or their interpretation. It is possible that the increased number of protocol violations due to compliance issues in the Olo 5mcg and Olo 10mcg group compared to placebo could affect trial results. As this would potentially understate a treatment effect for the 5 and 10mcg groups, it is not a large concern.

Patient Disposition

A total of 621 patients were enrolled in this trial. Of these, 405 patients were randomized of whom 96% completed this trial. Premature discontinuation was most common in the Olo 5mcg and placebo group. The most common reason for discontinuation was an adverse event. AEs as a reason for discontinuation was most common in the Olo 5mcg group. In the placebo, Olo 2, 5, 10, 20 mcg groups, 1 (1.3%), 1 (1.2%), 5 (6.3%), 0, and 2 (2.5%) patients withdrew due to AEs, respectively. However, AEs related to study disease worsening leading to discontinuation were low and similar between groups. Lack of efficacy as a reason for discontinuation was most common in the placebo group. Patient disposition data are summarized in Table 13.

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Table 13 Trial 1222.5 Patient disposition

| | Placebo | Olo 2mcg | Olo 5mcg | Olo 10mcg | Olo 20mcg | Total |
|--|-------------|-------------|-------------|-------------|-------------|--------------|
| Enrolled | | | | | | 621 |
| Not entered/randomized | | | | | | 216 |
| Entered/randomized | 79 (100.00) | 81 (100.00) | 80 (100.00) | 86 (100.00) | 79 (100.00) | 405 (100.00) |
| Treated | 79 (100.00) | 81 (100.00) | 80 (100.00) | 86 (100.00) | 79 (100.00) | 405 (100.00) |
| Not prematurely discontinued from trial medication | 74 (93.67) | 80 (98.77) | 73 (91.25) | 85 (98.84) | 76 (96.20) | 388 (95.80) |
| Prematurely discontinued from trial medication | 5 (6.33) | 1 (1.23) | 7 (8.75) | 1 (1.16) | 3 (3.80) | 17 (4.20) |
| Adverse event | 1 (1.27) | 1 (1.23) | 5 (6.25) | 0 (0.00) | 2 (2.53) | 9 (2.22) |
| AE study dis. worse | 1 (1.27) | 0 (0.00) | 1 (1.25) | 0 (0.00) | 1 (1.27) | 3 (0.74) |
| AE-oth. dis. worse | 0 (0.00) | 1 (1.23) | 2 (2.50) | 0 (0.00) | 0 (0.00) | 3 (0.74) |
| AE-other | 0 (0.00) | 0 (0.00) | 2 (2.50) | 0 (0.00) | 1 (1.27) | 3 (0.74) |
| Lack of efficacy | 2 (2.53) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 2 (0.49) |
| Non compl prot. | 0 (0.00) | 0 (0.00) | 1 (1.25) | 0 (0.00) | 0 (0.00) | 1 (0.25) |
| Lost to follow-up | 1 (1.27) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.25) |
| Consent withdrawn | 1 (1.27) | 0 (0.00) | 1 (1.25) | 0 (0.00) | 0 (0.00) | 2 (0.49) |
| Other | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (1.16) | 1 (1.27) | 2 (0.49) |

Source: Trial 1222.5 CSR; Table 10.1:1; pp74

Reviewer comment:

Overall discontinuations were highest in the placebo and Olo 5mcg group. While this discrepancy could affect results, the given the overall small numbers of discontinuation, the effect is not likely to be significant.

Demographics:

In this trial, the majority of patients were Caucasian males with a mean age of 63 years, a 47 pack year smoking history, and a COPD diagnosis for 7.6 years. In general most demographic characteristics were similar across treatment groups. Baseline FEV1 and reversibility were also similar between groups. This information is summarized in Table 14.

Table 14. Trial 1222.5. Baseline patient characteristics

| | Placebo | Olo 2mcg | Olo 5mcg | Olo 10mcg | Olo 20mcg | Total |
|--------------------|-----------|-----------|-----------|-----------|-----------|------------|
| Number of patients | 79 | 81 | 80 | 86 | 79 | 405 |
| Gender [N (%)] | | | | | | |
| Male | 39 (49.4) | 42 (51.9) | 56 (70.0) | 51 (59.3) | 46 (58.2) | 234 (57.8) |
| Female | 40 (50.6) | 39 (48.1) | 24 (30.0) | 35 (40.7) | 33 (41.8) | 171 (42.2) |
| Age [years] | | | | | | |
| Mean | 62.66 | 63.81 | 63.25 | 63.55 | 63.19 | 63.30 |

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| SD | 9.74 | 8.63 | 9.47 | 7.92 | 9.00 | 8.92 |
|----------------------------------|-----------|-----------|------------|-----------|------------|-------------|
| Race [N (%)] | | | | | | |
| White | 78 (98.7) | 76 (93.8) | 72 (90.0) | 82 (95.3) | 73 (92.4) | 381 (94.1) |
| Black | 1 (1.3) | 5 (6.2) | 8 (10.0) | 3 (3.5) | 6 (7.6) | 23 (5.7) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.2) | 0 (0.0) | 1 (0.2) |
| Smoking history [N(%)] | | | | | | |
| Ex-smoker | 38 (48.1) | 41 (50.6) | 46 (57.5) | 40 (46.5) | 38 (48.1) | 203 (50.1) |
| Current smoker | 41 (51.9) | 40 (49.4) | 34 (42.5) | 46 (53.5) | 41 (51.9) | 202 (49.9) |
| Pack-year history | | | | | | |
| Mean | 50.03 | 46.01 | 49.01 | 43.57 | 47.63 | 47.18 |
| SD | 25.01 | 20.87 | 25.12 | 18.47 | 23.25 | 22.63 |
| Diagnosis duration [years] | | | | | | |
| Mean | 7.78 | 7.65 | 7.89 | 7.65 | 6.84 | 7.57 |
| SD | 5.42 | 5.73 | 5.75 | 5.72 | 5.18 | 5.55 |
| Diagnosis duration [N(%)] | | | | | | |
| <1 year | 4 (5.1) | 3 (3.7) | 2 (2.5) | 4 (4.7) | 8 (10.1) | 21 (5.2) |
| 1 to <10 years | 52 (65.8) | 54 (66.7) | 55 (68.8) | 60 (69.8) | 48 (60.8) | 269 (66.4) |
| 10 to <20 years | 19 (24.1) | 21 (25.9) | 18 (22.5) | 18 (20.9) | 22 (27.8) | 98 (24.2) |
| ≥20 years | 4 (5.1) | 3 (3.7) | 5 (6.3) | 4 (4.7) | 1 (1.3) | 17 (4.2) |
| FEV1 (%predicted) | | | | | | |
| Mean | 53.9 | 55.2 | 52.8 | 55 | 54.0 | 54.2 |
| SD | 12.7 | 13.4 | 13.6 | 12.9 | 13.3 | 13.2 |
| FEV1 %change post bronchodilator | | | | | | |
| Mean | 14.4 | 15.9 | 19.9 | 17.5 | 17.8 | 17.1 |
| SD | 14.0 | 12.0 | 16.5 | 12.7 | 15.8 | 14.3 |

Source: Trial 1222.5 CSR; Table 11.2:1 and 11.2:2; pp77 and 79

Compliance:

Overall, compliance was high. Patient compliance was balanced across all treatment groups and ranged between 93-95%. Approximately 80% of patients took study medication between 80-120% of the time. Only 4% of patients took more than 120% of the time, while 13% percent took their medication less 80% of the time.

Reviewer Comment:

Overall the patient demographics and compliance were similar between groups.

Primary Endpoint

The primary endpoint of this trial was trough FEV1 response after 4 weeks of treatment. At all olodaterol doses, increase in trough FEV1 response compared to placebo was statistically significant. Additionally, there was a clear dose response with an increasing treatment effect with increasing doses. These data are summarized in Table 15.

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Table 15.Trial 1222.5. Primary Endpoint. Trough FEV1 response after 4 weeks.

| Treatment | N (total=405) | Trough FEV1 [L] Response (SE) | Difference from placebo (SE) |
|------------|------------------|----------------------------------|---------------------------------|
| Placebo | 79 | -0.014 (0.021) | |
| Olo 2 mcg | 81 | 0.046 (0.021) | 0.061 (0.027) |
| Olo 5 mcg | 80 | 0.082 (0.021) | 0.097 (0.027) |
| Olo 10 mcg | 86 | 0.109 (0.021) | 0.123 (0.026) |
| Olo 20 mcg | 79 | 0.118 (0.021) | 0.132 (0.027) |

all p-values <0.023 compared to placebo

Source: Trial 1222.5 CSR; Table 11.4.1.1:1; pp81

Secondary Endpoints

The first secondary endpoint was trough FEV1 response after 1 and 2 weeks of treatment. As with the primary endpoint, all olodaterol doses demonstrated a statistically significant improvement compared to placebo. However, a dose response was not as evident at these earlier time points.

Table 16.Trial 1222.5. Trough FEV1 response after 1 and 2 weeks of treatment.

| | Treatment | Trough FEV1 [L] Response (SE) | Difference from placebo (SE) |
|----------------------|------------|----------------------------------|---------------------------------|
| 1 week of treatment | Placebo | -0.029 (0.019) | |
| | Olo 2 mcg | 0.059 (0.018) | 0.088 (0.025) |
| | Olo 5 mcg | 0.108 (0.019) | 0.137 (0.025) |
| | Olo 10 mcg | 0.099 (0.018) | 0.128 (0.024) |
| | Olo 20 mcg | 0.140 (0.019) | 0.169 (0.025) |
| 2 weeks of treatment | Placebo | -0.023 (0.020) | |
| | Olo 2 mcg | 0.062 (0.020) | 0.085 (0.026) |
| | Olo 5 mcg | 0.099 (0.020) | 0.121 (0.026) |
| | Olo 10 mcg | 0.102 (0.020) | 0.125 (0.026) |
| | Olo 20 mcg | 0.105 (0.020) | 0.128 (0.026) |

*all p-values ≤ 0.0011 for difference from placebo

Source: Trial 1222.5 CSR; Table 11.4.1.1:1; pp81

For other FEV1 related secondary endpoints [FEV1 AUC (0-3 hours), FEV1 (0-6), and FEV1 peak response] similar results were reported. For all endpoints, all doses of olodaterol demonstrated statistically significant treatment effect compared to placebo. A similar pattern was also evident for FVC related secondary endpoints.

For the secondary endpoint of rescue medication use (PRN salbutamol/albuterol), all doses demonstrated a decrease in rescue medication compared to placebo. However, the difference was not statistically significant for any olodaterol dose. The findings for the COPD symptom scores were similar. For the Physician Global Evaluation, at week 4, only the 10mcg group had significantly better scores than placebo.

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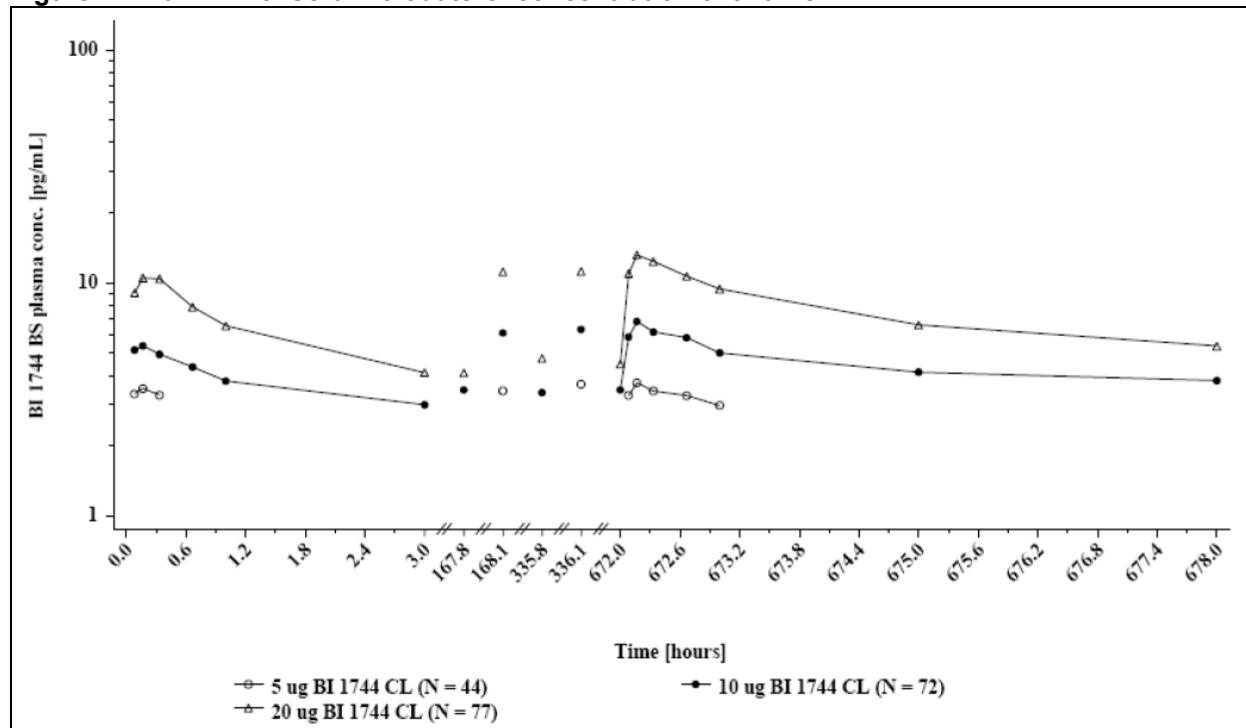
Reviewer Comment:

Based on the primary endpoint, all doses of olodaterol demonstrated a statistically significant bronchodilator effect compared to placebo. This effect demonstrated a clear dose response. As with trial 1222.3, the incremental benefit of increasing doses appeared less pronounced the higher the dose. Based on the primary endpoint, the 20mcg dose has only a minimal incremental benefit compared to the 10mcg dose. For the secondary endpoints of trough FEV1 response at week 1 and 2, the results were similar; however, the dose response was not as evident. This was especially true at week one. With regard to rescue medication use, while there was some numerical improvement, it was not statistically significant. The results for the symptom score and Physician Global Assessment score are of questionable value because the scores are highly subjective in nature, and have not been validated as an efficacy endpoints.

Pharmacokinetics

Following inhalation, serum levels of olodaterol could only be detected in 7 of 81 patients given Olo 2mcg. In patients receiving 5mcg, levels were quantifiable up to 20 minutes post-dose on day 1 and up to 40 minutes on day 29 in approximately 1/3 of patients. For the Olo 10 and 20mcg groups, 1/3 of patients had detectable serum levels 3 hours post-dose on day 1 and up to 6 hours on day 29. For the 5, 10, and 20mcg groups, the maximum plasma concentration was observed around 10 minutes post-dose (single and repeated doses). The decline after peak was rapid. Serum concentration data is summarized in Figure 4.

Figure 4. Trial 1222.5. Serum olodaterol concentration over time



BI1774 CL=Oladaterol

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Source: Trial 1222.5 CSR; Figure 11.5.2.1.1:1

Reviewer Comment:

These PK results are consistent with trial 1222.3.

Safety:

Exposure:

A total of 326 patients were exposed to olodaterol and 79 to placebo. The mean exposure time was 29 days and was similar across groups.

Deaths and SAEs

There were no deaths in this trial. There were 8 SAEs reported in the Olodaterol dose groups (2 per dose), and none in the placebo group. In the 2 mcg group, one SAE was due to lung cancer and one due to a COPD exacerbation and pleural effusion (s/p motorcycle accident). In the 5 mcg group, there was one SAE of diverticulitis and one of hip fracture s/p fall. In the 10 mcg group, there was one report of COPD exacerbation and one of humerus fracture s/p fall. In the 20 mcg group, there was one report of COPD exacerbation and one upper GI bleed

Treatment Emergent AEs

All AEs occurring after the first dose of trial medication until 12 days after the last dose were considered treatment emergent AEs (TEAEs) in the review of this trial. Overall, the total on treatment AEs were similar across treatment groups ranging between 30-40%. Total overall AEs were highest in the Olo 5 mcg group [33 (41.3%)] and lowest in the Olo 10 mcg group [26 (30.2)]. For the placebo group, AEs were reported in 29 patients (37%). The most frequent common AEs (>3% in any group) were in the RTM SOC. By preferred term, the most common AE was cough. Aside from headache and dyspnea, all other common AEs demonstrated an imbalance when comparing placebo to at least one olodaterol dose group. These results are summarized in Table 17.

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Table 17. Trial 1222.5. Common TEAEs (>3%)

| System organ class/ Preferred term | Placebo N(%) | BI 1744 R2 N(%) | BI 1744 R5 N(%) | BI 1744 R10 N(%) | BI 1744 R20 N(%) |
|---|-----------------|--------------------|--------------------|---------------------|---------------------|
| Number of patients | 79 (100.0) | 81 (100.0) | 80 (100.0) | 86 (100.0) | 79 (100.0) |
| Infections and infestations | | | | | |
| Nasopharyngitis | 1 (1.3) | 2 (2.5) | 6 (7.5) | 4 (4.7) | 2 (2.5) |
| Upper respiratory tract infection | 0 (0.0) | 2 (2.5) | 1 (1.2) | 4 (5.1) | 1 (1.3) |
| Bronchitis | 0 (0.0) | 1 (1.2) | 3 (3.8) | 2 (2.3) | 0 (0.0) |
| Nervous system disorders | | | | | |
| Headache | 4 (5.1) | 3 (3.7) | 1 (1.3) | 3 (3.5) | 1 (1.3) |
| Respiratory, thoracic and mediastinal disorders | | | | | |
| Dyspnea | 6 (7.6) | 3 (3.7) | 2 (2.5) | 0 (0.0) | 3 (3.8) |
| Cough | 2 (2.5) | 4 (4.9) | 6 (7.5) | 2 (2.3) | 2 (2.5) |
| Chronic Obstructive Pulmonary Disease | 2 (2.5) | 3 (3.7) | 2 (2.5) | 4 (4.7) | 2 (2.5) |

BI1774 R10=Olo 10mcg, BI1744 R5=Olo 5mcg, BI1744 R2=Olo 2mcg

Source: Trial 1222.5 CSR; Table 12.2.2:1; pp119

Reviewer Comment:

With regard to AEs, olodaterol was fairly well tolerated. While SAEs were more frequent in the olodaterol treatment groups compared to placebo, the overall number was small and only COPD exacerbation occurred more than once. Additionally, the 3 SAEs of COPD exacerbation are not necessarily surprising given the patient population, and the remaining 5 SAEs were not likely related to olodaterol. Overall TEAEs were also fairly even distributed across groups. With regard to common TEAEs, in general, they were more frequent in the olodaterol groups compared to placebo. However, there was no clear dose response as the highest olodaterol dose performed similarly to placebo.

Labs:

In general hematologic and chemistry lab values were stable from baseline to end of treatment. For most labs, fewer than 2 patients per group demonstrated significantly increased or decreased values. However, there were two exceptions; sodium and CPK. Sodium was increased in 5 patients (6.4%) in the 20mcg group, one in the placebo, and none in all other groups. With regard to serum CPK (levels taken at 1 and 3 hours post-dose), more patients in the Olo 20 mcg group [9 (12.9%)] had elevated CPKs compared to placebo [4 (6%)]. For all other olodaterol doses, there were fewer patients with CPK elevations compared to placebo. Serum potassium levels were also specifically monitored around dosing (1 and 3 hours post-dose). On day 29, there were no differences in serum potassium levels between olodaterol groups and placebo, although the 20mcg group had a trend toward decreased levels. After the 1st dose and on day 8, the 20mcg group had a statistically significant decrease in average serum potassium levels (0.96mmol/L) compared to placebo. However, this was not the case for all other olodaterol doses. None of the laboratory changes were associated with AEs.

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Vitals signs

The number of patients with changes from baseline in blood pressure was comparable between oladaterol groups and placebo treatment periods. There was also no significant differences in pulse rates based on mean values. However, for all oladaterol dose groups except 2mcg more patients with normal baseline pulse were noted to have elevated pulse rates at any point during the trial compared to placebo. However, there was not a dose response. New or worsening of ECG changes were not noted.

Reviewer comment:

Overall, oladaterol did not appear to have a significant effect on lab values in most patients. Although the highest dose of oladaterol appeared to decreased serum potassium levels after the 1st dose and at day 8, this effect did not persist at the end of treatment; nor was this effect seen in any other dose groups. This is reassuring as the proposed dose is 5mcg once daily. The potassium results are not surprising given that oladaterol is a beta-agonist, and decreased potassium is a known pharmacodynamic effect.

Overall Reviewer Comment:

Based on the primary and secondary endpoints, oladaterol at doses from 2mcg to 20mcg once daily have a significant bronchodilatory effect compared to placebo. Further, there is dose response, although the incremental benefit for increasing doses decreases at doses greater than 5mcg. There is little additional benefit from the 20mcg dose. These efficacy results are consistent with trial 1222.3. With regard to safety, oladaterol was fairly well tolerated and no adverse events demonstrated a dose response. However, the statistically significant decreases in potassium and increases in CPK at the 20mcg dose, suggest that this dose is unnecessarily high. The efficacy and safety data suggest that a dose <20mcg is optimal.

5.3.3 Trial 1222.26 (COPD)

Administrative Information

- **Study title:** Randomized, double-blind, 4-way cross-over study to determine the 24-hour FEV1-time profile of orally inhaled oladaterol, delivered with the Respimat inhaler, after 3 weeks of once daily (5 mcg, 10mcg) or twice daily (2 mcg, 5mcg) administration in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 2/16/2009-7/20/2009
- **Study sites:** Belgium (3 sites) and Netherlands (2 sites)
- **Study report date:** 3/11/2010

Objectives/Rationale

- To determine the 24-hour FEV1 time profile of oladaterol after 3 weeks of once or twice daily dosing.

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Study Design and Conduct

Overview

This was double-blind, randomized, 4-way crossover, dose interval trial in patients with moderate to severe stable COPD. The objective of this trial was to determine optimum dosing interval (qD versus BID). Each treatment period lasted 3 weeks with no washout period between. The doses of olodaterol used were 2 mcg BID, 5 mcg BID, 5 mcg qD, and 10 mcg qD. PFTs were performed at baseline (prior to any test article) and at the end of each 3 week treatment period. There was no placebo group as patients were compared to their own baseline.

Patients were seen in clinic at -8 days (visit 1), day 0 (visit 2), and weeks 3, 6, 9, 12 and 14 (visits 3, 4, 5, 6, 7, respectively). Prior to visit 1, informed consent was obtained and washout of restricted medications began (visit 0). After washout of medications, at visit 1, eligible patients began the one week baseline period. At visit 2, eligible patients were randomized to treatment sequences. 24-hour baseline spirometry was also performed at visit 2. At visits 3-6, treatment for the following treatment periods were dispensed. 24 hour spirometry was also performed at these visits. Patients were seen for an end of trial visit 14 days after the last treatment period. Trial assessment schedule is summarized in Table 18.

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Table 18. Trial 1222.26. Assessment schedule

| Trial Periods | Screening | | Treatment ¹ | | | | Follow-up | |
|--|-----------------|-----------------|----------------------------|----------------------------|----------------------------|----------------------------|-----------------|---------|
| | | | Period 1 | Period 2 | Period 3 | Period 4 | | |
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7/EOT |
| Week | | -1 | | 3 | 6 | 9 | 12 | 14 |
| Day2 | | -8 | 0/1 | 21/22 | 42/43 | 63/64 | 84/85 | V6 + 14 |
| Informed consent and subject information | X ³ | | | | | | | |
| Demographics | X | | | | | | | |
| Medical History | X | | | | | | | |
| Smoking status | X | | | | | | | |
| In-/Exclusion Criteria | X | X | | | | | | |
| Physical examination | X | | X | X | X | X ⁴ | | |
| Laboratory tests (fasting) | X | | X | X | X | X ⁴ | | |
| Pregnancy testing ⁵ | X | X | X | X | X | | X | |
| 12-lead ECG | X | | X | X | X | X ⁴ | | |
| Training in use of Respimat® inhaler | X | X ⁶ | | | | | | |
| Randomization | | X (Day 1) | | | | | | |
| Collect trial medication | | | X ⁷ (Day 21) | X ⁷ (Day 42) | X ⁷ (Day 63) | X ⁷ (Day 84) | | |
| Dispense trial medication | | | X ⁸ (Day 1) | X ⁸ (Day 22) | X ⁸ (Day 43) | X ⁸ (Day 64) | | |
| Dispense rescue medication | X | X | X | X | X | X | X | |
| Administer trial medication | | | X ⁹ (Day 1) | X ⁹ | X ⁹ | X ⁹ | X ⁹ | |
| Issue patient diary | X | X | X | X | X | X | X | |
| Collect patient diary | | | X | X | X | X | X | X |
| PFTs (FEV ₁ /FVC) | X ¹⁰ | X ¹¹ | X ¹² | X ¹² | X ¹² | X ¹² | | |
| PK sampling (plasma/urine) | | | X ¹³ | X ¹³ | X ¹³ | X ¹³ | X ¹³ | |
| Vital signs (seated) ¹⁴ | X | X | X | X | X | X | X | |
| Adverse events | X | X | X | X | X | X | X | X |
| Concomitant therapy | X | X | X | X | X | X | X | X |
| Compliance check | | | | X | X | X | X | |
| Drug accountability | | | X | X | X | X | X | |
| Trial medication termination | | | | X | X | X | X | |
| Trial completion | | | | | | | X | |

¹ No wash-out between each treatment period (see footnotes 7, 8, 9)

² Visits 2–6 require the patient to remain in the clinic for an overnight stay in order to complete the 24 hour PFTs; the days refer to the first and second day of each clinic visit

³ All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions

⁴ To be completed whenever trial participation ends

⁵ Women of child-bearing potential: serum pregnancy test at Visit 1; urine pregnancy test at Visits 2–5 and Visit 7

⁶ At Visit 2, the patient again will be instructed in the use of the Respimat® inhaler, but the patient should not inhale from the placebo inhaler at this visit

⁷ Last dose of trial medication for respective treatment period will be evening dose on the first day of the clinic visit (i.e., Day 21, 42, 63, 84); medication is collected after this evening dose

⁸ After completion of 24 hour PFTs, dispense medication for next 3 week treatment period

⁹ After completion of 24 hour PFTs, and dispensing of medication, administer first (morning) dose of next treatment period. Evening Respimat® device should also be primed prior to the patient leaving the clinic.

¹⁰ Pre- and post-bronchodilator (400 µg salbutamol (albuterol))

¹¹ Pre-treatment baseline 24 hour FEV₁-time profile: timing of PFT measurements need to be scheduled relative to the planned timing of the morning dose of trial medication during treatment (see footnote 12)

¹² Pre-morning dose PFT: 10 mins prior to inhalation of morning dose of study medication

Post-morning dose PFTs: 30 mins, 1, 2, 3, 4, 6, 8, 10 hrs and 11 hrs 50 mins post-morning dose

Evening dose: 12 hours post-morning dose

Post-evening dose PFTs: 30 mins, 1, 2, 10, 11 hrs and 11 hrs 50 mins post-evening dose

¹³ plasma: Day 1: prior to drug administration a.m.

Day 21, 42, 63, 84: prior to drug administration a.m., and 10 (-2/+5) minutes post-dose a.m.

urine: Day 1: prior to drug administration a.m.

Day 21, 42, 63, 84: 0–12 hours post dose a.m. and p.m.

¹⁴ In conjunction with pulmonary function testing (up to 6 hrs post-morning dose)

Source: Trial 1222.26 CSR; Table 9.5:1;pp48

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Study Population

This study included 47 COPD patients. Patients were randomized using a validated system which uses a pseudo-random number generator.

Key Inclusion/Exclusion Criteria

See trial 1222.5 (section 5.3.2)

Treatments

Treatment Groups

Olodaterol 2mcg twice daily (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 5mcg twice daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Concomitant Medications/Prohibited Medications:

All medications taken by patients were recorded in the CRF. During the treatment period, patients were allowed to be on salbutamol (albuterol) PRN. If short acting bronchodilator medication was needed during 24 hour serial spirometry, the PFTs were discontinued. Long acting beta-agonists (LABA) were not to be taken 12 hours prior to PFTs. Short acting bronchodilators (beta-adrenergic and anticholinergic) were not be taken 8 hours prior to PFTs. Inhaled corticosteroids (ICS) were not allowed 1 hour prior to PFTs. The morning dose of study medication was not to be taken prior to pre-dose PFTs. Long acting anticholinergics were only allowed during the follow-up period, but were prohibited during the baseline and treatment periods.

Patients on ICS/LABA combination therapies were switched to ICS alone 48 hours prior to visit 1. Patients on fixed dose anticholinergic/short acting beta-agonist (SABA) were switched to Atrovent prior to baseline period and allowed to use salbutamol PRN.

Patients on Anti-leukotrienes were only allowed if they were prescribed for conditions other than asthma.

Medications for COPD exacerbations were allowed as necessary. However, patients were discontinued for COPD exacerbations. The prohibited and allowed medications are summarized in Table 12 in section 5.3.2 (Trial 1222.5).

Reviewer comment:

Given the objective, the trial design is reasonable. Based on the previous COPD dose ranging trials, it is reasonable to explore total daily doses (TDD) of 5 and 10mcg. The inclusion/exclusion criteria are also reasonable. At the time this study was conducted, a 2.5 mcg dose was not available; although the 2 mcg BID dose offers a reasonable (if slightly lower) approximation. Note that the 2.5 mcg BID regimen is tested in the asthma dose interval trial (Trial 1222.29).

Efficacy Parameters

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Primary Endpoint

The co-primary endpoints were FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 3 weeks of treatment. Response was defined as the change from baseline as determined at visit 2.

Secondary Endpoints

The secondary endpoints will include the following parameters:

- 1) FEV AUC (0-24 hours), peak FEV1, and trough FEV1 response after 3 weeks of treatment
- 2) FVC AUC (0-12 hours), FVC AUC (12-24 hours), peak FVC, and trough FVC response after 3 weeks of treatment
- 3) Trough FVC response after 1, 2, and 4 weeks of treatment
- 4) FEV1, FVC AUC (0-3 hours) and peak(0-3) response after the 1st dose and after 1 and 2 weeks of treatment
- 5) Individual FEV1 and FVC measurements [L] at each time point over 24 hours after 3 weeks of treatment

Peak FEV1 and Peak FVC were defined as the highest values within 3 hours of post-morning dose of trial medication. Trough FEV1 and trough FVC were defined as the value immediately prior to morning dose of medication.

Safety Assessments:

Monitored safety parameters included the following and were assessed as per Table 18.

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs
- Physical examinations
- Clinical laboratory evaluations
 - Labs will include a complete blood count, chemistry panel, and urinalysis
- Vital signs (blood pressure and pulse rate)
- ECG (pre-dose at each visit)

Pharmacokinetic Assessments:

Blood and urine were also sampled to calculate the following parameters

- Serum concentration at steady state
- Serum concentration immediately prior to dosing
- Amount eliminated from urine at steady state
- Fraction eliminated from urine at steady state

Compliance Assessments

Compliance was based on entries in patient diaries. Each time a patient took study medication, they made an entry.

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Ethics:

This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Reviewer Comment:

The chosen co-primary and secondary endpoints are appropriate and typical for a trial attempting to determine optimum dose interval. The safety parameters are also reasonable.

Statistical Analysis

Sample Size

Based on previous trials, BI assumed a standard deviation in FEV1 AUC (0-12 hours) of 0.16 liters and for FEV1 AUC (12-24 hours) of 0.14 liters. Based on this BI estimated that randomization of 48 patients would yield 90% power to detect a 90mL difference in FEV AUC (0-12 hours) and a 80mL difference in FEV1 AUC (12-24 hours) (one sided alpha of 0.025). This assumes a 25% discontinuation rate.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and evaluable post-dosing data for at least the co-primary endpoints. The per protocol (PP) data set consisted of the FAS minus patients with important protocol deviations. Important protocol deviations were defined as deviations that may have a distorting influence on the primary endpoint or could affect patient safety or rights. The safety population was made up of all treated patients.

Missing Data

For missing spirometry data due to rescue medication use, the missing data was estimated using the least favorable observation from that day. If the timing of the rescue medication was unknown, data for the entire visit was considered missing. Data missing for other reasons will be imputed using linear interpolation of adjacent data points, or with the last observed data if sufficient data is not available for interpolation.

Efficacy Analysis

The co-primary variables to be analyzed were FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 3 weeks of treatment. The variable was analyzed using ANCOVA. P-values were not corrected for multiple comparisons.

The secondary efficacy variables were analyzed using ANCOVA in a manner similar to the primary efficacy variable.

Safety Analysis

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The safety analysis was descriptive. All events were coded with the MedDRA 10.1 dictionary. All events with an onset after the first dose of study medication up to 12 days after the last dose were assigned to the treatment period for evaluation. In this review, these were considered treatment emergent AEs. Other AEs were assigned to the follow-up period or screening period as appropriate. Laboratory values were assigned in a similar manner. Results were summarized by treatment group.

Reviewer Comment:

As the statistical analysis was not corrected for multiplicity, all comparisons should be considered exploratory/descriptive. As this is a dose ranging trial, this analysis may be acceptable.

Results:

Protocol Amendments:

There were no amendments. However, prior to database lock, there were changes to the data analysis plan. To model for missing data, BI used a mixed effect repeated measures model (MMRM). The FAS definition was modified due to use of the MMRM such that the FAS consisted of all patients with baseline data and evaluable post-dosing data for at least one period. Additionally, the FEV1 AUC (0-24 hours) was change from secondary endpoint to a key secondary endpoint.

Protocol Violations:

A total of 5 patients had important protocol deviations which were drug administration outside of time window, inclusion criteria not met, primary endpoint data missing/recoded outside time window, and study drug taken prior to coming to clinic for visit.

Patient Disposition

A total of 56 patients enrolled in this trial, and 47 were randomized. All 47 received at least one dose of medication. Only one patient discontinued from this trial (AE, worsening of COPD). This occurred during the Olo 2mcg dosing period. This patient had only been exposed to Olo 5mcg otherwise. The FAS consistent of all 47 patients, and the PP population consisted of the 42 patients without important protocol deviations.

Demographics/Baseline characteristics

The patients in this trial were predominantly Caucasian males, with an average age of 66 years with a 39 pack year history. The mean duration of COPD diagnosis was 12 years. Mean baseline FEV1 was 45% predicted with a 14.8% improvement following bronchodilator therapy. Means FEV1/FVC ratio was 44%.

Compliance

Based on diary entries, compliance ranged from 99.9-100% for each treatment period. One hundred percent (100%) of patients took study medication >80% of the time.

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Reviewer comment:

The potential impact of the protocol amendments on interpretation will be discussed with biostatistics. As this is complete crossover design, it is also unlikely that the protocol violations will affect data interpretation. However, the sponsor also analyzed the co-primary endpoint in the PP population. The patient demographics and baseline spirometry was also typical of a COPD trial.

Primary Endpoint:

The co-primary endpoints were FEV AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 3 weeks of therapy. For all dose regimens, the FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) at 3 weeks demonstrated a statistically significant improvement from baseline values (p-values not corrected for multiple comparisons). These endpoints were compared between each of the treatment periods. For FEV1 AUC (0-12 hours), the 5mcg once daily has a greater treatment effect compared to 2mcg BID. For all other treatment period comparisons, there are no statistically significant differences. For FEV1 AUC (12-24 hours), the twice daily periods have a greater treatment effect when comparing 10mcg qD to 5mcg BID and 5mcg qD to 5mcg BID. Otherwise, there are no statistically significant differences. The results are summarized in Table 19.

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Table 19. Trial 1222.26. Comparisons of co-primary endpoints between dose regimens

| Parameter | Dose | | Difference | p-value |
|----------------------|-----------|-----------|------------|---------|
| | 10 mcg QD | 5 mcg QD | | |
| FEV1 0-12 | 0.204 | 0.209 | -0.006 | 0.7046 |
| FEV1 12-24 | 0.149 | 0.155 | -0.006 | 0.709 |
| FEV1 0-24 | 0.176 | 0.182 | -0.006 | 0.6789 |
| FEV1 trough response | 0.087 | 0.108 | -0.021 | 0.2902 |
| | | | | |
| | 10 mcg QD | 5 mcg BID | | |
| FEV1 0-12 | 0.204 | 0.189 | 0.015 | 0.3011 |
| FEV1 12-24 | 0.149 | 0.201 | -0.052 | 0.0006 |
| FEV1 0-24 | 0.176 | 0.195 | -0.019 | 0.1753 |
| FEV1 trough response | 0.087 | 0.129 | -0.042 | 0.0353 |
| | | | | |
| | 5 mcg QD | 2 mcg BID | | |
| FEV1 0-12 | 0.209 | 0.155 | 0.54 | 0.0003 |
| FEV1 12-24 | 0.155 | 0.167 | -0.012 | 0.4111 |
| FEV1 0-24 | 0.182 | 0.16 | 0.022 | 0.1161 |
| FEV1 trough response | 0.108 | 0.093 | 0.015 | 0.4553 |
| | | | | |
| | 5 mcg QD | 5 mcg BID | | |
| FEV1 0-12 | 0.209 | 0.189 | 0.021 | 0.1582 |
| FEV1 12-24 | 0.155 | 0.201 | -0.047 | 0.0019 |
| FEV1 0-24 | 0.182 | 0.195 | -0.013 | 0.3444 |
| FEV1 trough response | 0.108 | 0.129 | -0.021 | 0.2875 |

source: Trial 1222.26 CSR; Table 11.4.1.1:1; pp74

p-values not corrected for multiple comparisons

Secondary Endpoints

The key secondary endpoint was FEV1 AUC (0-24 hours) response after 3 weeks of treatment. Based on this endpoint, there were no significant differences between olodaterol regimens; however, all regimens demonstrate statistically significant improvements from baseline. For the secondary endpoint of trough FEV1 response, the only statistically significant difference between regimens was between the 10mcg qD and 5mcg BID regimens. The 5mcg BID regimen had a greater treatment effect. Otherwise, no other statistically significant differences were seen between regimens. However, as with the primary and key secondary endpoint, all regimens were improved from baseline. As with the primary endpoints, no adjustments were made for multiple comparisons. These results are summarized in Table 19.

For the secondary endpoint of peak FEV1 response after 3 weeks, all doses were improved from baseline. However, the only statistically significant difference between groups was found when comparing the 10mcg qD to the 2mcg BID regimens (10mcg qD>2mcg BID).

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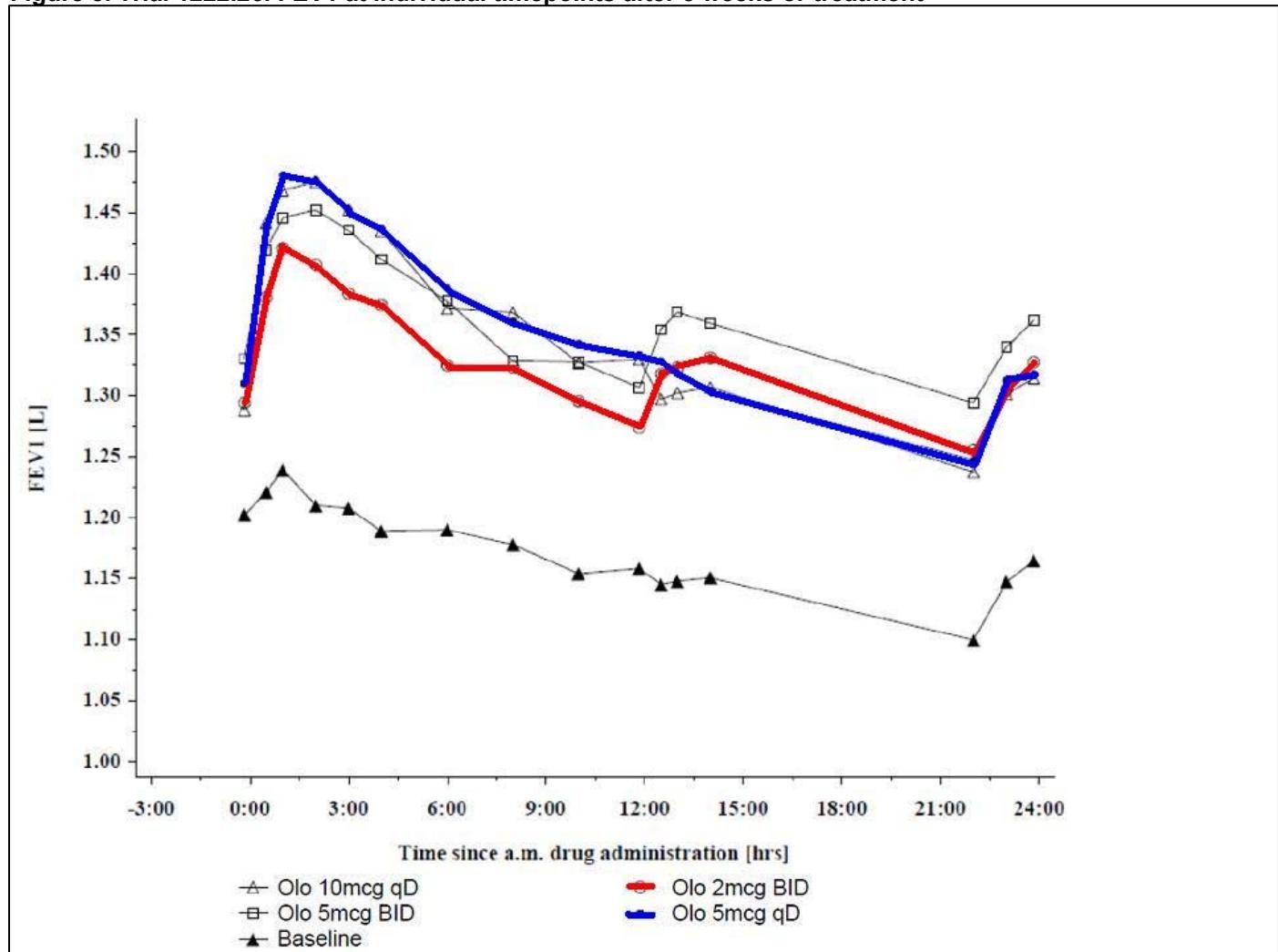
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The results for the secondary endpoint of individual FEV₁ measurement at each time point over 24 hours after 3 weeks of treatment is summarized in Figure 5.

Figure 5. Trial 1222.26. FEV₁ at individual timepoints after 3 weeks of treatment



source:modified from Trial 1222.26 CSR; Figure 11.4.1:1;pp72

The results for the FVC related endpoints were consistent with the analogous FEV₁ related endpoints. These results are summarized visually in the individual FVC measurements at each time point over 24 hours after 3 weeks of treatment (Figure 6).

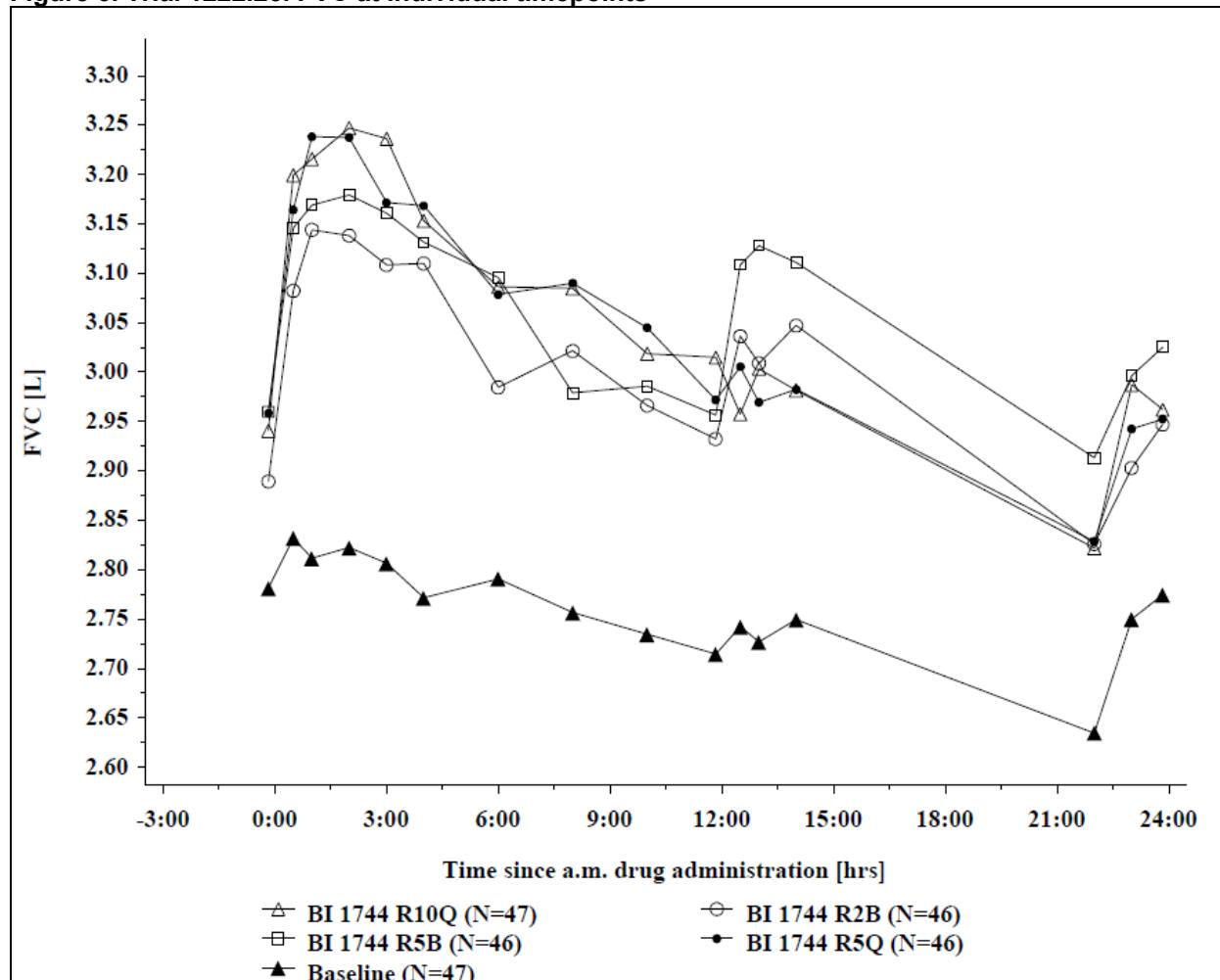
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Figure 6. Trial 1222.26. FVC at individual timepoints



Source: Trial 1222.26 CSR; Figure 11.4.2.3:1

BI1744 R10Q=Olo 10mcg qD, BI1744 R5B=Olo 5mcg BID, BI1744 R2B=Olo 2mcg BID

BI1744 R5Q=Olo 5mcg qD

Reviewer Comments:

In contrast to trial 1222.5 where there was a clear dose response for the primary endpoint, in this trial (1222.26), there is no such dose response. The 10mcg qD dose appears equivalent/slightly less effective compared to the 5 mcg qD. Additionally, the FEV1 AUC (0-12 hours) response is similar when comparing the 10mcg qD and 5mcg BID dose. Taken together, this implies that a single daily dose of 10 mcg and 5 mcg may be equivalent. This is not entirely inconsistent with previous COPD dose ranging trials as the incremental benefit of olodaterol waned at doses ≥ 5 mcg. This is also consistent with the sponsor's phase 3 data. The trial results also imply that BID dosing may be more optimal than qD dosing based on the FEV1 AUC (12-24 hours) when comparing the 10mcg qD dose to 5mcg BID. However, when comparing the 2mcg BID to 5mcg qD dosing, on a whole, the once daily dosing appeared superior. Given these

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findings, dose ranging and dose regimen trials in asthmatics as well as further exploration of dose in the Phase 3 trials, as the sponsor has done, are important in determining the most appropriate dose/dosage regimen for this compound.

Pharmacokinetics:

Prior to olodaterol dosing (visit 2), 3 patients had detectable serum olodaterol levels. As these patients had no previous exposure to olodaterol, the sponsor assumed that this was due to contamination during sample handling. Pre-dose serum olodaterol concentrations (pg/mL) after 3 weeks of treatment were 2.92 and 2.97 for the 5mcg BID and 10mcg qD treatment periods, respectively. For the 2mcg BID and 5mcg qD periods, less than a 1/3 of patients had detectable levels. Serum olodaterol concentrations (pg/mL) at steady state were 3.52, 4.28, and 5.78 for the 5mcg qD, 5mcg BID, and 10mcg qD periods, respectively.

Safety:

Exposure:

Forty-seven (47) patients received at least one dose of olodaterol. When broken down by treatment period, 47 patients received Olo 2mcg BID, 46 patients received Olo 5mcg BID, 47 patients received Olo 5mcg qD, and 46 patients received Olo 10mcg qD. Mean exposure across treatment periods was similar and ranged from 20.7-21 days.

Deaths and SAEs:

There were no deaths reported in this trial. One patient had an SAE (COPD exacerbation and pneumonia) during the 2mcg BID treatment period. The patient fully recovered. This patient was also discontinued from this trial.

Treatment Emergent AEs

As there was no washout period between treatment periods, the definition of TEAE for the first 3 treatment periods differed from the last period. For the first 3 periods, TEAEs were defined as those that occurred after the 1st dose until the last dose of the treatment period. For the 4th period, TEAEs were defined as those that occurred after the 1st dose and up to 12 days after the last dose.

The overall occurrence of TEAEs was higher for the Olo 5 mcg BID compared to other doses (28% versus 20-23%). No dose response was seen for any AE based on SOC. However, based on preferred term, the higher total daily doses (TDD) of olodaterol had more frequent occurrences of nasopharyngitis (2.1% for 4-5mcg TDD versus 6.5% for 10mcg TDD). Common TEAEs (occurring in ≥2 patients) are summarized in Table 20.

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Table 20. Trial 1222.26. Treatment emergent adverse events occurring in ≥2 patients per treatment period

| | Number of patients (%) | | | | |
|-----------------------------------|------------------------|-----------------------|------------------------|------------------------|------------|
| | Olodaterol 2 µg bid | Olodaterol 5 µg qd | Olodaterol 5 µg bid | Olodaterol 10 µg qd | Total |
| Number of patients | 47 (100.0) | 47 (100.0) | 46 (100.0) | 46 (100.0) | 47 (100.0) |
| Patients with AEs | 11 (23.4) | 11 (23.4) | 13 (28.3) | 9 (19.6) | 29 (61.7) |
| Nasopharyngitis | 1 (2.1) | 1 (2.1) | 3 (6.5) | 3 (6.5) | 6 (12.8) |
| Cough | 0 (0.0) | 1 (2.1) | 0 (0.0) | 2 (4.3) | 3 (6.4) |
| Dyspnoea | 0 (0.0) | 3 (6.4) | 1 (2.2) | 0 (0.0) | 3 (6.4) |
| Upper respiratory tract infection | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) | 2 (4.3) |
| Dysphonia | 0 (0.0) | 1 (2.1) | 0 (0.0) | 2 (4.3) | 2 (4.3) |
| Arthralgia | 2 (4.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) |
| Muscle spasms | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) | 2 (4.3) |
| Fatigue | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 2 (4.3) |

Source: Trial 1222.26 CSR; Table 12.2.2.2:1; pp91

Labs:

Based on shift tables, in general hematologic and chemistry lab values were stable from baseline to end of treatment. However, for all 4 treatment periods, 3-6% of patients with baseline normal/low fasting glucose levels had end of treatment fasting glucose higher than the upper limit of normal. However similar percentages of patients were also noted to have glucoses shift from baseline normal/high to below the lower limit of normal at the end of treatment. Additionally, for CPK, in all but the Olo 10mcg qD treatment periods, 6-8% of patients' serum levels shifted from a normal baseline to above normal at end of treatment. A similar trend was apparent for potassium (2.3-4.4% of patients), in all groups except Olo 5mcg BID. No patients had shifts in values from normal to high for potassium. No AEs related to lab values were reported.

Vitals signs

The number of patients with changes in blood pressures or pulse rates were similar between treatment groups. Based on shift table analysis for SBP, DBP, and pulse rate, there did not appear to be any dose related effects. New or worsening of ECG changes were not noted.

Reviewer Comment:

Given the lack of a washout period and lack of placebo group for comparison it is difficult to interpret the AE data. However, based on SAEs, olodaterol was relatively well tolerated. With regard to TEAEs, only nasopharyngitis demonstrated a consistent dose response. The increases in glucose and potassium seen in the shift table analysis are not surprising given olodaterol's mechanism of action. The lack of AEs related to labs values is reassuring.

Reviewer Overall Comments:

At all dose regimens studied, olodaterol appears to have a bronchodilaotry effect. Although statistical analysis did not account for multiple comparisons, this is consistent

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with previous COPD trial data. There also appears to be no added benefit to olodaterol doses >5mcg daily. With regard to dose interval, based on the totality of the efficacy data, when comparing 4-5mcg TDD divided BID or qD, the qD interval appears to be more optimal, although confirmation of this with data in asthmatics is necessary. Olodaterol was also fairly well tolerated, however, it is difficult to make any safety conclusions as this was a small trial and there was no placebo arm.

5.3.4 Trial 1222.4 (Asthma)

Administrative Information

- **Study title:** Randomized, double-blind, placebo-controlled, 5-way cross-over study to assess the efficacy (bronchodilation) and safety of a single dose of orally inhaled olodaterol (2 mcg, 5 mcg, 10 mcg, 20 mcg) in patients with intermittent asthma
- **Study dates:** 1/10/06-10/2/06
- **Study sites:** Canada (4 sites)
- **Study report date:** 4/4/11

Objectives/Rationale

- To evaluate the dose-dependent bronchoprotective effect of a single inhalation of olodaterol, against methacholine-induced bronchoconstriction.
- To characterize the PK of olodaterol following inhalation with the Respimat inhaler

Study Design and Conduct

Overview

This was a randomized, double-blind, placebo-controlled, 5-way cross-over, single-dose, dose-ranging trial in patients with intermittent asthma. Patients were randomized to receive a sequence of single doses of placebo, olodaterol 2mcg, 5mcg, 10mcg and 20mcg. Each treatment was separated by a washout period of 14-21 days. Following administration of trial medication patients received a series of methacholine challenges. These challenges occurred 0.5, 4, 8, 24, and 32 hours post-dose. PK sampling was performed at prior to dosing, and at 10, 20, 30, and 60 minutes post-dose; and at 1, 2, 4, and 8 hours post-dose.

Study Population

This study included 31 asthma patients.

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Key Inclusion Criteria

1. Diagnosis of intermittent asthma per GINA guidelines
2. Pre-bronchodilator FEV1 $\geq 80\%$
3. Demonstrated bronchial hyperresponsive to inhaled methacholines with a PC_{log20} FEV1 $\leq 8\text{mg/mL}$ at baseline visit

Key Exclusion Criteria

1. Significant disease other than asthma
2. Clinically relevant abnormal baseline labs
3. Patients who have undergone thoracotomy with pulmonary resection.
4. Patients being treated with medication that prolong QT/QTc interval, oral beta-adrenergics, beta-blockers, or oral steroids at unstable doses (<6 weeks on a stable dose or at doses $>10\text{mg}$ of prednisone per day or 20mg every other day).
5. A diagnosis of paroxysmal tachycardia or hyperthyrosis
6. Baseline prolongation of QT/QTc interval.
7. A history of additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalemia, family history of long QT).
8. Women of childbearing potential not using a highly effective method of birth control (<1% failure rate).

Treatments:

Olodaterol 2mcg once daily (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Olodaterol 20mcg once daily (2 actuations of 10mcg/actuation)

Placebo

All treatments were delivered via a Respimat device.

Concomitant/Prohibited medications

Patients were not allowed to have been on oral corticosteroids, inhaled corticosteroids, LABA, ICS/LABA, short or long-acting anticholinergics, anti-leukotriene medications, inhaled cromolyn, or theophylline within 3 months prior to the first study visit.

Efficacy Parameters

Primary Endpoint:

The primary endpoint was Log₂(PC₂₀FEV1) at 24 hours following a single dose of olodaterol where PC₂₀FEV1 was defined as the provocative concentration of methacholine required to produce a 20% decrease in FEV1

Secondary Endpoints:

The secondary endpoint was Log₂(PC₂₀FEV1) at 30 minutes, and 4, 8, and 32 hours post-dose.

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Safety Parameters:

The monitored safety variables include AEs, pulse rate, blood pressure, clinical labs, ECGs, and physical examinations

Pharmacokinetic Parameters:

The following PK parameters were evaluated after the last dose when feasible:

1. Maximum serum concentration
2. Time to maximum serum concentration
3. AUC from time point 0 to the last quantifiable data point during the first dosing interval
4. AUC between time points in the first dosing interval
5. Amount and fraction eliminated in the plasma from 0 to 3 hours

Reviewer comment:

The primary endpoint of Log2 (PC20FEV1) is not a standard endpoint and is not typically used in COPD/asthma development programs. However, as this was an early phase trial and dosing was confirmed in later trials with endpoints more typical endpoints, this is acceptable.

Results:

Disposition:

A total of 48 patients were enrolled and 31 were randomized. Five patients total discontinued from this trial. The most common reason for discontinuation overall was withdrawal of consent [2 patients(6.5%)]. The remaining patients who discontinued, discontinued for isolated reasons.

Demographics:

The patients in this trial were predominantly white (87%), females (55%) with a mean age of 29 years. The average time of asthma diagnosis was 16 years. Mean FEV1 % predicted was 97%.

Primary endpoint:

For the primary endpoint, PC20s were improved 24 hours following olodaterol administration. The difference from placebo was statistically significant and followed a clear dose response. These results are summarized in Table 21.

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Table 21. Trial 1222.4. Log₂ PC20 FEV1 24 hours after olodaterol administration

| Treatment | N | Log ₂ PC20 FEV1(SE) [mg/mL] | Difference from placebo (SE)* |
|------------|----|---|----------------------------------|
| Placebo | 29 | 0.793 (0.182) | |
| Olo 2 mcg | 28 | 1.950 (0.186) | 1.157 (0.252) |
| Olo 5 mcg | 27 | 2.504 (0.190) | 1.711 (0.255) |
| Olo 10 mcg | 30 | 3.236 (0.179) | 2.443 (0.248) |
| Olo 20 mcg | 29 | 3.777 (0.183) | 2.984 (0.251) |

*all p-values <0.0001 compared to placebo

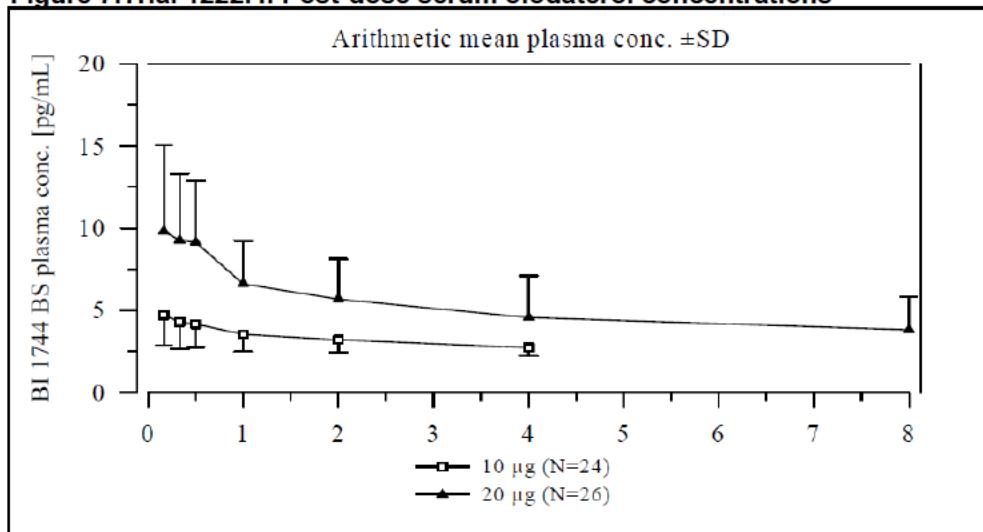
Source: Trial 1222.4 CSR; table 11.4.1.1:1; pg 84

Results for the secondary endpoints were consistent with the primary endpoint.

Pharmacokinetic endpoints:

For the 2mcg dose group, no patients had detectable levels of olodaterol at any time point. For the 5mcg group, the majority of patients did not have detectable levels at anytime post-dose. In the 10 and 20mcg groups, levels were detectable in most patients post dose. The results for the 10 and 20mcg doses are summarized in Figure 7.

Figure 7.Trial 1222.4. Post-dose serum olodaterol concentrations



*BI 1744=olodaterol

Source: Trial 1222.4 CSR; table 11.5.2.1.1:1; pg90

Reviewer comment:

These results demonstrated that olodaterol increased Log₂(PC₂₀FEV1) in a dose responsive manner and that the PK appeared generally dose proportional. The treatment response did not appear to plateau as in the COPD dose-ranging trials.

Safety:

Deaths and SAEs

There were no deaths nor SAEs reported in this trial.

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Adverse events (AE)

AEs were assigned to treatments if they occurred on test day and up to 14 days after. Overall AEs occurred most commonly after treatment with placebo (27.6%) compared to after treatment with olodaterol (7.1%-20.7%). Based on preferred term (PT), the most AEs were headache and cough. There was no evidence for dose dependence for any AE. No AEs lead to discontinuation from the trial.

Clinical Labs

Olodaterol exposure was not associated with statistically significant changes in mean lab value, except for potassium. The Olo 20mcg group demonstrated a small, but statistically significant decrease in serum potassium levels (4.14 mmol/L) compared to placebo (4.34 mmol/L, p<0.0005) at 1 hour post-dose. Similar findings were seen at 2 and 8 hours post-dose. This was not seen for the 2 and 5mcg olodaterol doses. However, the 10mcg olodaterol dose did demonstrate a statistically significant decrease in serum potassium levels at 8 hours post-dose, but not at 1 or 2 hours post-dose.

Reviewer comment:

As this was small single dose cross-over trial, safety conclusions cannot be made. However, the statistically significant increase in serum potassium levels for Olo 20mcg at up to 8 hours post-dosing indicate that the 20mcg dose will likely result in adverse reactions known to be associated with beta2-adrenergic agents.

5.3.5 Trial 1222.6 (Asthma)

Administrative Information

- **Study title:** Randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy (bronchodilation) and safety of 4 weeks of once daily treatment of orally inhaled olodaterol (2 mcg, 5 mcg, 10 mcg, 20 mcg) delivered by the Respimat inhaler in patients with asthma
- **Study dates:** 5/9/07-10/3/08
- **Study sites:** Canada (1 site), Germany (1 site), U.S. (1 site), and France (1 site)
- **Study report date:** 10/28/09

Objectives/Rationale

- To determine the optimum daily dose(s) of olodaterol on asthmatic patients.

Study Design and Conduct

Overview

This was a 4-week multi-center, randomized, double-blind placebo controlled, parallel group dose ranging trial in patients with asthma who demonstrated reversibility on PFTs. Patients were randomized to receive either placebo or olodaterol at doses of 2, 5, 10, or 20 mcg once daily. Following the screening phase and subsequent 4 week

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baseline period, patients were randomized into the double-blind treatment period. During the double-blind phase patients had weekly study visits.

Prior to visit 1, informed consent was obtained and washout of restricted medication began. At visit 1 (week -4 to -6), medication washout was confirmed and pre and post-bronchodilator spirometry was performed to assess for reversibility. Patients were also issued an eDiary to record medication use and symptoms. Patients who were determined to be eligible entered the 4 week baseline period. At visit 2, patient eligibility was assessed. Eligible patients were randomized into treatment groups and study drug initiated. At visits 3, 4, and 5 (week 2, 3, and 4, respectively) spirometry was performed pre and post-dose. During these visits unsupervised PFTs were also performed up to 12 hours post-dosing using the Viasys AM2+ device. At visit 6 (week 8), predose PFTs (-10 minutes) were performed. In addition to spirometry, clinical labs, ECGs, AE review, and eDiary review were performed during all visits. The study schedule is summarized in Table 22. Timing of procedures for visits 2, 3, 4, and 5 are summarized Table 23.

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Table 22. Trial 1222.6. Assessment schedule

| Trial Periods | Screening | Treatment | | | | Follow-up |
|--|----------------|------------------|----------------|----------------|------------------|--------------------|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 |
| Week | -4 to -6 | - | 1 | 2 | 3 | 4 |
| Day | -28 to -42 | 1 | 8 + 2 | 15 + 2 | 22 + 2 | 29 + 2 |
| Informed consent ¹ | X | | | | | |
| Demographics | X | | | | | |
| Medical history | X | | | | | |
| Review in-/exclusion criteria | X | X | | | | |
| Physical examination | X | | | | X ^{2,6} | |
| Laboratory test | X ³ | X ^{3,4} | X ³ | X ³ | | X ^{2,3,6} |
| Pregnancy test ⁵ | X | X | X | X | | X ⁶ |
| Respimat® training | X | X ⁸ | | | | |
| Randomisation | | X | | | | |
| Medication washout compliance assessment | X | X | X | X | | X |
| Pulmonary Function Testing | X | X | X | X | | X ⁶ |
| Reversibility Testing | X | | | | | |
| Administer trial medication ⁷ | | X | X | X | | X |
| 12-lead ECG | X | X | X | X | | X ⁶ |
| Issue AM2+ / e-diary | X | X | X | X | | X |
| Dispense trial drug | | X | X | X | | |
| Dispense rescue medication | X | X | X | X | | X |
| Pharmacokinetics | | X | X | X | | X |
| Compliance check | | | X | X | | X |
| Asthma Control Questionnaire | | X | | | | X |
| Vital signs (seated) | X | X | X | X | | X ⁶ |
| Collect and review e-diary | | X | X | X | | X ⁶ |
| Telephone contact with patient | | | | X | | |
| Adverse events | X | X | X | X | X | X ⁶ |
| Concomitant therapy | X | X | X | X | X | X ⁶ |
| Drug accountability | | X | X | X | | X |
| Trial medication termination | | | | | X | |
| Conclude patient participation | | | | | | X ⁶ |

¹ All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions

² If findings, repeat at follow-up (Visit 6).

³ Fasting (at least 8 hours)

⁴ Up to 2 additional blood samples at Visit 2 required for genotype analysis (β 2-receptor polymorphisms)

⁵ To be completed on all women of childbearing potential. A serum β HCG will be performed at Visit 1. A urine pregnancy test will be performed prior to trial medication administration at Visits 2-5, and at follow-up (Visit 6).

⁶ To be completed whenever trial participation ends (including discontinued patients).

⁷ At Visit 2, trial drug administered between 7:00-10:00 a.m.. At Visits 3-5, trial drug administered within \pm 30 minutes of the time of trial drug administration at Visit 2 AND between 7:00-10:00 a.m.

⁸ At Visit 2, the patient again will be instructed in the use of the Respimat® inhaler. Note: the patient should not inhale from the placebo inhalers at this visit.

Source: Trial 1222.6 report U09-1850-01 (protocol and amendments); pp6

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Table 23. Trial 1222.6. Procedure timing at visits 2, 3, 4, and 5

TIMING OF PROCEDURES^{*}: VISIT 2

| | Time (relative to dosing) | | | | | | | | | | | | | | |
|--|---------------------------|----------------|------|---|----|-----|-----|-----|-----|----------------|----|----------------|----------------|----------------|----------------|
| | -1h | -30' | -10' | 0 | 5' | 10' | 20' | 30' | 40' | 1h | 2h | 3h | 6h | 9h | 12h |
| Administer trial medication | | | | X | | | | | | | | | | | |
| Asthma Control Questionnaire | X | | | | | | | | | | | | | | |
| 12-lead ECG | | X | | | | X | | | | | | X | | | |
| Vital signs (seated) | X | X | | | | | | X | | X | X | X | | | |
| PK plasma sampling | | X | | | X | X | X | | | X | X | | X | | |
| Pharmacogenetics | | X ⁴ | | | | | | | | | | | | | |
| Safety laboratory testing | | X | | | | | | | | | | | | | |
| Abbreviated laboratory testing ¹ | | | | | | | | | | X | | X | | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "supervised" clinic spirometer | X ² | | X | | | | | X | | X ² | X | X ² | | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "unsupervised" Viasys AM2+ | X ² | | | | | | | | | X ² | | X ² | X ³ | X ³ | X ³ |
| PK urine sampling | | X | | ← | | | | | | → | | | | | |

TIMING OF PROCEDURES^{*}: VISITS 3 & 4

| | Time (relative to dosing) | | | | | | | | | | | | | | |
|--|---------------------------|----------------|------|---|----|-----|-----|-----|-----|----------------|----|----------------|----------------|----------------|----------------|
| | -1h | -30' | -10' | 0 | 5' | 10' | 20' | 30' | 40' | 1h | 2h | 3h | 6h | 9h | 12h |
| Administer trial medication | | | | X | | | | | | | | | | | |
| 12-lead ECG | | X | | | | X | | | | | | X | | | |
| Vital signs (seated) | X | | X | | | | | X | | X | X | X | | | |
| PK plasma sampling | | X ⁴ | | | | X | | | | | | | | | |
| Safety laboratory testing | | X | | | | | | | | | | | | | |
| Abbreviated laboratory testing ¹ | | | | | | | | | | X | | X | | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "supervised" clinic spirometer | X ² | | X | | | | | X | | X ² | X | X ² | | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "unsupervised" Viasys AM2+ | X ² | | | | | | | | | X ² | | X ² | X ³ | X ³ | X ³ |
| PK urine sampling | | | | ← | | | | | | → | | | | | |

TIMING OF PROCEDURES^{*}: VISIT 5

| | Time (relative to dosing) | | | | | | | | | | | | | | |
|--|---------------------------|----------------|------|---|----|-----|-----|-----|-----|----------------|----|----------------|----------------|----------------|----------------|
| | -1h | -30' | -10' | 0 | 5' | 10' | 20' | 30' | 40' | 1h | 2h | 3h | 6h | 9h | 12h |
| Administer trial medication | | | | X | | | | | | | | | | | |
| Asthma Control Questionnaire | X | | | | | | | | | | | | | | |
| 12-lead ECG | | X | | | | X | | | | | | X | | | |
| Vital signs (seated) | X | | X | | | | | X | | X | X | X | | | |
| PK plasma sampling | | X ⁴ | | | X | X | X | | | X | X | | X | X | |
| Safety laboratory testing | | X | | | | | | | | | | | | | |
| Abbreviated laboratory testing ¹ | | | | | | | | | | X | | X | | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "supervised" clinic spirometer | X ² | | X | | | | | X | | X ² | X | X ² | X ² | | |
| Pulmonary Function Testing (FEV ₁ , FVC, PEF): "unsupervised" Viasys AM2+ | X ² | | | | | | | | | X ² | | X ² | X ³ | X ³ | X ³ |
| PK urine sampling | | | | ← | | | | | | → | | | | | |

Whenever more than one procedure is performed at the same timepoint, PK sampling should always be performed as close to that timepoint as possible. The order of procedures should be as follows: PK plasma sampling (safety and abbreviated blood samples can be taken at the same time), vital signs, supervised PFTs and unsupervised PFTs. ECGs can be done either before or after these procedures, whichever is more convenient.

¹ Potassium

² "Supervised" spirometry always to be performed first (**very important**)

³ Performed at home

⁴ Blood sampling should be performed within 30 minutes before but as close to the next drug administration as possible

Source: Trial 1222.6 report U09-1850-01 (protocol and amendments); pp7-9

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Study Population

This study included 296 asthma patients. Patients were randomized using a validated system which uses a pseudo-random number generator.

Key Inclusion Criteria

4. ≥18 years of age
5. Diagnosis of asthma per GINA guidelines
6. Pre-bronchodilator FEV1 ≥60% predicted and <90%
7. Reversibility following bronchodilator treatment defined as a ≥12% increase in FEV1 and 200mL within 15 minutes of salbutamol treatment (performed at visit 1).
8. Patients must have been taking ICS for at least 12 weeks prior to screening and must have been receiving a stable low/moderate dose for at least 6 weeks prior to screening.

Key Exclusion Criteria

9. Significant disease other than asthma
10. Clinically relevant abnormal baseline labs
11. Smoking history of greater than 10 pack-years
12. Patient with significant disease other than COPD.
13. Clinical relevant abnormal baseline lab values
14. Patients with a history of myocardial infarction within 1 year of the screening visit, a diagnosis of clinical relevant cardiac arrhythmia, active tuberculosis, clinically evident bronchiectasis, a history of cor pulmonale, Cystic Fibrosis, or a history of life threatening pulmonary obstruction.
15. Patients who have undergone thoracotomy with pulmonary resection.
16. Patients being treated with medication that prolong QT/QTc interval, oral beta-adrenergics, beta-blockers, or oral steroids at unstable doses (<6 weeks on a stable dose or at doses >10mg of prednisone per day or 20mg every other day).
17. A diagnosis of paroxysmal tachycardia or hyperthyroidism
18. Baseline prolongation of QT/QTc interval.
19. A history of additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalemia, family history of long QT).
20. Women of childbearing potential not using a highly effective method of birth control (<1% failure rate).

Treatments:

Olodaterol 2mcg once daily (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Olodaterol 20mcg once daily (2 actuations of 10mcg/actuation)

Placebo

All treatments were delivered via a Respimat device.

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Concomitant/Prohibited medications

All medication used within 3 months preceding the screening visit and throughout the trial was recorded in the eCRF. Patients were allowed to use salbutamol as rescue medication; however, if it was required during PFTs, the PFTs were discontinued. For exacerbations, patients were allowed to take any medication deemed necessary by the treating physician. Other concomitant medications were restricted as summarized in Table 24.

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Table 24. Trial 1222.6. Permitted and restricted medications

| Drug Class | Sub-class | Prior to study | Baseline Period | Study Period | |
|----------------------------------|--|----------------------------|----------------------------|----------------------------|----------------------------|
| | | | | Treatment Period | Follow up Period |
| Corticosteroids | Inhaled corticosteroids (low/moderate dose) ¹ | required | required | required | required |
| | Inhaled corticosteroids (high dose) | not permitted ² | not permitted ³ | not permitted ³ | not permitted ³ |
| | Oral corticosteroids | not permitted ² | not permitted ³ | not permitted ³ | not permitted ³ |
| Other asthma controllers | Combination ICS/LABA (Advair/Seretide; Symbicort) | not permitted ² | not permitted | not permitted | permitted |
| | Cromolyn sodium / nedocromil sodium | permitted | permitted | permitted | permitted |
| | Antihistamines, antileukotrienes | permitted | permitted | permitted | permitted |
| | Methylxanthines | not permitted ² | not permitted | not permitted | not permitted |
| Beta-adrenergics / Beta-blockers | Inhaled short-acting beta-adrenergics | permitted | rescue | rescue | rescue |
| | Inhaled long-acting beta-adrenergics | not permitted ² | not permitted | study medication | permitted |
| | Oral beta-adrenergics | not permitted ² | not permitted | not permitted | not permitted |
| | Beta blockers | not permitted ² | not permitted | not permitted | not permitted |
| Anticholinergics | Short-acting anticholinergics (inhalation aerosol and nasal spray) | permitted | not permitted | not permitted | not permitted |
| | Long-acting anticholinergics | not permitted | not permitted | not permitted | not permitted |
| Miscellaneous | Other investigational drugs | not permitted ⁴ | not permitted | not permitted | not permitted |

Source: Trial 1222.6 report U09-1850-01 (protocol and amendments);table 4.2.2:1; pp48

¹ Patient must have been taking ICS for at least 12 weeks prior to screening, and must have been receiving a stable low/moderate dose for at least 6 weeks prior to screening

² 6 weeks prior to screening

³ Permitted for treatment of asthma exacerbation where necessary

⁴ Wash-out of 1 month or 6 half-lives, whichever is greater

Reviewer Comment:

The overall trial design, inclusion/exclusion criteria, and restricted medications are reasonable for a dose ranging trial in asthmatics.

Efficacy Parameters

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Primary Endpoint:

Trough FEV1 response after 4 weeks of treatment with olodaterol was the primary endpoint. Trough FEV1 was defined as the mean of FEV1 one hour prior to study drug and 10 minutes prior to study drug. Response was defined as change from baseline. Baseline was defined as the mean of the 2 pre-dose FEV1 measurements (-1 hour and -10 minutes) taken at visit 2.

Secondary Endpoints:

The key secondary endpoint was mean peak expiratory flow rate (PEFR) response during the last week of treatment. Response was defined as change in mean weekly morning PEFR from baseline. Baseline was defined as the mean PEFR for the last week prior to the randomization visit.

Other Secondary Endpoints include the following:

1. Trough FEV1 response [L] after 1 and 2 weeks of treatment
2. Trough FVC (forced vital capacity) response [L] after 1, 2 and 4 weeks of treatment
3. FEV₁, FVC (supervised) AUC(0-6) and peak(0-3) response [L] after 4 weeks of treatment
4. FEV₁, FVC (supervised) AUC (0-3 hours) and peak(0-3) response [L] after the first dose and after 1 and 2 weeks of treatment
5. FEV₁, FVC (unsupervised) AUC(0-6) and AUC(6-12) response [L] after 4 weeks of treatment
6. FEV₁, FVC (unsupervised) AUC (0-3 hours) and AUC(3-12) response [L] after the first dose and after 1 and 2 weeks of treatment
7. Individual FEV₁ and FVC (supervised) measurements [L] at each time point
8. Individual FEV₁ and FVC (unsupervised) measurements [L] at each time point
9. Weekly mean evening PEF (peak expiratory flow rate) response [L/min]
10. Weekly mean pre-dose morning PEF response [L/min]
11. Peak expiratory flow variability (the difference between the highest morning PEF value and the highest evening PEF value of one day divided by the arithmetic mean of these two PEF values, weekly means)
12. Weekly mean number of occasions of rescue therapy used per day (prn salbutamol [albuterol]) as assessed by the e-Diary (e-Diary incorporated in AM2+)
13. Asthma Control Questionnaire

Note that for all secondary endpoints 'response' is defined as in the primary endpoint.

Safety Parameters:

The monitored safety variables include AEs, pulse rate, blood pressure, clinical labs, ECGs, and physical examinations. These were assessed as per Table 22 and Table 23.

Marked changes in pulse or blood pressure were defined as follows:

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1. Systolic BP (SBP) increase of 25 mmHg above baseline
2. SBP decrease to <100 mmHg if not at that level at baseline, and a decrease of greater than 10 mmHg below baseline
3. Diastolic BP(DBP) increase to >90 mmHg
4. DBP increase of greater than 10 mmHg above baseline,
5. DBP decrease to <60 mmHg if not at that level at baseline, and a decrease of greater than 10 mmHg below baseline
6. A pulse rate increase to > 100 bpm if not at that level at baseline
7. A pulse rate increase of greater than 10% above baseline,
8. A pulse rate decrease to <60 bpm if not at that level at baseline, and a decrease of greater than 10 bpm below baseline.

Pharmacokinetic Parameters:

The following PK parameters were evaluated in this trial after the first dose

6. Maximum serum concentration
7. Time to maximum serum concentration
8. AUC from time point 0 to the last quantifiable data point during the first dosing interval
9. AUC between time points in the first dosing interval
10. Amount and fraction eliminated in the plasma from 0 to 3 hours

The following PK parameters were evaluated after the last dose when feasible:

1. Maximum serum concentration at steady state
2. Time to maximum concentration at steady state
3. Minimum concentration at steady state
4. Time to minimum concentration at steady state
5. Pre-dose concentration at steady state
6. Half-life
7. Clearance
8. Volume of distribution

Compliance:

Compliance was assessed using patients' eDiary. The eDiary was reviewed at each visit. Patients also returned all dispensed Respimat inhalers and cartridges to research personnel.

Reviewer Comment:

The primary endpoint is typical and appropriate for an asthma dose ranging trial. The secondary endpoints are also generally appropriate. However, the utility of unsupervised PFTs is questionable. The PK, safety, and compliance parameters are appropriate.

Ethics:

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This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

Based on previous trials, BI assumed a standard deviation for trough FEV1 of 0.55 liters. Based on this, BI estimated that a sample size of 80 patients would yield 90% power to detect a 29mL difference from placebo with a two sided p-value of 0.05. This assumes a 25% discontinuation rate.

Missing Data

For missing spirometry data, values were estimated using other recorded values for that day. If the value was missing due to rescue medication use, then the least favorable value from that day was used. Estimations were made by linear interpolation of the adjacent data, or by last observed carried forward if no subsequent data was available. However if a single pre-dose measurement was missing, the other pre-dose measurement was used. If both were missing then, pre-dose data from the prior visit was used.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and evaluable post-dosing data following at least 5 days of randomized treatment for at least one endpoint. The per protocol (PP) data set that consisted of all FAS minus patients with important protocol deviations. The safety population was made up of all treated patients.

Efficacy Analysis

The primary endpoint was to be analyzed using ANCOVA. Analysis was to occur in a step-wise fashion to control for type 1 error. The first comparison was to be between Olo 20mcg and placebo. If that difference were to be statistically significant, then the next lower dose was to be compared to placebo, and so on. If a dose did not demonstrate a statistically significant difference from placebo, subsequent analysis of lower doses would continue, however, would be considered descriptive. Secondary endpoints were to be analyzed in a manner similar to the primary endpoint.

Safety Analysis

All safety data was analyzed in a descriptive manner.

Results:

Protocol Amendments:

After initial submission of this protocol, there were 3 amendments. The first was submitted 6/11/07. Changes included additional time points for ECG, vital signs, and

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PFTs. A second amendment was submitted on 7/27/07. Changes included changing the upper limit of bilirubin and creatinine for exclusionary criteria and allowing for genotyping of select cytochrome P 450 enzymes. The 3rd amendment was submitted on 3/26/08. Changes included changing the washout period for LABAs from 6 weeks to 2 weeks, and a reduction in sample size.

Protocol Violations

Important protocol violations were defined as violations that could potentially affect the efficacy parameters or safety of the patients. They occurred in 29% of patients in this trial. The most common violations were related to poor compliance ('compliance out of range'). This was higher in the olodaterol groups (12-18%) as compared to placebo (7.4%). However, missing or unreliable compliance data was more common in the placebo group (7.4%) compared to all olodaterol groups (1.6-3.3%). Note that patients in the poor compliance group and missing compliance data group did not overlap. Otherwise, protocol violations were generally similar across treatment groups.

Disposition:

A total of 426 patients were enrolled and 296 were randomized. Seven patients total discontinued from this trial. Discontinuation was most common in the Olo 2mcg group with 3 (4.9%) patients withdrawing. The most common reason for discontinuation overall was withdrawal of consent [3 patients(1%)]. The other 4 patients who discontinued, discontinued for isolated reasons.

Reviewer Comment:

The protocol amendments are unlikely significantly affect data interpretation. The changes were reasonable. The percentages of patients with important protocol violations, while higher than previous trials, were generally evenly distributed across treatment groups. As such systematic bias is unlikely. With regard to the unbalanced compliance related protocol violations, if one groups together the 'compliance out of range' and 'compliance missing or not reliable' categories, the compliance related PVs are generally even across groups. The number of patients who discontinued in this trial was low and is unlikely to affect data interpretation.

Demographics:

The patients in this trial were predominantly white (87%), females (57%) with a mean age of 45.2 years. The average time of asthma diagnosis was 22 years. Mean FEV1 % predicted was 74% with an FEV1/FVC ratio of 69%. Average reversibility based on FEV1 was 19%. These values were all similar between groups. Demographic information is summarized in Table 25.

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Table 25. Trial 1222.6. Demographic information

| | Placebo | BI 1744 2 µg | BI 1744 5 µg | BI 1744 10 µg | BI 1744 20 µg | All patients |
|------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Number of patients [N (%)] | 54 (100.0) | 61 (100.0) | 60 (100.0) | 60 (100.0) | 61 (100.0) | 296 (100.0) |
| Sex [N (%)] | | | | | | |
| Male | 20 (37.0) | 22 (36.1) | 30 (50.0) | 26 (43.3) | 28 (45.9) | 126 (42.6) |
| Female | 34 (63.0) | 39 (63.9) | 30 (50.0) | 34 (56.7) | 33 (54.1) | 170 (57.4) |
| Age [years] | | | | | | |
| Mean (SD) | 43.6 (14.1) | 45.4 (15.1) | 46.2 (13.0) | 46.3 (14.5) | 44.6 (13.0) | 45.2 (13.9) |
| Median (range) | 44.0 (19-74) | 45.0 (20-91) | 47.0 (20-74) | 45.0 (19-79) | 46.0 (18-67) | 46.0 (18-91) |
| Age class [N (%)] | | | | | | |
| 18 to 30 years | 9 (16.7) | 11 (18.0) | 8 (13.3) | 9 (15.0) | 9 (14.8) | 46 (15.5) |
| 31 to 39 years | 15 (27.8) | 12 (19.7) | 12 (20.0) | 13 (21.7) | 10 (16.4) | 62 (20.9) |
| 40 to 50 years | 16 (29.6) | 17 (27.9) | 15 (25.0) | 13 (21.7) | 19 (31.1) | 80 (27.0) |
| 51 to 65 years | 8 (14.8) | 14 (23.0) | 22 (36.7) | 20 (33.3) | 22 (36.1) | 86 (29.1) |
| >65 years | 6 (11.1) | 7 (11.5) | 3 (5.0) | 5 (8.3) | 1 (1.6) | 22 (7.4) |
| Race [N (%)] | | | | | | |
| White | 45 (83.3) | 56 (91.8) | 53 (88.3) | 51 (85.0) | 53 (86.9) | 258 (87.2) |
| Black | 7 (13.0) | 1 (1.6) | 4 (6.7) | 5 (8.3) | 8 (13.1) | 25 (8.4) |
| Asian | 2 (3.7) | 4 (6.6) | 3 (5.0) | 4 (6.7) | 0 (0.0) | 13 (4.4) |
| Height [cm] | | | | | | |
| Mean (SD) | 167.9 (9.9) | 166.9 (11.1) | 168.5 (9.0) | 168.1 (8.9) | 169.2 (9.7) | 168.1 (9.7) |
| Median (range) | 167.5 (152-194) | 165.0 (147-196) | 169.5 (154-194) | 168.0 (152-186) | 169.0 (147-189) | 168.0 (147-196) |
| Weight [kg] | | | | | | |
| Mean (SD) | 80.7 (21.6) | 75.2 (17.8) | 81.7 (18.4) | 74.8 (15.0) | 78.6 (19.2) | 78.1 (18.5) |
| Median (range) | 78.0 (42.6- 132.0) | 71.2 (48.5- 122.0) | 81.5 (47.0- 145.1) | 73.3 (49.0- 123.8) | 77.3 (43.0- 135.2) | 76.1 (42.6- 145.1) |
| Alcohol history [N (%)] | | | | | | |
| Non-drinker | 28 (51.9) | 32 (52.5) | 34 (56.7) | 29 (48.3) | 27 (44.3) | 150 (50.7) |
| Average consumption | 26 (48.1) | 29 (47.5) | 26 (43.3) | 31 (51.7) | 34 (55.7) | 146 (49.3) |
| Smoking status [N (%)] | | | | | | |
| Never smoked | 41 (75.9) | 38 (62.3) | 48 (80.0) | 44 (73.3) | 44 (72.1) | 215 (72.6) |
| Ex-smoker | 10 (18.5) | 16 (26.2) | 10 (16.7) | 14 (23.3) | 15 (24.6) | 65 (22.0) |
| Current smoker | 3 (5.6) | 7 (11.5) | 2 (3.3) | 2 (3.3) | 2 (3.3) | 16 (5.4) |
| Smoking history [pack years] | | | | | | |
| N | 13 | 23 | 12 | 16 | 17 | 81 |
| Mean (SD) | 3.6 (2.44) | 4.8 (2.71) | 5.5 (2.80) | 5.9 (2.74) | 3.4 (2.60) | 4.6 (2.78) |
| Median (range) | 4.0 (0.3-8.0) | 5.0 (0.2-10.0) | 6.0 (0.5-9.0) | 5.5 (1.0-10.0) | 3.0 (0.1-8.0) | 5.0 (0.1-10.0) |

Source: Trial 1222.6 CSR; Table 11.2:1; pp81

BI1744=olodaterol

Compliance:

Compliance was based on eDiary entries. Overall the mean compliance was similar between groups ranging between 87-91%. 78-85% of patients took their medication 80-120% of the time.

Reviewer Comment:

Patient demographic information was generally balanced across treatment groups, as was baseline spirometry data. The characteristics of the trial population were typical for asthmatics. While the compliance in this trial was not poor, it is lower than what one would expect in a 4 week trial and was also lower than the analogous COPD dose ranging trials. This could potentially dilute the treatment effect.

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Primary Endpoint:

The primary endpoint was trough FEV1 response after 4 weeks of treatment. Only the Olo 20mcg group was significantly different than placebo. For all other olodaterol dose groups, while there was a trend for improvement compared to placebo, the improvement was not statistically significant. There was no apparent dose response. These results are summarized in Table 26.

Table 26. Trial 1222.6. Primary endpoint. Trough FEV1 response after 4 weeks of treatment

| Treatment | N (total=296) | Trough FEV1 [L] Response (SE) | Difference from placebo (SE) |
|------------|------------------|----------------------------------|------------------------------|
| Placebo | 53 | 0.004 (0.033) | |
| Olo 2 mcg | 61 | 0.083 (0.032) | 0.080 (0.045) |
| Olo 5 mcg | 59 | 0.090 (0.032) | 0.086 (0.045) |
| Olo 10 mcg | 60 | 0.080 (0.032) | 0.076 (0.045) |
| Olo 20 mcg | 61 | 0.150 (0.032) | 0.147 (0.044)* |

source: Trial 1222.6 CSR; table 11.4.1.1:1; pp86.

*p-value<0.05

Secondary endpoints:

The key secondary endpoint was PEFR response after 4 weeks of treatment. Compared to placebo, all olodaterol doses demonstrated a statistically significant treatment effect. A dose response was also apparent. Results are summarized in Table 27.

Table 27. Trial 1222.6. Key secondary endpoint. PEFR response after 4 weeks of treatment

| Treatment | N (total=296) | PEFR Response [L/min](SE) | Difference from placebo (SE) |
|------------|------------------|------------------------------|------------------------------|
| Placebo | 53 | 368.18 (5.713) | |
| Olo 2 mcg | 61 | 348.42 (5.377) | 16.238 (7.843) |
| Olo 5 mcg | 59 | 396.06 (5.419) | 27.878 (7.875) |
| Olo 10 mcg | 60 | 404.26 (5.465) | 36.072 (7.906) |
| Olo 20 mcg | 61 | 411.13 (5.377) | 42.943 (7.848) |

source: Trial 1222.6 CSR; Table 11.4.1.2.1:1; pp88

p-values <0.05

For the secondary endpoints of trough FEV1 response after 1 and 2 weeks of treatment, the results were similar to the primary endpoint. For the secondary endpoints of trough FVC response after 1, 2, and 4 weeks of treatment, the results mirrored the trough FEV1 response results.

FEV AUC(0-6) response demonstrated a statistically significant improvement compared to placebo after 4 weeks of treatment with 20mcg olodaterol (difference from placebo =0.232 L). For the 10mcg dose, there was no statistically significant difference, and as per the statistical analysis plan, comparisons of lower doses to placebo were only

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descriptive in nature (though p-values were provided). For the analogous FVC AUC (0-6) response data, only the 20mcg olodaterol dose showed a statistically significant difference from placebo (0.191L). For FEV AUC (0-3 hours) response after 1, 2 and 4 weeks of treatment, at all time points and for all doses, olodaterol groups demonstrated statistically significant improvement compared to placebo. For all the AUC related endpoints, there was no dose response. The numerical difference from placebo for the 10mcg dose was consistently less than the 5mcg dose.

For the secondary endpoints of peak FEV1 response at 0-3 hours post-dose at day 1 and week 1, all doses demonstrated a statistically significant response compared to placebo. For the same parameter at week 2 and 4, only the 20mcg dose demonstrated a statistically significant difference from placebo. For the 10mcg dose at weeks 2 and 4, a statistically significant difference was not seen, and as per the statistical analysis plan, the comparisons to placebo for the 2 and 5mcg doses were only descriptive in nature. For the analogous endpoint for FVC, the results were similar. As with FEV1, only the 20mcg dose consistently demonstrated a statistically significant difference from placebo for all time points. However, the 10mcg dose never demonstrated a statistically significant difference from placebo for any of the timepoints, as such only descriptive analysis was performed for the lower doses. As with the AUC data, there was no consistent dose response for the FEV1 and FVC peak response at 0-3 hours post dose.

The sponsor endpoints which included unsupervised spirometric measurements did not yield any statistically significant results.

For the secondary endpoint of weekly mean PEFR response after 4 weeks of treatment, all doses demonstrated a statistically significant difference from placebo (in liters/minute; Olo 2mcg=23, Olo 5mcg=25, Olo 10mcg=37, and Olo 20mcg=43). The results were similar after 1, 2, and 3 weeks of treatment, though the differences were greater in magnitude. For pre-dose morning PEFR response, the difference from placebo at weeks 1, 2, 3, and 4 were all statistically significant and similar in magnitude to the weekly mean PEFR responses. However, as with the FEV and FVC data, there was no apparent dose response.

With regard to rescue medication usage, at weeks 1, 2 and 3, all olodaterol dose groups has statistically significantly less rescue medication use compared to placebo. The differences from placebo were all generally ≤ 1 dose/day. After 4 weeks of treatment the differences from placebo were only statistically significant for the 20mcg. The magnitude of the differences was modest ranging from 0.287-0.593 fewer doses of rescue medications/day.

The sponsor also analyzed change from baseline in ACQ total score compared to placebo after 4 weeks of therapy. For both the 10 and 20mcg doses, there was a statistically significant improvement compared to placebo of 0.33 and 0.28, respectively. The 2 and 5mcg doses demonstrated a numerical improvement compared to placebo,

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however, the difference did not reach statistical significance. Note that overall, the improvements are minimal and of questionable clinical significance.

Reviewer Comment:

For the primary endpoint of trough FEV1 response, a statistically significant difference from placebo was only seen for the 20mcg dose, though there were similar trends for the lower doses. There was no trend for a dose response. These data were inconsistent with the COPD dose ranging trials. For the key secondary endpoint (PEFR response), however, all doses demonstrated a statistically significant difference from placebo. It should be noted that in general FEV1 is considered a more robust endpoint parameter than PEFR.

The results for the FVC and FEV1 related secondary endpoints were consistent with the primary endpoint in that only the 20mcg dose consistently demonstrated statistically significant differences from placebo. For all other doses, the results were variable. There was also no consistent dose response.

These results are not consistent with the COPD dose ranging trials, where in general, all doses demonstrated a statistically significant treatment effect and a dose response. This lack of consistency may have to do with the size of the trial, the higher percentage of protocol violations, and the lower compliance rates.

Pharmacokinetic endpoints:

For the 2mcg dose group, only 1 patient had a detectable level of olodaterol at any time point. For the 5mcg group, less than 1/3 had detectable levels post-dose on day 1; however at more than 1/3 had detectable levels post-dose on day 29. For the 10 and 20mcg dose groups, in more than 1/3 of patients, plasma concentrations could be detected up to 3 hours post-dose on day 1 and up to 6 hours post-dose on day 29. For the 5, 10, and 20mcg doses, maximum plasma concentrations were observed between 10 and 20 minutes post dosing. Thereafter, decline was rapid. For the 10 and 20mcg doses, steady state was reached at 6 hours post-dose (day 29). The half life at steady state was 28 hours for the 20mcg dose. Half life was not calculated for the other doses due to insufficient data. These results are summarized graphically in Figure 8.

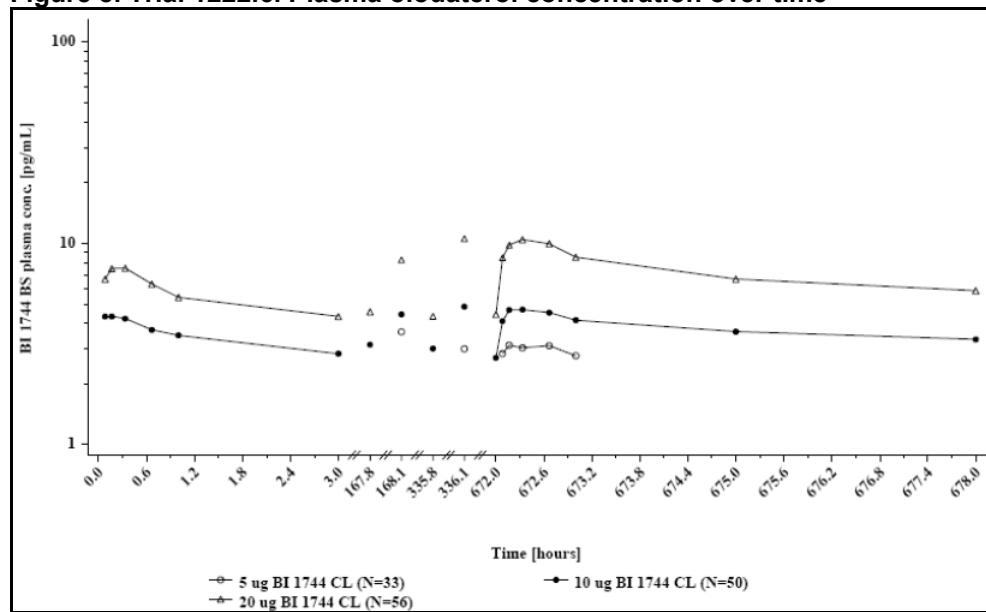
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Figure 8. Trial 1222.6. Plasma olodaterol concentration over time



source: Trial 1222.6 CSR; Figure 11.5.2.1.1:1; pp109

BI1744=olodaterol

Safety:

Exposure:

Approximately 242 patients were exposed to olodaterol and 54 to placebo for a mean duration of 29 days. Approximately 89% of patients were exposed for >28 days.

Exposures were similar between all groups.

Deaths and SAEs

There were no deaths reported in this trial. There were 2 SAEs reported. One patient in the Olo 10mcg group reported pneumonia and one patient in the Olo 20mcg group reported dizziness, palpitations, hyperhidrosis, and chest pain. The patient in the 20mcg group had a known history of palpitations; however, it had not previously been associated with dizziness or chest pain. Both patients required hospitalization and fully recovered. In both cases study drug was continued during these events.

Treatment Emergent AEs

Any AE occurring after the first dose of study drug until 12 days after the last dose is referred to as a TEAE in the review of this trial. Overall the occurrence of TEAEs was slightly lower in the placebo group (28%) compared to olodaterol groups (30-40%).

Based on system organ class, the most common TEAEs were infections and infestation; respiratory mediastinal and thoracic; and nervous system disorders. In general, AEs based on SOC were comparable between groups, though nervous system disorders were more common in the Olo 20mcg group (19.7%) compared to all others (5-11.7%). The most common TEAEs based on preferred term were headache and nasopharyngitis.

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These occurred with similar incidence across groups. Tremor and anxiety only occurred in Olo 20mcg group, and palpitations occurred more frequently in this group compared to all other groups. Asthma exacerbations were most frequent in the placebo group. A summary of TEAEs by preferred term that occurred in ≥2 patients can be found in Table 28.

Table 28. Trial 1222.6. Treatment emergent AEs that occurred in ≥2 patients

| | Placebo N(%) | Olo 2mcg N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Olo 20mcg N(%) |
|-----------------------------|-----------------|------------------|------------------|-------------------|-------------------|
| Number of patients | 54 (100.0) | 61 (100.0) | 60 (100.0) | 60 (100.0) | 61 (100.0) |
| Patients with AEs | 15 (27.8) | 23 (37.7) | 24 (40.0) | 18 (30.0) | 24 (39.3) |
| Headache | 3 (5.6) | 4 (6.6) | 4 (6.7) | 3 (5.0) | 5 (8.2) |
| Nasopharyngitis | 4 (7.4) | 4 (6.6) | 5 (8.3) | 3 (5.0) | 2 (3.3) |
| Asthma | 4 (7.4) | 2 (3.3) | 2 (3.3) | 1 (1.7) | 2 (3.3) |
| Dizziness | 1 (1.9) | 3 (4.9) | 1 (1.7) | 0 (0.0) | 2 (3.3) |
| Sinusitis | 2 (3.7) | 2 (3.3) | 1 (1.7) | 2 (3.3) | 0 (0.0) |
| Pharyngolaryngeal pain | 2 (3.7) | 3 (4.9) | 1 (1.7) | 0 (0.0) | 0 (0.0) |
| Cough | 1 (1.9) | 1 (1.6) | 2 (3.3) | 1 (1.7) | 1 (1.6) |
| Tremor | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (8.2) |
| Respiratory tract infection | 1 (1.9) | 0 (0.0) | 1 (1.7) | 0 (0.0) | 2 (3.3) |
| Back pain | 0 (0.0) | 0 (0.0) | 2 (3.3) | 0 (0.0) | 1 (1.6) |
| Neck pain | 0 (0.0) | 1 (1.6) | 2 (3.3) | 0 (0.0) | 0 (0.0) |
| Palpitations | 0 (0.0) | 0 (0.0) | 1 (1.7) | 0 (0.0) | 2 (3.3) |
| Anxiety | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (3.3) |

source: Trial 1222.6 CSR; Table 12.2.2.2:1; pp135

One patient withdrew due to an AE (Olo 5mcg) reported as premature ventricular contractions.

Reviewer comments:

Although there were only 2 SAEs, the report of dizziness/palpitation/chest pain is of concern. Although the patient had a history of palpitations, they had not previously been associated with other symptoms. Given what is known about LABAs, it is possible that olodaterol was a precipitating factor in the event. The AE of premature ventricular contractions is also of concern, given the potential cardiac safety issues with LABAs. With regard to TEAEs, none demonstrated a clear dose response; however, palpitations and anxiety occurred only in the olodaterol groups and more frequently in the highest dose group. Given the small number of events and short exposure times, it is difficult to make definitive conclusions. In the analysis of the safety data set for this development program specific attention is paid to similar SAEs and AEs.

Labs:

Based on shift tables, in general hematologic and chemistry lab values were stable from baseline to end of treatment. However, patients in the 20mcg group experienced a higher incidence of decreased hemoglobin compared to placebo (16.7% versus 4.5%) when comparing baseline to last value. In addition, patients in the 10 mcg group

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experienced a higher incidence of low minimum post-baseline red blood cell counts compared to placebo (15.3% vs. 5.9%) and elevated maximum post-baseline chloride levels (18.6% vs. 12.0%). Patients in both the 10mcg and 20mcg groups also showed a higher incidence of increased creatine phosphokinase (18.3% and 13.1%, respectively), compared to placebo (3.8%). No abnormal CK-MB (the isoenzyme for heart muscle elevation) values were noted. With regard to potassium levels, at weeks 8, 15, and 29, there were no statistically significant decreases noted in olodaterol groups compared to placebo. However at the day 1 dose, the 10mcg dose group had a statistically significant decrease compared to placebo at one hour post-dose; however, this was not seen at later time points. For the 20mcg dose group, a decrease in potassium compared to placebo at both 1 and 3 hours post-dose on day 1. The magnitude of the difference from placebo was approximately 1mmol/L. Shift table analysis comparing baseline to end of treatment serum potassium levels did not reveal any significant differences from placebo.

Vitals signs

The number of patients with changes in blood pressures or pulse rates were generally similar between treatment groups. However, there was a tendency in the 20mcg group for increased post-dose pulse rate at some of the clinic visits. Using shift table analysis, a higher proportion of patients in the 20 mcg group experienced a diastolic BP increase from within the normal range to above the upper limit of normal (26.2%) compared to the placebo group (9.3%) or other olodaterol dose groups (5% to 18.0%). Additionally, when comparing 'marked' changes from baseline, differences were noted between olodaterol and placebo groups. This was most notable for marked increases in blood pressures. These findings are summarized in Table 29.

Table 29. Trial 1222.6. Patients with marked changes in blood pressure (BP) and pulse rate

| Number of patients (%) | Placebo (N=54) | Olo 2mcg (N=61) | Olo 5mcg (N=60) | Olo 10mcg (N=60) | Olo 20mcg (N=61) |
|------------------------|-------------------|--------------------|--------------------|---------------------|---------------------|
| Systolic BP | | | | | |
| Increase | 1 (1.9) | 6 (9.8) | 7 (11.7) | 3 (5.0) | 7 (11.5) |
| Decrease | 7 (13.0) | 10 (16.4) | 5 (8.3) | 8 (13.3) | 12 (19.7) |
| Diastolic BP | | | | | |
| Increase | 2 (3.7) | 9 (14.8) | 8 (13.3) | 4 (6.7) | 12 (19.7) |
| Decrease | 3 (5.6) | 8 (13.1) | 1 (1.7) | 8 (13.3) | 7 (11.5) |
| Pulse rate | | | | | |
| Increase | 1 (1.9) | 2 (3.3) | 3 (5.0) | 1 (1.7) | 4 (6.6) |
| Decrease | 9 (16.7) | 12 (19.7) | 7 (11.7) | 11 (18.3) | 8 (13.1) |

source: Trial 1222.6 CSR; Table 12.5.1:1; pp142

There were no notable changes on ECG for PR interval, QRS interval, nor QTcF interval based on mean values. However, when comparing QTcB intervals, there was a trend in the 10 and 20mcg groups for an increase over the 3 hours following dosing. When analyzing the QTcF changes divided into categories (change from baseline >30msec or >60msec), at the end of treatment more patients treated with Olo 5mcg and

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Olo 10mcg had QTcF interval changes of >30msec compared to placebo. This was true for ECGs taken 40, 60, and 180 minutes after dosing, but not for ECGs taken 30 minutes pre-dose and 10 minutes post-dose. There was no clear dose response. This is summarized in Table 30. With regard to ECG morphology, there was a slightly higher incidence of T wave abnormalities in the 10 and 20mcg groups up to 1 hour post-dose on study day 1. These abnormalities were not associated with AE reports.

Table 30. Trial 1222.6 QTcF Changes from Baseline at the End of Treatment Period

| | | | Placebo | Olo 2mcg | Olo 5mcg | Olo 10mcg | Olo 20mcg |
|-------------|-------|----------|------------|------------|------------|------------|------------|
| Test day 29 | -0:30 | N | 52(100.00) | 58(100.00) | 57(100.00) | 58(100.00) | 61(100.00) |
| | | >30 msec | 4(7.69) | 1(1.72) | 1(1.75) | 0(0.00) | 1(1.64) |
| | | >60 msec | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) |
| | 0:10 | N | 51(100.00) | 56(100.00) | 58(100.00) | 57(100.00) | 59(100.00) |
| | | >30 msec | 2(3.92) | 2(3.57) | 0(0.00) | 2(3.51) | 1(1.69) |
| | | >60 msec | 1(1.96) | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) |
| | 0:40 | N | 51(100.00) | 55(100.00) | 56(100.00) | 53(100.00) | 57(100.00) |
| | | >30 msec | 1(1.96) | 3(5.45) | 2(3.57) | 2(3.77) | 2(3.51) |
| | | >60 msec | 1(1.96) | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) |
| | 1:00 | N | 51(100.00) | 56(100.00) | 57(100.00) | 53(100.00) | 57(100.00) |
| | | >30 msec | 1(1.96) | 1(1.79) | 3(5.26) | 2(3.77) | 2(3.51) |
| | | >60 msec | 1(1.96) | 0(0.00) | 0(0.00) | 1(1.89) | 0(0.00) |
| | 3:00 | N | 52(100.00) | 58(100.00) | 58(100.00) | 58(100.00) | 59(100.00) |
| | | >30 msec | 2(3.85) | 1(1.72) | 4(6.90) | 5(8.62) | 0(0.00) |
| | | >60 msec | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) | 0(0.00) |

source: Trial 1222.6 CSR; Table 15.3.4.2.2:7; pp493

Reviewer Comment:

The significance of the shift table analysis results for hemoglobin, red blood cells, and sodium is of unclear significance. The results for CPK are consistent with previous trials, where increases from baseline were noted. The results for serum potassium are not surprising given that olodaterol is a LABA. It is reassuring that the magnitude of serum potassium changes was small and is likely of little clinical significance. However, it is notable that for the above mentioned lab parameters, the changes from baseline were most obvious in the higher olodaterol dose groups. With regard to the vital sign changes (SBP, DBP, pulse rate), there appears to be a dose response, if the 10mcg dose is ignored. Interestingly, in the efficacy analysis, when a dose response was not demonstrated, it was frequently due to the 10mcg dose group. The observed imbalance in QTcF changes from baseline is somewhat surprising as in BI's TQT study, no significant QT effect was detected, although there was some indication that with increasing doses, the QTc increased. Although this is concerning, the overall numbers are small. This is scrutinized when analyzing the combined safety data sets.

Overall Comments:

The efficacy results of this trial were not consistent with the previous COPD dose-ranging trials. Only the 20mcg olodaterol dose consistently demonstrated a statistically significant treatment effect compared to placebo. Additionally, based on most endpoints, there was no dose effect. The disparate results may in part be related to higher number of protocol violations and lower compliance. Given this unexpected result, the trial is not helpful in terms of dose ranging. With regard to safety, olodaterol appeared relatively well tolerated, however there were several (S)AEs that were of some concern (i.e.

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chest pain/palpitations and premature ventricular contractions) given the potential cardiac safety issues with LABAs. Although it is reassuring that the number of the (S)AEs was low, the total exposure was also relatively low. The potential QTcF effects are also concerning. In the analysis of the combined safety data sets, special attention will be given to cardiac related AEs and ECGs.

5.3.6 Trial 1222.27 (Asthma)

Administrative Information

- **Study title:** A Randomized, Double-Blind, Placebo- and Active-Controlled, Incomplete Crossover Efficacy and Safety Comparison of 4-week Treatment Periods of Once Daily Treatment of 4 Doses of Olodaterol Inhalation Solution Delivered by the Respimat in Patients with Asthma
- **Study dates:** 2/22/10-1/14/2011
- **Study sites:** Austria (4 sites), Germany (9 sites), Poland (4 sites), Romania (2 sites), Slovakia (4 sites), Slovenia (4 sites)
- **Study report date:** 1/25/2012

Objectives/Rationale

- To determine the optimum daily dose(s) of olodaterol on asthmatic patients.
- To compare the 24-hour FEV1 profile of olodaterol with Foradil

Study Design and Conduct

Overview

This was a 16 week, multi-center, randomized, double-blind, placebo and active controlled, double dummy, 4-period incomplete block dose ranging trial in patients with asthma who demonstrated reversibility on PFTs. Patients were randomized to receive a sequence of 4 out of a possible 6 treatments (Olo 2, 5, 10, 20 mcg qD, placebo, and Foradil 12mcg BID). Each treatment period was for 4 weeks. There was no washout between treatment periods. PFTs were conducted at baseline (prior to any treatment) and at the end of each 4 week treatment period.

At the initial screening visit (visit 0), consent was obtained. If patients were on LABAs, they were washed out. If patients were on an ICS/LABA combination, while the LABA was washed out, they remained on an equivalent dose of ICS. When patients returned for visit 1 (week -2) baseline assessments such as ACQ and PFTs were obtained.

Appropriate medication washout was also verified. Patients were given an AM2+ device as their eDiary and instructed how to record PEFR. Rescue medication was also dispensed (salbutamol). Following the 14 day baseline period, patients returned for visit 2 (week 0). At this visit eligible patient were randomized to a treatment sequence. To be eligible, patients must have completed the eDiary at least 80% of the time during the baseline period. Patients then began the treatment phase. After 4 weeks of treatment, they returned to clinic for visit 3. At that visit, pre and post-dose PFTs were performed, as well as other trial assessments. The next dose of study medication was also

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dispensed. Patient then returned to clinic every 4 weeks for visits 4, 5, and 6 (weeks 8, 12, and 16, respectively) for similar assessments and new trial medication. The assessment schedule is summarized Table 31.

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Table 31. Trial 1222.27. Assessment schedule

| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|---------------------------|--------------------|
| Week | -1 | 0 | 1 | 4 | 6 | 8 | 10 | +2 |
| Day | -14 | 1 | 15 | 29 | 43 | 57 | 71 | +4 |
| | -14 | -4 | -4 | -4 | -4 | -4 | -4 | -4 |
| Informed consent | X | | | | | | | |
| Pharmacogenomics | | | | X ¹ | | | | |
| Demographics | X | | | | | | | |
| Medical history | X | | | | | | | |
| Review in-/exclusion criteria | X | X | | | | | | |
| Physical examination | X | | | | | | X ¹¹ | X ¹² |
| Vital signs (seated) | X ¹⁰ | X ¹⁰ | X ¹³ | X ¹⁰ | X ¹⁰ | X ¹⁰ | X ^{11,17} | X ¹² |
| Laboratory test ³ | X ¹³ | | X ¹⁵ | X ¹⁶ | X ¹⁶ | X ¹⁶ | X ^{11,15,} 17 | X ^{12,13} |
| Pregnancy test ⁴ | X | X | X | X | X | X | X ¹³ | X |
| Urinary cotinine | X | | | | | | | |
| Randomisation | X | | | | | | | |
| Collect and review e-diary | | X ¹⁴ | X ^{14,17} | X ¹⁴ |
| Medication washout compliance check | X | X | X | X | X | X | X | |
| Medication compliance check | | | X | X | X | X | X | |
| Pulmonary Function Testing ⁵ | X | X | X | X | X | X | X ¹¹ | X |
| Reversibility Testing ⁶ | X | | | | | | | |
| Administer trial medication ⁶ | | X | X | X | X | X | X | |
| 12-lead ECG ¹¹ | X | X | X | X | X | X | X ¹³ | X ¹² |
| Pharmacokinetics ¹³ | | | X | X | X | X | X | |
| Issue Peak Flow Meter / e-diary | X ¹⁸ | X | X | X | X | X | X ¹⁹ | |
| Dispense trial drug | | X | X | X | X | X | X ¹⁷ | |
| Collect trial drug | | | X | X | X | X | X ¹⁷ | |
| Dispense rescue medication | X | X | X | X | X | X | X ¹⁹ | |
| Telephone contact to patient ⁷ | | | X | X | X | X | X | |
| ACQ | X | X | X | X | X | X | X | X |
| AQLQ (S) | | X | X | X | X | X | X | X |
| Training in use of inhalers | X | X ¹ | X ⁷ | |
| Adverse events | X | X | X | X | X | X | X ¹³ | X |
| Concomitant therapy | X | X | X | X | X | X | X ¹³ | X |
| Drug accountability | | X | X | X | X | X | X ¹³ | |
| Trial medication termination | | | | | | | X ¹⁷ | |
| Conclude patient participation | | | | | | | X ¹ | |

1 All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication wash out and restrictions. A separate consent for pharmacogenomic sampling should be signed if patients are participating in the pharmacogenomic substudy.

2 Patients to be contacted every two weeks in between visits during the treatment period to collect safety information and 1 day prior to Visits 3, 4, 5 and 6 to ensure correct trial drug administration.

3 1 additional blood sample at Visit 3, or later Visit as necessary, required for genotype analysis at any visit (optional)

4 To be completed on all patients of childbearing potential. A serum BHCG test will be performed at Visit 1. A urine pregnancy test will be performed prior to trial medication administration at Visits 2-6 and at follow-up (Visit 7).

5 To be completed whenever trial participation ends (including discontinued patients).

6 At Visit 2, trial drug administered in fixed sequence (1. from Respimat[®] 2 from Aerolizer[®] 3. iCS) between 18:00-20:00. At Visits 3, 4, 5 and 6 trial drug administered within <=30 minutes of the time of trial drug administration at Visit 2 AND between 18:00-20:00 pm Study medication via the Aerolizer[®] to be delivered immediately after study medication delivered via the Respimat[®]. At Visits 3, 4, 5 and 6 trial drug administration in fixed sequence (1.from Aerolizer[®] 2. iCS) will occur between 06:00 am and 08:00 am and 12 hours (>30 minutes) after the time of the pm trial drug administration. The dosing (bid od am/od pm) of the iCS is determined by the former use as the patient was instructed by her/his treating physician.

7 The patient should not inhale from the Respimat[®] and Aerolizer[®] training inhalers at Visits 2, 3, 4, 5 and 6.

8 Visit 2: PFTs performed up to one hour pre-dose and at Visits 3, 4, 5 and 6 up to 24 hours post dose (pm). See chart below for timings

9 Reversibility testing using 4 puffs Salbutamol (100 µg per actuation).

10 Vital signs measured in all patients at Screening Visit (Visit 1) and repeated at the withdrawal visit if the patient does not complete all study visits. In addition, vital signs will be performed in all patients at Visits 2, 3, 4, 5 and 6. See chart below for timings.

11 Triplicate 12-lead ECG recordings in all patients at Screening Visit (Visit 1). 12-lead ECG to be performed at Visit 2 and repeated at the withdrawal visit if the patient does not complete all study visits. In addition, 12-lead ECG recording will be performed pre-dose and post-dose (pm) in all patients at Visits 3, 4, 5 and 6 (see chart below for timings).

12 To be performed if findings at Visit 6 or at premature withdrawal visit.

13 Samples to be taken prior to inhalation

14 e-Diary compliance check

15 PK blood sampling post drug administration at Visits 3, 4, 5 and 6. See chart below for timings.

16 Abbreviated laboratory tests only at Visits 3, 4, 5 and 6 pre and post-dose (pm) for collection of potassium levels. See below for timings.

17 To be performed at the following any premature withdrawal of a patient. A single PFT should be performed in this case.

18 Training to be given on Peak Flow Meter / e-diary (AM2+ device) at Visit 2

Source: Trial 1222.27 report U11-2137-01 (protocol and amendments);pp7-8

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The assessment schedule at visit 3, 4, 5, and 6 is summarized in Table 32.

Table 32. Trial 1222.27. Assessment schedule at visits 3, 4, 5, and 6

| Hours -1 to 11:50 | Timing in relation to evening inhalation of study drug (Respiimat®) (0 hours) within ±30 minutes of the time of trial drug administration at Visit 2 AND between 18:00-20:00 pm Study medication via the Aerolizer® to be delivered immediately after study medication delivered via the Respiimat®. Morning trial drug administration will occur between 06.00 am and 08.00 am and 12 hours (±30 minutes) after the time of the pm trial drug administration. | | | | | | | | | | | | |
|---|---|-----------------|------|-----------------|-----|-----------------|-----|-----------------|-----------------|-----------------|-----------------|-----------------|--------|
| | -1hr | -30' | -10' | 0 | 10' | 20' | 30' | 40' | 1h | 2h | 3h | 4h | 11h50' |
| AQLQ(s) | X ¹ | | | | | | | | | | | | |
| ACQ | X ² | | | | | | | | | | | | |
| Administer trial medication | | | | X ¹² | | | | | | | | | |
| Administer ICS | | | | X ⁹ | | | | | | | | | |
| 12-lead ECG | | X ¹¹ | | | | | | X ¹¹ | X ¹¹ | | | X ¹¹ | |
| Vital signs ³ | X | | X | | | | X | | X | X | X | | |
| Physical examination | X ⁴ | | | | | | | | | | | | |
| Safety laboratory testing ⁴ | X ⁴ | | | | | | | | | | | | |
| Abbreviated laboratory testing ⁵ | X | | | | | | | X ¹¹ | | X ¹¹ | | | |
| Urine pregnancy test | X ⁶ | | | | | | | | | | | | |
| Pulmonary function testing ⁷ | X | | X | | | X ¹⁰ | | | X | X | X | X | X |
| PK plasma sampling | | | | | | | | | X ¹¹ | | X ¹¹ | | |
| Hours 12-23:50 | Timing in relation to evening inhalation of study drug (Respiimat®) (0 hours) within ±30 minutes of the time of trial drug administration at Visit 2 AND between 18:00-20:00 pm Study medication via the Aerolizer® to be delivered immediately after study medication delivered via the Respiimat®. Morning trial drug administration will occur between 06.00 am and 08.00 am and 12 hours (±30 minutes) after the time of the pm trial drug administration. | | | | | | | | | | | | |
| | 12h | 12h30' | 13h | 14h | 15h | 16h | 18h | 20h | 22h | 23h | 23h50' | | |
| Administer trial medication | X ⁸ | | | | | | | | | | | | |
| Administer ICS | X ⁹ | | | | | | | | | | | | |
| Pulmonary function testing ⁷ | | X | X | X | X | X | X | X | X | X | X | X | |

* Whenever more than one procedure is performed at the same timepoint, pulmonary function tests should always be performed as close to that timepoint as possible. The order of procedures should be as follows: ECGs should be completed first (i.e 10 minutes prior to the other procedures) followed by vital signs and pulmonary function testing, followed by PK plasma sampling (safety and abbreviated blood samples can be taken at the same time).

- 1. First procedure to be undertaken on arrival at clinic
- 2. Second procedure to be undertaken on arrival at clinic
- 3. To be completed immediately prior to PFTs with patient sitting for 5 minutes
- 4. To be completed prior to inhalation of medication (pm) at Visit 6
- 5. Blood sample for Potassium
- 6. To be completed prior to inhalation of medications
- 7. FEV1, FVC and PEF completed using the MasterScope®.
- 8. Inhalation from the Aerolizer® only.
- 9. From patients own ICS (max 10 minutes after Aerolizer® inhalation)
- 10. ± 3 minutes
- 11. ±10 minute
- 12. Administration of medication in fixed sequence (1. from Respiimat® 2. from Aerolizer® 3. iCS (see also footnote 9). Inhalation from Respiimat® followed immediately by Aerolizer®

Source: Trial 1222.27 report U11-2137-01 (protocol and amendments);pp 9-10

Study Population

A total of 198 asthmatic patients were randomized. Treatment sequences were assigned using an IVRS system.

Key Inclusion Criteria

1. 18-70 years of age, diurnally active
2. Diagnosis of asthma per GINA guidelines and at treatment steps 3 or 4 at least 3 month prior to visit 1.
3. Pre-bronchodilator FEV1 ≥60% predicted and <90% at visit 1

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4. Reversibility following bronchodilator treatment defined as a ≥12% increase in FEV1 and 200mL within 15 minutes of salbutamol treatment (performed at visit 1).
5. Patients must have been taking ICS for at least 12 weeks prior to screening and must have been receiving a stable medium to high dose or a low to high dose ICS+LABA for at least 6 weeks prior to screening.
6. At visit 2, all patients must be symptomatic with an ACQ ≥1.5
7. Current non-smokers or ex-smokers with a <10 year pack history.

Key Exclusion Criteria

1. Significant disease other than asthma
2. Patient who has been hospitalized for an asthma exacerbation within the past 3 months or had an admission to an intensive care unit for asthma within 3 years of visit 1
3. Clinically relevant abnormal baseline labs
4. Patients with a history of myocardial infarction within 1 year of the screening visit, a diagnosis of clinical relevant cardiac arrhythmia, active tuberculosis, clinically evident bronchiectasis, a history of cor pulmonale, Cystic Fibrosis, or a history of life threatening pulmonary obstruction.
5. Patients who have undergone thoracotomy with pulmonary resection.
6. Patients being treated with medication that prolong QT/QTc interval, oral beta-adrenergics, beta-blockers, or oral steroids at unstable doses (<6 weeks on a stable dose or at doses >10mg of prednisone per day or 20mg every other day).
7. A diagnosis of paroxysmal tachycardia or hyperthyroidism
8. Baseline prolongation of QT/QTc interval.
9. A history of additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalemia, family history of long QT).
10. Women of childbearing potential not using a highly effective method of birth control (<1% failure rate).
11. Patients being treated with any of the following concomitant medications:
 - Long acting beta-agonists (LABAs) within 48 hours prior to screening
 - Oral or other systemic corticosteroids in the 6 weeks prior to screening
 - Anti-IgE antibodies (e.g. omalizumab) for 6 months prior to screening
 - Medications that prolong the QT/QTc interval
 - Oral beta-adrenergics for 6 weeks prior to screening
 - Beta-blockers (topical beta-blockers for ocular conditions are allowed)
 - Methylxanthines and antileukotrienes in the 6 weeks prior to screening
 - Short-acting anticholinergics (inhalation aerosol and nasal spray) including fixed dose anticholinergic/ beta-adrenergics (e.g. Combivent/ Berodual) within 8 hours prior to screening
 - Long-acting anticholinergics (e.g. Tiotropium (Spiriva)) in the 6 weeks prior to screening
12. Patients with frequent seasonal exacerbations of asthma (defined as one or more seasonal exacerbations every year for the past three years)

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13. Patients with any asthma exacerbation or respiratory tract infection in the four weeks prior to the Screening Visit (Visit 1) or during the 2 week baseline period. In the case of an asthma exacerbation during the baseline period patients may be randomised four weeks following the last administered dose of additional medication prescribed to control the exacerbations.
14. Patients whose compliance using the AM2+ device is less than 80% during baseline period
15. Patients that are predominantly night active (e.g. working night shift)

Treatments:

Olodaterol 2mcg once daily (2 actuations of 1mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Olodaterol 20mcg once daily (2 actuations of 10mcg/actuation)

Foradil 12mcg BID

Placebo (double dummy)

All treatments will be delivered via a Respimat device.

Concomitant/restricted medications

All medication used within 3 months preceding the screening visit and throughout the trial was recorded in the eCRF. Patients were allowed to use salbutamol as rescue medication, however if it was required during PFTs, the PFTs could have been discontinued at the discretion of the investigator. For exacerbations, patients were allowed to take any medication deemed necessary by the treating physician. Other concomitant medications were restricted as summarized in Table 33.

Table 33. Trial 1222.27 Restricted and prohibited medications

| Drug Class | Sub-Class | Prior to study | Study Period | | |
|-----------------|----------------------|---|-----------------|------------------|------------------|
| | | | Baseline period | Treatment period | Follow up period |
| Corticosteroids | ICS | REQUIRED Patients must have been taking ICS for at least 12 weeks prior to screening, and must have been receiving a stable dose for at least 6 weeks prior to screening | REQUIRED | REQUIRED | REQUIRED |
| | Oral corticosteroids | not permitted* | not permitted. | not permitted | not permitted |
| Other asthma | Combination | not permitted. | not permitted | not permitted | permitted |

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| | | | | | |
|-----------------------------------|--|---|--|--|---|
| controllers | ICS/LABA (e.g. Advair/ Seretide; Symbicort) | Fixed dose combination LABA/ ICS should be split into the equivalent monotherapy once the patient has enrolled but at least 48 hours prior to Visit 1. | | | |
| | Cromolyn sodium / nedocromil sodium | permitted | permitted | permitted | permitted |
| | Antihistamines | permitted | permitted | permitted | permitted |
| | Antileukotrienes | not permitted* | not permitted | not permitted | not permitted |
| | Methylxanthines | not permitted* | not permitted | not permitted | not permitted |
| Beta-adrenergics Beta-blockers | Inhaled SABA | permitted | Rescue (prior to all visits at least an 8- hour washout) | Rescue (prior to all visits at least an 8- hour washout) | Rescue (prior to all visits at least an 8-hour washout) |
| | Inhaled LABA | not permitted* | not permitted | Study medication | permitted |
| | Oral beta- adrenergics | not permitted* | not permitted | not permitted | not permitted |
| | Beta blockers | not permitted* | not permitted | not permitted | not permitted |
| Anticholinergic | Short-acting anticholinergics including fixed dose anticholinergic/ β adrenergics | permitted | not permitted. At least 8 hour washout prior to Visit 1. | not permitted | not permitted |
| | Long-acting anticholinergics | not permitted* | not permitted | not permitted | not permitted |
| Miscellaneous | Regular Anti-IgE treatment (e.g. Omaluzimab) | not permitted* | not permitted | not permitted | not permitted |
| | Mucolytics | permitted | permitted | permitted | permitted |
| | Immunotherapy (desensitization) | not permitted if started within last 2 years and are not on stable dose | not permitted | not permitted | not permitted |

Source: Trial 1222.27 report U11-2137-01 (protocol and amendments);table 4.2.2:1; pp45-46

* not permitted from 6 weeks prior to screening

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Reviewer Comment:

The overall trial design, inclusion/exclusion criteria, and restricted medications are reasonable for a dose ranging trial in asthmatics.

Efficacy Parameters

Primary Endpoint

The primary endpoint for this trial was FEV₁ AUC (0-24 hours) response after 4 weeks of treatment. The FEV₁ AUC (0-24 hours) was calculated from spirometric data from the clinic visit at the end of each 4 week treatment period, and divided by 24 hours to report in liters. Baseline FEV₁ from visit 2 (defined as mean of FEV₁ at -1hour and -10minutes pre-dose) was subtracted from FEV₁ AUC (0-24 hours) to determine FEV₁ AUC (0-24 hours) response. However, in this trial FEV₁ AUC (0-24 hours) data prior to trial medication was not collected.

Secondary Endpoints

The secondary endpoints are as follows:

1. PEFR at the end of each dosing interval measured by patients at home using the AM2+ device
2. FEV₁ AUC (0-12 hours) and FEV₁ AUC (12-24 hours) measured following each dosing determined at the end of each 4 week treatment period.
3. Peak FEV₁ (L) (within 24 hours post-dose) measured following the evening trial-drug inhalation at the end of each 4 week treatment period.
4. Trough FEV₁ (L) at the end of each 4 week treatment period. Trough FEV₁ is defined as the mean of the two FEV₁ values (performed at 1 hour and 10 minutes prior to the evening trial-drug inhalation) at the end of the dosing interval.
5. Trough forced vital capacity (FVC) (L) at the end of each dosing interval (as defined above for FEV₁) determined at the end of each 4 week treatment period.
6. FVC AUC (0-12 hours) and FVC AUC (12-24 hours) and peak FVC (L) (within 24 hours post dose) measured following each dosing determined at the end of each 4 week treatment period.
7. Individual FEV₁, FVC (L) and PEFR L/min measurements peak, trough, AUC (0-24 hours) where possible after the first two weeks of each period of randomized treatment.
8. PEFR variability: PEFR variability (L/min) is the absolute difference between morning and evening PEF value divided by the mean of these two values (weekly and overall means obtained after the first two weeks of each period of treatment will be compared).
9. Use of rescue medication during the entire study period
10. Asthma Quality of Life Questionnaire (AQLQ (S)) at the end each period of treatment.
11. Asthma Control Questionnaire (ACQ) at the end each period of treatment
12. FEV₁ (L): mean pre-dose morning and evening FEV₁ measured by patients at home as measured using the AM2+ device during the entire study period.

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13. Weekly mean number of night time awakenings as assessed by the patient's electronic diary.
14. Asthma symptoms and quality of life as assessed by the patient's electronic diary.
15. Asthma symptom free days: Asthma symptom free day is defined as a day with no reported symptoms and no use of rescue medication.

Data from the first 2 weeks of each treatment period was used as there was no washout period between treatment periods.

Safety Parameters:

The monitored safety parameters include AEs, vital signs, clinical labs, and ECGs. These were assessed as per Table 31 and Table 32. Note that abbreviated lab testing included serum potassium. 'Marked' changes in vital signs were defined as in trial 1222.6.

Compliance:

Treatment compliance was assessed using the eDiary entries and returned medications

Reviewer Comment:

The primary endpoint is typical and appropriate for an asthma dose ranging trial. The secondary endpoints are also generally appropriate. The safety and compliance parameters are appropriate.

Ethics:

This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

Based on BI's previous experience, the standard deviation for pair differences in FEV1 AUC (0-24 hours) was estimated to be 250mL. Based on this, BI estimated that a sample size of 84 patients would yield 95% power to detect a 100mL difference from placebo assuming a paired t-test with a 2.5% one-sided significance level. However, as this was an incomplete block cross-over design, BI targeted a sample size of 150 patients.

Missing Data

Spirometry:

During the baseline period, pre-dose missing data were replaced with non-missing pre-dose values recorded at the same visit. If both pre-dose values were missing at visit 2, baseline was imputed using the mean of the pre-bronchodilator values from visit 1.

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During the treatment period, trough data missing at an individual time point at visit 3-6 was replaced with the non-missing pre-dose data recorded at the same visit. Post-dose data missing due to worsening symptoms were replaced with the least favorable non-missing data recorded during the same visit. Post-dose data missing at random were either linearly interpolated if the preceding and subsequent data point was available or were imputed using last observation carried forward. If a patient discontinued or was excluded from the trial due to worsening of symptoms such that there were not 4 week measurements, data was imputed from the patients least favorable non-missing data.

Patient Recorded Data:

During the baseline period, if fewer than four values were measured in the week immediately preceding the first treatment, enough earlier values were added to obtain four. If fewer than four values were measured in the entire period prior to first inhalation of treatment, all the available data was used.

During the treatment period, data that was missing or excluded due to worsening of symptoms after the first two weeks of the treatment period was replaced with the least favorable non-missing value recorded within the same treatment period (excluding data from the first two weeks of the period). Data missing at random (not due to worsening of symptoms or use of rescue medication) after the first two weeks of the treatment period with no subsequent non-missing values recorded within the same treatment period was imputed using the last observation carried forward technique (LOCF).

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and evaluable post-dosing data following at least 5 days of randomized treatment for at least one endpoint. The per protocol (PP) data set that consisted of all FAS minus patients with important protocol deviations. The safety population was made up of all treated patients.

Efficacy Analysis

Analysis occurred in a step-wise fashion to control for type 1 error. The first comparison was between Olo 20mcg and placebo. If that difference was statistically significant, then the next lower dose was compared to placebo, and so on. If a dose did not demonstrate a statistically significant difference from placebo, subsequent analysis of lower doses continued, however, was considered descriptive. Analysis was performed on the FAS and the PP population.

All secondary analyses was performed only on the FAS. Secondary endpoints related to clinic visit spirometry will be analyzed in a manner similar to the primary endpoint. For patient eDiary derived endpoints, analysis was considered exploratory and no correction for multiplicity was made.

Safety Analysis

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All safety data was analyzed in a descriptive manner.

Results

Amendments:

After initial submission of this protocol, there were 3 amendments. Database lock was 2/18/2011. The first amendment was submitted on 1/8/2010 and primarily corrected typographical errors and made some minor changes. The 2nd amendment was submitted 10/21/2010. The changes were minor. The most notable was allowing for ICS/LABA use during the 2 week follow-up period after all treatment periods were completed. Additionally, instructions were added to account for possible delay in trial medication resupply. In the event that there was a delay in medication resupply, patients were instructed to continue taking medication from their current kit. The 3rd amendment was submitted 2/16/11. This amendment most notable modified the calculation of primary and secondary efficacy variables involving AUCs. The primary efficacy variable was initially defined as FEV1 AUC (0-24 hours) where the analysis would adjust for baseline value, however, in the amendment, the variable for analysis was to be FEV AUC (0-24 hours) after 4 weeks of treatment – baseline FEV1. A similar change was made for the secondary efficacy variables. This amendment was made to make this protocol more consistent with other BI protocols.

Protocol Violations:

Of the total randomized patients, 31 were identified as having important protocol violations. Five patients who should have been excluded due to exclusion criteria were included. Fifteen patients who did not meet inclusion criteria were included. Four patients were dispensed wrong trial medication, 3 were non-compliant, 3 had major deviations in PFT timing, and 5 were classified as other.

Disposition

A total of 317 patients enrolled in this trial and 198 patients were randomized. The most common reason for non-randomization was inclusion/exclusion criteria. Of the 198 patients, 182 (92%) patient completed. The most common reasons for discontinuation were AEs and non-compliance. Discontinuation was most common during the Olo 10mcg treatment period and least frequent during the Olo 2mcg treatment period. A total of 186 patients were included in the FAS for efficacy analysis. Patient disposition is summarized in Table 34.

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Table 34. Trial 1222.27. Patient disposition

| | Placebo N (%) | Olodaterol 2 µg N (%) | Olodaterol 5 µg N (%) | Olodaterol 10 µg N (%) | Olodaterol 20 µg N (%) | Formoterol N (%) | Total N (%) |
|------------------------------|------------------|-----------------------------|-----------------------------|------------------------------|------------------------------|---------------------|----------------|
| Treated | 125 (100.0) | 121 (100.0) | 130 (100.0) | 127 (100.0) | 124 (100.0) | 125 (100.0) | 198 (100.0) |
| Not prematurely discontinued | 123 (98.4) | 121 (100.0) | 127 (97.7) | 122 (96.1) | 120 (96.8) | 123 (98.4) | 182 (91.9) |
| Prematurely discontinued | 2 (1.6) | 0 | 3 (2.3) | 5 (3.9) | 4 (3.2) | 2 (1.6) | 16 (8.1) |
| Adverse event | 2 (1.6) | 0 | 3 (2.3) | 2 (1.6) | 1 (0.8) | 0 | 8 (4.0) |
| AE-oth. disease worsening | 1 (0.8) | 0 | 0 | 1 (0.8) | 0 | 0 | 2 (1.0) |
| AE-other | 1 (0.8) | 0 | 3 (2.3) | 1 (0.8) | 1 (0.8) | 0 | 6 (3.0) |
| Non-compliant with protocol | 0 | 0 | 0 | 2 (1.6) | 0 | 1 (0.8) | 3 (1.5) |
| Lost to follow-up | 0 | 0 | 0 | 1 (0.8) | 0 | 0 | 1 (0.5) |
| Consent withdrawn | 0 | 0 | 0 | 0 | 2 (1.6) | 0 | 2 (1.0) |
| Other | 0 | 0 | 0 | 0 | 1 (0.8) | 1 (0.8) | 2 (1.0) |

source: Trial 1222.27 CSR; Table 10.1:2;pp 82

Reviewer Comment:

The protocol amendments are unlikely significantly affect data interpretation. The changes were reasonable. As this is crossover design, it is also unlikely that the protocol violations will affect data interpretation. The number of patients who discontinued was low and is unlikely to affect data interpretation.

Demographics

The patients in this trial were primarily 40-65 year old (66.2%, average age 45) white (99%) females (56.6%) who had never smoked. The average duration of asthma diagnosis was 20 years. At baseline average FEV1 was 73.2% predicted with a mean improvement of 23.7% following bronchodilation. Average FEV1/FVC ratio was 66 pre-bronchodilator and 72 post-bronchodilator. This summarized in Table 35.

Table 35. Trial 1222.26. Patient baseline characteristics

| Variable | Category | Total (N=198) |
|--------------------------|----------------|---------------|
| Sex [N (%)] | Male | 86 (43.4) |
| | Female | 112 (56.6) |
| Age [years] | Mean (SD) | 45.0 (11.8) |
| Age group [N (%)] | <40 years | 62 (31.3) |
| | 40 to 50 years | 62 (31.3) |
| | 51 to 65 years | 69 (34.8) |
| | >65 years | 5 (2.5) |
| Race [N (%)] | White | 196 (99.0) |
| | Asian | 2 (1.0) |
| Height [cm] | Mean (SD) | 170.2 (9.5) |
| Weight [kg] | Mean (SD) | 80.7 (15.5) |
| BMI [kg/m ²] | Mean (SD) | 27.9 (5.3) |
| Alcohol history [N (%)] | Non-drinker | 70 (35.4) |
| | Drinks | 128 (64.6) |
| Smoking history [N (%)] | Never smoked | 146 (73.7) |

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| | | |
|-------------------------|----------------|-------------|
| | Ex-smoker | 51 (25.8) |
| | Current smoker | 1 (0.5) |
| Asthma Duration [years] | Mean (SD) | 20.4 (13.2) |
| FEV1 [%predicted] | | |
| Baseline | Mean (SD) | 73 (8.3) |
| Post-Bronchodilator | Mean (SD) | 90 (10.4) |
| Response | Mean | 23.7 |

Source: Trial 1222.27 CSR; Tables 11.2.1:1, 11.2.2:1, 11.2.2:2; pp86-88

Compliance:

For all treatment period, compliance based on eDiary was high and was approximately 99% in all groups. Greater than 98% of patients were compliant with trial medication >80% of the time.

Reviewer Comment:

Patient demographic information and baseline spirometry data was typical for an asthma population. Compliance in this trial was very high and, as such, will not affect data interpretation.

Efficacy

Primary endpoint:

The primary endpoint was FEV1 AUC (0-24 hours) response after 4 weeks of treatment. Across all treatment groups, there was a statistically significant treatment effect compared to placebo ($p<0.0001$). Additionally, there was a clear dose response. The magnitude of the treatment effect was similar or greater than Foradil. These results are summarized in Table 36.

Table 36. Trial 1222.27. Primary endpoint. FEV1 AUC (0-24 hours) response after 4 weeks of treatment

| Treatment | N (total =198) | FEV1 AUC (0-24 hours) [L] Response (SE) | Difference from placebo (SE) |
|------------|-------------------|--|---------------------------------|
| Placebo | 122 | -0.004 (0.025) | |
| Olo 2 mcg | 119 | 0.135 (0.025) | 0.140 (0.022) |
| Olo 5 mcg | 126 | 0.178 (0.025) | 0.182 (0.021) |
| Olo 10 mcg | 121 | 0.201 (0.025) | 0.205 (0.022) |
| Olo 20 mcg | 119 | 0.225 (0.025) | 0.229 (0.022) |
| Foradil | 122 | 0.164 (0.025) | 0.169 (0.022) |

source: Trial 1222.27 CSR; Table 11.4.1.1:1; pp93

p-values all <0.0001

Secondary Endpoints

For the secondary endpoints of FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 4 weeks of treatment, all doses of olodaterol demonstrated a statistically significant difference from placebo. As with the primary endpoint, a dose response was

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noted both secondary endpoints. Trough FEV1 also demonstrated a similar pattern. For all doses, there was a statistically significant improvement compared to placebo. These results are summarized in Table 37.

Table 37. Trial 1222.27. Secondary endpoints. FEV AUC (0-12 hours), FEV1 (12-14), and trough FEV1 response after 4 weeks of treatment

| Treatment | Trough FEV [L] Response (SE) | Difference from placebo (SE) |
|------------|---------------------------------|---------------------------------|
| Placebo | 0.013 (0.026) | |
| Olo 2 mcg | 0.116 (0.026) | 0.103 (0.023) |
| Olo 5 mcg | 0.146 (0.026) | 0.133 (0.023) |
| Olo 10 mcg | 0.182 (0.026) | 0.169 (0.023) |
| Olo 20 mcg | 0.211 (0.026) | 0.199 (0.023) |
| Foradil | 0.115 (0.026) | 0.103 (0.023) |
| | FEV1 AUC (0-12 hours) [L] | |
| Placebo | -0.039 (0.026) | |
| Olo 2 mcg | 0.124 (0.026) | 0.163 (0.024) |
| Olo 5 mcg | 0.173 (0.026) | 0.212 (0.024) |
| Olo 10 mcg | 0.194 (0.026) | 0.233 (0.024) |
| Olo 20 mcg | 0.211 (0.026) | 0.250 (0.024) |
| Foradil | 0.145 (0.026) | 0.184 (0.024) |
| | FEV AUC (12-24 hours) [L] | |
| Placebo | 0.031 (0.026) | |
| Olo 2 mcg | 0.147 (0.026) | 0.115 (0.022) |
| Olo 5 mcg | 0.183 (0.025) | 0.151 (0.021) |
| Olo 10 mcg | 0.208 (0.026) | 0.177 (0.022) |
| Olo 20 mcg | 0.238 (0.026) | 0.207 (0.022) |
| Foradil | 0.183 (0.026) | 0.152 (0.022) |

Source: Trial 1222.27 CSR; Tables 11.4.1.1:1 &11.4.1.2.1:1; pp 93 & 97

For the secondary endpoint of peak FEV1 response within 24 hours of the last dose in each 4 week treatment period, all olodaterol doses demonstrated a statistically significantly improvement compared to placebo. For the Olo 2, 5, 10, 20mcg, and Foradil groups, the differences from placebo were (in liters) 0.102, 0.135, 0.161, 0.180, and 0.166, respectively. P-values were all less than 0.001. As with the other secondary endpoints, there was a clear dose response.

FVC related secondary endpoints included the analogous parameters as were used for FEV1. The results were similar, however with the FVC data, the dose response was not as evident. Select FVC related secondary endpoints are summarized in Table 38.

Table 38. Trial 1222.27. FVC AUC (0-24 hours) and trough FVC response after 4 weeks of treatment

| Treatment | FVC AUC (0-24) | Difference from placebo |
|-----------|----------------|-------------------------|
|-----------|----------------|-------------------------|

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| | hours) [L] | (SE) |
|------------|---------------------------------|---------------------------------|
| Placebo | -0.026 (0.028) | |
| Olo 2 mcg | 0.056 (0.028) | 0.082 (0.023) |
| Olo 5 mcg | 0.109 (0.028) | 0.136 (0.023) |
| Olo 10 mcg | 0.102 (0.028) | 0.128 (0.023) |
| Olo 20 mcg | 0.131 (0.028) | 0.157 (0.023) |
| Foradil | 0.070 (0.028) | 0.097 (0.023) |
| Treatment | Trough FVC [L] Response (SE) | Difference from placebo (SE) |
| Placebo | -0.022 (0.029) | |
| Olo 2 mcg | 0.015 (0.029) | 0.037 (0.026) |
| Olo 5 mcg | 0.069 (0.029) | 0.091 (0.025) |
| Olo 10 mcg | 0.088 (0.029) | 0.110 (0.025) |
| Olo 20 mcg | 0.107 (0.029) | 0.129 (0.026) |
| Foradil | 0.029 (0.029) | 0.051 (0.025) |

Source: Trial 1222.27 CSR; Table 11.4.1.2.1:3 and 11.4.1.2.1:4; pp100 and 102
all p-values <0.05

Results for FVC AUC (0-12 hours) and FVC AUC (12-24 hours) response were consistent with the FVC AUC (0-24 hours) response data.

Reviewer Comment:

The results for the primary and FEV1 related secondary endpoints were remarkably consistent. All doses demonstrated a statistically significant improvement compared to placebo. There was also a clear dose response. Additionally, the incremental benefit of olodaterol decreases with increasing doses. However, this was not as marked as in the COPD dose ranging trials.

Note that for the endpoints discussed below, the analysis did not correct for multiplicity.

With regard to rescue medication usage at week 4 of treatment, all olodaterol dose groups has less rescue medication use compared to placebo ($p<0.05$). The differences from placebo were marginal for the olodaterol doses and range between -0.656 to -0.398 puffs/day. The magnitude of the differences were modest ranging from 0.287-0.593 fewer doses of rescue medications/day. The treatment effect for the olodaterol doses were similar to Foradil.

The sponsor also analyzed change from baseline in ACQ total score compared to placebo after 4 weeks of therapy. For all doses, there was a statistically significant improvement compared to placebo ($p<0.05$) of which all were <0.5 . As such, the improvements are minimal and of questionable clinical significance.

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The sponsor also analyzed change from baseline in AQLQ(S). The change from baseline for all olodaterol groups was less than the MCID of 0.5, though the differences were statistically significant.

With regard to symptom free days, both olodaterol and Foradil groups had a higher percentage of symptom free days compared to placebo (placebo=18.5%, Foradil=23.7%, olodaterol doses=21-26%).

Reviewer Comments:

The differences from placebo for the non-spirometric endpoints were marginal at best, and do not give support to the efficacy of olodaterol.

Safety:

Exposure:

A total of 198 patients received at least one dose of study medication. The mean exposure per treatment period was approximately 30 days and was similar across all treatments. The overall mean exposure was 111.5 days out of a possible 113 days (29 days for treatment period 1 and 28 days for treatment periods 2-4).

Deaths and SAEs

There were no deaths reported in this trial. There were 2 SAEs reported. One patient experienced appendicitis while being treated with Olo 10mcg. One patient had a cerebral infarction that occurred 3 days after the last dose of trial drug. This patient had a history of hypercholesterolemia and previous infarct 3 years prior. This patient had received Foradil, Olo 20mcg, Olo 5mcg and Olo 2mcg.

Withdrawal due to AEs

Six patients withdrew prematurely due to AEs. Withdrawals occurred during the treatment period for all doses except Olo 20mcg. AEs leading to withdrawal included metrorrhagia in one placebo period patient; headache in one Olo 2mcg period patient; dizziness/headache/muscle spasms in one Olo 5mcg period patient; palpitations in another Olo 5mcg period patient; tooth in infection in one Olo 10mcg period patient; and hypertension in two other Olo 10mcg period patients.

Reviewer Comment:

Based on the patient narrative, it appears unlikely that the SAEs were treatment related. However some of the AEs that lead to discontinuation were likely related to olodaterol use (i.e. palpitation and hypertension).

TEAEs

In this trial TEAEs were defined as AEs that occurred after first dose in a treatment period until the day before the next treatment period. Overall, AE were more common during olodaterol treatment periods (10%-16%) compared to placebo periods (4.8%) or formoterol (6.4%). The most common AEs by SOC were infections and infestations,

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respiratory mediastinal and thoracic, and nervous system. By preferred term, the most common AEs were nasopharyngitis and dyspnea. This is summarized in Table 39.

Table 39. Trial 1222.27. Treatment Emergent AEs occurring during treatment periods (>1%)

| System organ class Preferred term | Placebo N (%) | Olodaterol 2 µg N (%) | Olodaterol 5 µg N (%) | Olodaterol 10 µg N (%) | Olodaterol 20 µg N (%) | Formoterol N (%) |
|--|------------------|-----------------------------|-----------------------------|------------------------------|------------------------------|---------------------|
| Number of patients | 125 (100.0) | 121 (100.0) | 130 (100.0) | 127 (100.0) | 124 (100.0) | 125 (100.0) |
| Patients with any AE | 6 (4.8) | 12 (9.9) | 18 (13.8) | 20 (15.7) | 16 (12.9) | 8 (6.4) |
| Infections and infestations | 1 (0.8) | 5 (4.1) | 4 (3.1) | 8 (6.3) | 4 (3.2) | 4 (3.2) |
| Nasopharyngitis | 0 | 4 (3.3) | 2 (1.5) | 3 (2.4) | 4 (3.2) | 3 (2.4) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.8) | 1 (0.8) | 3 (2.3) | 5 (3.9) | 2 (1.6) | 1 (0.8) |
| Dyspnoea | 0 | 0 | 0 | 2 (1.6) | 0 | 0 |
| Nervous system disorders | 1 (0.8) | 1 (0.8) | 2 (1.5) | 3 (2.4) | 4 (3.2) | 0 |
| Headache | 1 (0.8) | 1 (0.8) | 2 (1.5) | 3 (2.4) | 1 (0.8) | 0 |
| Musculoskeletal and connective tissue disorders | 0 | 2 (1.7) | 2 (1.5) | 2 (1.6) | 1 (0.8) | 0 |
| Skin and subcutaneous tissue disorders | 0 | 1 (0.8) | 0 | 1 (0.8) | 2 (1.6) | 1 (0.8) |
| Psychiatric disorders | 2 (1.6) | 1 (0.8) | 1 (0.8) | 0 | 1 (0.8) | 0 |
| Gastrointestinal disorders | 0 | 0 | 2 (1.5) | 1 (0.8) | 1 (0.8) | 0 |
| General disorders and administration site conditions | 0 | 0 | 2 (1.5) | 0 | 0 | 1 (0.8) |

source: Trial 1222.27 CSR; Table 12.2.2.1:1; pp119

Because there was no washout period between treatment periods, the sponsor also analyzed the safety data for AEs that occurred only during week 3 and 4 of the treatment periods. The findings were similar.

Reviewer Comment

Lack of a washout period between treatment periods potentially makes interpretation of the safety data difficult. However, based on the available data, there does appear to be clear imbalance in AEs when comparing olodaterol to placebo. There also appears to be a dose response AEs based on the nervous system disorders SOC.

Clinical Labs

Except for potassium, labs were drawn at baseline and at end of treatment period only. Based on shift table analysis, for uric acid and CK, shifts from normal to high occurred more frequently on the Foradil group (uric acid=10.3%, CK=23.1%) than when on placebo (uric acid=0%, CK=3.7%) or olodaterol. Otherwise, there were no notable changes in clinical lab values.

As olodaterol is a beta-agonist, serum potassium was assessed more frequently than other clinical labs. In addition to the standard assessments, levels were drawn 1 hour pre-dose and 1 and 3 hours post-dose at the end of each treatment period. One hour post-dose, for the 5, 10, and 20mcg olodaterol doses, there were statistically significant reductions in serum potassium levels compared to placebo ($p<0.05$). This was not the

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case when comparing Foradil to placebo. The decreases in the olodaterol groups were modest with a difference from placebo of approximately 0.1mmol/L. However, at 3 hours post-dose, there were no statistically significant differences in potassium levels when comparing olodaterol groups to placebo.

Vital Signs

The number of patients with changes in blood pressures or pulse rates were generally similar between treatment groups. However, the frequency of patient with a marked increase in SBP and DBP was higher in the olodaterol groups compared to placebo. With regard to pulse rate, the frequency of marked change was similar between groups. These findings are summarize in Table 40.

Table 40. Trial 1222.27. Blood pressure and pulse rate shift

| Number of patients (%) | Placebo (N=125) | Olo 2mcg (N=121) | Olo 5mcg (N=130) | Olo 10mcg (N=127) | Olo 20mcg (N=124) | Foradil (N=125) |
|------------------------|--------------------|---------------------|---------------------|----------------------|----------------------|--------------------|
| Systolic BP | | | | | | |
| Increase | 1 (0.8) | 4 (3.3) | 5 (3.9) | 7 (5.6) | 2 (1.6) | 4 (3.2) |
| Decrease | 1 (0.8) | 1 (0.8) | 3 (2.3) | 2 (1.6) | 2 (1.6) | 6 (4.8) |
| Diastolic BP | | | | | | |
| Increase | 4 (3.2) | 10 (8.3) | 6 (4.7) | 14 (11.2) | 7 (5.7) | 8 (6.5) |
| Decrease | 1 (0.8) | 0 | 1 (0.8) | 3 (2.4) | 0 | 1 (0.8) |
| Pulse rate | | | | | | |
| Increase | 1 (0.8) | 1 (0.8) | 2 (1.6) | 1 (0.8) | 0 | 0 |
| Decrease | 10 (8.1) | 8 (6.6) | 5 (3.9) | 3 (2.4) | 4 (3.3) | 6 (4.8) |

Source: Trial 1222.27 CSR; Table 12.5.1:1; pp126

ECG

ECGs were perform 30 minutes prior to dosing, and 40, 60 and 180 minutes after dosing during study visits. There were no notable changes on ECG for PR intervals or QRS intervals. However, for the QTcF interval, at the 10 and 20mcg doses, there was a mean increase from baseline. This increase was most notable at post-dose hour 1. The increase for the Olo 10mcg dose was 3.56msec and 4.23msec for the Olo 20mcg dose. Foradil did not appear to affect QTcF based on mean values. When analyzing the QTcF divided into categories (change from baseline <30msec, ≥30msec, or ≥60msec), more patients treated with olodaterol had QTcF interval changes of ≥30msec compared to placebo. There was no clear dose response, however at every time point except -30 minutes, QTcF increases of ≥30msec were more frequent for all olodaterol doses compared to placebo. In contrast, at only the 40 minute time point were QTcF increases ≥30msec more frequent for Foradil versus placebo. This data is summarized in Table 41.

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Table 41. Trial 1222.27. QTcF changes from baseline at the end of treatment

| Test day | Planned time | Placebo | Olo 2ug | Olo 5ug | Olo 10ug | Olo 20ug | Form 12ug |
|----------|--------------|---|--|--|--|--|--|
| 29 | -0:30 N | 125 (100.0) Change from baseline < 30 msec 122 (97.6) Change from baseline >= 30 msec 3 (2.4) Change from baseline >= 60 msec 0 (0.0) | 120 (100.0) 113 (94.2) 7 (5.8) 0 (0.0) | 128 (100.0) 124 (96.9) 4 (3.1) 0 (0.0) | 125 (100.0) 122 (97.6) 3 (2.4) 0 (0.0) | 122 (100.0) 120 (98.4) 2 (1.6) 0 (0.0) | 125 (100.0) 123 (98.4) 2 (1.6) 0 (0.0) |
| | 0:40 N | 123 (100.0) Change from baseline < 30 msec 121 (98.4) Change from baseline >= 30 msec 2 (1.6) Change from baseline >= 60 msec 0 (0.0) | 120 (100.0) 115 (95.8) 5 (4.2) 0 (0.0) | 128 (100.0) 125 (97.7) 3 (2.3) 0 (0.0) | 122 (100.0) 117 (95.9) 5 (4.1) 0 (0.0) | 117 (100.0) 113 (96.6) 4 (3.4) 0 (0.0) | 123 (100.0) 117 (95.1) 6 (4.9) 0 (0.0) |
| | 1:00 N | 123 (100.0) Change from baseline < 30 msec 120 (97.6) Change from baseline >= 30 msec 3 (2.4) Change from baseline >= 60 msec 0 (0.0) | 118 (100.0) 115 (97.5) 3 (2.5) 0 (0.0) | 128 (100.0) 124 (96.9) 4 (3.1) 0 (0.0) | 122 (100.0) 116 (95.1) 6 (4.9) 0 (0.0) | 120 (100.0) 116 (96.7) 4 (3.3) 0 (0.0) | 123 (100.0) 121 (98.4) 2 (1.6) 0 (0.0) |
| | 3:00 N | 123 (100.0) Change from baseline < 30 msec 119 (96.7) Change from baseline >= 30 msec 4 (3.3) Change from baseline >= 60 msec 0 (0.0) | 118 (100.0) 110 (93.2) 7 (5.9) 1 (0.8) | 127 (100.0) 122 (96.1) 5 (3.9) 0 (0.0) | 121 (100.0) 116 (95.9) 5 (4.1) 0 (0.0) | 119 (100.0) 114 (95.8) 5 (4.2) 0 (0.0) | 122 (100.0) 118 (96.7) 4 (3.3) 0 (0.0) |

source: Trial 1222.27 CSR; Table 15.3.4.2.2-5; pp498

Reviewer Comment

With regard to clinical labs, the effect of olodaterol compared to placebo was minimal. With regard to vital signs, as with the trial 1222.6, marked increases in SBP and DBP were clearly more frequent in olodaterol groups. However, no dose response was evident. For QTcF, there were only minimal changes based on mean values. However, when comparing the percentage of patients who had increases of ≥30msec, although the percentage were low, increases were more frequent in the olodaterol groups compared to placebo. This is similar to what was seen in trial 1222.6, however, the effect was more prominent in this trial. It is possible that this is related to a cumulative dose effect as this was a crossover trial without washout periods. ECG data from the combined data sets will be closely scrutinized for QTc prolongation and related AEs.

Overall Comments:

The efficacy results from this trial were remarkably consistent across endpoints. All doses of olodaterol demonstrated a clear bronchodilator effect compared to placebo, and there was a clear dose effect. As with this COPD dose ranging trials, the incremental benefit appeared to decrease with increasing doses. However, this phenomenon was not as clear in this asthma trial compared to the COPD trial. With regard to AEs olodaterol was fairly well tolerated, however, it is of concern that several patients withdrew due to AEs that could have potentially been related to olodaterol. Additionally, there was an obvious imbalance when comparing overall common TEAEs between placebo and olodaterol dose groups, and for the nervous system disorder SOC, there was a dose effect. However, as there was no washout period between treatment periods, interpretation of safety data is difficult.

5.3.7 Trial 1222.29 (Asthma)

Administrative Information

- **Study title:** Randomized, Double-Blind, Cross-over Study to Compare the 24-hour FEV1-time Profile of Orally Inhaled Olodaterol, delivered with the Respimat Inhaler, after 3 Weeks of Olodaterol Once Daily 5mcg, Twice Daily

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2.5mcg and Placebo or after 3 Weeks of Olodaterol Once Daily 10mcg, Twice Daily 5mcg and Placebo Administration in Patients with Moderate to Severe Persistent Asthma

- **Study dates:** 3/7/2011-12/19/2011
- **Study sites:** Austria (4 sites), Germany (10 sites), Hungary (4 sites), Slovakia (4 sites), Slovenia (2 sites), and U.S. (12 sites)
- **Study report date:** 4/4/2012

Objectives/Rationale

- To compare the 24-hour FEV1 profile of olodaterol versus placebo after 3 weeks of treatment with Olo 2.5mcg BID, Olo 5mcg qD, Olo 5mcg BID, Olo 10mcg qD, or placebo.
- To conduct an exploratory comparison between active treatments.

Study Design and Conduct

Overview

This was a 17 week, multi-center, randomized, double-blind, placebo controlled, trial including two parallel 3-way crossovers in patient with moderate to severe persistent asthma. Following the screening period, patients were randomized to receive a treatment sequence consisting of 3 week treatment periods with Olo 2.5mcg BID, Olo 5mcg qD, and placebo; or Olo 5mcg BID, Olo 10mcg qD, and placebo. There were a total of 12 possible treatment sequences. Between each 3 week treatment period, there was a 2 week washout period.

This trial consisted on 8 trial visits. At visit 1a (week), informed consent was obtained and medication washout began. At visit 1b, medication washout compliance was verified and baseline data was collected. Pre- and post-bronchodilator spirometry was also performed. Patients were also given an AM3 device for use as an eDiary. Following visit 1a, the baseline period began and lasted 2 weeks. During this time patients recorded their PEFR, asthma symptoms, and medication use. At visit 2 (week 0), the treatment period began. Eligible patients were randomized to a treatment sequence and trial medication was dispensed. Following randomization, patients were seen in clinic at weeks 3, 5, 8, 10, and 13 (visits 3, 4, 5, 6, and 7, respectively). At visits 4 (week 5) and 6 (week 10), trial medication was dispensed. During trial visits 3, 5, and 7, 24-hour post-dose spirometry was performed, in addition to other safety and efficacy assessments. The assessments at visits 2, 4, and 6 were similar, however did not include 24-hour spirometry. The assessment schedule is summarized in Table 42.

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Table 42. Trial 1222.29. Assessment schedule

| Visit | 1a | 1b | 2 | 2T | 3 | 4 | 4T | 5 | 6 | 6T | 7 ¹⁷ | 8 |
|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------|--------------------|--------------------|
| Week | -2 | 0 | 2 | 3 | 5 | 7 | 8 | 10 | 12 | 13 | 15 | |
| Day | ≥ -16 | -14 | 1 +14 | 11 ±2 | 22/23 +4 | 36 ±2 | 46 ±2 | 57/58 +4 | 71 ±2 | 81 +2 | 92/93 +4 | 106 +4 |
| Informed consent | X ² | | | | | | | | | | | |
| Pharmacogenetic | | X ³ | | | | | | | | | | |
| ACQ | X | X | | X | | | X | | | X | X | |
| Medication washout compliance check | X | X | | X | X | | X | X | | X | | |
| Demographics | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Collect and review e-diary | | | X ¹⁴ | | X ¹⁴ | X ¹⁴ | | X ¹⁴ | X ¹⁴ | | X ^{14,15} | X ¹⁴ |
| Review in-/exclusion criteria | X | X | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | X ¹⁵ | X ¹⁵ |
| 12-lead ECG ¹¹ | X | X | | X | X | | X | X | | | X ¹⁵ | X ¹⁵ |
| Vital signs (seated) | X ¹⁰ | X ¹⁰ | | X ¹⁰ | X ¹⁰ | | X ¹⁰ | X ¹⁰ | | | X ^{10,15} | X ¹⁵ |
| Laboratory test (including urinalysis) ³ | X ¹³ | | | X ¹³ | | | X ¹³ | | | | X ^{13,15} | X ^{13,15} |
| Pregnancy test ⁴ | X | X | | X | X | | X | X | | | X ¹⁵ | X |
| Randomisation | X | | | | | | | | | | | |
| Medication compliance check | | | | X | X | X | X | X | X | X | | |
| Pulmonary Function Testing ⁸ | X | X | | X | X | | X | X | | | X ¹⁵ | X |
| Reversibility Testing ⁹ | X | | | | | | | | | | | |
| Administer trial medication | | X | | X | X | | X | X | | X | | |
| Collect investigational product | | | | X | | | X | | | | X ¹⁵ | |
| Issue Peak Flow Meter / e-diary | X ¹⁶ | X | | X | X | | X | X | | | X ¹⁵ | |
| Dispense investigational product | | X | | | X | | | X | | | | |
| Dispense rescue medication | X | X | X | | X | X | | X | X | | X ¹⁵ | |
| Telephone contact to patient | | | X | | | X | | | X | | | |
| Training in use of inhalers | X | X ¹ | | X ¹ | X ¹ | | X ¹ | X ¹ | | | X ¹ | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X ¹⁵ | X |
| Concomitant therapy | X | X | X | X | X | X | X | X | X | X | X ¹⁵ | X |
| Drug accountability | X | X | | X | X | | X | X | | | X ¹⁵ | X |
| Trial medication termination | | | | X | | | X | | | | X ¹⁵ | |
| Conclude patient participation | | | | | | | | | | | X ² | |

¹ All patients signed an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication wash-out and restrictions. A separate consent for pharmacogenetic sampling was signed if patients were participating in the pharmacogenetic substudy.

² Patients were contacted 10 days after dispensation of investigational product to collect safety information and 1 day prior to Visits 3, 5 and 7 to ensure correct investigational product administration and compliance.

³ One additional blood sample was required for genotype analysis at Visit 2 or any later visit in those patients who consented to pharmacogenetic sampling.

⁴ Completed on all patients of childbearing potential. A serum β-HCG test was performed at Visit 1b. A urine pregnancy test was performed prior to trial medication administration at Visits 2 to 7 and at follow-up (Visit 8).

⁵ Completed whenever trial participation ended (including discontinued patients).

⁶ At Visit 2, investigational product administered in fixed sequence (1. from Respimat® 2, ICS) between 07:00 and 9:00. At Visits 3, 5 and 7 investigational product administered within ±30 min of the time of investigational product administration at Visit 2 AND between 07:00-9:00 a.m. and after 12 h (± 5 min) p.m. on the first day of the visit. The posology (b.i.d./q.d. a.m./q.d. p.m.) of the ICS remained the same as the patient's previous use. See chart below for timings.

⁷ The patient was not to inhale from the Respimat® training inhalers at Visits 2, 3, 4, 5, 6 and 7.

⁸ Visit 1b PFTs performed prior to and after reversibility testing; Visit 2, 4, 6: PFTs performed at 1h and 10 min pre-dose and 3 h post dose (a.m.); at Visits 3, 5 and 7 at 1h and at 10 min pre-dose and up to 24 h post dose (a.m.). See chart below for timings. At Visit 8, one PFT was performed. Visits 3, 5, 7 required the patient generally to remain in the clinic for an overnight stay in order to complete the 24 h PFTs.

⁹ Reversibility testing using 4 puffs salbutamol/albuterol (100 µg per actuation).

¹⁰ Vital signs measured in all patients at Screening Visit (Visit 1b), Visits 2 to 7 and 8 and at the withdrawal visit if the patient did not complete all study visits. See chart below for timings.

¹¹ 12-lead ECGs were performed at Visit 1b to 7 and at Visit 8 if findings at Visit 7, and at the withdrawal visit if the patient did not complete all study visits (see chart below for timings).

¹² Performed if clinically relevant findings at Visit 7 or clinically relevant findings at premature withdrawal Visit.

¹³ Samples taken prior to inhalation of morning pulmonary medication

¹⁴ e-diary compliance check

¹⁵ Performed following premature withdrawal of a patient. A single PFT was performed.

¹⁶ Training for Peak Flow Meter / e-diary (AM3 device) at Visit 1b.

¹⁷ Or premature withdrawal visit (excluding 24-h lung function measurements and accompanying investigations)

Source: Trial 1222.29 CSR; Table 9.5.8.1; pp61

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The specific assessment schedules for visit 2-7 are summarized in Table 43.

Table 43. Trial 1222.29. Assessment schedule on visits 2 through 7

| Procedures on Visits 2-7 | | -1h | -10' | 0 | 30' | 1h | 2h | 3h |
|---|----------------|-----|------|----------------|-----|----|----|----|
| ACQ | X ¹ | | | | | | | |
| Administer trial medication | | | | X ⁶ | | | | |
| Administer ICS | | | | X ⁵ | | | | |
| 12-lead ECG | X | | | | | | | |
| Vital signs ² | X | X | | X | X | X | X | |
| Physical examination | X ³ | | | | | | | |
| Safety laboratory testing | X ³ | | | | | | | |
| Urine pregnancy test | X | | | | | | | |
| Pulmonary function testing ⁴ | X | X | | X | X | X | X | |
| AM3® * measurement | | | | | | | | |

¹ First procedure undertaken on arrival at clinic

² Completed immediately prior to PFTs with patient sitting for 5 min

³ Completed prior to inhalation of medication (a.m.) at Visit 3, 5 and 7; physical examination only at Visit 7.

⁴ FEV₁, FVC and PEF completed using the MasterScope®.

⁵ From patient's own ICS (immediately after Respimat® inhalation)

⁶ Administration of medication in fixed sequence (1. Inhalation from Respimat® followed immediately by ICS if applicable)

Additional procedures on Visits 3, 5, and 7

| | 4h | 6h | 8h | 10h | Between 11h and 11h 30' | 11h50' | 12h | 12h30' | 13h | 14h | 22h | 23h | Between 23h and 23h 30' | 23h50' |
|---|----|----|----|-----|-------------------------|----------------|-----|--------|-----|-----|-----|-----|-------------------------|--------|
| Administer trial medication | | | | | | X ³ | | | | | | | | |
| Administer ICS | | | | | | X ² | | | | | | | | |
| Pulmonary function testing ¹ | X | X | X | X | | X | | X | X | X | X | | | X |
| AM3® measurement | | | | | X | | | | | | | | X | |

¹ FEV₁, FVC and PEF completed using the MasterScope®.

² From patient's own ICS (immediately after Respimat® inhalation)

³ Administration of medication was in fixed sequence (inhalation from Respimat® followed immediately by ICS if applicable)

Source: Trial 1222.29 CSR; Tables 9.5.8:2 and 9.5.8:3; pp63

Study Population

Key Inclusion Criteria

1. 18-70 years of age
2. Diagnosis of asthma per GINA guidelines at least 3 month prior to visit 1b.

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3. Pre-bronchodilator FEV1 ≥60% predicted and <90% at visit 1b.
4. Reversibility following bronchodilator treatment defined as a ≥12% increase in FEV1 and 200mL within 15 minutes of salbutamol treatment (performed at visit 1).
5. Patients must have been taking ICS for at least 12 weeks prior to screening and must have been receiving a stable medium to high dose or a low to high dose ICS+LABA for at least 6 weeks prior to visit 1b.
6. Current non-smokers or ex-smokers with a <10 year pack history.

Key Exclusion Criteria

1. Significant disease other than asthma
2. Patient who has been hospitalized for an asthma exacerbation within the past 3 months or had an admission to an intensive care unit for asthma within 3 years of visit 1
3. Clinically relevant abnormal baseline labs
4. Patient with significant disease other than COPD.
5. Clinical relevant abnormal baseline lab values
6. Patients with a history of myocardial infarction within 1 year of visit 1b, a diagnosis of clinical relevant cardiac arrhythmia, active tuberculosis, clinically evident bronchiectasis, a history of cor pulmonale, Cystic Fibrosis, or a history of life threatening pulmonary obstruction.
7. Patients who have undergone thoracotomy with pulmonary resection.
8. Patients being treated with medication that prolong QT/QTc interval, oral beta-adrenergics, beta-blockers, or oral steroids at unstable doses (<6 weeks on a stable dose or at doses >10mg of prednisone per day or 20mg every other day).
9. A diagnosis of paroxysmal tachycardia or hyperthyroidism
10. Baseline prolongation of QT/QTc interval.
11. A history fo additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalemia, family history of long QT).
12. Women of childbearing potential not using a highly effective method of birth control (<1% failure rate).
 - Patients being treated with any of the following concomitant medications:
 - long acting beta-agonists (LABAs) within 48 hours prior to screening
 - oral or other systemic corticosteroids in the 6 weeks prior to screening
 - Anti-IgE antibodies (e.g. omalizumab) for 6 months prior to screening
 - medications that prolong the QT/QTc interval
 - oral β-adrenergics for 6 weeks prior to screening
 - β-blockers (topical β -blockers for ocular conditions are allowed)
 - Methylxanthines and antileukotrienes in the 6 weeks prior to screening
 - Short-acting anticholinergics (inhalation aerosol and nasal spray) including fixed dose anticholinergic/ β adrenergics (e.g. Combivent/ Berodual) within 8 hours prior to screening
 - Long-acting anticholinergics (e.g. Tiotropium) in the 6 weeks prior to screening
13. Patients with frequent seasonal exacerbations of asthma (defined as one or more seasonal exacerbations every year for the past three years)

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14. Patients with any asthma exacerbation or respiratory tract infection in the four weeks prior to the Screening Visit (Visit 1b) or in the 3 weeks prior to visit 2.

Key Removal Criteria:

1. The patient experiences an asthma exacerbation requiring an overnight hospitalization
2. Drop in FEV1 below 40% predicted
3. Prolongation of QT or QTc after randomization
4. Administrative reasons such as protocol violations and non-compliance
5. If any exclusion criteria was met during the course of the trial.

Treatments:

Olodaterol 2.5mcg twice daily (2 actuations of 1.25mcg/actuation)

Olodaterol 5mcg once daily (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg once daily (2 actuations of 5mcg/actuation)

Olodaterol 5mcg twice daily (2 actuations of 2.5mcg/actuation)

Placebo

All treatments will be delivered via a Respimat device.

Concomitant/restricted medications

All medication used within 3 months preceding the screening visit and throughout the trial was recorded in the eCRF. Patients were allowed to use albuterol as rescue medication, however if albuterol was required during PFTs, the PFTs could have been discontinued at the discretion of the investigator. For exacerbations, patients were allowed to take any medication deemed necessary by the treating physician. Other concomitant medications were restricted as summarized in Table 44.

Table 44. Trial 1222.29 Restricted and prohibited medications

| Drug Class | Sub-Class | Prior to study | Study Period | | |
|--------------------------|---|---|-----------------|------------------|------------------|
| | | | Baseline period | Treatment period | Follow up period |
| Corticosteroids | ICS | REQUIRED Patients must have been taking ICS for at least 12 weeks prior to screening, and must have been receiving a stable dose for at least 6 weeks prior to screening | REQUIRED | REQUIRED | REQUIRED |
| | Oral corticosteroids | not permitted* | not permitted. | not permitted | not permitted |
| Other asthma controllers | Combination ICS/LABA (e.g. Advair/Seretide; | not permitted. Fixed dose combination LABA/ICS should be split | not permitted | not permitted | permitted |

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| | | | | | |
|-----------------------------------|---|---|---|---|---|
| | Symbicort) | into the equivalent monotherapy once the patient has enrolled but at least 48 hours prior to Visit 1. | | | |
| | Cromolyn sodium / nedocromil sodium | permitted | permitted | permitted | permitted |
| | Antihistamines | permitted | permitted | permitted | permitted |
| | Antileukotrienes | not permitted* | not permitted | not permitted | not permitted |
| | Methylxanthines | not permitted* | not permitted | not permitted | not permitted |
| Beta-adrenergics Beta-blockers | Inhaled SABA | permitted | Rescue (prior to all visits at least an 8-hour washout) | Rescue (prior to all visits at least an 8-hour washout) | Rescue (prior to all visits at least an 8-hour washout) |
| | Inhaled LABA | not permitted 48 hour prior to screening | not permitted | Study medication | permitted |
| | Oral beta-adrenergics | not permitted* | not permitted | not permitted | not permitted |
| | Beta blockers | not permitted* | not permitted | not permitted | not permitted |
| Anticholinergic | Short-acting anticholinergics including fixed dose anticholinergic/ β adrenergics | permitted | not permitted. At least 8 hour washout prior to Visit 1b. | not permitted | not permitted |
| | Long-acting anticholinergics | not permitted* | not permitted | not permitted | not permitted |
| Miscellaneous | Regular Anti-IgE treatment (e.g. Omalizumab) | not permitted* | not permitted | not permitted | not permitted |
| | Mucolytics | permitted | permitted | permitted | permitted |
| | Immunotherapy (desensitization) | not permitted if started within last 2 years and are not on stable dose | not permitted | not permitted | not permitted |

Source: Trial 1222.29 protocol and amendments (U12-1132-01), Table 4.2.2.1:1; pp154

* not permitted from 6 weeks prior to screening

Reviewer Comment:

The overall trial design, inclusion/exclusion criteria, and restricted medications are reasonable for a dose ranging trial in asthmatics.

Efficacy Parameters

Primary Endpoint

The primary endpoint for this trial was FEV1 AUC (0-24 hours) response after 3 weeks of treatment. The FEV1 AUC (0-24 hours) response was calculated as the FEV1 AUC (0-24 hours) minus baseline FEV1. Baseline FEV1 was determined at visit 2.

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Key Secondary Endpoints

The key secondary efficacy endpoints were FEV1 AUC (0-12 hours) and FEV AUC (12-24 hours) response after 3 weeks of treatment.

Other secondary endpoints included the following:

1. PEFR at the end of each dosing interval measured by patients at home using the AM3.
2. Peak FEV1 (L) (within 24 hours post-dose) measured following the morning trial-drug inhalation at the end of each 3 week treatment period.
3. Trough FEV1 (L) at the end of each 3 week treatment period. Trough FEV1 is defined as the mean of the two FEV1 values (performed at 1 hour and 10 minutes prior to the evening trial-drug inhalation) at the end of the dosing interval.
4. Trough forced vital capacity (FVC) (L) at the end of each dosing interval (as defined above for FEV1) determined at the end of each 3 week treatment period.
5. FVC (AUC0-12h) and FVC (AUC12-24h) response and peak FVC (L) (within 24 hours post dose) measured following each dosing determined at the end of each 3 week treatment period.
6. PEFR AUC (0-12 hours), PEFR AUC (12-24 hours), and PEFR AUC (0-24 hours) response and peak PEFR (within 24 hours post dose) measured following each dosing determined at the end of each 3 week treatment period.
7. Individual FEV1, FVC (L) and PEFR measurements
8. Use of rescue medication during the entire study period
9. Asthma Control Questionnaire (ACQ) at the end each period of treatment
10. FEV1 (L): mean pre-dose morning and evening FEV1 measured by patients at home as measured using the AM3 device during the entire study period.
11. Weekly mean number of night time awakenings as assessed by the patient's electronic diary.
12. Asthma symptoms and quality of life as assessed by the patient's electronic diary.

Safety Parameters:

The monitored safety parameters include AEs, vital signs, clinical labs, and ECGs. These were assessed as per Table 42 and Table 43. Note that abbreviated lab testing included serum potassium.

Compliance:

Treatment compliance was assessed using the eDiary entries and returned medications

Reviewer Comment:

The primary endpoint is typical and appropriate for an asthma dose ranging trial. The secondary endpoints are also generally appropriate. The safety and compliance parameters are appropriate.

Ethics:

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This study was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this study protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

Based on BI's previous experience, the standard deviation for pair differences in FEV1 AUC (0-24 hours) was estimated to be 250mL. Based on this, BI estimated that a sample size of 180 patients would yield 95% power to detect a 100mL difference from placebo assuming a paired t-test with a 2.5% one-sided significance level. This projected sample size took into account the crossover design of this trial.

Missing Data

If there was only a one pre-dose spirometric value at a visit, then baseline was defined as that value. If both pre-dose values were missing, then baseline remained missing.

Post-dose data missing due to worsening symptoms were replaced with the least favorable non-missing data recorded during the same visit. Post-dose data missing at random was either linearly interpolated if the preceding and subsequent data point was available or was imputed using last observation carried forward. If a patient discontinued or was excluded from the trial due to worsening of symptoms such that there were not 4 week measurements, data will be imputed from the patients least favorable non-missing data.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients with baseline data and evaluable post-dosing data following at least 5 days of randomized treatment for at least one endpoint. The per protocol (PP) data set that consisted of all FAS minus patients with important protocol deviations. The safety population was made up of all treated patients.

Efficacy Analysis

Analysis of the primary endpoint occurred in a step-wise fashion to control for type 1 error. The first comparison was between Olo 10mcg qD and placebo. If that difference were to be statistically significant, then 5mcg BID was to be compared to placebo, followed by 5mcg qD to placebo, and 2.5mcg BID to placebo. If a dose did not demonstrate a statistically significant difference from placebo (one-side p-values 2.5%), subsequent analysis of lower doses would continue, however, would be considered exploratory. Analysis was performed on the FAS.

Provided that all doses demonstrated a statistically significant improvement compared to placebo for the primary endpoint, then the key secondary endpoints would be

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analyzed in a similar manner. For each dose, the FEV1 AUC (0-12 hours) response was analyzed first, followed by FEV AUC (12-24 hours) response.

Comparisons between once daily and twice daily dosing were performed in a descriptive manner.

Safety Analysis

All safety data was analyzed in a descriptive manner.

Results

Amendments:

After initial submission of this protocol, there were 1 amendment submitted on 2/4/2011. The amendment correct typographical errors, as well as added changed inclusion/exclusion criteria to allow for patients on allergen desensitization therapy if started within 2 years, and on a stable dose.

Protocol Violations:

Of the total randomized patients (206), 30 patients were identified as having important protocol violations. Of these, 11 patient violations related to inclusion criteria violations, 7 were related to timing deviations in PFT performance, 9 were related to non-compliance, and 1 was related to exclusion criteria violation.

Disposition

A total of 279 patients enrolled in this trial and 206 patients were randomized. The most common reason for non-randomization was inclusion/exclusion criteria. Of the 206 patients, 199 (96.6%) patients completed the planned treatment in all 3 treatment periods. Seven (7) patients discontinued prematurely; 1 in the placebo group, 1 in the Olo 5mcg BID group, 1 in the Olo 10mcg qD group, 2 in the Olo 2.5mcg BID group, and 2 in the Olo 5mcg qD group. The reasons for discontinuation were non-compliance (3 patients), withdrawal of consent (2 patients) and adverse events (2 patients). Four patients were excluded from the FAS analysis, as they lacked baseline primary endpoint data.

Reviewer Comment:

The protocol amendments are unlikely to significantly affect data interpretation. The changes were reasonable. The percentage of patients with important protocol violations was similar to previous trials. It is possible that the inclusion of these patients in the FAS could affect results, however the sponsor also performed a sensitivity analysis using the PP population. The number of patients who discontinued in this trial was low and is unlikely to affect data interpretation.

Demographics

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The patients in this trial were primarily <40 year old (35.4%) white (92.7%) females (69.9%) who had never smoked. The average duration of asthma diagnosis was 24.7 years. At baseline average FEV1 was 73.1% predicted with a mean improvement of 18% following bronchodilation. Average FEV1/FVC ratio was 66.3 pre-bronchodilator and 72 post-bronchodilator. This is summarized in Table 45.

Table 45. Trial 1222.29. Patient baseline characteristics

| Variable | Category | Total (N=198) |
|--------------------------|------------------------|---------------|
| Sex [N (%)] | Male | 97 (47.1) |
| | Female | 109 (52.9) |
| Age [years] | Mean (SD) | 43.7 (12.2) |
| Age group [N (%)] | <40 years | 73 (35.4) |
| | 40 to 50 years | 66 (32.0) |
| | 51 to 65 years | 60 (29.1) |
| | >65 years | 7 (3.4) |
| Race [N (%)] | White | 191 (92.7) |
| | Black/African American | 15 (7.3) |
| Height [cm] | Mean (SD) | 171.8 (9.2) |
| Weight [kg] | Mean (SD) | 83.1 (16.7) |
| BMI [kg/m ²] | Mean (SD) | 28.2 (5.7) |
| Alcohol history [N (%)] | Non-drinker | 65 (31.6) |
| | Drinks | 141 (68.4) |
| Smoking history [N (%)] | Never smoked | 144 (69.9) |
| | Ex-smoker | 62 (30.1) |
| Asthma Duration [years] | Mean (SD) | 24.7 (14.6) |
| FEV1 [%predicted] | Baseline | 73.1 (7.9) |
| | Post-Bronchodilator | 89.2 (11.7) |
| | Response | 18 |

Source: Trial 1222.29 CSR; Tables 11.2.1:1, 11.2.2:1, 11.2.2:2; pp82-84

Compliance:

For all treatment period, compliance based on eDiary was high and was approximately 99% in all groups. Greater than 98% of patients were compliant with trial medication >80% of the time.

Reviewer Comment:

The baseline demographics and spirometry data is typical for asthmatic patients. The compliance in this trial was very high.

Efficacy

Primary endpoint:

The primary endpoint was FEV1 AUC (0-24 hours) response after 3 weeks of treatment. Across all treatment groups, there was a statistically significant treatment effect

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compared to placebo ($p<0.0001$). These results are summarized in Table 46. When the sponsor analyzed the primary endpoint in the PP population, the results were essentially the same. In addition, the 10mcg total daily dose (TDD) groups also demonstrated a greater difference from placebo than the 5mcg TDD groups. When comparing qD and BID regimens with the same TDD, the BID dose interval demonstrated a greater FEV1 AUC (0-24 hours) response compared to placebo versus the qD dose interval. However, in the sponsors exploratory analyses, there was no statistically significant difference between qD and BID dose regimens provided that the TDDs were the same.

Key Secondary Endpoints:

The key secondary endpoints were FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 3 weeks of treatment. As with the primary endpoint, for both key secondary endpoints, all olodaterol groups demonstrated a statistically significant treatment effect compared to placebo ($p<0.0001$). Additionally, the 10mcg TDD groups had a numerically greater treatment effect compared to the 5mcg TDD. These results are summarized in Table 46.

Table 46. Trial 1222.29. Primary and key secondary endpoints

| Interval | Treatment Group | FEV1 AUC response (interval) | Difference from placebo |
|-------------|-----------------|------------------------------|-------------------------|
| 0-24 hours | Placebo | 0.022 (0.020) | |
| | Olo 2.5 mcg BID | 0.213 (0.024) | 0.191 (0.020) |
| | Olo 5 mcg qD | 0.173 (0.024) | 0.150 (0.020) |
| | Olo 5 mcg BID | 0.250 (0.024) | 0.228 (0.020) |
| | Olo 10 mcg qD | 0.231 (0.024) | 0.209 (0.020) |
| 0-12 hours | Placebo | 0.052 (0.020) | |
| | Olo 2.5 mcg BID | 0.242 (0.024) | 0.190 (0.020) |
| | Olo 5 mcg qD | 0.212 (0.024) | 0.160 (0.020) |
| | Olo 5 mcg BID | 0.266 (0.024) | 0.214 (0.020) |
| | Olo 10 mcg qD | 0.272 (0.024) | 0.219 (0.020) |
| 12-24 hours | Placebo | -0.010 (0.020) | |
| | Olo 2.5 mcg BID | 0.186 (0.025) | 0.196 (0.022) |
| | Olo 5 mcg qD | 0.135 (0.025) | 0.144 (0.022) |
| | Olo 5 mcg BID | 0.233 (0.025) | 0.242 (0.022) |
| | Olo 10 mcg qD | 0.189 (0.025) | 0.198 (0.022) |

Source: Trial 1222.29 CSR; Tables 11.4.1.1:1, 11.4.1.2:1:pp 88 and 92

p-values all <0.0001

Reviewer Comment:

Based on the primary and key secondary endpoints, olodatral at all dose regimens has demonstrated a bronchodilatory effect. This results is consistent with previous dose ranging trials. Additionally, the BID dosing appears to have a greater treatment effect

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compared to the qD dosing when the TDD is held constant. This finding differs from the COPD dose interval trial 1222.26, where the differences between BID and qD dosing was marginal.

Other Secondary Endpoints

This trial also evaluated multiple other spirometric endpoints, including measurements taken at home using the AM3 device. Results from at home or unsupervised spirometry are not reviewed.

For the secondary endpoints of peak FEV1 response and trough FEV1 response all doses of olodaterol demonstrated statistically significant differences from placebo (p-values<0.0001). For peak FEV1 response, the differences from placebo (in liters) ranged between 0.153 to 0.222 liters. Both peak and trough responses were higher for the BID versus qD regimens when the TDDs were equivalent. These data are summarized in Table 47.

Table 47. Trial 1222.29. Peak FEV1 and trough FEV1 response after 3 weeks of treatment

| | Treatment Group | FEV1 response [L] Mean (SE) | Difference from placebo [L] |
|-------------------------|-----------------|--------------------------------|--------------------------------|
| Peak FEV1 response | Placebo | 0.227 (0.021) | |
| | Olo 2.5 mcg BID | 0.410 (0.027) | 0.183 (0.023) |
| | Olo 5 mcg qD | 0.380 (0.027) | 0.153 (0.023) |
| | Olo 5 mcg BID | 0.449 (0.027) | 0.222 (0.023) |
| | Olo 10 mcg qD | 0.437 (0.026) | 0.210 (0.023) |
| Trough FEV1 response | Placebo | 0.033 (0.022) | |
| | Olo 2.5 mcg BID | 0.189 (0.027) | 0.156 (0.024) |
| | Olo 5 mcg qD | 0.134 (0.027) | 0.101 (0.024) |
| | Olo 5 mcg BID | 0.229 (0.027) | 0.196 (0.024) |
| | Olo 10 mcg qD | 0.205 (0.027) | 0.172 (0.024) |

source: Trial 1222.29 CSR; Table 11.4.1.2.1:2; pp94

p-values all <0.0001

These data are summarize graphically in Figure 9, where individual pre- and post-dose FEV1 measurements taken after 3 weeks of treatment were plotted against time.

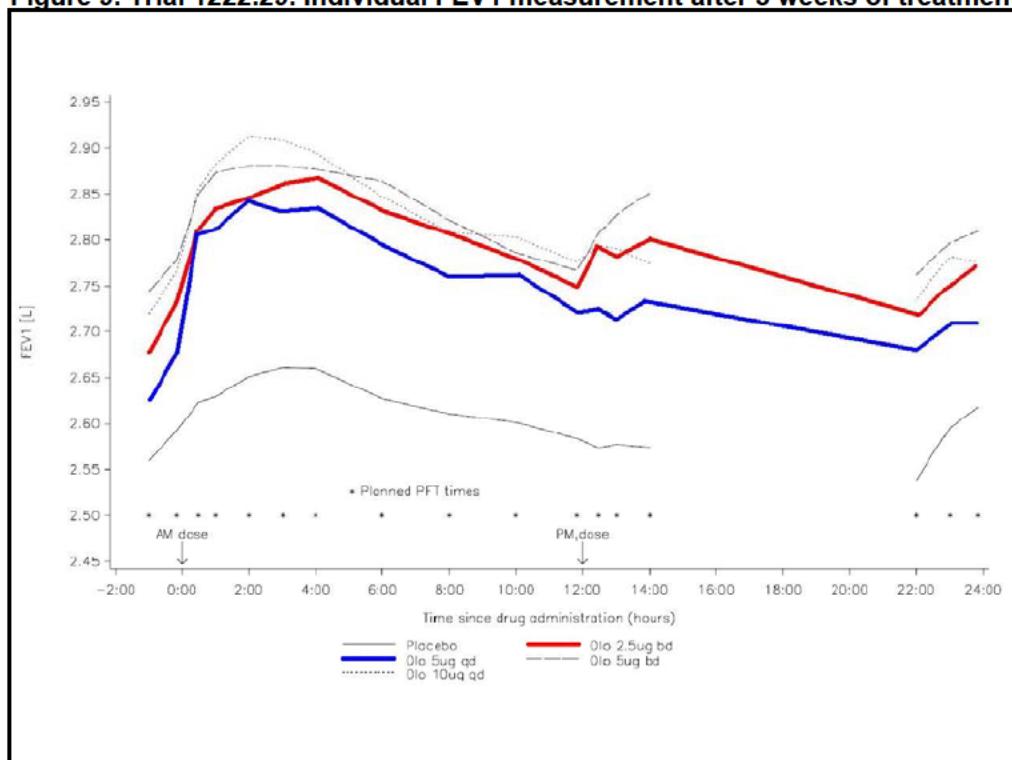
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Figure 9. Trial 1222.29. Individual FEV1 measurement after 3 weeks of treatment



source: Trial 1222.29 CSR; Figure 11.4.1.2.1:1; pp93

Note that this figure was modified from sponsor source material. In the sponsor figure, the data points between hours 14 and 22 were not connected for the Olo 2.5mcg BID or Olo 5mcg qD doses. The original figure was black and white.

FVC related secondary endpoints included the analogous parameters as were used for FEV1. Results for FVC AUC (0-12 hours) and FVC AUC (12-24 hours) response were consistent with the FVC AUC (0-24 hours) response data. Select FVC related secondary endpoints are summarized in Table 48.

Table 48. Trial 1222.29. FVC AUC (0-24 hours) and trough FVC response after 3 weeks of treatment

| Treatment | FEV1 AUC (0-24 hours) [L] | Difference from placebo (SE) |
|-----------------|------------------------------|------------------------------|
| Placebo | -0.029 (0.021) | |
| Olo 2.5 mcg BID | 0.116 (0.026) | 0.145 (0.022) |
| Olo 5 mcg qD | 0.099 (0.026) | 0.128 (0.022) |
| Olo 5 mcg BID | 0.127 (0.026) | 0.156 (0.022) |
| Olo 10 mcg qD | 0.111 (0.026) | 0.140 (0.022) |
| Treatment | Trough FEV [L] Response (SE) | Difference from placebo (SE) |
| Placebo | -0.013 (0.024) | |
| Olo 2.5 mcg BID | 0.096 (0.031) | 0.110 (0.028) |

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| | | |
|---------------|---------------|---------------|
| Olo 5 mcg qD | 0.079 (0.031) | 0.092 (0.028) |
| Olo 5 mcg BID | 0.105 (0.031) | 0.118 (0.028) |
| Olo 10 mcg qD | 0.098 (0.031) | 0.111 (0.028) |

Source: Trial 1222.29 CSR; Table 11.4.1.2.1:3 and 11.4.1.2.1:4; pp95 and 98
all p-values <0.0001

For secondary endpoints related to PEFR [i.e. PEFR AUC (0-12 hours), PEFR AUC (12-24 hours), and PEFR AUC (0-24 hours) response and peak PEFR (within 24 hours post dose) at the end of each 3 week treatment period], results were consistent with both the FEV1 and FVC data.

With regard to rescue medication usage throughout the trial, all olodaterol dose groups has statistically significantly less rescue medication use compared to placebo. The magnitude of the differences were modest ranging from 0.637 to 0.546 fewer doses of rescue medications/day.

The sponsor also analyzed change from baseline in ACQ total score compared to placebo after 3 weeks of therapy. For all doses, there were statistically significant improvements compared to placebo which were all <0.5. As such, the improvements are minimal and of questionable clinical significance.

With regard to symptom free days, olodaterol dose groups had a higher percentage of symptom free days compared to placebo (placebo=23.6%, olodaterol doses=28-36%).

Reviewer Comments:

The results for the non-key spirometric secondary endpoints, are remarkably consistent with the primary and key secondary endpoints. All dose regimens demonstrate a statistically significant improvement compared to placebo. As with the primary endpoint, there also appears to be increased benefit when dosing olodaterol BID versus qD when the TDD is held constant. It is of interest that when comparing the 2.5 mcg BID regimen to the 5 mcg QD regimen, the peak effect after each dose is higher for the 2.5mcg BID regimen, which is an unexpected result. This may be due to accumulation over time due to the cross-over design, though there was a 2 week washout period between treatment periods. The treatment effect with regard to non-spirometric endpoints, however, is marginal.

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Safety:

Exposure:

A total of 206 patients received at least one dose of study medication. The mean exposure per treatment period ranged between 22.8-23.4 days. In each treatment period, the majority of patients (58-70%) were exposed for 16-22 days.

Deaths, SAEs, withdrawal due to AEs

There were no deaths during this trial. There were 4 reported SAEs. Three were related to hospitalizations due to falling (patient was inebriated), to gastroenteritis, and to diverticulosis. The fourth SAE was due to a meniscal tear requiring arthroscopy. Two patients withdrew due to AEs; one for asthma exacerbation (Olo 5mcg BID treatment period) and one for weight gain (Olo 2.5mcg BID treatment period).

TEAEs

In this trial TEAEs were defined as AEs that occurred after first dose in a treatment period until 12 days after the last dose in a treatment period. Overall, AEs occurred with similar frequency during oldaterol treatment periods (12.7%-18.8%) and placebo periods (16.4%). The most common AEs by SOC were infections and infestations, respiratory mediastinal and thoracic, and nervous system. By preferred term, the most common AEs were headache and asthma. This is summarized in Table 49.

Table 49. Trial 1222.29. Treatment emergent AEs occurring during treatment periods (>1%)

| System organ class Preferred term | Placebo N (%) | Olodaterol 2.5 µg b.i.d. N (%) | Olodaterol 5 µg q.d. N (%) | Olodaterol 5 µg b.i.d. N (%) | Olodaterol 10 µg q.d. N (%) | Total N (%) |
|---|------------------|--------------------------------------|----------------------------------|------------------------------------|-----------------------------------|----------------|
| Number of patients | 201 (100.0) | 101 (100.0) | 101 (100.0) | 101 (100.0) | 102 (100.0) | 206 (100.0) |
| Patients with any AE | 33 (16.4) | 15 (14.9) | 15 (14.9) | 19 (18.8) | 13 (12.7) | 73 (35.4) |
| Infections and infestations | 14 (7.0) | 2 (2.0) | 4 (4.0) | 9 (8.9) | 4 (3.9) | 29 (14.1) |
| Sinusitis | 1 (0.5) | 0 | 0 | 0 | 4 (3.9) | 5 (2.4) |
| Nasopharyngitis | 3 (1.5) | 0 | 0 | 1 (1.0) | 0 | 4 (1.9) |
| Upper respiratory tract infection | 3 (1.5) | 1(1.0) | 0 | 1 (1.0) | 0 | 4 (1.9) |
| Cystitis | 1 (0.5) | 0 | 0 | 2 (2.0) | 0 | 2 (1.0) |
| Respiratory, thoracic and mediastinal disorders | 9 (4.5) | 3 (3.0) | 2 (2.0) | 3 (3.0) | 2 (2.0) | 19 (9.2) |
| Asthma | 4 (2.0) | 1 (1.0) | 1 (1.0) | 2 (2.0) | 1 (1.0) | 9 (4.4) |
| Rhinitis allergic | 0 | 2 (2.0) | 0 | 0 | 0 | 2 (1.0) |
| Nervous system disorders | 6 (3.0) | 2 (2.0) | 4 (4.0) | 0 | 3 (2.9) | 13 (6.3) |
| Headache | 5 (2.5) | 1 (1.0) | 2 (2.0) | 0 | 3 (2.9) | 9 (4.4) |
| Injury, poisoning, and procedural complications | 2 (1.0) | 3 (3.0) | 0 | 3 (3.0) | 1 (1.0) | 9 (4.4) |
| Investigations | 2 (1.0) | 1 (1.0) | 1 (1.0) | 0 | 2 (2.0) | 6 (2.9) |
| Musculoskeletal and connective tissue disorders | 0 | 2 (2.0) | 1 (1.0) | 1 (1.0) | 0 | 4 (1.9) |
| Eye disorders | 1 (0.5) | 0 | 0 | 2 (2.0) | 0 | 2 (1.0) |
| Skin and subcutaneous tissue disorders | 0 | 0 | 2 (2.0) | 0 | 0 | 2 (1.0) |

source: Trial 1222.29 CSR; Table 12.2.2.1:1; pp114

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With regard to SAEs and AEs, olodaterol was relatively well tolerated. None of the SAEs were likely related to study medication. It is also not unexpected to have asthmatics withdraw from a trial due to an exacerbation. With regard to TEAEs, there were no clear imbalances overall, or with regard to specific AEs. This is in contrast to trial 1222.27, where overall AEs were more frequent in the olodaterol groups.

Clinical Labs:

Labs were drawn at baseline and at end of treatment period only. Based on shift table analysis, there were no notable shifts in clinical lab values. However, for the 10mcg TDD groups compared to placebo, there were more patients who had normal serum glucose at baseline that increased to above the upper limits of normal after 3 weeks of treatment (placebo=5.7%, 5mcg BID=8.5%, and 10mcg qD=11.5%). There were 5 patients who had reported AEs due to clinical labs. In the placebo group, there was one case of blood in the urine and 1 case of increased CPK. In the 5mcg qD period, there was one case of increased blood creatinine. In the 10mcg qD period, one patient had increase AST and GGT and another had increased blood glucose.

Vital Signs:

The number of patients with changes in blood pressures or pulse rates was low and generally similar between treatment groups. The frequency of patients with a marked increase in SBP, DBP, or pulse rate was also similar between groups.

ECG:

ECGs were performed 60 minutes prior to dosing during study visits. There were no notable changes on ECG for PR, QRS, or QTc intervals.

Reviewer Comment

With regard to clinical labs and vital signs, olodaterol was well tolerated. In contrast to the other asthma dose-ranging trials, there were also no changes noted on ECG. This is likely related to decreased frequency of ECG monitoring.

Overall Reviewer Comment

As with the previous asthma and COPD dose ranging trials, this trial is supportive of a bronchodilator effect for olodaterol at all studies dose regimens. The results also indicate that BID dosing may offer a greater treatment benefit compared to qD. This is in contrast to the COPD dose ranging trial 1222.6, where the treatment effect differences in BID and qD dosing was marginal. Although BID dosing may confer a greater treatment effect in asthmatics (but not necessarily in COPD patients), the optimum TDD does not change. Based on the totality of the dose ranging data, 5mcg is likely the optimum TDD. With regard to safety, olodaterol was well tolerated in this trial.

5.3.8 Trial 1222.11 (COPD 48 Week Trial)

Administrative Information

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- **Study title:** Randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled olodaterol (5mcg [2 actuations of 2.5mcg] and 10mcg [2 actuations of 5mcg]) delivered by the Respimat inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 11/05/2008-9/21/2010
- **Study sites:** Australia (5 sites), New Zealand (4), China (11 sites), Germany (8 sites), Taiwan (5 sites), U.S. (21 sites)
- **Study report date:** 12/28/2011

Objectives/Rationale

- To assess the long-term efficacy and safety of olodaterol (5mcg and 10mcg once daily) compared to placebo in patients with COPD

Study Design and Conduct

Overview

This was a multi-center, randomized, double-blind placebo-controlled, 48-week parallel group trial to assess the safety and efficacy of two doses of olodaterol (5mcg qD and 10mcg qD) for the treatment of COPD. These COPD patients had FEV1 of <80% predicted and were current smokers, or had at least a 10 pack year smoking history. Asthmatics were excluded. The trial had a total of 11 visits. Consistent with standard of care, background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics, and methylxanthines were permitted in all treatment groups.

Consent was obtained from patients at visit 0, and patients were informed of restricted medications (primarily other LABAs) and began medication washout if indicated. At the screening visit (visit 1, week -2), medication washout was verified and baseline information collected. Baseline spirometry was also performed. Eligible patients then began a 2-week run-in period. Prior to the end of the run-in period, a subset of patients received baseline 24-hour Holter monitoring (N=50/arm). At visit 2, patients were randomized into the 48-week double-blind treatment portion of the trial. During the double-blind treatment period, patients were instructed to record PEFR, symptoms, test medication use, and rescue medication use in their eDiaries. After the randomization visit, there were 9 additional clinic visits (weeks 2, 6, 12, 18, 24, 32, 40, 48, and 50). The primary efficacy endpoint was assessed at 12 weeks (day 85); the remainder of the trial was primarily for collection of safety data. PFTs were performed at each clinic visit. At the week 12 visit, a subset of patients received additional post-dose PFTs to characterize the 12-hour FEV1 curve. After the final visit at week 48, there was a solicited vital status follow-up phone call at 50 weeks for all patients including those who prematurely discontinued from the trial. Unsolicited vital status updates were also reported after the trial period. Patients were allowed to continue with inhaled corticosteroids and anticholinergics for the duration of the trial. Note that randomization was stratified based on tiotropium use. Because of this, patients who started on

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tiotropium during the trial were discontinued. The trial schedule and assessments are summarized in Table 50.

Table 50. Trial 1222.11. Assessment schedule

| Visit Number Week Day | Screening | | Treatment period | | | | | | | | | | Follow-up |
|---|----------------|----------------|------------------|----------------|----------------|----------------|----------------|----------------|----------------|------------------|------------------|-----------------|-----------|
| | 0 -2 -14 | 1 0 -1 | 2 0 1 | 3 2 15 | 4 6 43 | 5 12 85 | 6 18 127 | 7 24 169 | 8 32 225 | 9 40 281 | 10 48 337 | 11 +2 +14 | |
| Informed consent | X ¹ | | | X ¹ | | | | | | | | | |
| Pharmacogenomics | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | |
| COPD characteristics | X | | | | | | | | | | | | |
| Inclusion / exclusion criteria | X | | X | | | | | | | | | | |
| Physical examination | X | | | | | | X | | | X ⁶ | X ⁷ | | |
| Vital signs (seated) | X ² | X ² | X ² | X ¹ | X ² | X ^{2,5} | | |
| Laboratory tests (fasted) | X | X | | | X | | X | | | | X ³ | X ¹ | |
| Laboratory test post-dosing | | | | X ⁸ | X ⁸ | | | | | | | | |
| 12-lead ECG | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ^{2,8} | X ⁷ | | |
| Holter monitoring (subset of patients) | | X ² | | | | X ² | X ² | | |
| Training in use of MDI & Respimat® | X | X | | | | | | | | | | | |
| Issue Electronic Peak Flow Meter / Diary | X | | | | | | | | | | | | |
| Download Electronic Peak Flow Meter / Diary | | | X | X | X | X | X | X | X | X | X | X | |
| Randomisation | | | X | | | | | | | | | | |
| Medication washout check | X | | X | X | X | X | X | X | X | X | X | | |
| Dispense Respimat® test medication inhaler | | | X | X | X | X | X | X | X | X | X | | |
| Collect Respimat® test medication inhaler | | | | X | X | X | X | X | X | X | X | | |
| Dispense rescue medication as needed | X | | X | X | X | X | X | X | X | X | X | | |
| Administration of test medication in clinic | | | X | X | X | X | X | X | X | X | X | | |
| Drug accountability check | | | | X | X | X | X | X | X | X | X | | |
| PFTs (FEV ₁ / FVC) | X ⁴ | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ² | X ² | | |
| EQ-5D | | X | X | X | X | X | X | X | X | X | X | | |
| Healthcare Resource Utilisation | | X | X | X | X | X | X | X | X | X | X | X | |
| Review smoking status | X | | | | | | X | | | X ⁶ | | | |
| Pharmacokinetic plasma sample | | | X ⁸ | X ⁸ | X ⁸ | X ⁸ | | | | | | | |
| Patient's Global Rating | | | | X | X | | X | | | X | | X ¹⁰ | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant medication | | X | X | X | X | X | X | X | X | X | X | X | |
| Health Status Check | | | | | | | | | | | X ¹⁰ | | |
| Termination of trial medication | | | | | | | | | | | X | | |

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions. Two blood samples will be taken from those patients eligible to be in the study and who signed the specific informed consent related to pharmacogenetic testing. Participation in the pharmacogenetic testing is voluntary and not a prerequisite for participation in the study.
2. Measured prior to each pulmonary function test at all visits. For patients in the 12-hr PFT sub-study at Visit 5, vital signs will be measured up to and including the 3 hours pulmonary function test.
3. 12-lead ECG recording in all patients at Screening Visit (Visit 1) and repeated at the withdrawal visit if the patient does not complete all study visits. In addition, 12-lead ECG recording will be performed pre-dose and at 40 minutes post dose in all patients at Visits 2, 4, 5, 7 and 10. Holter monitoring will be performed in a subset of 150 patients (i.e., 50 patients per treatment group) prior to randomisation (Visit 2*, Day -1 in flow chart) and at Visits 5, 7, 9 and 10.
4. Reversibility testing using 4 puffs salbutamol (100 µg per actuation) [note: reversibility is not an inclusion criterion].
5. Visit 2, 3, 4, 5, 7, 10: PFTs will be performed at 10 minutes prior to drug administration and at 5 minutes, 15 minutes, 30 minutes, 1, 2 and 3 hours post dose.
- At Visits 2, 4 and 5: An additional PFT measurement will be performed 1 hour prior to drug administration
- Visits 6, 8, 9: PFTs performed 10 minutes prior to drug administration only (i.e., trough measurement only).
- At Visit 5: in a sub-set of patients, pulmonary function testing will be performed pre-dose (-1 hour and -10 minutes prior to test-drug inhalation) and at 5, 15 and 30 minutes, and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after inhalation of study medication. Patients not in the sub-set will perform PFTs at Visit 5 at 5, 15 and 30 minutes, and at 1, 2 and 3 hours after inhalation of study medication.
6. To be completed by all patients including those who discontinue early.
7. To be performed only if relevant findings at Visit 10.
8. In selected countries, pharmacokinetic plasma samples will be drawn 10 minutes (- 2 min/+ 5 min) post dose at Visits 4, 5 and 6. One PK sample will be drawn at Visit 2 prior to drug administration.
9. Potassium will be tested at 1 hour and 3 hours post dosing
10. To be completed only for patients who discontinue early. Patients will be contacted at their predicted 24 week (Visit 7) date (if they discontinue prior to 24 weeks of treatment), and at the predicted exit date from the trial (48 weeks plus 14 days i.e. Visit 11)

Source: Trial 1222.11 protocol and amendment report U10-3192-01; pp 6-7

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Trial Population

The trial consisted of 625 randomized COPD patients. They were randomized using an interactive voice randomization system (IVRS). Randomization was stratified based on tiotropium use. If the number of patients on tiotropium at baseline exceeded 30% in any region, then enrollment into the tiotropium strata was curtailed. Tiotropium was not discontinued in any patients for the purposes of enrolling in the trial.

Key Inclusion Criteria

1. All patients signed an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which included medication washout and restrictions.
2. All patients had a diagnosis of chronic obstructive pulmonary disease and met the following spirometric criteria: Patients had relatively stable airway obstruction with a post-bronchodilator <80% of predicted normal and a post-bronchodilator FEV1/FVC <70% predicted at Visit 1.
3. Male or female patients, 40 years of age or older
4. Patients were current or ex-smokers with a smoking history of more than 10 pack-years. Patients who had never smoked cigarettes were excluded.
5. Patients were able to perform technically acceptable pulmonary function tests (both supervised) and PEFR measurements, and were able to maintain records (Patient Daily e-Diary) during the study period as required in the protocol.
6. Patients were able to inhale medication in a competent manner from the Respimat inhaler and from a metered dose inhaler (MDI).

Key Exclusion Criteria

1. Patients with a significant disease other than COPD
2. Patients with clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis; all patients with an AST (SGOT) >2x ULN, ALT (SGPT) >2x ULN, bilirubin >2x ULN or creatinine >2x ULN were excluded regardless of clinical condition (a repeat laboratory evaluation was not be conducted in these patients)
3. Patients with a history of asthma. For patients with allergic rhinitis or atopy, source documentation was required to verify that the patient did not have asthma. If a patient had a total blood eosinophil count 600/mm³, source documentation was required to verify that the increased eosinophil count was related to a non-asthmatic condition.
4. Patients with any of the following conditions:
 - a diagnosis of thyrotoxicosis (due to the known class side effect profile of beta-agonists)
 - a diagnosis of paroxysmal tachycardia (>100 beats per minute [due to the known class side effect profile of beta-agonists])
5. Patients with any of the following conditions:
 - a history of myocardial infarction within 1 year of Screening Visit (Visit 1)
 - unstable or life-threatening cardiac arrhythmia.
 - have been hospitalized for heart failure within the past year.
 - known active tuberculosis

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- a malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years (patients with treated basal cell carcinoma are allowed)
 - a history of life-threatening pulmonary obstruction
 - a history of cystic fibrosis
6. Clinically evident bronchiectasis
 7. A history of significant alcohol or drug abuse
 8. Patients who had undergone thoracotomy with pulmonary resection (patients with a history of thoracotomy for other reasons could have been evaluated as per exclusion criterion No. 1)
 9. Patients being treated with any of the following concomitant medications:
 - oral beta-adrenergics
 - oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day
 10. Patients who regularly used daytime oxygen therapy for more than one hour per day and in the investigator's opinion would have been unable to abstain from the use of oxygen therapy during clinic visits
 11. Patients who had completed a pulmonary rehabilitation program in the six weeks prior to the Screening Visit (Visit 1) or patients who were currently in a pulmonary rehabilitation program
 12. Patients who had taken an investigational drug within one month or six half lives (whichever is greater) prior to Screening Visit (Visit 1)
 13. Patients with known hypersensitivity to beta-adrenergics drugs, EDTA or any other component of the Respimat inhalation solution delivery system
 14. Pregnant or nursing women
 15. Women of childbearing potential not using two effective methods of birth control (one barrier, one non-barrier method). Female patients would be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation, or postmenopausal for at least two years
 16. Patients who had previously been randomized in this study or were currently participating in another study
 17. Patients who were unable to comply with pulmonary medication restrictions prior to randomization

Enrollment Cautions:

1. Extreme caution was used when including patients:
 - with cardiovascular disorders, especially coronary insufficiency and hypertension
 - being treated with monoamine oxidase inhibitors or tricyclic antidepressants
2. Caution was used when including patients on treatment with non potassium-sparing diuretics
3. Patients should not have been normally taking beta-blockers. However, under certain circumstances, e.g., prophylaxis after myocardial infarction, there may be no

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acceptable alternatives to the use of beta-adrenergic blocking agents in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

4. The randomization of patients with any respiratory infection or COPD exacerbation in the 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period should be postponed. Patients may be randomized 6 weeks following recovery from the infection or exacerbation.

Reviewer Comment:

The trial design was typical for a phase 3 COPD trial. The inclusion/exclusion criteria were also appropriate for a COPD trial.

Treatments

Treatment Groups

Olodaterol 5mcg qD (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg qD (2 actuations of 5mcg/actuation)

Placebo

All were administered using the Respimat inhaler.

Concomitant/Restricted Medications:

Medications taken by the patient within 3 months of the screening visit were recorded in the electronic case report form (eCRF). All medications used during the trial were also recorded in the eCRF. Use of SABAs were allowed as necessary; however, if a patient required SABA treatment during PFTs, the testing was stopped. Temporary increases in the dose or addition of oral steroids and theophylline were allowed; however, PFTs could not be performed within 7 days of the last dose. PFTs could be postponed up to 14 days. The use of antibiotics was not restricted. However, PFTs would have been postponed for at least 2 days, but not more than 7 days. Medication limitations are summarized in Table 51.

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Table 51. Trial 1222.11. Restricted and prohibited medications

| Drug Class | Sub-class | Prior to study | Study Period | | |
|----------------------------------|---|----------------|-----------------|------------------|------------------|
| | | | Baseline Period | Treatment Period | Follow up Period |
| Corticosteroids | Inhaled corticosteroids ¹ | permitted | permitted | permitted | permitted |
| | Oral corticosteroids ¹ [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent)] | permitted | permitted | permitted | permitted |
| Beta-adrenergics / beta-blockers | Inhaled short-acting beta-adrenergics | permitted | rescue | rescue | rescue |
| | Inhaled long-acting beta-adrenergics ² | permitted | not permitted | study medication | permitted |
| | Oral beta-adrenergics | not permitted | not permitted | not permitted | not permitted |
| | Beta blockers ¹ | permitted | permitted | permitted | permitted |
| Anticholinergics ³ | Short-acting anticholinergics (inhalation aerosol and nasal spray) | permitted | permitted | permitted | permitted |
| | Long-acting anticholinergics ¹ | permitted | permitted | permitted | permitted |
| Miscellaneous | Other investigational drugs ⁴ | not permitted | not permitted | not permitted | not permitted |
| | Oral cromolyn sodium / nedocromil sodium ⁵ | permitted | permitted | permitted | permitted |
| | Antihistamines, antileukotrienes ⁵ | permitted | permitted | permitted | permitted |
| | Methylxanthines ⁶ | permitted | permitted | permitted | permitted |
| | Mucolytics ¹ | permitted | permitted | permitted | permitted |

¹ if stabilized for at least six weeks prior to Visit 1

² at least a 48-hour washout of long-acting beta-adrenergics prior to Visit 1

³ short acting anticholinergic agents not to be taken within 8 hours of PFTs, long acting within 48 hours

⁴ washout of at least one month or six half lives (whichever is greater)

⁵ only allowed if prescribed for conditions other than asthma

⁶ at least a 24-hour washout of short-acting (BID or more frequent administration) theophylline preparations prior to all PFT visits least a 48-hour washout of long-acting (QD administration) theophylline preparation prior to all PFT visits.

Source: Trial 1222.11 protocol and amendment report U10-3192-01:pg32

Efficacy Parameters

Primary Endpoint

The co-primary endpoints for this trial were trough FEV1 response and FEV1 AUC (0-3 hours) response at week 12 (day 85). Trough FEV1 was defined as the mean of the FEV1 obtained at 1 hour prior to daily medication and 10 minutes prior to daily trial medication. FEV1 AUC (0-3 hours) was defined as area under the curve from 0 to 3 hours post-dose using the trapezoid rule, divided by the time duration. Response for both parameters was defined as change from baseline. Baseline was defined as the mean of the 2 pre-dose PFTs at visit 2.

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Secondary Endpoints

The secondary endpoints included the following:

1. FEV1 AUC (0-3 hours) response at day 1 and after 2, 6, 24 and 48 weeks
2. FEV1 AUC (0-12 hours) response after 12 weeks (in the subset of patients with available data)
3. Trough FEV1 response [L] after 2, 6, 18, 24, 32, 40, and 48 weeks
4. FVC (forced vital capacity) AUC (0-3 hours) response at day 1 and after 2, 6, 12, 24 and 48 weeks
5. Trough FVC response [L] after 2, 6, 12, 18, 24, 32, 40 and 48 weeks
6. FEV1 peak(0-3) response at day 1 and after 2, 6, 12, 24 and 48 weeks
7. FVC peak(0-3) response after 2, 6, 12, 24 and 48 weeks
8. FEV1 response [L] at 5, 15 and 30 minutes, and at 1, 2 and 3 hours after inhalation of study medication, after 2, 6, 12, 24 and 48 weeks
9. FVC response [L] at 5, 15 and 30 minutes, and at 1, 2 and 3 hours after inhalation of study medication, after 2, 6, 12, 24 and 48 weeks
10. FEV1 response [L] at 4, 5, 6, 8, 10 and 12 hours after inhalation of study medication, after 12 weeks (in the subset of patients with available data)
11. FVC response [L] at 4, 5, 6, 8, 10 and 12 hours after inhalation of study medication, after 12 weeks (in the subset of patients with available data)
12. Weekly mean pre-dose morning and evening peak expiratory flow rates (PEFs)[L/min]
13. Weekly mean number of puffs of rescue medication used per day (daytime/nighttime/ total) (PRN salbutamol)
14. Patient's Global Rating after 6, 12, 24 and 48 weeks
15. Time to first COPD exacerbation
16. Time to first COPD exacerbation leading to hospitalization
17. Time to first COPD exacerbation that did not lead to hospitalization, but included treatment with antibiotics and/or systemic steroids (moderate COPD exacerbation)
18. Number of COPD exacerbations, per patient year
19. Number of COPD exacerbations leading to hospitalization, per patient year
20. Number of moderate COPD exacerbations per patient year

For the secondary endpoints, AUC and response was defined as in the primary endpoint. Baseline was also defined as in the primary endpoint.

A COPD exacerbation was defined as “a complex of lower respiratory events/symptoms (increase of new onset) related to the underlying COPD, with a duration of three days or more, requiring a change in treatment” where a “complex of lower respiratory events / symptoms” meant at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing

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- Chest tightness

And where “a required change in treatment” included the following:

- Prescription of antibiotics and/or systemic steroids
- And/or significant change for prescribed respiratory medication (bronchodilators including theophyllines)

For the Patient’s Global Rating, patients were asked to assess their health at each visit compared to the day before the first dose of study drug. There were 7 possible responses which were ‘very much better’, ‘much better’, ‘a little better’, ‘no change’, ‘a little worse’, ‘much worse’, or ‘very much worse’. Each response was given a point value 1-7, with 1 being ‘very much better’ and 7 being ‘very much worse.’

Pharmacokinetic parameters

PK samples were also taken pre-dose at visit 2, and 10-minutes post-dose at visits 4, 5, and 6.

Safety parameters:

Monitored safety parameters will include the following:

- AEs, vital signs and clinical labs were performed as per the schedule listed in Table 50.
- ECGs were performed at baseline and screening. ECGs were also performed at visits 2, 4, 5, 7, and 10. ECGs were performed pre-dose and 40 minutes post-dose.
- 24-hour Holter monitoring was performed in 50 patients per treatment arm. Holter monitoring was performed at visit 2 and after completion of trial related testing on visits 5, 7, 9, and 10.

Compliance

Compliance was determined based on eDiary entries and in a subset of patients, returned medications.

Ethics:

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB’s approval.

Statistical Analysis

Sample Size

Based on the Applicant’s previous experience, the standard deviation for FEV1 AUC (0-3 hours) was estimated to be 226mL and for trough FEV1 was 225mL. It is estimated that a total of 76 patients/group would yield 90% power to detect a 120mL FEV1 AUC (0-3 hours) response with a one sided alpha of 0.025. To have 90% power to detect a 75mL

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difference in trough FEV1 between olodaterol and placebo, 191 patients/group were required. As such BI planned to randomize 200 patients/group.

Missing Data

Data missing due to worsening symptoms were replaced with the least favorable non-missing data recorded during the same visit. Post-dose data missing at random was either linearly interpolated if the preceding and subsequent data points were available or was imputed using last observation carried forward (LOCF). If the adjacent data points were not available, then data were also imputed using LOCF. If a patient discontinued or was excluded from the trial due to worsening of symptoms, data was imputed from the patient's least favorable non-missing data.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients who received study drug and had baseline data and at least one evaluable post-dosing data for either co-primary endpoint. The per protocol set (PPS) consisted of all FAS minus patients with important protocol deviations. If the PPS was <90% of the FAS, the primary analysis was to have been performed on the PPS as a sensitivity analysis. The safety population was made up of all treated patients.

Efficacy Analysis

The co-primary endpoints were analyzed in a hierarchical manner to protect against type 1 error. The analysis first compared FEV1 AUC (0-3 hours) response for the olodaterol 10mcg group to placebo, then compared trough FEV1 response. If the 10mcg dose was superior to placebo (one sided p-values 0.025), then the 5mcg dose was compared to placebo for the co-primary endpoints. The FEV1 AUC (0-3 hours) response and trough FEV1 response data was analyzed using a mixed effect model for repeated measures.

Analyses of the secondary endpoints were considered descriptive and the p-values did not account for multiple comparisons.

Results:

Protocol Amendments

There was one protocol amendment. This was submitted on 1/10/2010. This amendment included corrections of typographical errors and clarification of the timing of some trial assessments. The amendment also increased the sample size from 510 to 600 patients in response to results from other olodaterol trials and olodaterol/tiotropium fixed dose combination trials. Results from these trials demonstrated that when LABAs were used on a LAMA background the FEV1 responses were smaller than previously expected. As patients in these trials were allowed to be on tiotropium, BI readjusted the sample size to account for a smaller than expected treatment difference. As such, BI changed their proposed sample to 191 patients per group, which would yield 90% power to detect a difference of 75mL in trough FEV1 between olodaterol groups and

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placebo (one sided p-value of 0.025). Additionally, BI reduced the cap on the number of patients allowed to be on concomitant tiotropium (60% to 30%).

In addition to the above protocol changes, there were also changes to the planned statistical analysis. Notable changes are discussed. The FAS definition was modified to include all patients who received at least one dose of study medication and had both baseline and at least one post-baseline measurement at or before Day 85 for either co-primary endpoint. The previous definition required measurements for specifically the first co-primary endpoint. Moderate COPD exacerbation related secondary endpoints were also added. A pooled analysis of COPD exacerbations was also added (trials 1222.11, 1222.12, 1222.13, 1222.14). Note that this was changed in a subsequent amendment to the statistical analysis plan. These changes were made prior to database lock and were considered by the Applicant to be the 'planned' analysis.

The Applicant also made alterations to their statistical analysis plan following database lock. The treatment-by-tiotropium stratum interaction terms were removed from the statistical model after database lock and unblinding. This was removed because it resulted in the calculation of the adjusted means for treatment as the unweighted average of the means of each stratum. This reduced the treatment effect and increased variability. The Applicant provided numbers for both the pre-specified analysis and the amended analysis. Using the original analysis, olodaterol's treatment effect compared to placebo was of lesser magnitude compared to the amended analysis. The Applicant also did not perform analysis of the pooled data for COPD exacerbation, as the results across the individual trials were not consistent.

Reviewer Comment:

The changes to the protocol do not affect data interpretation. The pre-database lock changes to the statistical analysis plan were also reasonable. However, the changes made to the statistical analysis plan after database lock and unblinding are problematic. As these changes were made after unblinding, the results of this post-hoc analysis should not be used as the basis for efficacy conclusions. The co-primary endpoints were re-analyzed by FDA statisticians using the pre-specified analysis plan. Note that the sponsor's pre-specified analysis was not provided in the body of the clinical study report; it was provided in an appendix. As their results matched the FDA analysis, the sponsor performed pre-specified analysis will be presented.

Protocol Violations

A total of 27 (4.3%) patients had important protocol violations (IPV). An important protocol violation was defined as a violation that could potentially affect the interpretation of the efficacy of safety data. The most common violation was 'study medication taken significantly longer than planned treatment durations' (end of treatment plus 2 weeks). Important protocol violations are summarized in Table 52. Two patients (#3428 and 3040) received a different study drug treatment prior to the primary endpoint (visit 5, week 12) than was received at the beginning of the trial. These two

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patients were excluded from the PP population. Another patient (#3140), was issued the correct medication (Olo 5mcg) prior to the primary endpoint, but thereafter was dispensed the wrong dose (Olo 10mcg). This was not considered an important protocol deviation, as it would not have likely affected the primary endpoint.

Table 52. Trial 1222.11. Important protocol violations

| | Placebo [N(%)] | Olo 5mcg [N(%)] | Olo 10mcg [N(%)] | Total [N(%)] |
|--|-------------------|--------------------|---------------------|-----------------|
| Randomized | 209 (100) | 208 (100) | 207 (100) | 625 (100) |
| Total with IPV | 6 (2.9) | 10 (4.8) | 11 (5.3) | 27 (4.3) |
| Exclusion criteria affecting efficacy and possibly safety | 0 | 3 (1.4) | 1 (0.5) | 2 (0.3) |
| Exclusion criteria affecting safety only | 0 | 1 (0.5) | 1 (0.5) | 2 (0.3) |
| Study drug not taken on day prior to primary endpoint clinic visit | 0 | 1 (0.5) | 4 (1.9) | 5 (0.8) |
| Study medication taken longer than planned duration | 5 (2.4) | 5 (2.4) | 5 (2.4) | 15 (2.4) |
| Incorrect trial medication dispensed | 1 (0.5) | 1 (0.5) | 0 | 2 (0.3) |
| Primary endpoint data missing | 0 | 0 | 1 (0.5) | 1 (0.2) |

source: Trial 1222.11 CSR; Table 15.1.2:1; pp155; IPV=important protocol violations

Disposition

Of the 859 enrolled patients, 625 were randomized. Of these, 504 (81%) completed the trial. Six-hundred twenty-four (624) patients received at least one dose of study medication. One patient was randomized prior to review of his ECG. Because the ECG was discovered to be abnormal, the patient was not treated. The most common reason for discontinuations were AEs, withdrawal of consent, and lack of efficacy.

Discontinuations were less common in the olodaterol groups compared to placebo. 'Lack of efficacy' as a reason for withdrawal was more common in placebo patients. Of the patients in the treated set, 620 were included in the FAS used for efficacy analysis. One hundred seventy five (175) received Holter monitoring. Although there was a PP data set defined, analysis was not performed using this set, per the analysis plan (PPS analysis was only performed if the difference between the FAS and PPS were >10%). Patient disposition and analysis populations are summarized in Table 53

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Table 53. Trial 1222.11. Patient disposition and analysis populations

| | Placebo N (%) | Olo 5mcg N (%) | Olo 10mcg N (%) | Total N (%) |
|---------------------------|------------------|-------------------|--------------------|----------------|
| Treated Set | 209 (100) | 208 (100) | 207 (100) | 624 (100) |
| Full Analysis Set (FAS) | 208 (99.5) | 206 (99) | 206 (99.5) | 620 (99.4) |
| Per Protocol Set (PPS) | 207 (99) | 202 (97.1) | 200 (96.6) | 609 (97.6) |
| 12-hour PFT set (TPS) | 71 (34) | 85 (40.9) | 85 (41.1) | 241 (38.6) |
| Holter set (HMS) | 52 (24.9) | 64 (30.8) | 59 (28.5) | 175 (28) |
| Completed | 159 (76.1) | 173 (83.2) | 172 (83.1) | 504 (80.8) |
| Premature discontinuation | 50 (23.2) | 35 (16.8) | 35 (16.9) | 120 (19.2) |
| Adverse events | 21 (10.1) | 17 (8.2) | 16 (7.7) | 54 (8.7) |
| AE study disease worse | 13 (6.2) | 7 (3.37) | 4 (1.93) | 24 (3.9) |
| AE-other disease worse | 2 (1.0) | 0 (0.00) | 3 (1.5) | 5 (0.8) |
| AE-other | 6 (2.9) | 10 (4.8) | 9 (4.4) | 25 (4.0) |
| Lack of efficacy | 13 (6.2) | 4 (1.9) | 1 (0.5) | 18 (2.9) |
| Non-compliance | 0 | 3 (1.44) | 2 (1) | 5 (0.8) |
| Lost to follow-up | 2 (1) | 1 (0.5) | 2 (1) | 5 (0.8) |
| Consent withdrawn | 11 (5.3) | 8 (3.9) | 11 (5.3) | 30 (4.8) |
| Other | 3 (1.4) | 2 (1) | 3 (1.5) | 8 (1.3) |

Source: Trial 1222.11 CSR; Tables 10.1:1 and 11.1:1; pp 71 and 74

Reviewer Comment:

Overall, there were more important protocol violations in the olodaterol groups compared to placebo. However, the overall numbers were small and are unlikely to affect interpretation. While there was an overall imbalance in discontinuations when comparing placebo to olodaterol groups, this was primarily driven by discontinuations in the placebo group due to lack of efficacy and worsening of COPD. As such, this imbalance implies that olodaterol has a treatment benefit. This difference in discontinuations is unlikely to exaggerate the treatment effect.

Demographics

Overall, patient demographics were similar between treatment groups. Most patients were white males with a mean age of 65. The average pack year history was 49 years and most patients were ex-smokers. The average time since COPD diagnosis was 8.4 years. Across all groups, 45-48% of patients were Global Initiative for Chronic Obstructive Lung Disease(GOLD) stage II and 40-45% were GOLD stage III. The average FEV1% predicted ranged between 41-43% across groups. These data are summarized Table 54.

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Table 54. Trial 1222.11. Patient demographics and baseline respiratory data

| | Placebo | Olo 5mcg | Olo 10mcg | Total |
|----------------------------------|------------|------------|------------|------------|
| Number of patients | 209 | 208 | 207 | 624 |
| Gender [N (%)] | | | | |
| Male | 152 (72.7) | 150 (72.1) | 155 (74.9) | 457 (73.2) |
| Female | 57 (27.3) | 58 (27.9) | 52 (25.1) | 167 (26.8) |
| Age [years] N | | | | |
| Mean | 65.8 | 64.0 | 65.0 | 64.9 |
| SD | 8.5 | 8.6 | 8.2 | 8.5 |
| Race [N (%)] | | | | |
| White | 130 (62.2) | 130 (62.5) | 131 (63.3) | 391 (62.7) |
| Black/African Amer. | 5 (2.4) | 3 (1.4) | 4 (1.9) | 12 (1.9) |
| Asian | 70 (33.5) | 72 (34.6) | 71 (34.3) | 213 (34.1) |
| Amer.Ind./Alaskan Nat. | 2 (1.0) | 1 (0.5) | 0 (0.0) | 3 (0.5) |
| Hawaiian/Pacif. Isle | 2 (1.0) | 2 (1.0) | 1 (0.5) | 5 (0.8) |
| Smoking history [N (%)] | | | | |
| Ex-smoker | 123 (58.9) | 133 (63.9) | 127 (61.4) | 383 (61.4) |
| Currently smoker | 86 (41.1) | 75 (36.1) | 80 (38.6) | 241 (38.6) |
| Smoking history [pack years] | | | | |
| Mean | 48.4 | 49.0 | 49.1 | 48.8 |
| SD | 26.5 | 31.9 | 37.5 | 32.2 |
| Trial diagnosis duration [years] | | | | |
| Mean | 8.6 | 8.4 | 8.4 | 8.4 |
| SD | 6.8 | 6.54 | 6.7 | 6.7 |
| FEV1 % predicted | | | | |
| Mean | 43.0 | 41.3 | 43.4 | 42.5 |
| SD | 14.4 | 14.4 | 15.4 | 14.7 |
| FEV1/FVC | | | | |
| Mean | 44.7 | 44.6 | 45.3 | 44.9 |
| SD | 11.5 | 12.4 | 11.3 | 11.7 |
| FEV1% change after albuterol | | | | |
| Mean | 15.6 | 18.3 | 15.9 | 16.6 |
| SD | 12.9 | 13.9 | 13.0 | 13.3 |

Source: Trial 1222.11 CSR; Table 11.2:1, 11.2:2, 11.2.5:1, 11.2.5:2; pp 76, 77, 80, 82

Across treatment groups, patients had similar numbers and types of concomitant medical diagnoses. The most common medical diagnoses were hypertension (40-47%), gastroesophageal reflux (17-22%), hyperlipidemia (15-18%), and osteoarthritis (14-17%). Cardiac disorders (by SOC and preferred term) were fairly evenly distributed across groups (28-34%).

Reviewer Comment:

The patients' demographic and baseline data was similar across groups and typical of most COPD trial populations.

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Compliance

Based on eDiary entries, compliance was high across groups, ranging from 96-97%. Greater than 95% of patients in each group took their medication 80-100% of the time.

Efficacy

Co-primary endpoints:

The co-primary endpoints for this trial were FEV1 AUC (0-3 hours) response and trough FEV1 response after 12 weeks of treatment. Note that the primary analysis plan was amended after database lock and unblinding. Based on the amended analysis plan both doses demonstrated statistically significant differences from placebo for both co-primary endpoints. There was no evidence of a dose response. The results of the sponsor's analysis are summarized in Table 55

Table 55. Trial 1222.11. Sponsor amended analysis of co-primary endpoint [FEV1 AUC (0-3 hours) response and trough FEV1 response after 12 weeks of treatment]

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|--------------------------------------|---------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | -0.007 (0.014) | | | -0.041 (0.014) | | |
| Olo 5 mcg | 0.165 (0.014) | 0.172 (0.019) | <0.0001 | 0.050 (0.014) | 0.091 (0.019) | <0.0001 |
| Olo 10 mcg | 0.169 (0.014) | 0.176 (0.019) | <0.0001 | 0.060 (0.014) | 0.101 (0.019) | <0.0001 |

Source: Trial 1222.11 CSR; Table 15.2.1.1.2:2 and 15.2.1.1.2:3; pp238 and 248

The sponsor also provided a sensitivity analysis for the co-primary endpoints using the originally planned pre-specified analysis. The magnitude of the response for both co-primary endpoints was decreased when compared to the amended analysis (Table 56). There was also no difference when comparing the 5mcg dose to the 10mcg dose.

Table 56. Trial 1222.11. Co-primary endpoint with sponsor pre-specified analysis

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|--------------------------------------|---------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | 0.002 (0.016) | | | -0.032 (0.016) | | |
| Olo 5 mcg | 0.167 (0.016) | 0.164(0.023) | <0.0001 | 0.052 (0.016) | 0.084(0.023) | 0.0002 |
| Olo 10 mcg | 0.157 (0.016) | 0.155(0.022) | <0.0001 | 0.048 (0.015) | 0.080(0.022) | 0.0003 |

Source: Trial 1222.11 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2.16 and 6.1.1.3.14; pp 527 and 689

When comparing the co-primary endpoints between patients in the tiotropium strata to non-tiotropium strata, the treatment difference from placebo was of greater magnitude in the non-tiotropium strata. The comparisons to placebo all had p-values <0.05; however, these comparisons were not corrected for multiplicity (Type I error) and since they were comparing subsets of patients, they were not powered to show a treatment response. These results are summarized in Table 57.

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Table 57. Trial 1222.11. Sponsor analysis by strata for co-primary endpoints

| Treatment Group | Tiotropium Strata | | | Non-tiotropium Strata | | |
|-----------------|--------------------------------------|------------------------|---------|--------------------------------------|------------------------|---------|
| | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | 0.018 (0.028) | | | -0.013 (0.015) | | |
| Olo 5 mcg | 0.168 (0.028) | 0.150 (0.040) | 0.0002 | 0.166 (0.015) | 0.179 (0.022) | <0.0001 |
| Olo 10 mcg | 0.131 (0.027) | 0.113 (0.039) | 0.0041 | 0.183 (0.015) | 0.196 (0.022) | <0.0001 |
| | | | | | | |
| | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.016 (0.028) | | | -0.048 (0.015) | | |
| Olo 5 mcg | 0.056 (0.028) | 0.072 (0.040) | 0.0720 | 0.048 (0.015) | 0.096 (0.021) | <0.0001 |
| Olo 10 mcg | 0.025 (0.026) | 0.041 (0.039) | 0.2893 | 0.071 (0.015) | 0.119 (0.021) | <0.0001 |

Source: Trial 1222.11 CSR; Tables 11.4.1.1.2 &11.4.1.1; pp 87 and 88

Reviewer Comment:

As the sponsor's amended primary analysis plan was altered after unblinding, those results cannot be used as primary evidence for efficacy. As such, their pre-specified analysis was used to assess efficacy. Based on those results, both doses of olodaterol demonstrated a statistically significant bronchodilatory effect. However, there was no incremental benefit to the higher dose. With regard to the by strata analysis the difference from placebo was greater for both co-primary endpoints for the non-tiotropium strata versus the tiotropium strata. This is not surprising as both olodaterol and tiotropium are bronchodilators.

Secondary Endpoints:

Note that unlike for the co-primary endpoints, the secondary endpoints did not have a pre-specified hierarchical analysis plan. Therefore, there was no protection against type I error and all the reported p-values for all secondary endpoints should be considered descriptive. Additionally, as with the primary analysis, the secondary analysis was revised post-database lock and unblinding.

Spirometric Secondary Endpoints:

This trial included multiple FEV1 related secondary endpoints. A subset of patients, received 12 hour post-dose spirometry at week 12. For these patients, FEV1 AUC (0-12 hours) response was compared between olodaterol groups and placebo. Results demonstrated that the olodaterol 10mcg and olodaterol 5mcg groups had a difference from placebo of 0.173L and 0.169L (p-values<0.0001), respectively. These results are summarized graphically in Figure 10. Sensitivity analysis using unadjusted means (original pre-specified analysis plan) demonstrated similar results.

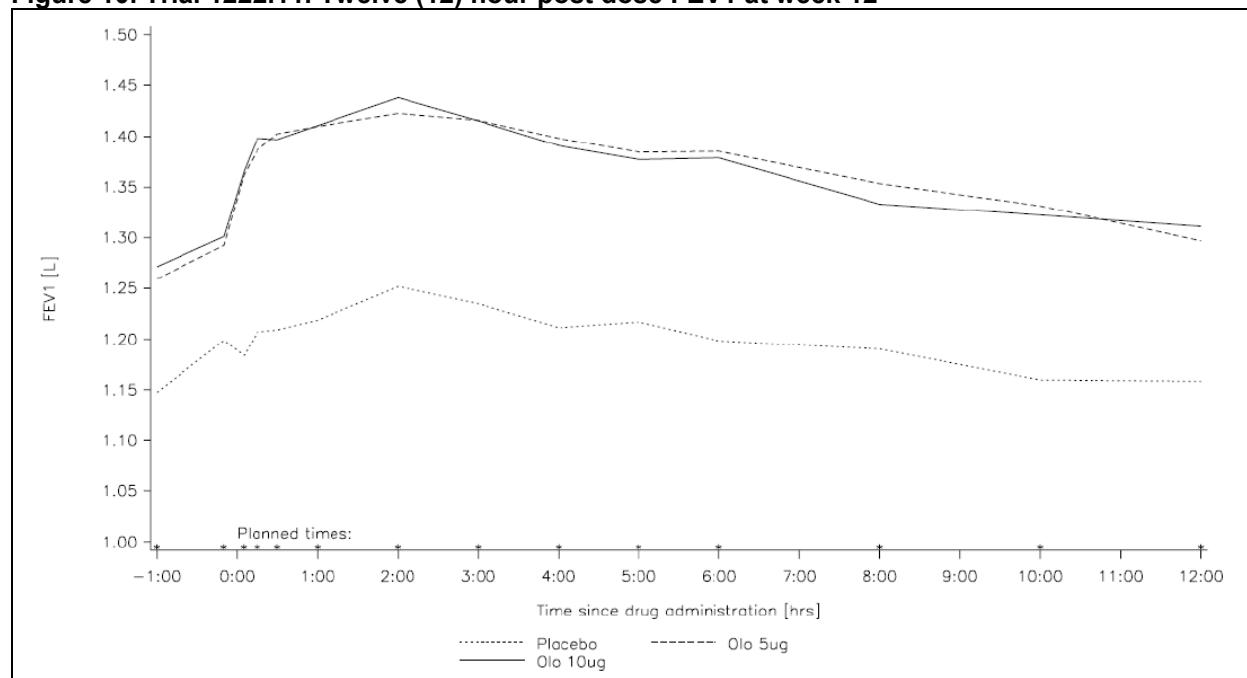
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Figure 10. Trial 1222.11. Twelve (12) hour post dose FEV1 at week 12



Source: Trial 1222.11 CSR; figure 11.4.1:2; pg 85

For the secondary endpoint of FEV1 AUC (0-3 hours) response after 48 weeks of treatment, the olodaterol 10mcg and olodaterol 5mcg dose groups had differences from placebo of 0.169L and 0.173L (p-values <0.0001), respectively. At days 1, 43, 85, 169, and 337 (weeks 0, 6, 12, 24, and 48, respectively), the results were similar, all with p-values <0.0001. The magnitude for the differences from placebo during these time points for the olodaterol 5mcg group were 0.165, 0.17, 0.172, 0.174, and 0.173L, respectively. For olodaterol 10mcg, the differences from placebo at the same time points were 0.175, 0.167, 0.176, 0.161, and 0.169L, respectively. These results are represented graphically in Figure 11.

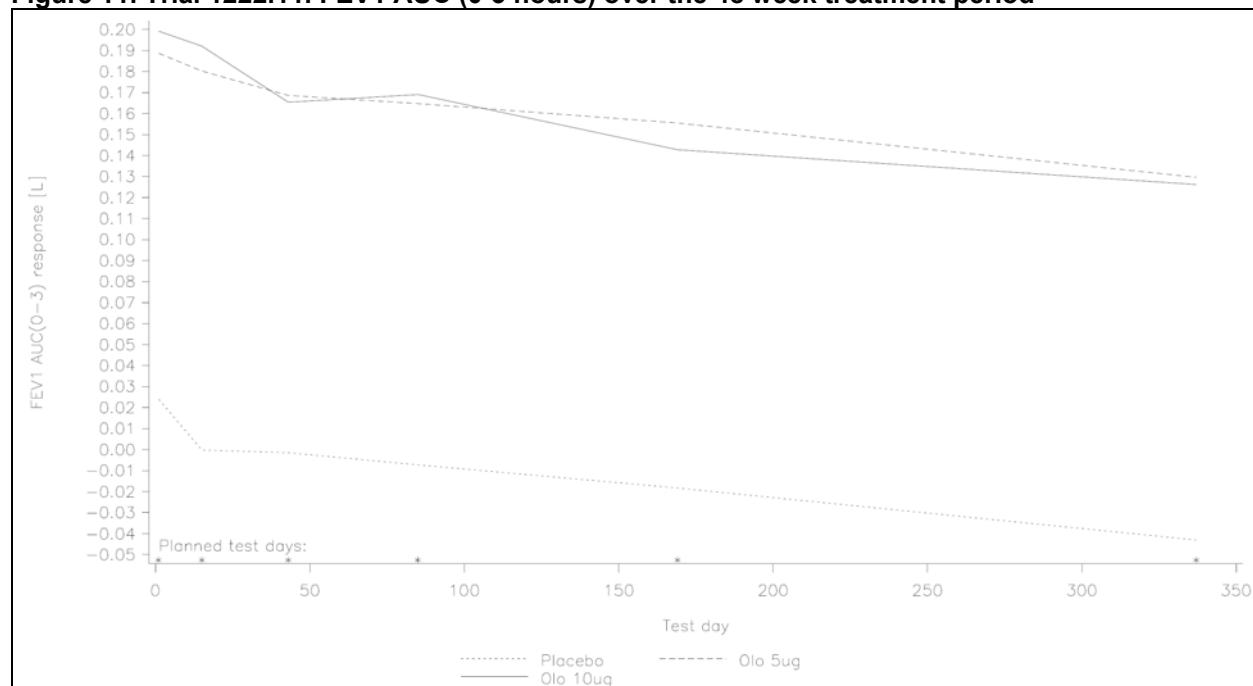
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Figure 11. Trial 1222.11. FEV1 AUC (0-3 hours) over the 48 week treatment period



Source: Trial 1222.11 CSR; Figure 11.4.1.2.1:1; pg 89

For the secondary endpoint of trough FEV1 response over the 48-week period, both olodaterol doses demonstrated an increase in response compared to placebo on all tested days [days 15, 43, 85, 169, and 337 (weeks 2, 6, 12, 24, and 48, respectively)]. The mean differences from placebo in liters for olodaterol 5mcg were 0.095, 0.095, 0.091, 0.086, and 0.091 at days 15, 43, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.111, 0.091, 0.101, 0.089, and 0.091 L, respectively. P-values for both doses at all time points were <0.0001. This is represented graphically in Figure 12.

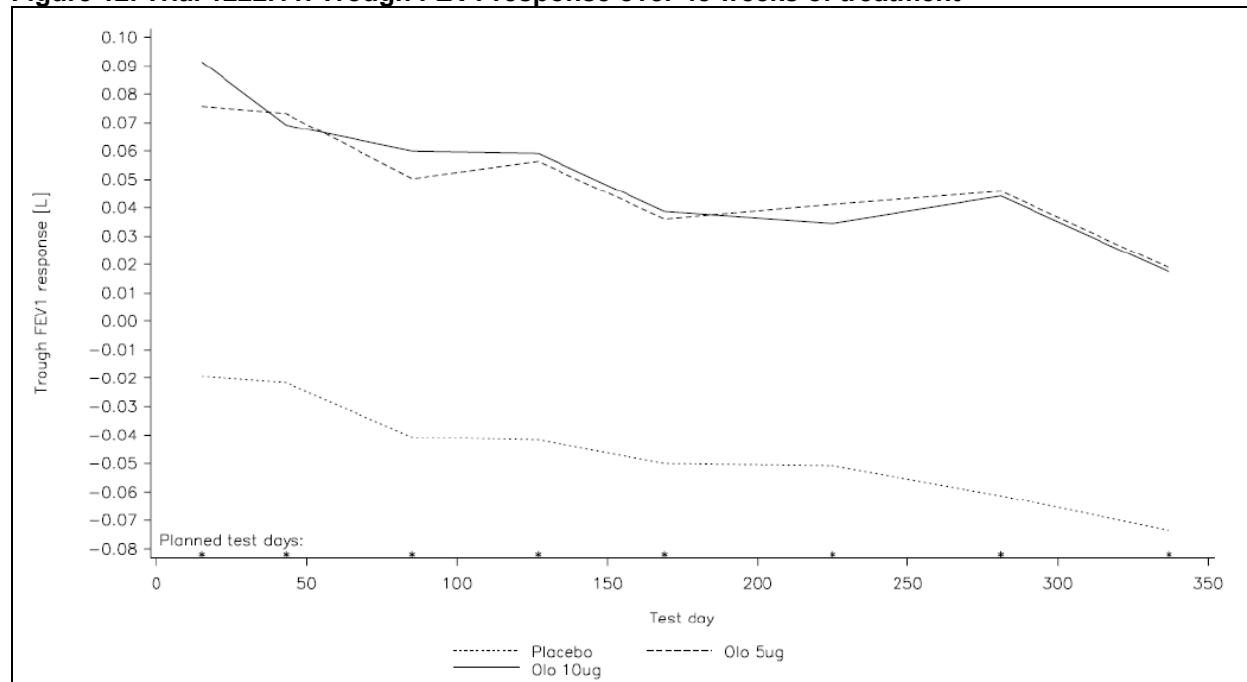
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Figure 12. Trial 1222.11. Trough FEV1 response over 48 weeks of treatment



Source: trial 1222.11 CSR; figure 11.4.1.2.1:2; pg 90

For the secondary endpoint FEV1 peak (0-3) response compared to placebo on all tested days, the mean differences from placebo in liters for olodaterol 5mcg were 0.155, 0.164, 0.175, and 0.169 at days 1, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.171, 0.165, 0.151, and 0.163, respectively. P-values for both doses at all time points were <0.0001.

The differences from placebo in FEV1 response for the olodaterol 5mcg group at 5, 15, 30, 60, 120, and 180 minutes post-dose on Day 1 were 0.115, 0.158, 0.162, 0.175, 0.171, and 0.167 L, respectively. For olodaterol 10mcg the differences from placebo were 0.115, 0.155, 0.160, 0.183, 0.189, and 0.185 L, respectively. The p-values at both doses were <0.0001. This is summarized graphically in Figure 13.

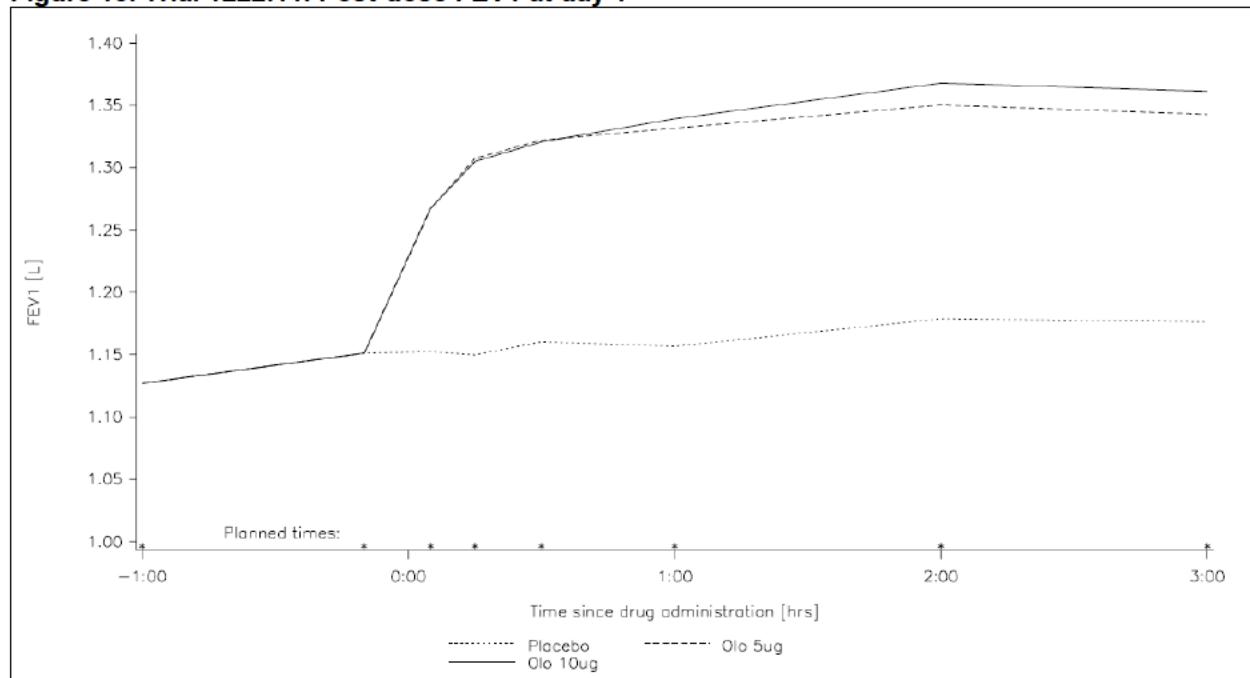
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Figure 13. Trial 1222.11. Post-dose FEV1 at day 1



Source: Trial 1222.11 CSR; figure 15.2.1.1.1:1; pg 212

Sensitivity analysis using unadjusted means (original pre-specified analysis plan) for the FEV1-related endpoints also demonstrated similar results.

The results for the FVC-related secondary endpoints were consistent with the results for the analogous FEV1-related secondary endpoints. For the trough FVC response at 12 weeks, both the olodaterol 5mcg and olodaterol 10mcg demonstrated improvements compared to placebo [0.115L ($p=0.002$) and 0.160L ($p<0.0001$), respectively]. The results were similar at all other time points. In comparison to the FEV1 data, there did appear to be an incremental benefit to the olodaterol 10mcg compared to olodaterol 5mcg.

For the FVC AUC (0-3 hours) response at 12 weeks, the olodaterol 5mcg and olodaterol 10mcg groups demonstrated improvements compared to placebo [0.115L and 0.160L (all p -values <0.0001), respectively]. Similar trends were seen at all other time points.

With regard to FVC peak (0-3) response at 12 weeks, both olodaterol 5mcg and olodaterol 10mcg demonstrated improvements compared to placebo [0.251L ($p<0.0001$) and 0.260L ($p<0.0001$), respectively]. Results were similar at other time points.

For weekly mean values from morning PEFR, both olodaterol groups demonstrated improvements from placebo. The magnitude of the mean differences from placebo at weeks 1, 12, 24, and 48 were 15.6 ($p <0.0001$), 13.0 ($p=0.0004$), 14.7 ($p=0.0003$), and 13.4 ($p=0.0018$) L/min for olodaterol 5mcg, respectively, and 17.7 ($p<0.0001$), 19.4

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($p<0.0001$), 15.1($p=0.0002$), and 15.5 ($p=0.0003$) L/min for olodaterol 10mcg, respectively. Results were similar for evening PEFR.

Reviewer Comment

The results for the secondary endpoints related to FEV1 and FVC were supportive of a bronchodilatory effect for olodaterol. As with the primary endpoint, there was no incremental benefit for the 10mcg dose over the 5mcg dose with regard to FEV1-related secondary endpoints. Over the 48 week treatment period, spirometric responses for the olodaterol groups compared to placebo appeared to exhibit a downward trend. These results implied that the bronchodilatory effect may wane over the 48-week treatment period. Additionally, when comparing the treatment effect between 6 and 12 weeks (days 43 and 85), the treatment effects were of similar magnitude. However, it should be noted that the secondary analysis was amended post-database lock/unblinding, and did not protect against type 1 error.

Non-spirometric secondary endpoints:

For the secondary endpoint of daily rescue medication use (measured weekly) over the 48-week treatment period, both olodaterol dose groups demonstrated less rescue medication use (albuterol) compared to placebo. At weeks 1, 12, 24, and 48, the difference from placebo ranged from 0.51 to 1.1 puffs per day for olodaterol 5mcg (p -values from 0.0048-0.0005) and from 0.56 to 1.5 puffs per day for olodaterol 10mcg (p -values <0.0001-0.002).

The results for the secondary endpoints of daytime and night-time rescue medication use over the 48-week treatment period were similar. At weeks 1, 12, 24, and 48, the mean differences from placebo for daytime rescue medication use in olodaterol 5mcg were 0.15 ($p=0.051$), 0.47 ($p=0.007$), 0.434 ($p=0.0025$), and 0.52 ($p=0.0045$) puffs/day respectively. For olodaterol 10mcg mean differences from placebo were 0.16 ($p=0.03$), 0.54 ($p=0.002$), 0.56 ($p<0.0001$), and 0.65 ($p<0.0004$), respectively. Results for nighttime rescue medication use were similar.

The number and time to first COPD exacerbation were also evaluated as secondary endpoints. For time to first COPD exacerbation, moderate COPD exacerbation, and first COPD exacerbation leading to hospitalization, there were no statistically significant differences between olodaterol and placebo groups. However, there was a trend for earlier exacerbations in the placebo group versus olodaterol groups based on hazard ratios (Table 58). There were also no statistically significant differences with respect to number of exacerbations between groups. However, there was a trend for fewer exacerbations (any and moderate) in both olodaterol groups versus placebo as demonstrated by hazard ratios <1.

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Table 58. Trial 1222.11. Hazard Ratio (HR) for time to first exacerbation

| | Treatment | Hazard ratio (SE) compared to placebo | p-values |
|-----------------|------------|--|----------|
| Any | Olo 5mcg | 0.73 (0.12) | 0.66 |
| | Olo 10mcg | 0.80 (0.13) | 0.80 |
| Hospitalization | Olo 5mcg | 0.66 (0.25) | 0.28 |
| | Olo 10mcg | 1.01 (0.34) | 0.98 |
| Moderate | Olo 5 mcg | 0.74 (0.14) | 0.12 |
| | Olo 10 mcg | 0.81 (0.15) | 0.26 |

Source: Trial 1222.11 CSR; table 15.2.4:1; pg 395

PK data

Post-dosing olodaterol levels were comparable on days 43, 85 and 127. The geometric mean concentration 10 minutes after inhalation was 1.6 fold higher in olodaterol 10mcg versus olodaterol 5mcg. Serum concentrations were also slightly higher in Asians compared to Whites. There was also no evidence of a relationship between olodaterol serum levels and serum potassium levels. It should be noted that 13 (1.8%) out of the 725 plasma samples from placebo patients had detectable levels of olodaterol. Two samples came from a placebo patient who dispensed the wrong trial medication. In addition to the 11 placebo samples that had detectable olodaterol, 21 (5.2%) of 407 samples taken from olodaterol patients taken prior to first trial drug administration also had detectable olodaterol levels.

Reviewer comment

The detection of olodaterol in patients who were not exposed to olodaterol is concerning. However, the overall numbers were small and this would likely dilute treatment effects rather than accentuate them. As such, this does not affect efficacy conclusions.

Safety

Exposure

A total of 624 patients received at least one dose of trial drug (209 placebo, 208 Olo 5mcg, 207 Olo 10mcg). Mean exposure was higher in the olodaterol groups (303-307 days) compared to placebo (286 days). The difference was likely related to the higher number of discontinuations in the placebo group compared to the olodaterol groups. Patient exposure is summarized in Table 59

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Table 59. Trial 1222.11. Patient exposure

| | Placebo | Olo 5mcg | Olo 10mcg | Total |
|----------------------------------|------------|------------|------------|------------|
| Extent of exposure (days) | | | | |
| N | 209 | 208 | 207 | 624 |
| Mean | 286.2 | 303.4 | 306.6 | 298.7 |
| SD | 107.1 | 88.2 | 83.1 | 93.7 |
| Min | 1 | 11 | 1 | 1 |
| Median | 337 | 337 | 337 | 337 |
| Max | 391 | 372 | 376 | 391 |
| Extent of exposure [N(%)] | | | | |
| <=15 days | 10 (4.8) | 4 (1.9) | 4 (1.9) | 18 (2.9) |
| 16 - 43 days | 9 (4.3) | 4 (1.9) | 5 (2.4) | 18 (2.9) |
| 44 - 85 days | 5 (2.4) | 8 (3.8) | 4 (1.9) | 17 (2.7) |
| 86 - 127 days | 7 (3.3) | 5 (2.4) | 3 (1.4) | 15 (2.4) |
| 128 - 169 days | 3 (1.4) | 3 (1.4) | 5 (2.4) | 11 (1.8) |
| 170 - 225 days | 5 (2.4) | 5 (2.4) | 2 (1.0) | 12 (1.9) |
| 226 - 281 days | 5 (2.4) | 2 (1.0) | 6 (2.9) | 13 (2.1) |
| 282-337 days | 108 (51.7) | 111 (53.4) | 117 (56.5) | 336 (53.8) |
| >=338 days | 57 (27.3) | 66 (31.7) | 61 (29.5) | 184 (29.5) |

Source: Trial 1222.11 CSR; table 12.1:1; pg 104

Deaths

Of the 624 randomized patients, five patients died during the on-treatment period [Olo 5mcg=3 (1.4%), Olo 10mcg=1 (0.5%), and placebo=1 (0.5%)]. The on-treatment period was defined as the period starting after study drug initiation and ending 12 days after last dose. Deaths are summarized in Table 60.

Table 60. Trial 1222.11. Patient deaths during the on-treatment period and at vital status follow-up

| Period | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---|-----------------|------------------|-------------------|
| Total | 3 (1.5) | 4 (1.9) | 2 (1) |
| On treatment | 1 (0.5) | 3 (1.4) | 1 (0.5) |
| Solicited vital status follow-up | 2 (1) | 1 (0.5) | 1 (0.5) |

*one unsolicited death was reported 3.5 months after the vital status follow-period

Source: Trial 1222.11 CSR; tables 12.3.1:1 and 12.3.1:2; pp108 and 109

Based on investigator assessment, the placebo patient died of an aortic aneurysm and the olodaterol 10mcg patient died of lung cancer (small cell). The mortality adjudication committee (MAC) concurred with the investigator assessment. For the olodaterol 5mcg deaths, per investigator the causes of death were lung infection, acute respiratory failure, and respiratory failure. Per the MAC, the cause of death for these 3 patients was COPD exacerbation.

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An additional 4 patients died after early discontinuation of study treatment (Placebo=2, Olo 5mcg=1, Olo 10mcg= 1) and were reported as part of the solicited vital status follow-up (Table 60). The olodaterol 10mcg patient died due to a small bowel obstruction and the olodaterol 5mcg patient died of multiorgan failure (COPD exacerbation per MAC). The placebo patients died of “unknown” and multiple organ failure (unknown and cerebrovascular accident per MAC).

SAEs

One hundred sixteen (116) patients experienced SAEs (placebo=16.3%, Olo 5mcg=18.8%, and Olo 10mcg=20.8%). The most common SAEs were COPD exacerbation [42 patients (6.7%)], pneumonia [8 patients (1.3%)], lobar pneumonia [3 patients (0.5%)], atrial fibrillation [3 patients (0.5%)], and fall [3 (0.5%)]. Of these, only COPD exacerbations and falls occurred more frequently in the olodaterol group(s). COPD exacerbations occurred in 14 placebo patients (6.7%), 10 olodaterol 5mcg patients (4.8%), and 18 olodaterol 10mcg patients (8.7%). The numbers of patients with falls in the placebo, olodaterol 5mcg, and olodaterol 10mcg groups were 0, 1 (0.5%), and 2 (1%), respectively.

There appeared to be a small numerical imbalance for SAEs under the SOC nervous system disorders [placebo=1 (0.5%), Olo 5mcg=4 (1.9%), and Olo 10mcg (2.4%)]. However, within this SOC, none of the adverse events (by preferred terms) followed a clear dose response. There was also a small numerical imbalance when analyzing the SOC cardiac disorders [placebo=4 (1.9%), Olo 5mcg=5 (2.4%), Olo 10mcg=5 (2.4%)]. Within the cardiac disorder SOC, atrial fibrillation exhibited a small imbalance [placebo=0, Olo 5mcg=1 patient (0.5%), Olo 10mcg= 2 patients (1%)]. As the numbers are small and are not adjusted for exposure, conclusions cannot be drawn based on this trial. These events will be further evaluated in the safety summary (section 7 Review of Safety)

All SAEs by SOC are summarized in Table 61. This table also includes PTs that occurred in ≥ 2 patients. Note that not all SAEs by PT are included. Additionally, if a PT that occurred in < 2 patients was similar to a PT that occurred in ≥ 2 patients, that PT was also listed in the SAE table (e.g. lobar pneumonia and lung infection).

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Table 61. Trial 1222.11. All serious adverse events by SOC (PTs listed when they occurred in ≥2 patients)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---|-----------------|------------------|-------------------|
| Total patients | 209 (100) | 208 (100) | 207 (100) |
| Total SAEs | 34 (16.3) | 39 (18.8) | 43 (20.8) |
| Infections Infestations | 6 (2.9) | 10 (4.8) | 4 (1.9) |
| Pneumonia | 4 (1.9) | 2 (1) | 2 (1) |
| Lobar pneumonia | 1 (0.5) | 1 (0.5) | 1 (0.5) |
| Lung infection* | 0 | 1 (0.5) | 0 |
| Infective COPD exacerbation | 1 (0.5) | 1 (0.5) | 0 |
| Urinary tract infection | 0 | 2 (1) | 0 |
| Osteomyelitis | 0 | 1 (0.5) | 1 (0.5) |
| Neoplasms benign and malignant | 2 (1) | 5 (2.4) | 8 (3.9) |
| Small cell cancer | 0 | 0 | 2 (0.3) |
| Lung adenocarcinoma | 1 (0.5) | 1 (0.5) | 0 |
| Endocrine disorder (goiter) | 0 | 0 | 1 (0.5) |
| Psychiatric disorder (bipolar) | 0 | 0 | 1 (0.5) |
| Eye disorder (amaurosis fugax) | 0 | 0 | 1 (0.5) |
| Nervous system disorder | 1 (0.5) | 4 (1.9) | 5 (2.4) |
| Carotid artery stenosis | 0 | 0 | 2 (0.3) |
| Syncope | 0 | 0 | 2 (0.3) |
| Cardiac disorders | 4 (1.9) | 5 (2.4) | 5 (2.4) |
| Atrial fibrillation | 0 | 1 (0.5) | 2 (1) |
| Coronary artery occlusion | 2 (1) | 0 | 0 |
| Coronary artery disease | 0 | 1 (0.5) | 1 (0.5) |
| Vascular disorders | 1 (0.5) | 3 (1.4) | 0 |
| Respiratory, thoracic, mediastinal | 16 (7.7) | 12 (5.8) | 18 (8.7) |
| COPD exacerbation | 14 (6.7) | 10 (4.8) | 18 (8.7) |
| Acute respiratory failure | 0 | 1 (0.5) | 0 |
| Respiratory failure | 1 (0.5) | 1 (0.5) | 0 |
| Pneumothorax | 1 (0.5) | 0 | 1 (0.5) |
| Gastrointestinal disorder | 6 (2.9) | 0 | 4 (1.9) |
| Gastritis | 2 (1) | 0 | 0 |
| Inguinal hernia | 1 (0.5) | 0 | 1 (0.5) |
| Hepatobiliary disorder (bile duct stone) | 0 | 0 | 1 (0.2) |
| Musculoskeletal disorder | 1 (0.5) | 4 (1.9) | 4 (1.9) |
| Musculoskeletal pain | 0 | 1 (0.5) | 1 (0.5) |
| Renal and urinary disorders | 0 | 1 (0.5) | 1 (0.5) |
| General disorders | 1 (0.5) | 0 | 2 (1) |
| Investigations | 0 | 0 | 1 (0.5) |
| Increased CPK | 0 | 0 | 1 (0.5) |
| Increased myoglobin | 0 | 0 | 1 (0.5) |
| Injury, poisoning, and procedural complications | 1 (0.5) | 4 (1.9) | 4 (1.9) |
| Fall | 0 | 1 (0.5) | 2 (1) |

*listed as the PT was similar to pneumonia and lobar pneumonia

Source: trial 1222.11 CSR; table 15.3.2.1:6; pp433-437

AEs leading to withdrawal

Fifty one patients (8.2%) withdrew due to AEs. This occurred more frequently in the placebo group [20 patients (9.6%)] compared to the olodaterol groups [Olo 10mcg=16 patients (7.7%), Olo 5mcg=15 patients (7.2%)]. The most common AE leading to discontinuation was COPD exacerbation [13 patients (2.1%)] and dyspnea [4 patients

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(0.6%)]. Both were more common in the placebo group compared to the olodaterol groups.

A summary of all AEs by SOC leading to discontinuation can be found in Table 62. Within a SOC if ≥2 patients withdrew due to the same AE based on PT, then the PT was listed. Additionally, if a PT that occurred in <2 patients was similar to a PT that occurred in ≥2 patients, that PT was also listed in the SAE table (e.g. lobar pneumonia and pneumonia).

Table 62. Trial 1222.11. All adverse events leading to discontinuation by SOC (PTs listed if they occurred in ≥2 patients)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---|-----------------|------------------|-------------------|
| Total patients | 209 (100) | 208 (100) | 207 (100) |
| Total AEs leading to discontinuation | 20 (9.6) | 15 (7.2) | 16 (7.7) |
| Infections Infestations | 2 (1) | 3 (1.4) | 0 |
| Pneumonia | 1 (0.5) | 0 | 0 |
| Lobar pneumonia | 0 | 2 (1) | 0 |
| Lung infection* | 0 | 1 (0.5) | 0 |
| Neoplasms benign and malignant | 2 (1) | 2 (1) | 5 (2.4) |
| Lung adenocarcinoma | 1 (0.5) | 1 (0.5) | 0 |
| Psychiatric disorder | 0 | 0 | 2 (0.5) |
| Nervous system disorder | 0 | 1 (0.5) | 0 |
| Eye disorder | 0 | 0 | 1 (0.5) |
| Cardiac disorders | 1 (0.5) | 2 (1) | 1 (0.5) |
| Atrial fibrillation | 0 | 1 (0.5) | 1 (0.5) |
| Vascular disorders | 2 (1) | 1 (0.5) | 0 |
| Respiratory, thoracic, mediastinal | 13 (6.2) | 6 (2.9) | 4 (1.9) |
| COPD exacerbation | 7 (3.3) | 2 (1) | 4 (1.9) |
| Acute respiratory failure | 0 | 1 (0.5) | 0 |
| Respiratory failure | 1 (0.5) | 1 (0.5) | 0 |
| Gastrointestinal disorder | 1 (0.5) | 0 | 2 (1) |
| Hepatobiliary disorder (bile duct stone) | 0 | 0 | 1 (0.2) |
| Musculoskeletal disorder | 0 | 1 (0.5) | 0 |
| General disorders | 0 | 1 (0.5) | 0 |
| Investigations | 0 | 1 (0.5) | 1 (0.5) |
| Increased CPK | 0 | 0 | 1 (0.5) |
| Increased myoglobin | 0 | 0 | 1 (0.5) |
| Injury, poisoning, and procedural complications | 0 | 2 (1) | 2 (1) |

*listed as the PT was similar to pneumonia and lobar pneumonia

Source: trial 1222.11 CSR; table 15.3.2.1:5; pp430-432

Common treatment emergent AEs (TEAEs)

In this trial, TEAEs were defined as AEs that occurred after the first dose in a treatment period until 12 days after the last dose in a treatment period. Overall, AEs occurred with similar frequency during olodaterol treatment periods (71-73%) and placebo periods (74%). The most common AEs by SOC were respiratory, mediastinal, and thoracic; infections and infestations; and gastrointestinal disorders. The most common AEs ($\geq 3\%$) based on preferred term were COPD exacerbation, URI, nasopharyngitis,

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bronchitis, hypertension, cough, and dyspnea. There was no evidence of dose response for any of these AEs. Common TEAEs (>3%) are summarized in Table 63.

Table 63. Trial 1222.11. Common treatment emergent AEs (>3%)

| System Organ Class/ Preferred Term | Placebo N (%) | Olodaterol 5 µg N (%) | Olodaterol 10 µg N (%) | Total N (%) |
|---|------------------|-----------------------------|------------------------------|----------------|
| Number of patients | 209 (100) | 208 (100) | 207 (100) | 624 (100) |
| Total with AEs | 155 (74.2) | 151 (72.6) | 146 (70.5) | 452 (72.4) |
| Infections and infestations | 69 (33.0) | 85 (40.9) | 62 (30.0) | 216 (34.6) |
| Upper respiratory tract infection | 15 (7.2) | 21 (10.1) | 13 (6.3) | 49 (7.9) |
| Nasopharyngitis | 13 (6.2) | 21 (10.1) | 13 (6.3) | 47 (7.5) |
| Bronchitis | 8 (3.8) | 11 (5.3) | 6 (2.9) | 25 (4.0) |
| Urinary tract infection | 4 (1.9) | 9 (4.3) | 5 (2.4) | 18 (2.9) |
| Sinusitis | 8 (3.8) | 1 (0.5) | 7 (3.4) | 16 (2.6) |
| Nervous system disorders | 10 (4.8) | 16 (7.7) | 22 (10.6) | 48 (7.7) |
| Dizziness | 4 (1.9) | 7 (3.4) | 4 (1.9) | 15 (2.4) |
| Vascular disorders | 16 (7.7) | 11 (5.3) | 13 (6.3) | 40 (6.4) |
| Hypertension | 12 (5.7) | 3 (1.4) | 8 (3.9) | 23 (3.7) |
| Respiratory, thoracic and mediastinal disorders | 103 (49.3) | 78 (37.5) | 84 (40.6) | 265 (42.5) |
| COPD | 71 (34.0) | 50 (24.0) | 67 (32.4) | 188 (30.1) |
| Cough | 8 (3.8) | 14 (6.7) | 7 (3.4) | 29 (4.6) |
| Dyspnoea | 11 (5.3) | 10 (4.8) | 4 (1.9) | 25 (4.0) |
| Gastrointestinal disorders | 32 (15.3) | 35 (16.8) | 28 (13.5) | 95 (15.2) |
| Diarrhoea | 7 (3.3) | 9 (4.3) | 4 (1.9) | 20 (3.2) |
| Nausea | 4 (1.9) | 5 (2.4) | 7 (3.4) | 16 (2.6) |
| Constipation | 7 (3.3) | 3 (1.4) | 6 (2.9) | 16 (2.6) |
| Musculoskeletal and connective tissue disorders | 20 (9.6) | 34 (16.3) | 28 (13.5) | 82 (13.1) |
| Back pain | 4 (1.9) | 4 (1.9) | 7 (3.4) | 15 (2.4) |
| Arthralgia | 2 (1.0) | 7 (3.4) | 1 (0.5) | 10 (1.6) |

Source: Trial 1222.11 CSR; table 12.2.2.2.1;pg107

Forty one patients experienced administration-related bronchospasm ($\geq 15\%$ decrease in FEV1 post-dose or rescue medication use). Administration-related bronchospasm was more common in placebo (13.4%) than olodaterol 5mcg or 10 mcg groups (2.4% and 3.9%, respectively).

Reviewer comment:

The deaths reported in this trial were not necessarily surprising given the patient population. The small imbalance seen in the total SAEs is of some concern, as is the small imbalance seen in the nervous system and cardiac disorder SOCs, and the atrial fibrillation PT. However, the overall numbers were small and analysis of the larger pooled safety data set would likely be more informative. The common AEs were typical for what one would expect in a COPD program.

Labs:

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Based on mean lab values, there were no notable changes in lab values except for CPK. Mean changes from baseline were -24U/L, 8U/L, and 59 U/L for the placebo, olodaterol 5mcg, and olodaterol 10mcg groups. More patients in the olodaterol groups also had normal CPK levels at baseline and above normal maximum in treatment values (placebo=6.4%, Olo 5mcg=17.5%, and Olo 10mcg=20.8%). One patient (Olo 10mcg) was discontinued due to an increased CPK (amaurosis fugax and increased myoglobin were also listed as the reasons discontinuation). When examining glucose and potassium, the number of patients per group who had normal baseline values and elevated maximum values were similar between groups. Based on mean values, there was also no difference between groups with regard to potassium values.

When examining potentially clinically significant changes in lab values as defined by the sponsor, numbers were generally similar between groups. Note that potentially clinically significant was defined by lab values and not clinical outcomes. However, for a small number of lab parameters changes were more frequent in olodaterol groups (Table 64).

Table 64. Trial 1222.11. Potentially clinical significant changes in lab parameters that were more frequent in olodaterol groups versus placebo

| | Placebo n/N(%) | Olo 5mcg n/N(%) | Olo 10mcg n/N(%) |
|------------------------|-------------------|--------------------|---------------------|
| Low Values | | | |
| Hematocrit | 0 | 1/197 (0.5) | 2/196 (1.0) |
| White blood cell count | 0 | 1/197 (0.5) | 0 |
| Sodium | 0 | 1/197 (0.5) | 4/197 (2.0) |
| Calcium | 0 | 0 | 1/197 (2.0) |
| High Values | | | |
| GGT | 3/187 (1.6) | 2/195 (1.0) | 5/192 (2.6) |
| Potassium | 0 | 0 | 1/201 (0.5) |

Source:Trial 1222.11 CSR; table 12.4.1.3:1; pg113

Reviewer comments:

The findings with regard to CPK were not necessarily surprising as it was likely a pharmacodynamic effect of olodaterol. These results were also consistent with what was seen in the dose ranging trials. It is also reassuring that the only CPK value that led to discontinuation was in the olodaterol 10mcg group and not at the proposed to be marketed dose (5mcg). With regard to potentially clinical significant lab changes, the numbers were very small, so results should be interpreted with caution.

Vital signs:

With regard to systolic blood pressure (SBP), there were no significant differences between groups based on change in mean values, shifts from normal to low, or shifts from normal to high. The same was true for diastolic blood pressure (DBP) and pulse rate.

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ECG

ECGs were assessed as mean changes from baseline, mean changes exceeding a pre-specified threshold (450, >480, or >500ms in QTcF interval), mean changes exceeding categorized change (>30ms or >60ms in QTcF interval), and notable changes. Notable changes were defined as in Table 65.

Table 65. Trial 1222.11. Definition for notable changes in heart rate, PR interval, and QRS interval

| Change | Criteria |
|-----------------------|--|
| Heart rate increase | ≥25% increase from baseline and on-treatment value > 100 bpm |
| Heart rate decrease | ≥25% decrease from baseline and on-treatment value < 50 bpm |
| PR interval increase | ≥25% increase from baseline and on-treatment value >200 ms |
| QRS interval increase | ≥10% increase from baseline and on-treatment value > 110 ms |

Based on these parameters, there were no notable changes from baseline. When analyzing the QTcF based on categorized change (>30ms or >60ms), the overall numbers were small for all time points. During the entire treatment period, there were only 4 reported increases of QTcF of >60ms. Reports of increases >30ms were more frequent; however, there was neither a clear dose-dependent nor time dependent effect. A prolonged PR interval was reported as an AE for one patient and a prolonged QTc interval was reported in 2 patients (one placebo, one Olo 5mcg). These patients did not discontinue treatment.

Holter monitoring

With regard to supraventricular couplets and supraventricular runs, changes from baseline at days 85, 169, 281, and 337 were variable within groups. Within groups, there were no apparent time-related trends. Between groups, there were also no consistent differences.

Based on shift table analysis of ventricular premature beats (VPB) and supraventricular premature beats (SVPB), almost all patients had similar numbers of SVPBs when comparing baseline values to last values on treatment.

Reviewer Comment:

With regard to vital signs, ECG, and holter data, no significant imbalances were seen. Notably, the olodaterol groups did not appear to have an increased frequency of QTcF prolongation as was implied in some of the asthma dose ranging trials. However, the pooled ECG and holter data from the 48-week trials will be analyzed in the combined safety section.

Overall reviewer comment on trial 1222.1:

Based on the sponsor analysis of the primary endpoints, both doses of olodaterol are effective bronchodilators. The 10 mcg dose of olodaterol offers no added benefit

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compared to the 5 mcg dose. It should be noted that the difference from placebo with respect to trough FEV1, is relatively small compared to other bronchodilators, however, this trial allowed for the use of all background COPD medications except for LABAs. As such, a patient could also have been on tiotropium. The trough FEV1 response in the non-tiotropium strata tended to be larger compared to the tiotropium-treated strata. With regard to maintenance of effect, the magnitude of the treatment effect (based on the primary endpoint) appeared to wane somewhat from 6-48 weeks. There appeared to be no statistically significant effect on exacerbations and some mild improvement in rescue medication use.

With regard to safety, the deaths were fairly well balanced. The most common SAEs were COPD exacerbation, pneumonia, lobar pneumonia, atrial fibrillation, and falls. Of these, only COPD exacerbations and falls occurred more frequently in the olodaterol group(s). No clear dose responses were demonstrated. Common AEs were typical of what one would expect in a COPD trial.

5.3.9 Trial 1222.12 (COPD 48-Week Trial)

Administrative Information

- **Study title:** Randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled olodaterol (5mcg [2 actuations of 2.5mcg] and 10mcg [2 actuations of 5mcg]) delivered by the Respimat inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 2/5/2009-9/27/2010
- **Study sites:** China (11 sites), Germany (7 sites), Taiwan (5 sites), U.S. (29 sites)
- **Study report date:** 01/09/2012

Objectives/Rationale

- To assess the long-term efficacy and safety of olodaterol (5mcg and 10mcg once daily) compared to placebo in patients with COPD

Study Design and Conduct

The design, conduct, inclusion/exclusion criteria, medication restrictions, endpoints, and statistical analysis plan were identical to trial 1222.11. The amendments to the protocol were also similar. As with trial 1222.11, the primary analysis plan was altered post-database lock and unblinding.

Results

Protocol Violations

A total of 25 (3.9%) patients had what the sponsor designated as important protocol violations (IPV). The most common violation was 'study medication taken significantly longer than planned treatment durations (end of treatment plus 2 weeks). One patient

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(#6947) received the incorrect study drug at the time of the primary endpoint. This patient was supposed to receive placebo, but received olodaterol 10mcg from day 43-85. This violation is most likely to bias against the efficacy of the drug, so is unlikely to have affected overall study results. Two additional patients received incorrect trial medication (subjects 6761 and 7024); however, as the incorrect medication was only administered outside the primary endpoint window, these were not considered major protocol violations. Important protocol violations are summarized in Table 66.

Table 66. Trial 1222.12. Important protocol violations

| | Placebo [N(%)] | Olo 5mcg [N(%)] | Olo 10mcg [N(%)] | Total [N(%)] |
|--|-------------------|--------------------|---------------------|-----------------|
| Randomized | 216 (100) | 209 (100) | 217 (100) | 644 *(100) |
| Total with important protocol violations | 13 (6.0) | 4 (1.9) | 8 (3.7) | 25 (3.9) |
| Inclusion criteria not met | 2 (0.9) | 1 (0.5) | 2 (0.9) | 5 (0.8) |
| Exclusion criteria affecting efficacy and possibly safety | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Exclusion Criteria affecting safety only | 1(0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Study drug not taken on day prior to primary endpoint clinic visit | 1(0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Study medication taken longer than planned duration | 9 (4.2) | 3 (1.4) | 4 (1.8) | 16 (2.5) |
| Incorrect trial medication dispensed | 1 (0.5) | 0 | 0 | 1(0.2) |

*only 642 patients received study medication; see Disposition

Source: Trial 1222.12 CSR; table 15.1.2:1; pg 162

Disposition

Of the 892 enrolled patients, 644 were randomized. Of the randomized patients, 541 (84.3%) completed the trial. Six-hundred forty three (643) patients received at least one dose of study medication. One patient was randomized but prior to first administration experienced an AE and decided to discontinue. Another patient did not sign the HIPAA form prior to enrolling. This was only noted after the patient had received olodaterol 5mcg for 1 month and reported 2 SAEs (pneumonia and pneumothorax). Because the patient did not sign the HIPAA form, he was withdrawn from the trial and his data excluded. As such, only 642 patients were included in the treated set. The most common reason for discontinuations were AEs, lack of efficacy, and withdrawal of consent. Discontinuations were less common in the olodaterol groups compared to placebo. ‘Lack of efficacy’ as a reason for withdrawal was more common in placebo-treated patients. Of the patients in the treated set, 637 were included in the FAS used for the efficacy analysis. Two-hundred-eighteen (218) patients received Holter monitoring. Although there was PPS, analysis was not performed using this set, per the analysis plan (PPS analysis was only performed if the difference between the FAS and PPS were >10%.) Patient disposition and analysis populations are summarized in Table 67.

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Table 67. Trial 1222.12. Patient disposition and analysis populations

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Total N(%) |
|---------------------------|-----------------|------------------|-------------------|---------------|
| Treated Set | 216 (100) | 209 (100) | 217 (100) | 642 (100) |
| Full Analysis Set (FAS) | 215 (99.5) | 207 (99) | 215 (99.1) | 637 (99.2) |
| Per Protocol Set (PPS) | 210 (97.2) | 206 (98.6) | 211 (97.2) | 627 (97.7) |
| 12-hour PFT set (TPS) | 98 (45.4) | 116 (55.5) | 107 (49.3) | 321 (50) |
| Holter set (HMS) | 74 (34.3) | 71 (34) | 73 (33.6) | 218 (34) |
| Completed | 175 (81.0) | 185 (88.5) | 181 (83.4) | 541 (84.3) |
| Premature discontinuation | 41 (18.98) | 24 (11.48) | 36 (16.59) | 101 (15.73) |
| Adverse events | 20 (9.26) | 10 (4.78) | 20 (9.22) | 50 (7.79) |
| AE study disease worse | 8 (3.70) | 3 (1.44) | 2 (0.92) | 13 (2.02) |
| AE-other disease worse | 3 (1.39) | 3 (1.44) | 2 (0.92) | 8 (1.25) |
| AE-other | 9 (4.17) | 4 (1.91) | 16 (7.37) | 29 (4.52) |
| Lack of Efficacy | 10 (4.63) | 5 (2.39) | 2 (0.92) | 17 (2.65) |
| Non-compliance | 2 (0.93) | 0 (0.00) | 0 (0.00) | 2 (0.31) |
| Lost to follow-up | 1 (0.46) | 2 (0.96) | 3 (1.38) | 6 (0.93) |
| Consent withdrawn | 3 (1.39) | 5 (2.39) | 8 (3.69) | 16 (2.49) |
| Other | 5 (2.31) | 2 (0.96) | 3 (1.38) | 10 (1.56) |

Source: Trial 1222.12 CSR; tables 10.1:1 and 11.1:1; pp72 and 75

Reviewer Comment:

Overall, there were more important protocol violations (IPV) in the placebo group compared to olodaterol groups. This is in contrast to trial 1222.11, where there were more IPVs in the olodaterol groups compared to placebo. However, the overall numbers were small and are unlikely to affect interpretation. With regard to discontinuations, they were less frequent in the olodaterol 5mcg group compared to placebo and olodaterol 10mcg. The difference between the placebo and olodaterol 5mcg group was driven primarily by increased discontinuation due to AEs and lack of efficacy in the placebo group. This may imply a treatment effect for olodaterol. It should be noted that 'lack of efficacy' as a reason for discontinuation was inversely related to dose. However, it should also be noted that 'AE-other' was much more common in olodaterol 10mcg compared to olodaterol 5mcg and placebo.

Demographics

Overall, patient demographics were similar between treatment groups. Most patients were white males with a mean age of 65. The average pack-year history was 50 years and most patient were ex-smokers (56%). The average time since COPD diagnosis was 7.6 years. Across all treatment groups, 43-49% of patients were GOLD II and 33-45% were GOLD III. The average FEV1% predicted was approximately 43% across groups. Demographic and baseline respiratory data are summarized in Table 68.

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Table 68. Trial 1222.12. Patient demographic and baseline respiratory data

| | Placebo | Olo 5mcg | Olo 10mcg | Total |
|----------------------------------|------------|------------|------------|------------|
| Number of patients | 216 | 209 | 217 | 642 |
| Gender [N (%)] | | | | |
| Male | 152 (70.4) | 152 (72.7) | 152 (70.0) | 456 (71.0) |
| Female | 64 (29.6) | 57 (27.3) | 65 (30.0) | 186 (29.0) |
| Age [years] N | 216 | 209 | 217 | 642 |
| Mean | 63.8 | 64.7 | 65.4 | 64.6 |
| SD | 8.3 | 8.1 | 9.7 | 8.8 |
| Race [N (%)] | | | | |
| Native American | 1 (0.5) | 0 (0.0) | 1 (0.5) | 2 (0.3) |
| Asian | 73 (33.8) | 68 (32.5) | 71 (32.7) | 212 (33.0) |
| Black | 3 (1.4) | 7 (3.3) | 9 (4.1) | 19 (3.0) |
| White | 139 (64.4) | 134 (64.1) | 136 (62.7) | 409 (63.7) |
| Smoking history [N (%)] | | | | |
| Ex-smokers | 125 (57.9) | 111 (53.1) | 125 (57.6) | 361 (56.2) |
| Currently smokers | 91 (42.1) | 98 (46.9) | 92 (42.4) | 281 (43.8) |
| Smoking history [pack years] | | | | |
| Mean | 47.8 | 52.3 | 50.8 | 50.3 |
| SD | 23.0 | 27.3 | 31.0 | 27.3 |
| Trial diagnosis duration [years] | | | | |
| Mean | 7.7 | 7.5 | 7.6 | 7.6 |
| SD | 6.4 | 6.9 | 6.5 | 6.6 |
| FEV1 % predicted | | | | |
| Mean | 43.1 | 42.9 | 43.0 | 43.0 |
| SD | 16.0 | 13.8 | 15.2 | 15.0 |
| FEV1/FVC | | | | |
| Mean | 45.3 | 46.7 | 44.7 | 45.5 |
| SD | 12.1 | 12.2 | 11.6 | 12.0 |
| FEV1% change after albuterol | | | | |
| Mean | 15.4 | 16.6 | 14.9 | 15.6 |
| SD | 13.1 | 17.2 | 14.9 | 15.1 |

source: Trial 1222.12 CSR; tables 11.2:1, 11.2:2, 11.2.5:1, 11.2.5:2; pp77, 78, 81, 82

Across treatment groups, patients had similar numbers and types of concomitant medical diagnoses. The most common medical diagnoses were hypertension (39-44%), gastroesophageal reflux (13-19%), hyperlipidemia (15-16%), osteoarthritis (12-13%), depression (10-13%), back pain (10-12%), anxiety (7-12%), and benign prostatic hyperplasia (9-11%). Cardiac disorders (by SOC and preferred term) were fairly evenly distributed across groups (27-31%). Baseline medications were also similar between groups; however, during the treatment period, more patients in the olodaterol groups (~22%) received oral steroids compared to placebo (15%).

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Reviewer Comment:

Overall, the patient demographics, baseline respiratory parameters, concomitant medications, and concomitant medical diagnoses were similar between groups. However it is worth noting that during the treatment period, both the 5 and 10mcg olodaterol groups had more use of oral steroids, which may imply that exacerbation was more frequent in the olodaterol groups. Interestingly, while the sponsor's analysis of the co-primary endpoints demonstrated a bronchodilator effect, no effect on exacerbation-related parameters was seen.

Compliance

Compliance was also similar between groups. Based on eDiary data, compliance ranged from 97-98% across all groups.

Efficacy

Co-primary endpoints:

The co-primary endpoints for this trial were FEV1 AUC (0-3 hours) response and trough FEV1 response. Note that the primary analysis plan was amended after database lock and unblinding. Based on the amended analysis plan, both doses demonstrated statistically significant differences from placebo for both co-primary endpoints. There was no evidence of a dose response. The results of the sponsor's analysis are summarized in Table 69.

Table 69. Trial 1222.12. Sponsor's amended analysis of co-primary endpoints [FEV1 AUC (0-3 hours) and trough FEV1 response after 12 weeks of treatment]

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|--------------------------------------|------------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | 0.008 (0.013) | | | -0.003 (0.014) | | |
| Olo 5 mcg | 0.159 (0.013) | 0.151(0.017) | <0.0001 | 0.044 (0.014) | 0.047(0.019) | 0.0116 |
| Olo 10 mcg | 0.152 (0.013) | 0.143(0.017) | <0.0001 | 0.045 (0.014) | 0.048(0.019) | 0.0095 |

Source: Trial 1222.12 CSR, table 11.4.1.1:1, 11.4.1.1:3; pp88 and 89

The sponsor also performed a sensitivity analysis using the original pre-specified analysis plan. In this analysis, neither olodaterol dose demonstrated a statistically significant difference from placebo with respect to trough FEV1. As with the amended analysis, there were minimal differences between olodaterol 5mcg and olodaterol 10mcg. These results are summarized in Table 70.

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Table 70. Trial 1222.12. Original pre-specified analysis of co-primary endpoints

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|--------------------------------------|------------------------|---------|---------------------------|------------------------|---------|
| Placebo | 0.021 (0.016) | | | 0.005 (0.17) | | |
| Olo 5 mcg | 0.155 (0.016) | 0.134(0.022) | <0.0001 | 0.038 (0.017) | 0.033 (0.024) | 0.1624 |
| Olo 10 mcg | 0.151 (0.016) | 0.130(0.022) | <0.0001 | 0.049 (0.016) | 0.045 (0.023) | 0.0563 |

Source: Trial 1222.12 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2.16 and 6.1.1.2.14; pp 549 and 711.

When comparing the co-primary endpoints between patients in the tiotropium strata to non-tiotropium strata, the treatment difference from placebo was of greater magnitude in the non-tiotropium strata. The comparisons to placebo all had p-values <0.05; however, these comparisons were not corrected for multiplicity (Type I error) and since they were comparing subsets of patients, are not powered for a treatment response. These results are summarized in Table 71.

Table 71. Trial 1222.12. Sponsor analysis by strata for co-primary endpoints

| Treatment Group | Tiotropium Strata | | | Non-tiotropium Strata | | |
|-----------------|--------------------------------------|------------------------|---------|--------------------------------------|------------------------|---------|
| | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | 0.044 (0.028) | | | -0.003 (0.014) | | |
| Olo 5 mcg | 0.151 (0.029) | 0.107 (0.040) | 0.0077 | 0.158 (0.014) | 0.161 (0.019) | <0.0001 |
| Olo 10 mcg | 0.152 (0.027) | 0.107 (0.039) | 0.0057 | 0.149 (0.014) | 0.152 (0.019) | <0.0001 |
| | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | 0.019 (0.030) | | | -0.009 (0.015) | | |
| Olo 5 mcg | 0.030 (0.030) | 0.011 (0.043) | 0.7990 | 0.047 (0.015) | 0.056 (0.021) | 0.0073 |
| Olo 10 mcg | 0.058 (0.029) | 0.039 (0.042) | 0.3489 | 0.041 (0.015) | 0.050 (0.021) | 0.0162 |

Source: Trial 1222.12 CSR; Tables 11.4.1.1:2 &11.4.1.1:4; pp 89 and 90

Reviewer Comment:

As the sponsor's amended primary analysis plan was altered after unblinding, these results cannot be used as primary evidence for efficacy. As such, the pre-specified analysis was used to assess efficacy. Based on those results, neither olodaterol 5mcg nor olodaterol 10mcg demonstrated a consistent bronchodilatory effect for both co-primary endpoints. Both failed for the co-primary endpoint of trough FEV1. It should also be noted that the treatment effect based on trough FEV1 response, whether looking at the pre-specified analysis or amended analysis, is much smaller in this trial compared to 1222.11. With regard to the by strata analysis, not surprisingly, the difference from placebo was greater for both co-primary endpoints for the non-tiotropium strata versus

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the tiotropium strata. This by-strata difference is not surprising as both olodaterol and tiotropium are bronchodilators. However, even examining the results for patients not on tiotropium, the treatment effect is modest.

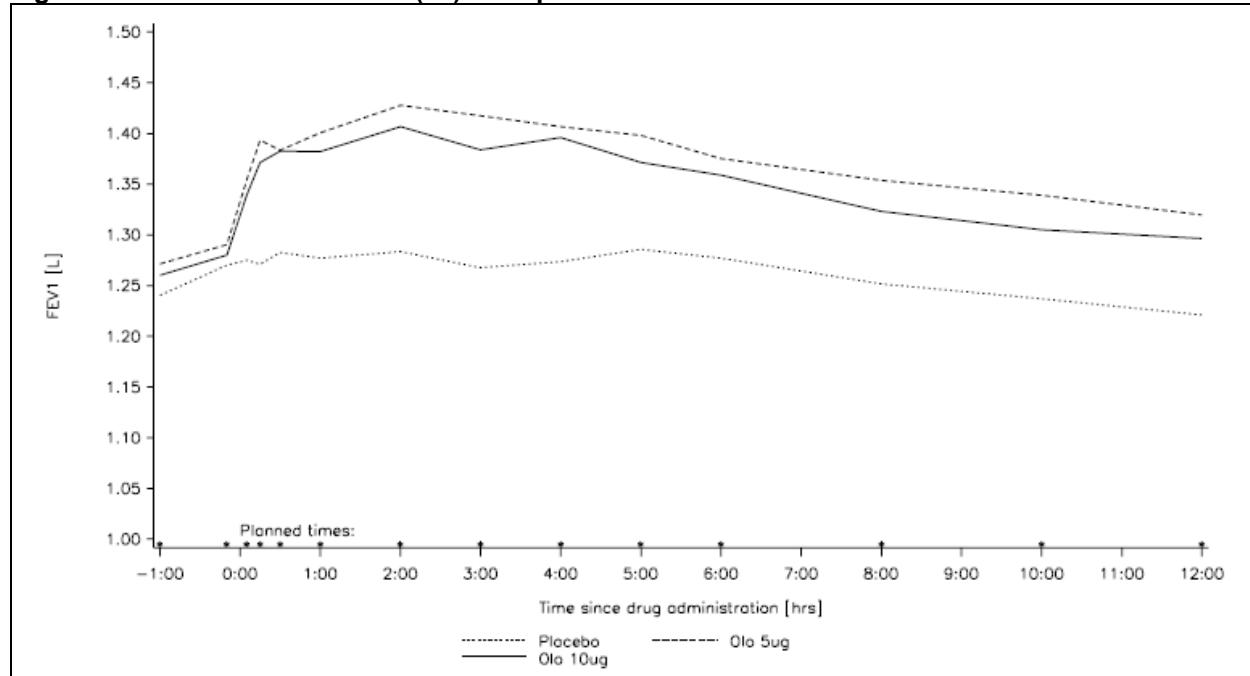
Secondary Endpoints

As with trial 1222.11, the secondary endpoints did not have a pre-specified hierarchical analysis plan. Therefore, there was no protection against type I error and all the reported p-values for all secondary endpoints should be considered descriptive. Additionally, as with the primary analysis, the secondary analysis was revised post-database lock and unblinding.

Spirometric Secondary Endpoints

This trial included multiple FEV1-related secondary endpoints. A subset of patients (TPS) received 12 hour post-dose spirometry at week 12. For these patients, FEV1 AUC (0-12 hours) response was compared between olodaterol groups and placebo. Results demonstrated that the olodaterol 10mcg and olodaterol 5mcg groups had a difference from placebo of 0.089L ($p=0.0011$) and 0.110L ($p<0.0001$), respectively. These results are summarized graphically in Figure 14. Sensitivity analysis using unadjusted means (original pre-specified analysis plan) demonstrated similar results.

Figure 14. Trial 1222.12. Twelve (12) hour post-dose FEV1 at week 12



Source: Trial 1222.12 CSR; figure 15.2.1.1.1:3; pg229

For the secondary endpoint of FEV1 AUC (0-3 hours) response after 48 weeks of treatment, the olodaterol 10mcg and olodaterol 5mcg dose groups had differences from placebo of 0.161L and 0.158L (p -values <0.0001), respectively. At days 1, 43, 85, 169,

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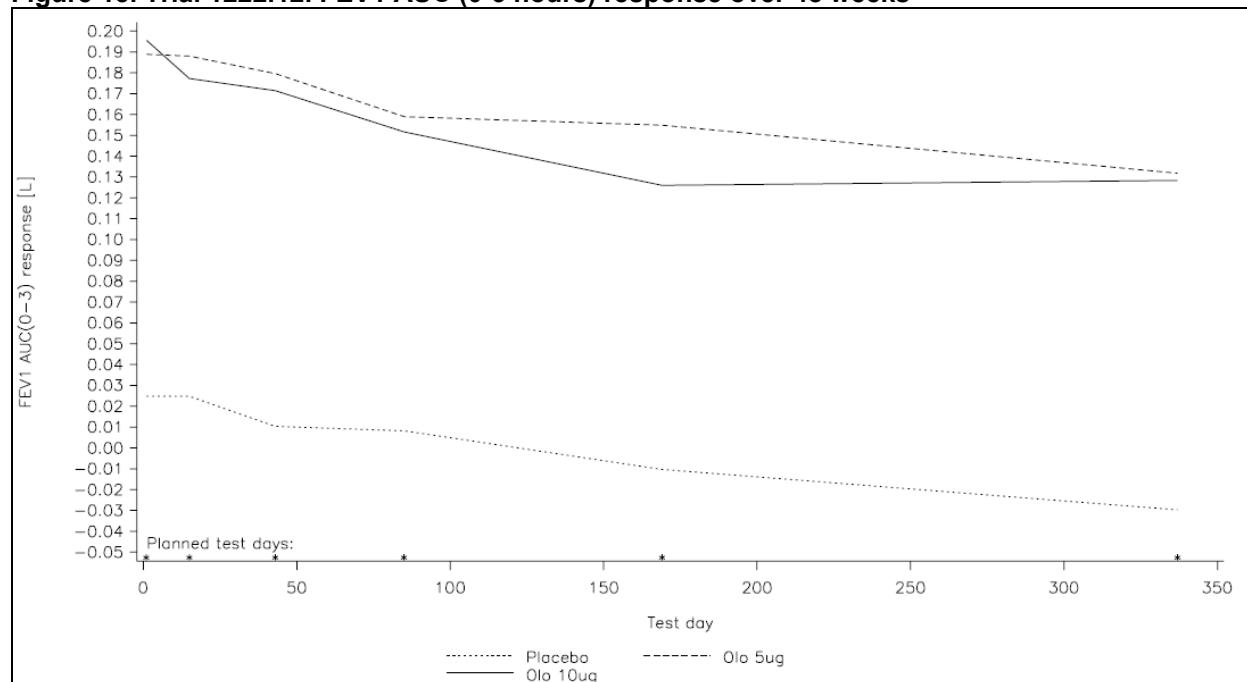
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and 337, the results were similar, all with p-values <0.0001. The magnitude for the differences from placebo for the olodaterol 5mcg group at days 1, 43, 85, 169, and 337 were 0.164, 0.169, 0.151, 0.165, and 0.161L, respectively. For olodaterol 10mcg, the differences from placebo at the same time points were 0.171, 0.161, 0.143, 0.136, and 0.158L, respectively. These results are represented graphically in Figure 15.

Figure 15. Trial 1222.12. FEV1 AUC (0-3 hours) response over 48 weeks



Source: Trial 1222.12 CSR; figure 15.2.1.2:1; pg242

For the secondary endpoint of trough FEV1 response over the 48 week period, both olodaterol doses demonstrated an increase in response compared to placebo on all tested days (days 15, 43, 85, 169, and 337). The mean differences from placebo in liters for olodaterol 5mcg were 0.053, 0.073, 0.047, 0.069, and 0.068 at days 15, 43, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.065, 0.085, 0.048, 0.058, 0.072, and 0.071L, respectively. P-values for both doses at all time points were <0.01. This is represented graphically in Figure 16. Note when using the original analysis, the differences from placebo were smaller and the p-values were larger.

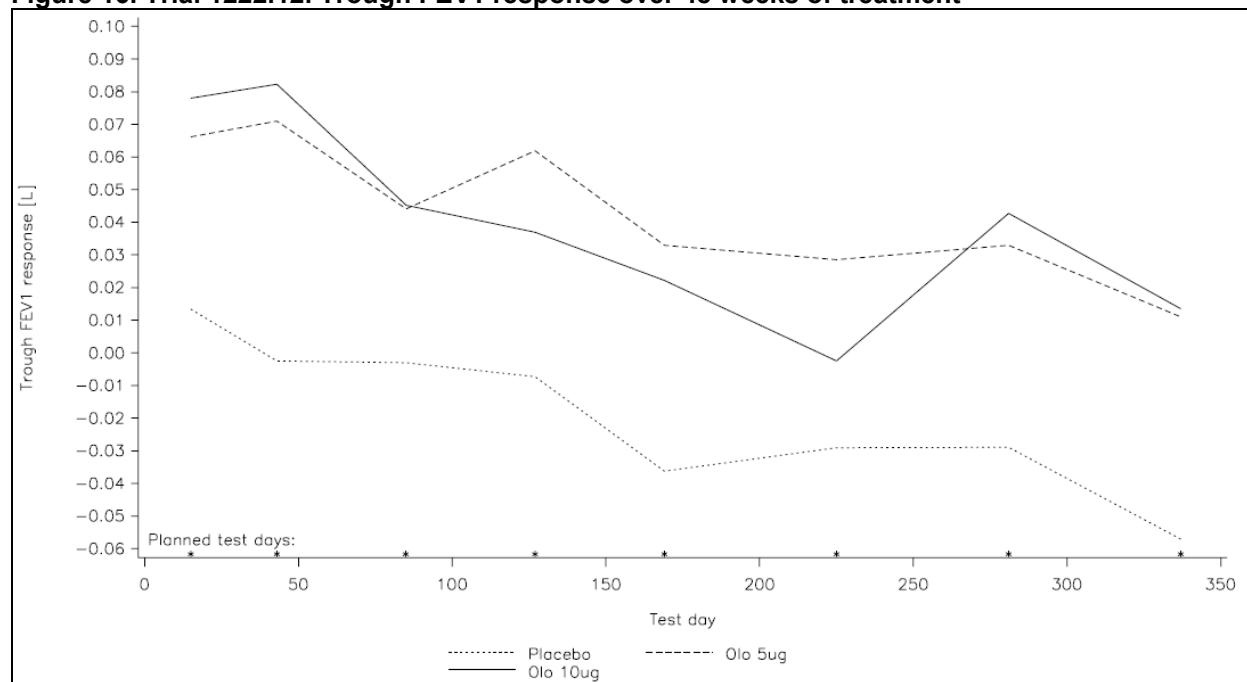
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Figure 16. Trial 1222.12. Trough FEV1 response over 48 weeks of treatment



Source: Trial 1222.12 CSR; figure 15.2.1.1.3:1; pg252

For the secondary endpoint FEV1 peak (0-3) response over the 48 week period, both olodaterol doses demonstrated an increase in response compared to placebo on all tested days. The mean differences from placebo in liters for olodaterol 5mcg were 0.168, 0.144, 0.164, and 0.155L at days 1, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.177, 0.130, 0.135, and 0.157, respectively. P-values for both doses at all time points were <0.0001.

The difference from placebo in FEV1 response for the olodaterol 5mcg group at 5, 15, 30, 60, 120, and 180 minutes post-dose on Day 1 were 0.120, 0.147, 0.159, 0.170, 0.173, 0.173 L. For olodaterol 10mcg the differences from placebo were 0.118, 0.144, 0.160 L, 0.169, 0.187, and 0.189 L, respectively. This is represented graphically in Figure 17. The unadjusted means for these data showed similar results. The p-values at both doses were <0.0001.

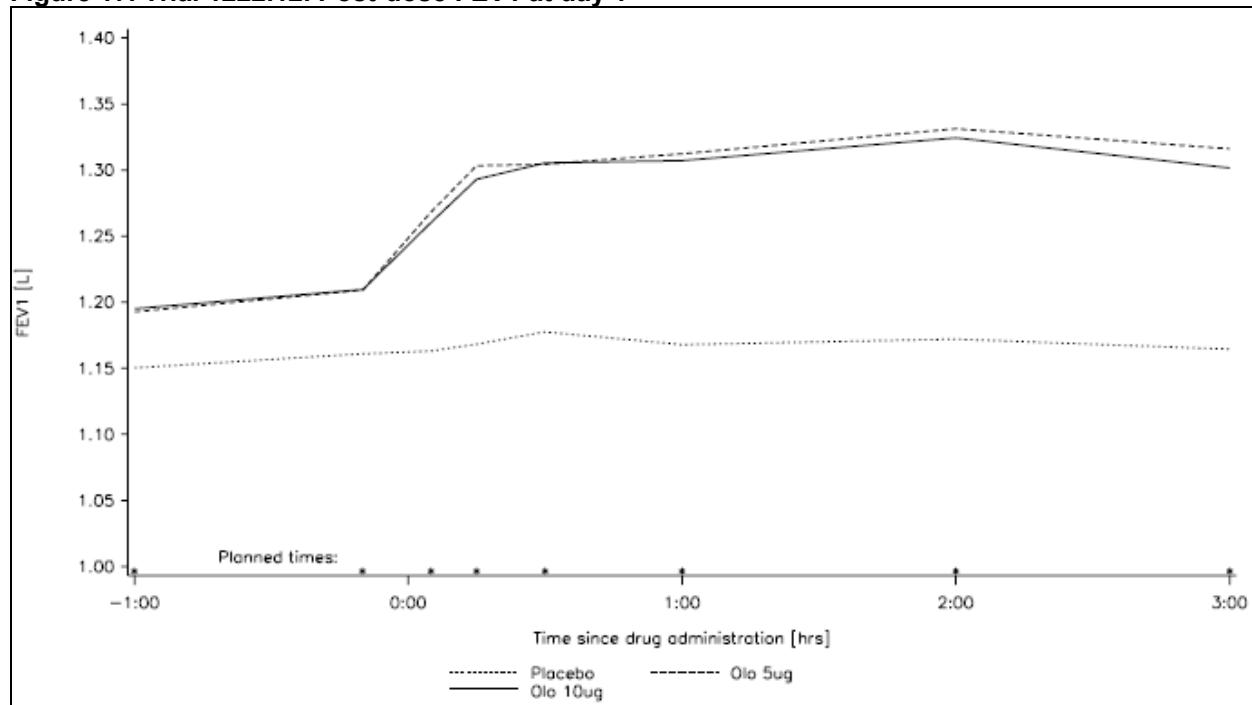
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Figure 17. Trial 1222.12. Post-dose FEV1 at day 1



Source: Trial 1222.12 CSR; figure 15.2.1.1.1:2; pg225

The results for the FVC-related secondary endpoints demonstrated similar trends to the results for the analogous FEV1-related secondary endpoints. For the trough FVC response at 12 weeks, both the olodaterol 5mcg and olodaterol 10mcg demonstrated improvements compared to placebo [0.032L ($p=0.3821$) and 0.048L ($p=0.197$)], respectively. The results were similar at all other time points. The difference from placebo never had a p-value <0.05 at any time point.

For the FVC AUC (0-3 hours) response at 24 weeks, the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.199L, 0.213L, and 0.241L (all p-values <0.0001), respectively]. Similar trends were seen at all other time points.

With regard to FVC peak (0-3) response at 12 weeks, both olodaterol 5mcg and olodaterol 10mcg demonstrated improvements compared to placebo [0.239L ($p<0.0001$) and 0.245L ($p<0.0001$)]. Results were similar at all other time points.

For weekly mean values from morning PEFR, both olodaterol groups demonstrated improvements from placebo. The magnitude of the mean differences from placebo at weeks 1, 12, 24, and 48 were 14.2 ($p<0.0001$), 15.2 ($p=0.0009$), 16.5 ($p=0.0002$), and 13.4 ($p=0.0072$) L/min for olodaterol 5mcg, respectively, and 18.4 ($p<0.0001$), 19.2 ($p<0.0001$), 19.8 ($p<0.0001$), and 20.9 ($p<0.0001$) L/min for olodaterol 10mcg, respectively. Results were similar for evening PEFR.

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Reviewer Comment

The results for the secondary endpoints related to FEV1 and FVC are supportive of a bronchodilatory effect for olodaterol. As with the primary endpoint, there was no incremental benefit for the 10mcg dose over the 5mcg dose. Over the 48-week treatment period, spirometric responses for the olodaterol groups compared to placebo exhibited some time point-to-time point variability, but had an overall downward trend. These results imply that the bronchodilatory effect may wane to some degree over the 48-week treatment period. From 6 weeks to 12 weeks, the treatment effect consistently decreased. This is in contrast to trial 1222.11, where there was no notable difference between weeks 6 and 12. It should be noted that although all the p-values were generally low (<0.05), the analysis was amended post-database lock/unblinding, and did not protect for type 1 error.

Non-spirometric secondary endpoints:

For the secondary endpoint of daily rescue medication use (measured weekly) over the 48 week treatment period, both olodaterol dose groups demonstrated less rescue medication (albuterol) use compared to placebo. At week 1, 12, 24, and 48, the difference from placebo ranged from 0.59 to 0.85 puffs per day for olodaterol 5mcg and from 0.6 to 1.2 puffs per day for olodaterol 10mcg (p-values all <0.05).

The results for the secondary endpoints of daytime and night-time rescue medication use over the 48 week treatment period were similar. At weeks 1, 12, 24, and 48, the mean differences from placebo for daytime rescue medication use in olodaterol 5mcg were 0.16 (p=0.0628), 0.33 (p=0.0040), 0.38 (p=0.0012), and 0.42 (p=0.0011) puffs/day, respectively. The magnitude of the mean differences from placebo at key study time points (Weeks 1, 12, 24, and 48) were 0.20 (p=0.0242), 0.43 (p=0.0001), 0.50 (p<0.0001), and 0.51 (p<0.0001) puffs/day for the olodaterol 10mcg group, respectively. Results for nighttime rescue medication use was similar, however, for both doses and at all time points, the p-values were <0.05.

The number and time to first COPD exacerbation were also evaluated as secondary endpoints. For time to first COPD exacerbation, moderate COPD exacerbation, and first COPD exacerbation leading to hospitalization, there were no statistically significant differences between olodaterol and placebo groups. There was also no trend for longer time to first exacerbation for olodaterol versus placebo. There same was true with respect to number of exacerbations between groups.

PK data

Post-dosing olodaterol levels were comparable on days 43, 85 and 127. The geometric mean concentration 10 minutes after inhalation was 1.8 fold higher in olodaterol 10mcg versus olodaterol 5mcg. Serum concentrations were also slightly higher in Asians compared to Whites. There was no evidence of a relationship between oldaterol serum levels and serum potassium levels. It should be noted that 7 (0.9%) out of the 768

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plasma samples from placebo patients had detectable levels of olodaterol. Two samples came from a placebo patient who was dispensed the wrong trial medication. In addition to the remaining 5 placebo samples that had detectable olodaterol, 10 (2.5%) of 408 samples taken from olodaterol patients taken prior to first trial drug administration also had detectable olodaterol levels.

Reviewer comment

The detection of olodaterol in patients who were not exposed to olodaterol is concerning. However, the overall numbers were small and this would likely dilute treatment effects rather than accentuate them. As such, this does not affect efficacy conclusions.

Safety

Exposure

A total of 642 patients received at least one dose of trial drug (216 placebo, 209 Olo 5mcg, 217 Olo 10mcg). Mean exposure was higher in the olodaterol groups (Olo 5mcg=316.2 days; Olo 10mcg=304.6 days) compared to placebo (295.4 days). The difference is likely related to the higher number of discontinuations in the placebo group compared to the olodaterol groups. Patient exposure is summarized in Table 72.

Table 72. Trial 1222.12. Patient exposure

| | Placebo | Olo 5mcg | Olo 10mcg | Total |
|---------------------------|------------|------------|------------|------------|
| Extent of exposure (days) | | | | |
| N | 216 | 209 | 217 | 642 |
| Mean | 295.4 | 316.2 | 304.6 | 305.3 |
| SD | 100.3 | 69.4 | 87.7 | 87.2 |
| Min | 4 | 12 | 1 | 1 |
| Median | 337 | 337 | 337 | 337 |
| Max | 430 | 386 | 392 | 430 |
| Extent of exposure [N(%)] | | | | |
| <=15 days | 10 (4.6) | 1 (0.5) | 5 (2.3) | 16 (2.5) |
| 16 - 43 days | 5 (2.3) | 2 (1) | 5 (2.3) | 12 (1.9) |
| 44 - 85 days | 5 (2.3) | 4 (1.9) | 5 (2.3) | 14 (2.2) |
| 86 - 127 days | 6 (2.8) | 6 (2.9) | 4 (1.8) | 16 (2.5) |
| 128 - 169 days | 5 (2.3) | 1 (0.5) | 2 (0.9) | 8 (1.2) |
| 170 - 225 days | 4 (1.9) | 4 (1.9) | 7 (3.2) | 15 (2.3) |
| 226 - 281 days | 1 (0.5) | 3 (1.4) | 1 (0.5) | 5 (0.8) |
| 282-337 days | 117 (54.2) | 123 (58.9) | 122 (56.2) | 362 (56.4) |
| >=338 days | 63 (29.2) | 63 (31.1) | 66 (30.4) | 194 (30.2) |

Source: Trial 1222.12 CSR; table 12.1:1; pp108

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Deaths

Of the 642 patients who received treatment, five patients died during the on-treatment period [Olo 5mcg=0, Olo 10mcg=4 (1.8%), and placebo=1 (0.5%)]. Deaths are summarized in Table 73. The on-treatment period was defined as starting when the first dose of study medication was administered and ending 12 days after the last dose. Based on investigator assessment, the placebo patient died of pneumonia; per MAC the cause of death was COPD exacerbation. For the olodaterol 10mcg groups, the causes of death per investigator were legionella pneumonia, lung cancer, respiratory failure, and sudden cardiac death. Per MAC, the causes of death were pneumonia, lung cancer, COPD exacerbation, and unknown, respectively.

Table 73. Trial 1222.12. Deaths on treatment and during vital status follow-up period

| Period | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|----------------------------------|-----------------|------------------|-------------------|
| Total | 3 (1.5) | 1 (0.5) | 5 (2.3) |
| On treatment | 1 (0.5) | 0 | 4 (1.8) |
| Solicited vital status follow-up | 2 (1) | 1 (0.5) | 1 (0.5) |

*One Olo 10mcg patient died outside the vital status follow-up period

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

An additional 5 patients died after early discontinuation of study treatment (placebo=2, Olo 5mg=1, Olo 10mcg=2) and were reported as part of the solicited vital status follow-up period. Post-treatment was defined as anytime after the treatment period during the planned observation period of the study. For the olodaterol groups the causes of death were death (preferred term) (Olo 5mcg); and renal impairment and respiratory failure (Olo 10mcg). Per MAC, the causes of death were unknown, bladder cancer, and motor vehicle accident, respectively.

SAEs

One hundred one (101) patients experienced SAEs (placebo=14.8%, Olo 5mcg=15.3%, and Olo 10mcg=17.1%). The most common SAEs were COPD exacerbation (4.8%), pneumonia (1.9%), pneumothorax (0.8%), respiratory failure (0.6%), coronary artery disease (0.6%), aortic aneurysm (0.5%), traffic accident (0.5%), and lung infection (0.5%). No SAEs based on SOC or PT demonstrated a dose response. All SAEs by SOC are summarized in Table 74. This table also includes PTs that occurred in ≥2 patients. Additionally, if a PT that occurred in <2 patients was similar to a PT that occurred in ≥2 patients, that PT was also listed in the SAE table (e.g. atrial fibrillation and atrial flutter).

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Table 74. Trial 1222.12. All serious adverse events by SOC (PTs that occurred in ≥ 2 patients are included)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---|-----------------|------------------|-------------------|
| Total patients | 216 (100) | 209 (100) | 217 (100) |
| Total SAEs | 32 (14.8) | 32 (15.3) | 37 (17.1) |
| Infections Infestations | 6 (2.8) | 5 (2.4) | 10 (2.6) |
| Pneumonia | 4 (1.9) | 3 (1.4) | 5 (2.3) |
| Neoplasms benign and malignant | 3 (1.4) | 2 (1) | 2 (0.9) |
| Basal cell carcinoma | 1 (0.5) | 1 (0.5) | 0 |
| Blood and lymphatic | 0 | 0 | 1 (0.5) |
| Immune system | 1 (0.5) | 0 | 0 |
| Metabolism and nutrition | 0 | 2 (1) | 0 |
| Dehydration | 0 | 2 (1) | 0 |
| Nervous system disorder | 3 (1.4) | 2 (1) | 0 |
| Eye disorders | 0 | 0 | 1 (0.5) |
| Cardiac disorders | 4 (1.9) | 5 (2.4) | 3 (1.4) |
| Atrial fibrillation | 1 (0.5) | 1 (0.5) | 0 |
| Atrial flutter* | 0 | 1 (0.5) | 0 |
| Coronary artery disease | 1 (0.5) | 2 (1) | 1 (0.5) |
| Vascular disorders | 2 (0.9) | 3 (1.4) | 1 (0.5) |
| Aortic aneurysm | 0 | 3 (1.4) | 0 |
| Respiratory, thoracic, mediastinal | 15 (6.9) | 9 (4.3) | 15 (6.9) |
| COPD | 12 (5.6) | 7 (3.3) | 12 (5.5) |
| Acute respiratory failure | 0 | 1 (0.5) | 1 (0.5) |
| Respiratory failure | 1 (0.5) | 0 | 3 (1.4) |
| Pneumothorax | 2 (0.9) | 2 (1) | 1 (0.5) |
| Gastrointestinal disorder | 3 (1.4) | 3 (1.4) | 4 (1.8) |
| Inguinal hernia | 1 (0.5) | 1 (0.5) | 0 |
| Hepatobiliary disorder | 0 | 1 (0.5) | 1 (0.5) |
| Musculoskeletal disorder | 0 | 3 (1.4) | 5 (2.3) |
| Back pain | 0 | 0 | 2 (0.9) |
| Intervertebral disk protrusion | 0 | 1 (0.5) | 1 (0.5) |
| Reproductive disorders | 1 (0.5) | 0 | 1 (0.5) |
| General disorders | 1 (0.5) | 1 (0.5) | 2 (0.9) |
| Injury, poisoning, and procedural complications | 1 (0.5) | 4 (1.9) | 4 (1.8) |
| Fall | 0 | 1 (0.5) | 2 (1) |
| Road traffic accident | 1 (0.5) | 1 (0.5) | 1 (0.5) |

*included as the PT was similar to atrial fibrillation

Source: trial 1222.12 CSR; table 15.3.2.1:6; pp 438-441

AEs leading to withdrawal

Forty-seven patients withdrew due to AEs. This occurred more frequently in the placebo (8.8%) group and olodaterol 10mcg (8.8%) groups compared to the olodaterol 5mcg group (4.3%). The most common AEs leading to discontinuation was COPD exacerbation, respiratory failure, pneumonia, and atrial fibrillation. Within the cardiac disorder SOC, there were no imbalances between groups. Only patients in the placebo group withdrew due to atrial fibrillation, and more patients in the olodaterol groups (Olo 5mg=2, Olo 10mcg=1) withdrew due to ventricular tachycardia compared to placebo (0). A summary of all AEs by SOC leading to discontinuation can be found in Table 75. PTs were listed if they occurred in ≥ 2 patients.

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Table 75. Trial 1222.12. All adverse events leading to discontinuation by SOC (PTs that occurred in ≥2 patients are included)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---|-----------------|------------------|-------------------|
| Total patients | 216 (100) | 209 (100) | 217 (100) |
| Total AEs leading to discontinuation | 19 (8.8) | 9 (4.3) | 19 (8.8) |
| Infections Infestations | 3 (1.4) | 0 | 3 (1.4) |
| Pneumonia | 2 (0.9) | 0 | 1 (0.5) |
| Neoplasms benign and malignant | 2 (0.9) | 0 | 1 (0.5) |
| Psychiatric disorder | 0 | 0 | 2 (0.9) |
| Nervous system disorder | 1 (0.5) | 0 | 1 (0.5) |
| Eye disorders | 1 (0.5) | 0 | 1 (0.5) |
| Cardiac disorders | 4 (1.9) | 4 (1.9) | 1 (1.8) |
| Atrial fibrillation | 3 (1.4) | 0 | 0 |
| Ventricular tachycardia | 0 | 2 (1) | 1 (0.5) |
| Vascular disorders | 1 (0.5) | 1 (0.5) | 0 |
| Respiratory, thoracic, mediastinal | 6 (2.8) | 2 (1) | 7 (3.2) |
| COPD | 4 (1.9) | 2 (1) | 4 (1.8) |
| Acute respiratory failure | 0 | 0 | 1 (0.5) |
| Respiratory failure | 1 (0.5) | 0 | 2 (0.9) |
| Gastrointestinal disorder | 1 (0.5) | 0 | 1 (0.5) |
| Musculoskeletal disorder | 0 | 0 | 2 (0.9) |
| Renal and urinary disorders | 0 | 0 | 1 (0.5) |
| General disorders | 1 (0.5) | 1 (0.5) | 2 (0.9) |
| Sudden cardiac death | 0 | 0 | 1 (0.5) |
| Investigations | 3 (1.4) | 1 (0.5) | 0 |
| Injury, poisoning, and procedural complications | 0 | 1 (0.5) | 2 (0.9) |
| Road traffic accident | 0 | 1 (0.5) | 1 (0.5) |

Source: trial 1222.12 CSR; table 15.3.2.1:5; pp 435-437

Reviewer comment:

Deaths were fairly evenly distributed with no apparent imbalances. However, as with trial 1222.11, there was a mild imbalance with respect to overall SAEs. No dose responses were demonstrated when examining SAEs by PT or SOC. The overall numbers are small and analysis of the larger pooled safety data set would likely be more informative. With regard to discontinuations, there were no apparent imbalances.

Common TEAEs

TEAEs were defined as in trial 1222.11. The most common TEAEs (≥3%) based on preferred term were COPD exacerbation, URI, nasopharyngitis, bronchitis, headache, and hypertension. By SOC, infections and infestations demonstrated evidence suggestive of dose dependence. Within that SOC, the PTs of nasopharyngitis and URI demonstrated some evidence of dose dependence. The PT of ventricular extrasystoles also demonstrated some suggestion of dose dependence, with 2 (0.9%), 6 (2.9%), and 7 (3.2%), for placebo, olodaterol 5mcg, and olodaterol 10mcg, respectively; however the SOC of cardiac disorders did not. TEAE data is summarized in Table 76.

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Table 76. Trial 1222.12. Common treatment adverse events (>3%)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) |
|---------------------------------------|-----------------|------------------|-------------------|
| Number of patients | 216 (100) | 209 (100) | 217 (100) |
| Total with AEs | 146 (67.6) | 142 (67.9) | 163 (75.1) |
| Infections and infestations | 62 (28.7) | 71 (34.0) | 84 (38.7) |
| Nasopharyngitis | 18 (8.3) | 19 (9.1) | 25 (11.5) |
| Upper respiratory tract infection | 17 (7.9) | 20 (9.6) | 22 (10.1) |
| Pneumonia | 5 (2.3) | 4 (1.9) | 9 (4.1) |
| Bronchitis | 6 (2.8) | 7 (3.3) | 7 (3.2) |
| Sinusitis | 7 (3.2) | 3 (1.4) | 6 (2.8) |
| Nervous system disorders | 25 (11.6) | 23 (11.0) | 19 (8.8) |
| Headache | 11 (5.1) | 7 (3.3) | 4 (1.8) |
| Cardiac disorders | 13 (6.0) | 23 (11.0) | 21 (9.7) |
| Ventricular extrasystoles | 2 (0.9) | 6 (2.9) | 7 (3.2) |
| Vascular disorders | 10 (4.6) | 16 (7.7) | 10 (4.6) |
| Hypertension | 7 (3.2) | 8 (3.8) | 5 (2.3) |
| Respiratory, thoracic and mediastinal | 81 (37.5) | 68 (32.5) | 83 (38.2) |
| COPD | 55 (25.5) | 46 (22.0) | 59 (27.2) |
| Cough | 4 (1.9) | 10 (4.8) | 3 (1.4) |
| Musculoskeletal and connective | 18 (8.3) | 24 (11.5) | 25 (11.5) |
| Back pain | 3 (1.4) | 8 (3.8) | 8 (3.7) |

Source: Trial 1222.12 CSR; table 12.2.2.2:1; pg111

Forty-nine patients experienced respiratory events indicative of bronchoconstriction related to medication administration. Respiratory events indicative of bronchospasm were defined as a $\geq 15\%$ decrease in FEV1, rescue medication use, or cough/wheeze/dyspnea within 30 minutes post-dose. Of the 49 patients, 46 had $\geq 15\%$ decreased in FEV1, and 3 had rescue medication use. Administration-related bronchospasm was more common in placebo (14%) than olodaterol 5mcg or olodaterol 10mcg groups (3.3% and 5.5%, respectively).

Reviewer Comment:

The common TEAEs seen in this trial were typical for a LABA development program. Unlike in trial 1222.11, the infections and infestation SOC did demonstrate a dose response. However, it is reassuring that it was primarily driven by the nasopharyngitis and upper respiratory infections, rather than more severe infections.

Labs:

Based on mean lab values, there were no notable changes in lab values except for CPK. Mean changes from baseline were -14 U/L, 7 U/L, and 7 U/L for the placebo, olodaterol 5mcg, and olodaterol 10mcg groups. More patients in the olodaterol groups

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also had normal CPK levels at baseline and above normal maximum values (placebo=6.3%, Olo 5mcg=10.4%, and Olo 10mcg=18.7%).

When examining glucose and potassium, the number of patients per group who had normal baseline values and elevated maximum values were similar between groups. Based on mean values, there was also no difference between groups with regard to potassium values.

When examining potentially clinically significant changes in lab values as defined by the sponsor, numbers were generally similar between groups. Notably, potentially clinically significant elevations in potassium and glucose were similar between treatment groups.

Reviewer comments

The findings with regard to CPK are not necessarily surprising as it is likely a pharmacodynamic effect of olodaterol. These results are also consistent with what was seen in the dose ranging trials.

Vital signs:

With regard to SBP, there were no significant differences between groups based on change in mean values or shifts from normal to high. However, a higher percentage of olodaterol treated patients compared to placebo had shifts from normal to low (Olo 5mcg=19.1%, Olo 10mcg=18.9%, placebo=11.1%). With regard to DBP there were no significant differences between groups based on change in mean values, shifts from normal to low, or shifts from normal to high. For pulse rate, there were no significant differences between groups based on change in mean values, shifts from normal to high, or shifts from normal to low. However, more patients in the olodaterol groups had shifts in pulse from normal to markedly elevated compared to placebo (Olo 5mcg=7.2%, Olo 10mcg=6.0%, placebo=3.2%).

ECG

ECGs were assessed as mean changes from baseline, mean changes exceeding a pre-specified threshold (450, >480, or >500ms in the QTc interval), mean changes exceeding categorized change (>30ms or >60ms in the QTc interval), notable changes, and frequency of ECG abnormalities. Notable changes were defined as in trial 1222.11.

Based on these parameters, there were no notable changes from baseline. When analyzing the QTcF based on threshold values (>450ms, >480ms, and >500ms), no imbalances were identified, nor was there any evidence of dose response. However, during the entire treatment period, there were only 6 reported increases of QTcF of >500ms. Of these reported increases, 2 were in the placebo group and 4 were in the olodaterol groups (2 in each dose group). When analyzing the QTcF based on categorized change (>30ms or >60ms), the overall numbers were small for all time points. During the entire treatment period, there were only 11 reported increases of QTcF >60ms. All were in the olodaterol treatment groups. Reports of increases >30ms

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were more frequent; however, there was neither a clear dose-dependent nor time-dependent effect. A prolonged QT interval was reported as an AE for one patient (Olo 10mcg) and decreased T-wave amplitude was reported in 2 patients (both Olo 5mcg). Two placebo patients reported inverted T-waves. The patient with the prolonged QTc interval and one patient with T-wave inversion were discontinued.

Holter monitoring

With regard to supraventricular couplets, change from baseline at days 85, 169, 281, and 337 were highly variable within groups. Within groups, there were no apparent time related trends. Between groups, there were also no consistent differences. However, change from baseline at day 337 for supraventricular couplets was higher in both olodaterol groups compared to placebo (placebo=3.1, Olo 5mcg=43.5, and Olo 10mcg=29.6).

The results for supraventricular tachycardia runs were also variable when comparing change from baseline at day 85, 169, 281, 337, though not as variable as the supraventricular couplet data. Within groups, there were no apparent time-related trends, nor were there consistent differences between groups at each time point.

With regard to ventricular couplets, there were no consistent trends within or between groups. However, the change from baseline at days 169 and 281 was greater in the olodaterol groups compared to placebo. This difference was not maintained at day 337. With regard to ventricular runs, the differences between groups were minimal, and the mean number of runs in each group was small.

Based on shift table analysis of ventricular premature beats (VPB) and supraventricular premature beats (SVPB), most patients had similar numbers of SVPBs when comparing baseline values to last value on treatment.

Reviewer Comment:

With regard to vital signs, ECG, and holter data, no significant imbalances were seen. Notably, the olodaterol groups did not appear to have an increased frequency of QTcF prolongation as was implied in some of the asthma dose ranging trials. However, the pooled ECG and holter data from the 48 week trials will be analyzed in the combined safety section.

Overall Reviewer Comment on trial 1222.12

Based on the sponsor analysis of the co-primary endpoints, neither dose of olodaterol is effective at bronchodilation. While both doses did demonstrate a statistically significant treatment effect with respect to FEV1 AUC (0-3 hours), neither did with respect to trough FEV1, though there was a trend for an effect. Compared to trial 1222.11, the treatment effect on trough FEV1 was smaller in magnitude. As with trial 1222.11, this trial allowed for the use of all background COPD medications except for LABAs. As such, patients could also be on tiotropium. The trough FEV1 response in the non-

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tiotropium strata tended to be larger compared to the tiotropium treated strata. With regard to maintenance of effect, although there was time point to time point variability, the magnitude of the treatment effect (based on the primary endpoint) appeared to exhibit a downward trend from 6-48 weeks. There appeared to be no effect on exacerbations and some mild improvement in rescue medication use. With regard to safety, the deaths were fairly well balanced, and the common AEs were generally consistent with what one would expect in a COPD trial.

5.3.10 Trial 1222.13 (COPD 48 Week Trial)

Administrative Information

- **Study title:** Randomized, double-blind, double-dummy, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled olodaterol (5mcg [2 actuations of 2.5mcg] and 10mcg [2 actuations of 5mcg]) delivered by the Respimat inhaler, and 48 weeks of twice daily Foradil (12mcg) delivered by the Aerolizer in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 2/3/2009-12/10/2010
- **Study sites:** Argentina (4), Brazil (5), Canada (11), Croatia (4), Czech Republic (3), Denmark (3), Finland (3), Germany (12), Hong Kong (1), India (12), Italy (5), Malaysia (4), Norway (2), Philippines (3), South Korea (6), South Africa (2), Spain (6), Sweden (2), Thailand (3), Ukraine (3).
- **Study report date:** 01/27/2012

Objectives/Rationale

- To assess the long-term efficacy and safety of olodaterol (5mcg and 10mcg once daily) compared to placebo in patients with COPD

Trial Design, Trial population, Treatments

This trial was similar in design, conduct, inclusion/exclusion criteria, and prohibited/restricted medications as trials 1222.11 and 1222.12. However, this trial had an additional formoterol 12 mcg BID treatment arm.

Efficacy Parameters

Primary Endpoints

Similar to trials 1222.11 and 1222.12, the co-primary endpoints in this trial included FEV1 AUC (0-3 hours) and trough FEV1. However, in this trial, there was an additional co-primary endpoint of Mahler TDI focal score after 24 weeks of treatment. The TDI data was pooled with the TDI data from trial 1222.14 for analysis. In addition, for the primary analysis, all co-primary endpoints were assessed at 24 weeks, rather than 12 weeks (as in trials 1222.11 and 1222.12).

Secondary Endpoints

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The secondary endpoints in this trial were identical to trials 1222.11 and 1222.12 with the addition of the following key secondary and other secondary endpoints:

Key secondary endpoint

1. Total SGRQ after 24 weeks of treatment.
2. Trough FEV1 response and FEV1 AUC (0-3 hours) response after 24 weeks of treatment compared between olodaterol groups and formoterol.

Other secondary endpoints

1. SGRQ (total, impacts, activity and symptoms scores) after 12 and 48 weeks.
2. Mahler Dyspnea Indices (Focal, Functional Impairment, Magnitude of Task and Magnitude of Effort) after 6, 12, 18, 32, 40 and 48 weeks.

These additional endpoints were meant to be analyzed after combining data with trial 1222.14.

Safety Parameters, compliance, and ethics-see trials 1222.11 and 1222.12 (section 5.3.7 and 5.3.8)

Statistical Analysis

Sample Size

The sample size was estimated using an expected standard deviation of 0.226L for FEV1 AUC (0-3 hours), 0.225L for trough FEV1, and 2.8 units for TDI focal scores. To detect a difference of 120mL in FEV1 AUC (0-3 hours) response between olodaterol and placebo with 90% power, 76 patients per group were required (one-sided p-value of 0.025). To detect a difference of 90mL in FEV1 AUC (0-3 hours) response between olodaterol and placebo with 90% power, 168 patients per group were required (one-sided p-value of 0.025). To detect a difference of 0.7units in TDI focal score between olodaterol and placebo with 90% power, 338 patients per group were required (one-sided p-value of 0.025). To detect a difference of 50mL in trough FEV1 between olodaterol and formoterol with 90% power, 427 patients per group were required (one-sided p-value of 0.025). Based on this, the sponsor selected a sample size of 215 patients per group. This would yield 430 patients per group in the combined analysis from trial 1222.13/1222.14.

Missing Data

Spirometric data missing due to worsening symptoms were replaced with the least favorable non-missing data recorded during the same visit. Post-dose data missing at random was either linearly interpolated if the preceding and subsequent data points were available or was imputed using last observation carried forward.

For missing SGRQ data, missing data was imputed as outlined in the SGRQ scoring manual.

If one or more components of the TDI were missing at a visit, the TDI focal score at that visit was considered missing.

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If a patient discontinued due to worsening symptoms then subsequent missing data was imputed using the least favorable value observed at that point in time.

Analysis Populations- same as trials 1222.11/1222.12 (see section 5.3.7 and 5.3.8)

Primary Analysis

The analysis of the co-primary endpoints was performed on the FAS population. The co-primary endpoints were analyzed in a hierachal order to protect against type 1 error. Analysis of the co-primary endpoints were conducted in the following order:

- Superiority in mean FEV1 AUC (0-3hours) response in patients treated with olodaterol 10 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean FEV1 trough response in patients treated with olodaterol 10 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean FEV1 AUC (0-3 hours) response in patients treated with olodaterol 5 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean trough FEV1 response in patients treated with olodaterol 5 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean TDI focal score in patients treated with olodaterol 10 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean TDI focal score in patients treated with olodaterol 5 mcg compared with those treated with placebo, after 24 weeks

When a comparison failed to meet statistical significance, subsequent analysis was considered descriptive. Additionally, the TDI related primary endpoints were only analyzed using data combined with trial 1222.14.

Secondary Analysis

The key secondary endpoints were also to be analyzed in a hierachal manner to protect against type 1 error. Comparisons of olodaterol to formoterol for FEV1 AUC (0-3 hours) response and trough FEV1 response at 24 weeks were also performed in a hierachal manner following analysis of the key secondary endpoint analysis. All analysis was performed using combined data sets from this trial and 1222.14. Analysis occurred in the following order:

- Superiority in mean SGRQ total score in patients treated with olodaterol 10 mcg compared with those treated with placebo, after 24 weeks

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- Superiority in mean SGRQ total score in patients treated with olodaterol 5 mcg compared with those treated with placebo, after 24 weeks
- Superiority in mean FEV₁ AUC_{0-3h} response in patients treated with olodaterol 10 mcg compared with those treated with formoterol, after 24 weeks
- Superiority in mean FEV₁ trough response in patients treated with olodaterol 10 mcg compared with those treated with formoterol, after 24 weeks
- Superiority in mean FEV₁ AUC_{0-3h} response in patients treated with olodaterol 5 mcg compared with those treated with formoterol, after 24 weeks
- Superiority in mean FEV₁ trough response in patients treated with olodaterol 5 mcg compared with those treated with formoterol, after 24 weeks
- Superiority in mean TDI focal score in patients treated with olodaterol 10 mcg compared with those treated with formoterol, after 24 weeks
- Superiority in mean TDI focal score in patients treated with olodaterol 5 mcg compared with those treated with formoterol, after 24 weeks

Other analysis

Analysis for all other endpoints was not performed in a hierachal manner nor did it correct for multiple comparisons.

Results:

Protocol Amendments

There was a single amendment submitted for this protocol on 7/7/09. These changes were relatively minor and included revising the storage conditions for formoterol and the addition of Germany as a separate region defined for this trial; previously it had been grouped with Europe.

Changes to the analysis

As with trials 1222.11 and 1222.12, the following changes to the planned analysis were made. The FAS definition was modified to include all patients who received at least one dose and had both baseline and at least one post-baseline measurement at or before Day 85 for any co-primary endpoint. Moderate COPD exacerbation-related secondary endpoints were also added. A pooled analysis of COPD exacerbations was also added (trials 1222.11, 1222.12, 1222.13, 1222.14). These changes were made prior to database lock and were considered by the sponsor to be the 'planned' analysis. These amendments were consistent with the amendments made to trials 1222.11 and 1222.12.

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After unblinding, the sponsor altered their analysis of the COPD exacerbation related endpoints. Due to inconsistent results between trials, they considered it inappropriate to perform a pooled analysis.

Reviewer comment:

As compared to trials 1222.11 and 1222.12, there were no significant changes made to the statistical analysis plan after database lock and unblinding. It is unclear why the sponsor considered COPD exacerbation results inconsistent between trials, as there was consistently no statistically significant effect across all 48 week trials. The pre-specified analysis plan was consistent with the amended plan made after database lock and unblinding of trials 1222.11 and 1222.12.

Protocol Violations

A total of 86 (9.5%) patients had important protocol violations (IPV). The most common violations were 'prohibited medication during treatment period,' 'informed consent given too late,' and 'study drug not taken on the day prior to primary clinical endpoint.' 'study medication taken significantly longer than planned treatment durations' (end of treatment plus 2 weeks). Important protocol violations are summarized in Table 77.

Table 77. Trial 1222.13. Important protocol violations

| | Placebo [N(%)] | Olo 5mcg [N(%)] | Olo 10mcg [N(%)] | Formoterol 12mcg [N(%)] | Total [N(%)] |
|--|-------------------|--------------------|---------------------|-------------------------------|-----------------|
| Randomized | 225 (100) | 227 (100) | 225 (100) | 227 (100) | 906 (100) |
| Total with important protocol violations | 20 (8.9) | 22 (9.7) | 21 (9.3) | 23 (10.1) | 86 (9.5) |
| Exclusion criteria affecting efficacy and possibly safety | 3 (1.3) | 0 | 2 (0.9) | 1 (0.4) | 6 (0.7) |
| Informed consent given too late | 7 (3.1) | 5 (2.2) | 6 (2.7) | 7 (3.1) | 25 (2.8) |
| Incorrect trial medication taken on non-clinic days | 0 | 0 | 0 | 1 (0.4) | 1 (0.1) |
| Study drug not taken on day prior to primary endpoint clinic visit | 2 (0.9) | 7 (3.1) | 5 (2.2) | 5 (2.2) | 19 (2.1) |
| Study medication taken longer than planned duration | 1 (0.4) | 2 (0.9) | 1 (0.4) | 0 | 4 (0.4) |
| Prohibited medication taken during treatment period | 5 (2.2) | 7 (3.1) | 7 (3.1) | 8 (3.5) | 27 (3.0) |
| Primary endpoint data missing | 3 (1.3) | 1 (0.4) | 0 | 2 (0.9) | 6 (0.7) |
| Other PV affecting safety and possibly safety | 0 | 1 (0.4) | 1 (0.4) | 2 (0.9) | 4 (0.4) |

Source: trial 1222.13 CSR; table 15.1.2:1; pg180

In general the frequency of protocol deviations was similar between groups. However, there were fewer deviations in the placebo group related to the study drug not being taken on the day prior to the primary endpoint and prohibited medications taken during the treatment period. Use of prohibited medications was primarily related to use of expired formoterol or placebo, or the use of LABAs.

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Reviewer comment:

The protocol amendment does not affect interpretation of data. The IPVs in this trial were more frequent compared to 1222.11/1222.12, however, were in general balanced, except for the above 2 mentioned categories. While the imbalance IPVs could have impacted the treatment effect, the overall numbers are small. Additionally, for both categories of IPV, it is likely that, if there was an effect, in general it would have tended to attenuate the treatment effect.

Disposition

Of the 1212 enrolled patients, 906 were randomized. Of these, 904 received at least one dose of trial medication. Two patients were randomized, but not treated. One patient withdrew consent prior to dosing (10477), and one was withdrawn due to inability to perform spirometry prior to dosing (11580). Seven hundred twenty-nine (729) patients (80.6%) completed the trial (175 discontinued). The most common reasons for discontinuations were AEs and withdrawal of consent. Discontinuations were less common in the olodaterol groups compared to placebo. ‘Lack of efficacy’ and withdrawal of consent as reasons for withdrawal were more common in placebo patients compared to olodaterol and formoterol patients. Of the patients in the treated set, 885 were included in the FAS used for efficacy analysis. Two hundred seven (207) patients received Holter monitoring. Although there was a PPS defined, analysis was not performed using this set, per the analysis plan (PPS analysis was only to be performed if the difference between the FAS and PPS were >10%). Patient disposition and analysis populations are summarized in Table 78.

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Table 78. Trial 1222.13. Patient disposition and analysis populations

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total N(%) |
|-----------------------------|-----------------|------------------|-------------------|--------------------------|---------------|
| Treated Set | 225 (100) | 227 (100) | 225 (100) | 227 (100) | 904 (100) |
| Full Analysis Set (FAS) | 217 (96.4) | 222 (97.8) | 223 (99.1) | 223 (98.2) | 885 (97.9) |
| Per Protocol Set (PPS) | 211 (93.8) | 213 (93.8) | 215 (95.6) | 215 (94.7) | 854 (94.5) |
| Holter set (HMS) | 53 (23.6) | 52 (22.9) | 53 (23.6) | 49 (21.6) | 207 (22.9) |
| Completed | 168 (74.67) | 191 (84.14) | 186 (82.67) | 184 (81.06) | 729 (80.64) |
| Prematurely discontinued | 57 (25.33) | 36 (15.86) | 39 (17.33) | 43 (18.94) | 175 (19.36) |
| Adverse event: | 18 (8.00) | 16 (7.05) | 15 (6.67) | 20 (8.81) | 69 (7.63) |
| COPD worsening | 7 (3.11) | 11 (4.85) | 4 (1.78) | 4 (1.76) | 26 (2.88) |
| Other disease worsening | 0 (0.00) | 2 (0.88) | 0 (0.00) | 2 (0.88) | 4 (0.44) |
| Other | 11 (4.89) | 3 (1.32) | 11 (4.89) | 14 (6.17) | 39 (4.31) |
| Lack of Efficacy | 9 (4.00) | 2 (0.88) | 1 (0.44) | 3 (1.32) | 15 (1.66) |
| Noncompliance with protocol | 2 (0.89) | 3 (1.32) | 2 (0.89) | 3 (1.32) | 10 (1.11) |
| Lost to follow-up | 2 (0.89) | 2 (0.88) | 4 (1.78) | 0 (0.00) | 8 (0.88) |
| Consent withdrawn | 20 (8.89) | 9 (3.96) | 11 (4.89) | 14 (6.17) | 54 (5.97) |
| Other | 6 (2.67) | 4 (1.76) | 6 (2.67) | 3 (1.32) | 19 (2.10) |

Source: Trial 1222.13 CSR; tables 10.1:1 and 11.1:1; pp 80 and 84

Reviewer Comment:

There was an overall imbalance in discontinuations when comparing placebo to olodaterol and formoterol groups; this was primarily driven by increased discontinuations in the placebo group due to lack of efficacy and consent withdrawn. The imbalance in lack of efficacy implies that olodaterol has a treatment benefit. When reviewing the ‘consent withdrawn’ category, in 4, 0, 1, and 2 cases in the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups, respectively, the reasons for consent withdrawn were related to COPD worsening or COPD exacerbation. When combining these numbers with the AE of COPD worsening, the number for withdrawal due to AE COPD worsening for the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups were 11 (4.9%), 11 (4.9%), 5 (2.2%), and 6 (2.6%), respectively. Based on this, there appears to be an inverse dose relationship between withdrawals due to worsening COPD and olodaterol dose. As such, this implies that olodaterol may have a treatment benefit.

Demographics

Overall, patient demographics were similar between treatment groups. Most patients were white males with a mean age of 64 years. The average pack year history was 45 years, and most patients were not current smokers (65%). The average time since COPD diagnosis was 6.9 years. Approximately 54% of patients were GOLD II and 39% were GOLD III. The average FEV1% predicted was 45.3%. Demographic data are summarized in Table 79.

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Table 79. Trial 1222.13. Demographics and baseline respiratory data

| | Placebo | Olo 5mcg | Olo 10mcg | Formoterol 12mcg | Total |
|---|------------|------------|------------|------------------|------------|
| Number of patients | 225 | 227 | 225 | 227 | 904 |
| Gender [N (%)] | | | | | |
| Male | 180 (80.0) | 177 (78.0) | 170 (75.6) | 179 (78.9) | 706 (78.1) |
| Female | 45 (20.0) | 50 (22.0) | 55 (24.4) | 48 (21.1) | 198 (21.9) |
| Age [years] | | | | | |
| Mean | 64.0 | 63.7 | 62.6 | 64.8 | 63.8 |
| SD | 8.4 | 9.1 | 8.8 | 8.6 | 8.7 |
| Race [N (%)] | | | | | |
| White | 159 (70.7) | 160 (70.5) | 159 (70.7) | 163 (71.8) | 641 (70.9) |
| Black/African American | 2 (0.9) | 3 (1.3) | 0 (0.0) | 1 (0.4) | 6 (0.7) |
| Asian | 64 (28.4) | 63 (27.8) | 66 (29.3) | 62 (27.3) | 255 (28.2) |
| American Indian/Alaskan | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 1 (0.1) |
| Missing | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Smoking history [N (%)] | | | | | |
| Ex-smoker | 138 (61.3) | 159 (70.0) | 147 (65.3) | 144 (63.4) | 588 (65.0) |
| Currently smokes | 87 (38.7) | 68 (30.0) | 78 (34.7) | 83 (36.6) | 316 (35.0) |
| Smoking history [pack years] | | | | | |
| Mean | 46.2 | 45.2 | 43.4 | 45.8 | 45.1 |
| SD | 26.4 | 25.0 | 31.6 | 23.6 | 26.8 |
| Trial Diagnosis [years] | | | | | |
| Mean | 6.6 | 6.6 | 7.3 | 7.1 | 6.9 |
| SD | 5.2 | 4.7 | 5.9 | 5.6 | 5.4 |
| FEV1% predicted | | | | | |
| Mean | 44.4 | 46.4 | 44.2 | 46.4 | 45.3 |
| SD | 14.4 | 14.8 | 14.6 | 14.5 | 14.6 |
| FEV1/FVC [%] | | | | | |
| Mean | 44.1 | 46.1 | 44.0 | 45.6 | 45.0 |
| SD | 11.6 | 11.6 | 10.8 | 11.8 | 11.5 |
| FEV1 [% change from pre-bronchodilator] | | | | | |
| Mean | 14.1 | 14.9 | 14.9 | 15.8 | 14.9 |
| SD | 12.9 | 15.7 | 19.2 | 16.1 | 16.1 |

Source: Trial 1222.13 CSR; table 11.2:1, 11.2.3:1, 11.2.6:1, 11.2.6:2; pp 86, 87, 91, 93

Across treatment groups, patients had similar numbers and types of concomitant medical diagnoses. The most common medical diagnoses were hypertension (37-42%), hypercholesterolemia (6-9%), benign prostatic hyperplasia (5-8%), osteoarthritis (4-67%), reflux (5-7%), depression (4-6%), menopause (4-7%). Cardiac disorders (by SOC and preferred term) were fairly evenly distributed across groups (18-21%). Cardiac disorders were lower compared to trials 1222.11/1222.12.

In general, baseline medications were also similar between groups, though LABA use was higher in olodaterol 10mcg (40%) compared to olodaterol 5mcg (28.6%), formoterol (33.8%), and placebo (33.3%). Use of inhaled steroids was also more frequent in

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olodaterol 10mcg (52.9%) compared to olodaterol 5mcg (41.4%), formoterol (39.2%), and placebo (44%).

Reviewer Comment:

The patients' demographic and baseline data were similar across groups and typical of a COPD trial population. Overall, the population was fairly similar to that seen in trials 1222.11 and 1222.12.

Compliance

Based on eDiary entries, compliance was high across groups ranging from 97-98%. Greater than 96% of patients in each group took their medication 80-100% of the time.

Efficacy

Co-primary endpoints:

The spirometric co-primary endpoints for this trial were FEV1 AUC (0-3 hours) response and trough FEV1 response after 24 weeks of treatment. Both doses demonstrated statistically significant differences from placebo for both co-primary endpoints. There was minimal incremental benefit of the higher olodaterol dose. The results of the sponsor's analysis are summarized in Table 80

Table 80. Trial 1222.13. Co-primary endpoint [FEV1 AUC (0-3 hours) and trough FEV1 response after 24 weeks of treatment]

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|--------------------------------------|---------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | -0.009 (0.016) | | | -0.056 (0.015) | | |
| Olodaterol 5 mcg | 0.142 (0.015) | 0.151 (0.021) | <0.0001 | 0.021 (0.015) | 0.078 (0.021) | 0.0002 |
| Olodaterol 10 mcg | 0.156 (0.015) | 0.165 (0.021) | <0.0001 | 0.028 (0.015) | 0.085 (0.021) | <0.0001 |
| Formoterol | 0.168 (0.015) | 0.177 (0.021) | <0.0001 | -0.002 (0.015) | 0.054 (0.021) | 0.0088 |

Source: Trial 1222.13 CSR; tables 11.4.1.1.1:1 and 11.4.1.1.2:1; pp 96 and 98.

When comparing the spirometric co-primary endpoints between patients in the tiotropium strata to non-tiotropium strata, the treatment difference from placebo was greater in magnitude for the non-tiotropium strata for olodaterol 10mcg and formoterol, but not olodaterol 5mcg. The comparisons to placebo all had p-values <0.05 for FEV1 AUC (0-3 hours) response; however, for the trough FEV1, only the non-tiotropium strata was significantly different than placebo. It should be noted that these comparisons were not corrected for multiplicity (type 1 error), and since they were comparing subsets of patients, were not powered for a treatment response. These results are summarized in Table 81.

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Table 81. Trial 1222.13. Sponsor analysis by strata for co-primary endpoints

| Treatment Group | Tiotropium Strata | | | Non-tiotropium Strata | | |
|-----------------|--------------------------------------|------------------------|---------|--------------------------------------|------------------------|---------|
| | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | 0.022 (0.030) | | | -0.021 (0.018) | | |
| Olo 5 mcg | 0.181 (0.028) | 0.159 (0.041) | 0.0001 | 0.127 (0.017) | 0.148 (0.024) | <0.0001 |
| Olo 10 mcg | 0.120 (0.029) | 0.099 (0.042) | 0.0183 | 0.167 (0.017) | 0.188 (0.024) | <0.0001 |
| Formoterol | 0.164 (0.030) | 0.142 (0.042) | 0.0008 | 0.168 (0.017) | 0.189 (0.024) | <0.0001 |
| | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.053 (0.029) | | | -0.051 (0.017) | | |
| Olo 5 mcg | 0.040 (0.027) | 0.093 (0.040) | 0.0204 | 0.021 (0.017) | 0.072 (0.024) | 0.0028 |
| Olo 10 mcg | -0.011 (0.029) | 0.042 (0.041) | 0.3035 | 0.049 (0.016) | 0.099 (0.024) | <0.0001 |
| Formoterol | -0.019 (0.030) | 0.034 (0.042) | 0.4164 | 0.011 (0.016) | 0.062 (0.024) | 0.0103 |

Source: Trial 1222.13 CSR; Tables 11.4.1.1:2 &11.4.1.2:2; pp 97 and 99

For the third co-primary endpoint of Mahler TDI, at 24 weeks, no treatment group had statistically significant improvement compared to placebo. This was true for the both the total score and individual component scores.

Reviewer Comment:

For the co-primary endpoints of FEV1 AUC (0-3 hours) and trough FEV1 response at 24 weeks, both doses demonstrated a statistically significant difference from placebo. The treatment effect for olodaterol 10mcg and olodaterol 5mcg were similar. Additionally, both olodaterol doses had a similar treatment effect (numerically) to formoterol. With regard to the by strata analysis, the results were mixed. The difference from placebo was greater for both co-primary endpoints for the non-tiotropium strata versus the tiotropium strata for olodaterol 10mcg and formoterol, but not olodaterol 5mcg. It should also be noted that the treatment effect based on trough FEV1 response is larger in this trial compared to 1222.12 and similar to trial 1222.11. For the third co-primary endpoint of Mahler TDI score, there was no significant difference from placebo for Trial 1222.13; however, the sponsor had pre-specified that analysis would be performed on the pooled data with 1222.14.

Key Secondary Endpoints

Although the sponsor planned to pool data for analysis of the key secondary endpoints, in this report, they also provided analysis for data from this trial only. For the key secondary endpoint of SGRQ at week 24, only the olodaterol 10mcg demonstrated a statistically significant difference from placebo (-3.4, p=0.0155). The difference from placebo for both olodaterol 5mcg and formoterol was not statistically significant (-2.44, p=0.08 and -0.95, p=0.50; respectively).

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Comparisons to formoterol

For the spirometric co-primary endpoints, comparisons were also made between olodaterol groups and formoterol. As with the SGRQ, the sponsor planned to pool data for this analysis. However, in this report, they also provided analysis for data from this trial only. When comparing FEV1 AUC (0-3 hours) response at 24 weeks between olodaterol groups to formoterol, there were no statistically significant differences.

Numerical differences between the olodaterol 5 and 10mcg doses to formoterol were -0.026L and -0.12L, respectively, favoring formoterol. When comparing trough FEV1 response at 24 weeks between olodaterol groups and formoterol, there were also no statistically significant differences. Numerical differences between the olodaterol 5 and 10mcg doses to formoterol were 0.023L and 0.030L, respectively, favoring olodaterol.

Other secondary endpoints

For the following endpoints, there is no protection for type 1 error; therefore, the analysis was considered descriptive by the sponsor.

Spirometric Secondary Endpoints:

For the secondary endpoint of FEV1 AUC (0-3 hours) response after 48 weeks (337 days) of treatment, the olodaterol 10mcg, olodaterol 5mcg, and formoterol dose groups had differences from placebo of 0.145L, 0.146L, and 0.172L (p-values <0.0001), respectively. At days 1, 43, 85, 169, and 337, the results were similar, all with p-values <0.0001. The magnitude for the differences from placebo during these time points for the olodaterol 5mcg group were 0.168, 0.176, 0.178, 0.151, and 0.145L, respectively. For olodaterol 10mcg, the differences from placebo at the same time points were 0.168, 0.160, 0.170, 0.165, and 0.146L, respectively. For formoterol, the results for the same time points were 0.177, 0.192, 0.185, 0.177, and 0.172L. These results are represented graphically in Figure 18.

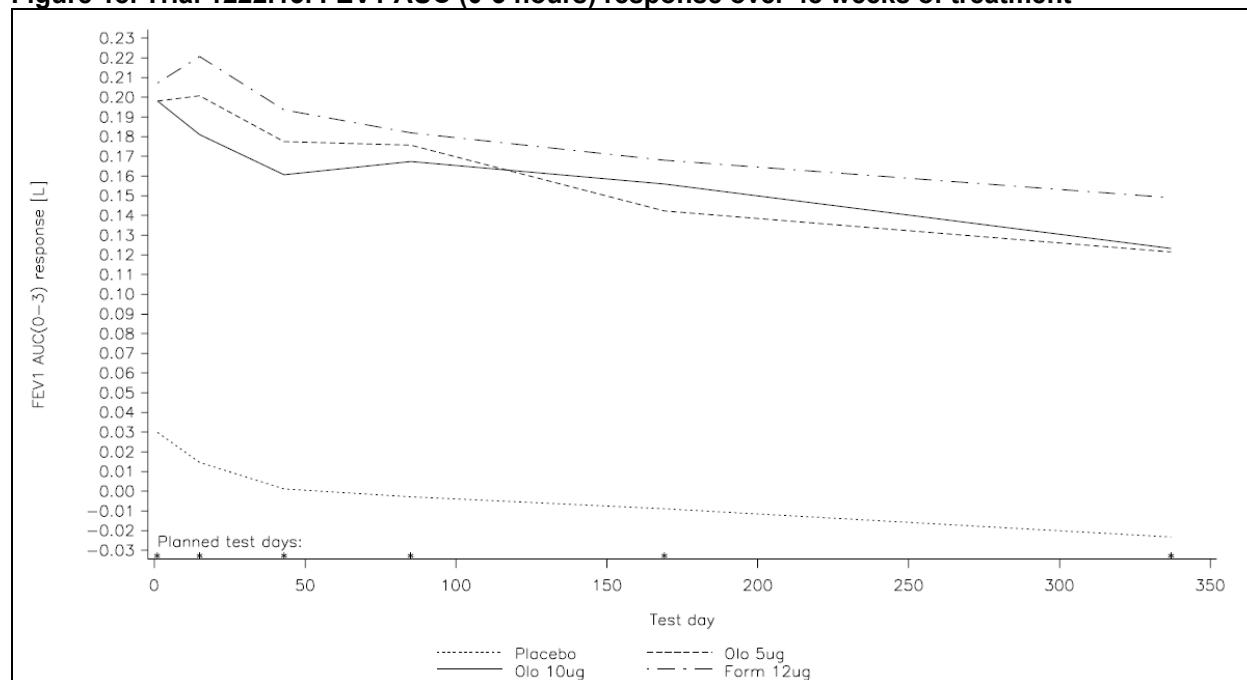
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Figure 18. Trial 1222.13. FEV1 AUC (0-3 hours) response over 48 weeks of treatment



Source: trial 1222.13 CSR; figure 15.2.1.1.2:1; pg 272

For the secondary endpoint of trough FEV1 response over the 48-week period, both olodaterol doses demonstrated an increase in response compared to placebo at key trial timepoints (days 15, 43, 85, 169, and 337). The mean differences from placebo in liters for olodaterol 5mcg were 0.087, 0.086, 0.083, 0.078, and 0.068L at the key study time points of days 15, 43, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.079, 0.075, 0.085, and 0.057L, respectively. For formoterol, the differences from placebo were 0.080, 0.059, 0.054, 0.059L. P-values for all treatment groups at these time points ranged between <0.0001 and 0.0426. This is represented graphically in Figure 19.

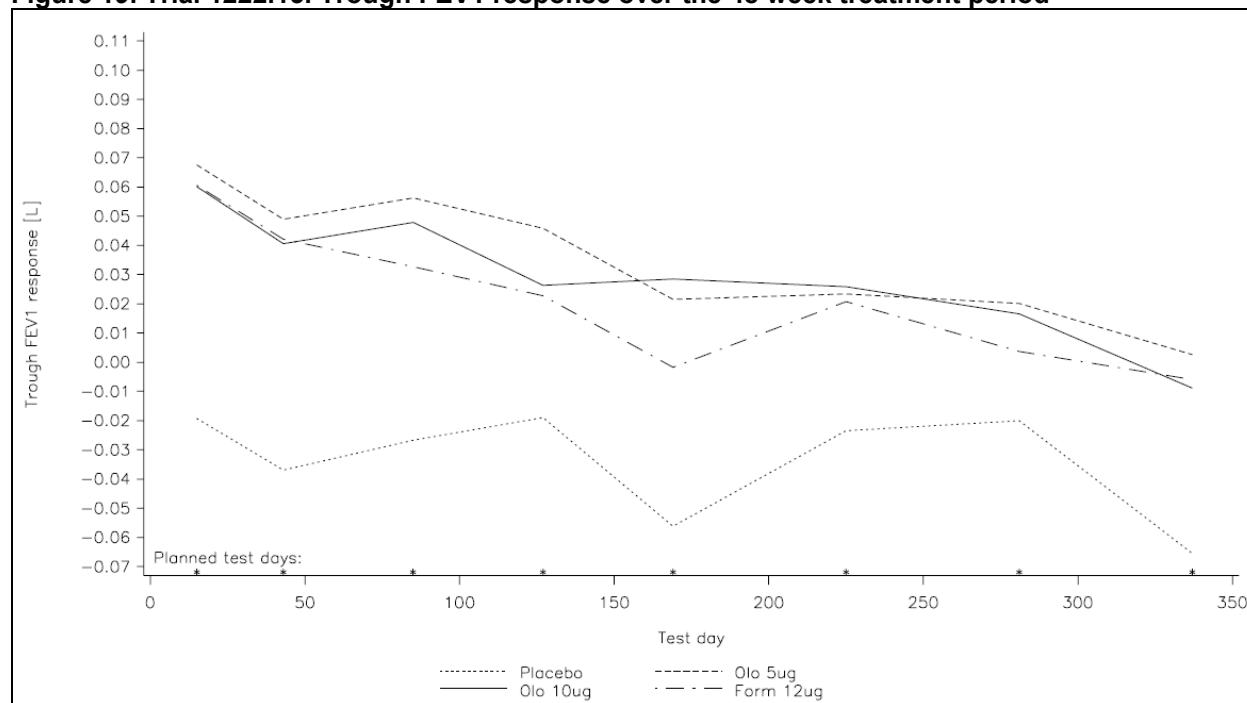
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Figure 19. Trial 1222.13. Trough FEV1 response over the 48 week treatment period



Source: Trial 1222.13 CSR; figure 15.2.1.3:1; pg 279

For the secondary endpoint FEV1 peak (0-3) response compared to placebo at all tested days, the mean differences from placebo in liters for olodaterol 5mcg were 0.163, 0.165, 0.148, and 0.139 at days 1, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.16, 0.159, 0.156 and 0.139, respectively. For the formoterol group, the differences from placebo in liters at the same time points were 0.17, 0.174, 0.167, and 0.162, respectively. P-values for both olodaterol doses and formoterol at all time points were <0.0001.

The difference from placebo in FEV1 response for the olodaterol 5mcg group at 5, 15, 30, 60, 120 and 180 minutes post-dose on Day 1 were 0.114, 0.145, 0.153, 0.178, 0.179, and 0.180L, respectively. For olodaterol 10mcg the differences from placebo were 0.111, 0.136, 0.149, 0.172, 0.186, and 0.183 L, respectively. For formoterol the differences from placebo were 0.131, 0.153, 0.160, 0.190, 0.192, and 0.177L, respectively. All p-values were <0.0001. This is represented graphically in Figure 20.

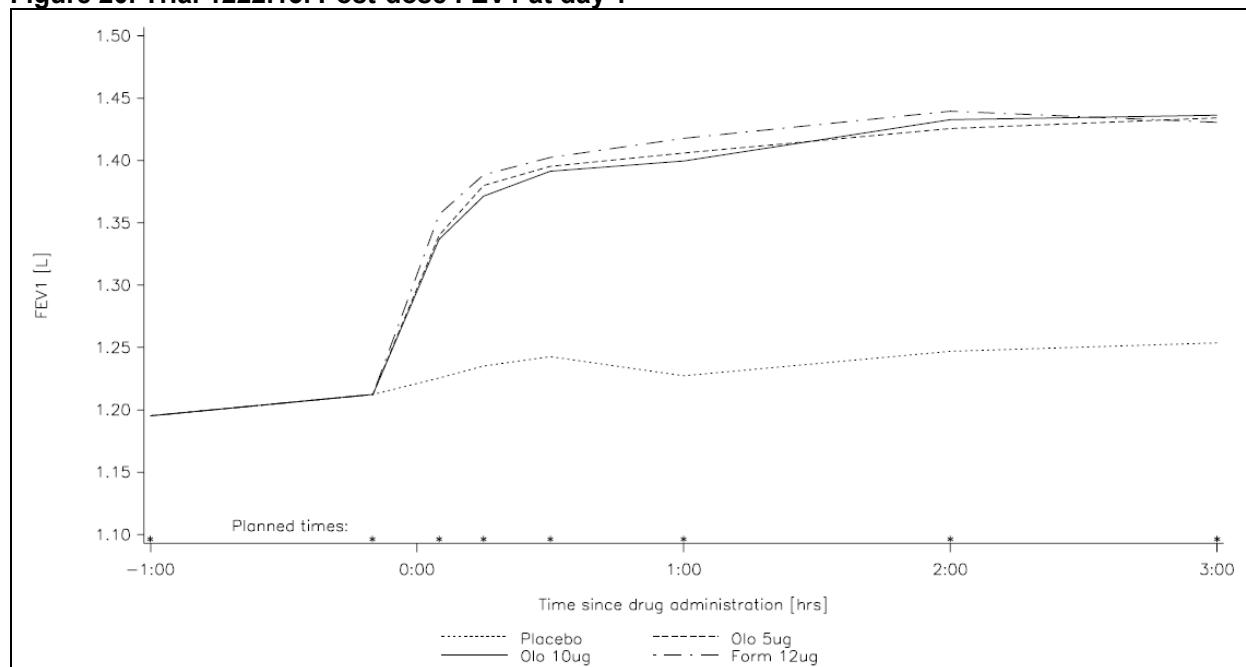
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Figure 20. Trial 1222.13. Post-dose FEV1 at day 1



Source: Trial 1222.13 CSR; figure 15.2.1.1:1; pg 233

Sensitivity analysis using unadjusted means (original pre-specified analysis plan from trials 1222.11 and 1222.12) for the FEV1_related endpoints also demonstrated similar results.

The results for the FVC related secondary endpoints were consistent with the results for the analogous FEV1 related secondary endpoints. For the trough FVC response at 24 weeks, the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.056L ($p=0.16$), 0.082L ($p<0.04$), and 0.019 ($p=0.6328$), respectively]. Similar trends were seen at all other time points, however p-values <0.05 were only seen for all three groups at weeks 6 and 12 (days 43 and 85).

For the FVC AUC (0-3 hours) response at 24 weeks (day 169), the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.182L, 0.215L, and 0.242L (all p-values <0.0001), respectively]. Similar trends were seen at all other time points.

With regard to FVC peak (0-3) response at 24 weeks, olodaterol 5mcg, olodaterol 10mcg, and formoterol all demonstrated improvements compared to placebo [0.173L ($p<0.0001$), 0.207L ($p<0.0001$), and 0.217L ($p<0.0001$), respectively]. Results were similar at days 1, 43, 85, and 337.

For weekly mean values from morning PEFR, both olodaterol groups demonstrated improvements from placebo. The magnitude of mean differences from placebo at key

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study time points (Week 1, 12, 24, and 48) was 20.6, 15.4, 15.1, and 13.3 L/min, respectively, for olodaterol 5mcg; 19.7, 17.6, 15.0, and 14.4 L/min, respectively, for olodaterol 10mcg; and 18.6, 18.5, 17.6, and 20.0 L/min, respectively, for formoterol. For these time points, the p-values were between 0.0057 to <0.0001. Results were similar for evening PEFR.

Reviewer Comment

The results for the secondary endpoints related to FEV1 and FVC were supportive of a bronchodilatory effect for olodaterol compared to placebo. As with the primary endpoint, there was no consistent incremental benefit for the 10mcg dose over the 5mcg dose with regard to FEV1 related secondary endpoints. Over the 48 week treatment period, spirometric responses for the olodaterol groups compared to placebo appeared decrease over time. At the day 337, for both the trough FEV1 response and FEV1 AUC (0-3 hours) response and at both olodaterol doses, there was a decrease in treatment effect. Note that for formoterol this was not observed. This implies that there may be some decrease in treatment effect overtime.

Non-spirometric secondary endpoints:

For the secondary endpoint of weekly mean daily rescue medication use over the 48-week treatment period, both olodaterol dose groups demonstrated less rescue medication use compared to placebo. At each weekly timepoint, the mean reduction for both olodaterol doses ranged from 0.733 to 1.413 fewer puffs/day with p-values ranging from <0.0001 to 0.0023). A similar trend was seen for formoterol (0.455 to 0.986 fewer puffs/day); p-values ranged from <0.0001 to 0.0758.

The results for the secondary endpoints of daytime and night-time rescue medication use over the 48-week treatment period were similar. For both olodaterol doses, the difference from placebo in weekly mean daytime rescue medication use ranged from 0.248 to 0.574 puffs/day with p-values ranging from <0.0001 to 0.04. A similar trend was seen for formoterol; however, as with the total daily rescue medication use, p-values sometime crossed the 0.05 threshold. Results for nighttime rescue medication use were similar.

The number and time to first COPD exacerbation were also evaluated as secondary endpoints. For time to first COPD exacerbation, moderate COPD exacerbation, and first COPD exacerbation leading to hospitalization, there were no statistically significant differences between olodaterol and placebo groups. There was also no trend for a treatment effect when comparing olodaterol to placebo. The results with respect to number of exacerbations between groups was also similar. When comparing formoterol to placebo for the same parameters, there was a trend for longer time to first exacerbation and time to first moderate exacerbation. The same trend was seen for number of exacerbations.

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PK data

Post-dosing olodaterol levels were comparable on days 43, 85 and 127. The geometric mean concentration 10 minutes after inhalation was 1.7 fold higher in olodaterol 10mcg versus olodaterol 5mcg. Serum concentrations were also slightly higher in Asians compared to Whites. There was also no evidence of a relationship between oldaterol serum levels and serum potassium levels. It should be noted that 4 (0.5%) out of the 784 plasma samples from placebo patients had detectable levels of olodaterol, and 2 (0.8%) out of 240 formoterol patients had detectable olodaterol levels. In addition 18 (4.1%) of 407 samples taken from olodaterol patients prior to first trial drug administration also had detectable olodaterol levels.

Reviewer comment

The detection of olodaterol in patients who were not exposed to olodaterol is concerning. However, the overall numbers were small and this would likely dilute treatment effects rather than accentuate them. As such, this does not affect efficacy conclusions.

Safety

Exposure

A total of 904 patients received at least one dose of trial drug. Mean exposure was higher in the olodaterol groups and formoterol group (296-306 days) compared to placebo (277 days). The difference is likely related to the higher number of discontinuations in the placebo group compared to the olodaterol groups. Patient exposure is summarized in Table 82.

Table 82. Trial 1222.13. Patient exposure

| | Placebo | Olo 5mcg | Olo 10mcg | Formoterol | Total |
|---------------------------|------------|------------|------------|------------|------------|
| Extent of exposure (days) | | | | | |
| N | 225 | 227 | 225 | 227 | 904 |
| Mean | 277.1 | 305.8 | 300.9 | 295.5 | 294.9 |
| SD | 111.7 | 79.7 | 88.1 | 96.5 | 95.2 |
| Min | 1 | 36 | 9 | 1 | 1 |
| Median | 336 | 336 | 337 | 337 | 336 |
| Max | 358 | 371 | 363 | 362 | 371 |
| Extent of exposure [N(%)] | | | | | |
| <=15 days | 12 (5.3) | 0 (0.0) | 3 (1.3) | 8 (3.5) | 23 (2.5) |
| 16 - 43 days | 7 (3.1) | 4 (1.8) | 7 (3.1) | 6 (2.6) | 24 (2.7) |
| 44 - 85 days | 10 (4.4) | 8 (3.5) | 6 (2.7) | 10 (4.4) | 34 (3.8) |
| 86 - 127 days | 9 (4.0) | 7 (3.1) | 5 (2.2) | 2 (0.9) | 23 (2.5) |
| 128 - 169 days | 4 (1.8) | 5 (2.2) | 4 (1.8) | 3 (1.3) | 16 (1.8) |
| 170 - 225 days | 6 (2.7) | 5 (2.2) | 7 (3.1) | 5 (2.2) | 23 (2.5) |
| 226 - 281 days | 9 (4.0) | 4 (1.8) | 5 (2.2) | 5 (2.2) | 23 (2.5) |
| 282-337 days | 115 (51.1) | 139 (61.2) | 125 (55.6) | 130 (57.3) | 509 (56.3) |
| >=338 days | 53 (23.6) | 55 (24.2) | 63 (28.0) | 58 (25.6) | 229 (25.3) |

Source: Trial 1222.13 CSR; table 12.1:1; pp119

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Deaths

Of the 904 patients who received at least one dose of trial drug, 17 patients died on-treatment. [(Olo 5mcg=3 (1.3%), Olo 10mcg=6 (2.7%), Foradil=4 (1.8%), and placebo=4 (1.8%)]. Patient deaths are summarized in Table 83.

Table 83. Trial 1222.13. Deaths during on treatment period and during off-treatment/solicited vital status follow-up

| Period | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol |
|---|-----------------|------------------|-------------------|------------|
| Total | 8 (3.6) | 5 (2.2) | 6 (2.7) | 6 (2.7) |
| On treatment | 4 (1.8) | 3 (1.3) | 6 (2.7) | 4 (1.8) |
| Off treatment/ Solicited vital status follow-up | 4 (1.8) | 2 (0.9) | 0 | 2 (0.9) |

Source. Trial 1222.13 CSR; table 12.3.1:1 and 12.3.1:2; pp 128 and 129.

In the olodaterol 5mcg group, 2 patients died of COPD exacerbations and one of lung cancer. There was concurrence between the investigator assessment and MAC. For the olodaterol 10mcg groups, the causes of death per investigator were pneumonia (n=3), lung cancer, esophageal cancer, and suicide. The MAC attributed 2 out of the 3 pneumonia deaths to COPD exacerbation, and was in agreement on the other causes of death. For the fomoterol group, the causes of death were cardiac failure, sudden death, lung adenocarcinoma, and ruptured aortic aneurysm. In the case of cardiac failure, the MAC assigned cause of death as unknown, and in the case of sudden death, assigned the cause as sudden cardiac death. In the placebo group, there were 4 deaths during the treatment period; the causes of death were cardiorespiratory arrest, death, acute respiratory failure/COPD, and sudden death. Per MAC, the causes were unknown, sudden cardiac death, sudden death, and sudden cardiac death, respectively.

An additional 8 patients died after early discontinuation of study treatment (placebo=4, Olo 5mg=2, fomoterol=2). Of these, 4 were reported during the vital status follow-up period (all placebo). The remaining four were reported during the off-treatment period (>12 days after last treatment, but before end of trial). For the olodaterol 5mcg group, the causes of death were cardio-respiratory arrest and COPD (per MAC, both were COPD exacerbation). For the fomoterol group, the causes of death were assigned as respiratory failure and cardiac death (per MAC, COPD exacerbation and unknown). In the placebo group, the causes of death were myocardial infarction, acute myocardial infarction, death, and acute respiratory failure/COPD/hemoptysis. Per MAC, the causes of death were COPD, sudden death, unknown, and massive hemoptysis.

SAEs

One hundred twenty three (123) patients experienced SAEs (placebo=13.8%, Olo 5mcg=14.5%, Olo 10mcg=11.6%, and fomoterol=14.5%). The most common SAEs were COPD exacerbation (4.5%), pneumonia (2%), gastroenteritis (0.4%) and infective exacerbation of COPD (0.4%), atrial fibrillation (0.4%), and acute respiratory failure

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(0.4%). Based on overall SAEs, there was no dose response. When examining the respiratory mediastinal, and thoracic SOC, there was mild imbalance. This appeared to be driven by the COPD exacerbations, which occurred more frequently in the olodaterol 10 mcg group. It should also be noted that the SAE atrial fibrillation also appeared to have a mild imbalance. As the numbers are small, conclusions cannot be drawn on the basis of this trial. These events will be further evaluated in section 7 Review of Safety.

Table 84 summarizes all SAEs. This table also includes PTs that occurred in ≥ 2 patients. Note that not all SAEs by PT are included. Additionally, if a PT that occurred in < 2 patients was similar to a PT that occurred in ≥ 2 patients, that PT was also listed in the SAE table (e.g. cardiac failure and cardiac failure acute).

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Table 84. Trial 1222.13. All serious adverse events by SOC (PTs listed if they occurred in ≥2patients)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol |
|---|-----------------|------------------|-------------------|------------|
| Total patients | 225 (100) | 227 (100) | 225 (100) | 227 (100) |
| Total SAEs | 31 (13.8) | 33 (14.5) | 26 (11.6) | 33 (14.5) |
| Infections Infestations | 10 (4.4) | 9 (4.0) | 9 (4.0) | 7 (3.1) |
| Pneumonia | 3 (1.3) | 5 (2.2) | 7 (3.1) | 3 (1.3) |
| Gastroenteritis | 3 (1.3) | 1 (0.4) | 0 | 0 |
| Infective exacerbation of COPD | 2 (0.9) | 0 | 1 (0.4) | 1 (0.4) |
| Bronchitis | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Neoplasms benign and malignant | 1 (0.4) | 3 (1.3) | 3 (1.3) | 5 (2.2) |
| Lung adenocarcinoma | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Prostate Cancer | 0 | 1(0.4) | 0 | 1 (0.4) |
| Blood and lymphatic | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Anemia | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Metabolism and nutrition | 2 (0.9) | 0 | 1 (0.4) | 1(0.4) |
| Dehydration | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Psychiatric disorder | 0 | 0 | 1 (0.4) | 0 |
| Nervous system disorder | 3 (1.3) | 2 (0.9) | 0 | 0 |
| Eye disorders | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Cardiac disorders | 6 (2.7) | 3 (1.3) | 2 (0.9) | 4 (1.8) |
| Atrial fibrillation | 0 | 1 (0.4) | 2 (0.9) | 1 (0.4) |
| Acute myocardial infarction | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Supraventricular tachycardia | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Cardiac Failure | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Cardiac Failure Acute* | 0 | 1 (0.4) | 0 | 0 |
| Cardiac Failure Congestive* | 0 | 0 | 1(0.4) | 0 |
| Vascular disorders | 1 (0.4) | 0 | 3 (1.3) | 3 (1.3) |
| Intermittent Claudication | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Respiratory, thoracic, mediastinal | 10 (4.4) | 11 (4.8) | 15 (6.7) | 9 (4.0) |
| COPD | 9 (4.0) | 10 (4.4) | 13 (5.8) | 9 (4.0) |
| Respiratory failure | 2 (0.9) | 0 | 0 | 0 |
| Acute Respiratory failure | 1 (0.4) | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Gastrointestinal disorder | 1 (0.4) | 1 (0.4) | 0 | 2 (0.9) |
| Hepatobiliary disorder | 2 (0.9) | 0 | 1 (0.4) | 0 |
| Musculoskeletal disorder | 1 (0.4) | 2 (0.9) | 0 | 1 (0.4) |
| Renal and urinary disorders | 2 (0.9) | 2 (0.9) | 0 | 1 (0.4) |
| Renal Failure | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Reproductive disorders | 0 | 0 | 0 | 1 (0.4) |
| Congenital, familial, & genetic disorder | 0 | 0 | 1 (0.4) | 0 |
| General disorders | 2 (0.9) | 3 (1.3) | 0 | 2 (0.9) |
| Sudden Death | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Investigations | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Injury, poisoning, and procedural complications | 3 (1.3) | 3 (1.3) | 3 (1.3) | 2 (0.9) |
| Fall | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Joint dislocations | 0 | 1 (0.4) | 1 (0.4) | 0 |

*included because the terms were similar to cardiac failure

Source: Trial 1222.13 CSR; table 15.3.2.1:6; pp 547-552

Sixty-five (65) patients withdrew due to AEs. This occurred more frequently in the placebo (7.1%) group compared to the olodaterol 10mcg (6.6%) and olodaterol 5mcg (6.7%) groups. However, discontinuations due to AEs were the most common in the

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fomoterol group (8.4%). The most common AEs leading to discontinuation was COPD, pneumonia, dyspnea, and lung cancer. No AEs demonstrated a dose response. A summary of all AEs by SOC leading to discontinuation occurring in ≥2 patients can be found in Table 85.

Table 85. Trial 1222.13. Adverse events leading to discontinuation

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Fomoterol N(%) |
|--------------------------------------|-----------------|------------------|-------------------|-------------------|
| Total patients | 225 (100) | 227 (100) | 225(100) | 227 (100) |
| Total AEs leading to discontinuation | 16 (7.1) | 16 (6.6) | 15 (6.7) | 19 (8.4) |
| Infections Infestations | 0 | 0 | 4 (1.8) | 1 (0.4) |
| Pneumonia | 0 | 0 | 3 (1.3) | |
| Neoplasms benign and malignant | 0 | 1 (0.4) | 2 (0.9) | 2 (0.9) |
| Lung adenocarcinoma | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Blood Lymphatic System | 0 | 0 | 1 (0.4) | 0 |
| Immune system | 0 | 1 (0.4) | 0 | 0 |
| Psychiatric disorder | | | | |
| Nervous system disorder | 2 (0.9) | 0 | 0 | 1 (0.4) |
| Headache | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Eye disorders | 1 (0.4) | 0 | 0 | 2 (0.9) |
| Cardiac disorders | 5 (2.2) | 1 (0.4) | 0 | 4 (1.8) |
| Acute myocardial infarction | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Vascular disorders | 0 | 0 | 0 | 1 (0.4) |
| Respiratory, thoracic, mediastinal | 6 (2.7) | 11 (4.8) | 5 (2.2) | 6 (2.6) |
| COPD | 5 (2.2) | 9 (4) | 4 (1.8) | 5 (2.2) |
| Dyspnea | 1 (0.4) | 2 (0.9) | 0 | 0 |
| Acute respiratory failure | 0 | 0 | 0 | 1 (0.4) |
| Gastrointestinal disorder | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Hepatobiliary disorder | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Skin and subcutaneous disorder | 0 | 0 | 1 (0.4) | 0 |
| Musculoskeletal disorder | 0 | 0 | 1 (0.4) | 0 |
| Reproductive System | 0 | 0 | 0 | 1 (0.4) |
| Congenital, familial, and genetic | 0 | 0 | 1 (0.4) | 0 |
| General disorders | 2 (0.9) | 1 (0.4) | 0 | 2 (0.9) |
| Sudden cardiac death | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Investigations | 0 | 0 | 2 (0.9) | 1 (0.4) |
| ECG QT prolonged | 0 | 0 | 1 (0.4) | 1 (0.4) |

Source: Trial 1222.13 CSR; table 15.3.2.1:6; pp 544-546

Reviewer comment:

With regard to deaths, there was no apparent imbalance based on sponsor analysis; however per MAC, COPD was a more common cause of death (on treatment) in olodaterol groups (Olo 5mcg=2, Olo 10mcg =2) compared to placebo(0) and formoterol (0). No similar trend was noted in previous trials. Given the small numbers, this may be a chance observation. There was also mild imbalance for SAEs in the SOC respiratory thoracic and mediastinal, which was driven by the PT COPD. A mild imbalance for the PT atrial fibrillation was also seen. However, as the numbers are small conclusions cannot be drawn on the basis of this trial. These events will be further evaluated in section 7 Review of Safety

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Common TEAEs

The most common TEAEs ($\geq 3\%$) based on preferred term were COPD, nasopharyngitis, and URI. The AEs of nasopharyngitis and pneumonia demonstrated some evidence of dose dependence. COPD and nasopharyngitis were least commonly reported in the placebo group.

Table 86. Trial 1222.13. Common TEAEs ($\geq 3\%$)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol N(%) |
|---|-----------------|------------------|-------------------|--------------------|
| Number of patients | 225 (100.0) | 227 (100.0) | 225 (100.0) | 227 (100.0) |
| Total with adverse events | 153 (68.0) | 160 (70.5) | 164 (72.9) | 149 (65.6) |
| Infections and infestations | 78 (34.7) | 77 (33.9) | 82 (36.4) | 69 (30.4) |
| Nasopharyngitis | 15 (6.7) | 22 (9.7) | 25 (11.1) | 23 (10.1) |
| Upper respiratory tract infection | 15 (6.7) | 17 (7.5) | 12 (5.3) | 11 (4.8) |
| Bronchitis | 9 (4.0) | 10 (4.4) | 8 (3.6) | 5 (2.2) |
| Pneumonia | 6 (2.7) | 8 (3.5) | 10 (4.4) | 5 (2.2) |
| Gastroenteritis | 7 (3.1) | 5 (2.2) | 2 (0.9) | 8 (3.5) |
| Influenza | 7 (3.1) | 8 (3.5) | 3 (1.3) | 5 (2.2) |
| Urinary tract infection | 1 (0.4) | 8 (3.5) | 3 (1.3) | 0 (0.0) |
| Nervous system disorders | 19 (8.4) | 15 (6.6) | 26 (11.6) | 11 (4.8) |
| Headache | 8 (3.6) | 5 (2.2) | 11 (4.9) | 6 (2.6) |
| Dizziness | 6 (2.7) | 3 (1.3) | 7 (3.1) | 3 (1.3) |
| Respiratory, thoracic and mediastinal disorders | 84 (37.3) | 94 (41.4) | 97 (43.1) | 77 (33.9) |
| COPD | 60 (26.7) | 77 (33.9) | 75 (33.3) | 62 (27.3) |
| Cough | 7 (3.1) | 7 (3.1) | 13 (5.8) | 13 (5.7) |
| Dyspnea | 11 (4.9) | 9 (4.0) | 13 (5.8) | 6 (2.6) |
| Gastrointestinal disorders | 33 (14.7) | 23 (10.1) | 25 (11.1) | 30 (13.2) |
| Diarrhea | 6 (2.7) | 3 (1.3) | 3 (1.3) | 7 (3.1) |
| Musculoskeletal disorders | 29 (12.9) | 34 (15.0) | 25 (11.1) | 32 (14.1) |
| Back pain | 8 (3.6) | 9 (4.0) | 6 (2.7) | 9 (4.0) |
| General disorders | 19 (8.4) | 20 (8.8) | 21 (9.3) | 14 (6.2) |
| Chest pain | 3 (1.3) | 2 (0.9) | 7 (3.1) | 6 (2.6) |

Source: Trial 1222.13 CSR; table 12.2.2.2:1; pg123

Reviewer Comment:

The common TEAEs seen in this trial were typical in a LABA development program. Unlike in trial 1222.12 and similar to 1222.11, the infections and infestation SOC did not demonstrate a dose response. However, the PTs nasopharyngitis and pneumonia within the SOC did have a mild dose response. COPD as a PT was also more frequent in the olodaterol groups compared to placebo. This is not necessarily surprising as olodaterol did not have an effect on exacerbations based on secondary endpoints. However, it should be noted that in 1222.11 and 1222.12, the TEAE of COPD was had similar frequency in olodaterol groups compared to placebo.

Labs:

Based on mean lab values, there were no notable changes in lab values except for CPK. Mean changes from baseline were -36 U/L, -13 U/L, 18 U/L and 21 U/L for the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups. Similar numbers of

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patients in the olodaterol groups also had normal CPK levels at baseline and above normal maximum values (placebo=12.1%, Olo 5mcg=15%, Olo 10mcg=13%, and formoterol=20.9%).

When examining glucose and potassium, the numbers of patients per group who had normal baseline values and elevated maximum values were similar between groups. When comparing mean difference from placebo in serum potassium (at day 43 and 85 at 1 and 3 hours post-dose) both olodaterol 5mcg and olodaterol 10mcg at day 85 and 3 hours post-dose were statistically significantly decreased compared to placebo ($p<0.02$). However, the magnitude of the difference is likely not clinically significant and ranged from 0.099 and 0.097 mM/L.

When examining potentially clinically significant changes in lab values as defined by the sponsor, numbers were generally similar between groups. However, the potentially clinically significant elevations in glucose were somewhat more frequent in the olodaterol groups compared to placebo (placebo= 1.6%, Olo 5mcg=3.3%, and Olo 10mcg=2.4%).

Vital signs:

With regard to SBP, there were no significant differences between groups based on change in mean values or shifts from normal to high or normal to low. With regard to DBP there were no significant differences between groups based on change in mean values, shifts from normal to low, or shifts from normal to high. For pulse rate, there were no significant differences between groups based on change in mean values or shifts from normal to high.

ECG

ECGs were assessed as mean changes from baseline, mean changes exceeding a pre-specified threshold (450, >480, or >500ms in QTc interval), mean changes exceeding categorized change (>30ms or >60ms in QTc interval), notable changes, and frequency of ECG abnormalities. Notable changes were defined as in trial 1222.11.

Based on these parameters, there were no notable changes from baseline. When analyzing the QTcF based on threshold values (>450ms, >480ms, and >500ms), no imbalances were identified, nor was there any evidence of dose response. However, during the entire treatment period, there were 14 reported increases of QTcF of >500ms, and none were in the placebo group (Olo 10mcg=8, Olo 5mcg=2, formoterol=4). When analyzing the QTcF based on categorized change (>30ms or >60ms), the overall numbers were small for all time points. During the entire treatment period, there were 15 reported increases of QTcF of >60ms (placebo=4, Olo 5mcg=5, Olo 10mcg=4, formoterol=2). Reports of increases >30ms were more frequent, however, there was no clear dose dependent nor time dependent effect. Based on ECG findings, 2 patients discontinued the trial [10322 (Olo 10mcg) and 12102 (formoterol)]. For both patients the PT was prolonged QT.

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Holter monitoring

With regard to supraventricular couplets, change from baseline at days 85, 169, 281, and 337 were variable within groups. Within groups, there were no apparent time-related trends. Between groups, there were also no consistent differences.

The results for supraventricular tachycardia runs were also variable when comparing change from baseline at day 85, 169, 281, and 337. Within groups, there was no apparent time-related trends, nor were there consistent differences between groups at each time point.

With regard to ventricular couplets, there were no consistent trends within groups. However, at all time points the mean number of ventricular couplets decreased compared to baseline versus for the olodaterol 5mcg in which they increased at all timepoints. Notably, ventricular couplets increased for olodaterol 10mcg, at all timepoints except for day 281. With regard to ventricular tachycardia runs, the differences between groups were minimal, and the mean change from baseline in the number of runs in each group was small.

Based on shift table analysis of ventricular premature beats (VPB) and supraventricular premature beats (SVPB), most patients had similar numbers of SVPBs when comparing baseline values to last value on treatment.

Reviewer Comment:

With regard to vital signs, ECG, and holter data, no significant imbalances were seen. These results were consistent with trials 1222.11 and 1222.12. Notably, the olodaterol groups did not appear to have an increased frequency of QTcF prolongation as was implied in some of the asthma dose ranging trials. However, the pooled ECG and holter data from the 48 week trials will be analyzed in the combined safety section.

Overall Reviewer Comment on trial 1222.13

Based on the sponsor analysis of the primary endpoints, both doses of olodaterol are effective bronchodilators. The 10 mcg dose of olodaterol offers no added benefit compared to the 5 mcg dose. It should be noted that the difference from placebo with respect to trough FEV1, is relatively small compared to other bronchodilators; however, this trial allowed for the use of all background COPD medications (including tiotropium) except for LABAs, which may have affected results. The trough FEV1 response in the non-tiotropium strata trended to be larger compared to the tiotropium treated strata for olodaterol 10mcg and formoterol, but not olodaterol 5mcg. It should be noted that compared to trial 1222.12, the treatment effect with respect to trough FEV1 response was larger and similar in magnitude to trial 1222.11. With regard olodaterol's effect over time, there appears to be a slight downward slope, which implies that the treatment effect may wane somewhat over time. With regard to SGRQ, based on analysis of this trial only, while there was a statistically significant effect, the effect is not likely clinical

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significant as it is less than 4, the MCID, for both olodaterol doses. Neither olodaterol dose appears to have any effect on the TDI score. There appears to be no effect on exacerbations and some mild improvement in rescue medication use. With regard to safety, the deaths were fairly well balanced between treatment groups. Based on investigator analysis, there were no imbalances between treatment groups for causes of death; however, based on MAC assessments COPD as a cause of death occurred only in the olodaterol groups during the treatment period. The most common SAEs were COPD exacerbation, pneumonia, gastroenteritis, infective exacerbation of COPD, atrial fibrillation, and acute respiratory failure. Common TEAEs were also fairly consistent with the COPD population. While some numerical imbalances were seen, overall numbers were small and conclusions cannot be drawn.

5.3.11 Trial 1222.14 (COPD 48 Week Trial)

Administrative Information

- **Study title:** Randomized, double-blind, double-dummy, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled olodaterol (5mcg [2 actuations of 2.5mcg] and 10mcg [2 actuations of 5mcg]) delivered by the Respimat inhaler, and 48 weeks of twice daily Foradil (12mcg) delivered by the Aerolizer in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 1/27/2009-12/08/2010
- **Study sites:** Argentina (5), Brazil (6), Canada (15), Czech Republic (4), Denmark (3), Finland (3), Germany (14), Hong Kong (1), India (12), Italy (5), Malaysia (3), Norway (2), Philippines (3), South Korea (6), Romania (3), Russia (3), South Africa (2), Spain (7), Sweden (3), Thailand (3).
- **Study report date:** 01/31/2012

Objectives/Rationale, Trial design, Trial population, treatments

The objectives, design, conduct, inclusion/exclusion criteria, prohibited/restricted medications, endpoints, and analysis plan of this trial were identical to trial 1222.13.

Results:

Protocol Amendments/Changes to analysis

There was a single amendment submitted for this protocol on 7/7/09. The changes were identical to those described in trial 1222.13.

Protocol Violations

A total of 120 (12.8%) patients had important protocol violations (IPV). The most common violation was 'prohibited medication during treatment period,' 'informed consent given too late,' and 'study drug not taken on the day prior to primary clinical endpoint.' Important protocol violations are summarized in Table 87.

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Table 87. Trial 1222.14. Important protocol violations

| | Placebo [N(%)] | Olo 5mcg [N(%)] | Olo 10mcg [N(%)] | Formoterol 12mcg [N(%)] | Total [N(%)] |
|--|-------------------|--------------------|---------------------|-------------------------------|-----------------|
| Randomized | 235 (100) | 232 (100) | 234 (100) | 233 (100) | 937 (100) |
| Total with important protocol violations | 36 (15.3) | 25 (10.8) | 28 (12.0) | 31 (13.3) | 120 (12.8) |
| Inclusion criteria not met | 1 (0.4) | 1 (0.4) | 0 | 2 (0.9) | 4 (0.4) |
| Exclusion criteria affecting efficacy and possibly safety | 2 (0.9) | 1 (0.4) | 3 (1.3) | 4 (1.7) | 10 (1.1) |
| Exclusion criteria affecting safety only | 1 (0.4) | 1 (0.4) | 0 | 2 (0.9) | 4 (0.4) |
| Informed consent given too late | 8 (3.4) | 7 (3.0) | 10 (4.3) | 5 (2.1) | 30 (3.2) |
| Study drug not taken on day prior to primary endpoint clinic visit | 4 (1.7) | 4 (1.7) | 2 (0.9) | 3 (1.3) | 13 (1.4) |
| Randomization order not followed | 1 (0.4) | 0 | 0 | 1 (0.4) | 2 (0.2) |
| Study medication taken longer than planned duration | 0 | 1 (0.4) | 2 (0.9) | 0 | 3 (0.3) |
| Incorrect trial medication taken on clinic days | 0 | 0 | 0 | 1 (0.4) | 1 (0.1) |
| Prohibited medication taken during treatment period | 17 (7.2) | 11 (4.7) | 11 (4.7) | 11 (4.7) | 50 (5.3) |
| Primary endpoint data missing | 2 (0.9) | 1 (0.4) | 0 | 1 (0.4) | 4 (0.4) |
| Other PV affecting safety and possibly safety | 3 (1.3) | 1 (0.4) | 2 (0.9) | 1 (0.4) | 7 (0.7) |

source: trial 1222.14 CSR; table 15.1.2:1; pp176; IPV= important protocol violations

In general the frequency of protocol deviations was similar between groups. However, more patients in the placebo group took prohibited medications during the treatment period compared to the other groups. Use of prohibited medications was primarily related to use of expired formoterol or placebo. Of the 17 placebo patients who took prohibited medications, in 13 cases it was due to having possibly taken expired placebo.

Reviewer comment:

The protocol amendment does not affect interpretation of data. The IPVs in this trial were in general balanced, except for use prohibited medications. However, it is unlikely that would have affected the results, as it was primarily due to use of expired formoterol/placebo kits.

Disposition

Of the 1257 enrolled patients, 937 were randomized. Of these 934 received at least one dose of trial medication (treated set). Three patients were randomized, but not treated. Two patients withdrew consent prior to dosing (14138 and 13497), and one was withdrawn due to findings on pre-dose ECG (13536) prior to dosing. Seven-hundred-seventy patients (82.4%) completed the trial. The most common reasons for discontinuations were AEs and withdrawal of consent. Discontinuations were least common in the olodaterol groups compared to formoterol and placebo. 'Lack of efficacy' and withdrawal of consent as reasons for withdrawal were more common in placebo patients compared to olodaterol and formoterol patients. Of the patients in the treated set, 928 were included in the FAS used for efficacy analysis. One-hundred-seventy-five

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(175) patients received Holter monitoring. Although there was a PPS defined, analysis was not performed using this set, per the analysis plan (PPS analysis was only performed if the difference between the FAS and PPS were >10%. Patient disposition and analysis populations are summarized in Table 88.

Table 88. Trial 1222.14. Patient disposition and analysis population

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total N(%) |
|-----------------------------|-----------------|------------------|-------------------|--------------------------|---------------|
| Treated Set | 235(100.00) | 232(100.00) | 234(100.00) | 233(100.00) | 934(100.00) |
| Full Analysis Set (FAS) | 233 (99.1) | 230 (99.1) | 233 (99.6) | 232 (99.6) | 928 (99.4) |
| Per Protocol Set (PPS) | 220 (93.6) | 223 (96.1) | 228 (97.4) | 218 (93.6) | 889 (95.2) |
| Holter set (HMS) | 47 (20) | 48 (20.7) | 49 (20.9) | 31 (13.3) | 175 (18.7) |
| Completed | 184 (78.3) | 195 (84.1) | 198 (84.6) | 193 (82.8) | 770 (82.4) |
| Prematurely discontinued | 51 (21.7) | 37 (16.0) | 36 (15.4) | 40 (17.2) | 164 (17.6) |
| Adverse event: | 19 (8.1) | 16 (6.9) | 16 (6.8) | 16 (6.9) | 67 (7.2) |
| COPD worsening | 5 (2.1) | 6 (2.6) | 4 (1.7) | 9 (3.9) | 24 (2.6) |
| Other disease worsening | 2 (0.9) | 1 (0.4) | 3 (1.3) | 1 (0.4) | 7 (0.8) |
| Other | 12 (5.1) | 9 (3.9) | 9 (3.9) | 6 (2.6) | 36 (3.9) |
| Lack of Efficacy | 8 (3.4) | 1 (0.4) | 3 (1.3) | 2 (0.9) | 14 (1.5) |
| Noncompliance with protocol | 2 (0.9) | 2 (0.9) | 0 | 2 (0.9) | 6 (0.6) |
| Lost to follow-up | 2 (0.9) | 1 (0.4) | 2 (0.9) | 3 (1.3) | 8 (0.9) |
| Consent withdrawn | 16 (6.8) | 8 (3.5) | 8 (3.4) | 13 (5.6) | 45 (4.8) |
| Other | 4 (1.7) | 9 (3.9) | 7 (3.0) | 4 (1.7) | 24 (2.6) |

source: Trial 1222.14 CSR; tables 10.1:1 and 11.1:1; pp78 and 82

Reviewer Comment:

There was an overall imbalance in discontinuations when comparing placebo to olodaterol and formoterol group; this was primarily driven by increased discontinuations in the placebo group due to lack of efficacy and consent withdrawn. A similar finding was seen in trial 1222.13. The imbalance in lack of efficacy implies that olodaterol has a treatment benefit. As with trial 1222.13, the reasons for withdrawal of consent were reviewed. The reasons (when available) were primarily due to patient preference or relocation. Of the patients who withdrew consent, only one (placebo) cited worsening disease. This is in contrast to trial 1222.13 where worsening of disease was more commonly cited as the reason for withdrawal of consent.

Demographics

Overall, patient demographics were similar between treatment groups. Most patients were white males with a mean age of 64 years. The average pack year history was 43 years and most patient were not current smokers (67%). The average time since COPD diagnosis was 6.6 years. Approximately 52% of patients were GOLD II and 39% were GOLD III. The average FEV1% predicted was 46%. Demographic data are summarized in Table 89.

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Table 89. Trial 1222.14. Patient demographics and baseline respiratory data

| | Placebo | Olo 5mcg | Olo 10mcg | Formoterol 12mcg | Total |
|---|------------|------------|------------|------------------|------------|
| Number of patients | 235 | 232 | 234 | 233 | 934 |
| Gender [N (%)] | | | | | |
| Male | 195 (83.0) | 187 (80.6) | 184 (78.6) | 192 (82.4) | 758 (81.2) |
| Female | 40 (17.0) | 45 (19.4) | 50 (21.4) | 41 (17.6) | 176 (18.8) |
| Age [years] | | | | | |
| Mean | 63.9 | 63.7 | 63.8 | 65.0 | 64.1 |
| SD | 7.8 | 8.8 | 8.5 | 8.2 | 8.3 |
| Race [N (%)] | | | | | |
| White | 156 (66.4) | 153 (65.9) | 158 (67.5) | 154 (66.1) | 621 (66.5) |
| Black/African American | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 2 (0.2) |
| Asian | 78 (33.2) | 78 (33.6) | 76 (32.5) | 78 (33.5) | 310 (33.2) |
| American Indian/Alaskan | 0 | 1 (0.4) | 0 | 1 (0.4) | 1 (0.1) |
| Smoking history [N (%)] | | | | | |
| Ex-smoker | 163 (69.4) | 144 (62.1) | 158 (67.5) | 161 (69.1) | 626 (67.0) |
| Currently smokes | 72 (30.6) | 88 (37.9) | 76 (32.5) | 72 (30.9) | 308 (33.0) |
| Smoking history [pack years] | | | | | |
| Mean | 41.2 | 40.7 | 43.6 | 44.5 | 42.5 |
| SD | 23.5 | 24.9 | 28.6 | 28.1 | 26.4 |
| Trial Diagnosis [years] | | | | | |
| Mean | 6.7 | 6.3 | 7.0 | 6.6 | 6.6 |
| SD | 5.9 | 5.7 | 6.4 | 6.4 | 6.1 |
| % predicted normal FEV1 | | | | | |
| Mean | 46.6 | 46.7 | 45.4 | 45.2 | 46.0 |
| SD | 14.9 | 14.8 | 14.6 | 15.3 | 14.9 |
| FEV1/FVC [%] | | | | | |
| Mean | 46.8 | 46.5 | 47.0 | 45.5 | 46.5 |
| SD | 12.0 | 11.2 | 10.7 | 11.2 | 11.3 |
| FEV1 [% change from pre-bronchodilator] | | | | | |
| Mean | 12.2 | 13.5 | 14.6 | 13.9 | 13.6 |
| SD | 11.9 | 14.3 | 12.9 | 13.6 | 13.2 |

Source: trial 1222.14CSR; table 11.2:1, 11.2.3:1, 11.2.6:1, 11.2.6:2; pp 84, 85, 89, 91

Across treatment groups, patients had similar numbers and types of concomitant medical diagnoses. The most common medical diagnoses were hypertension (34-37%), benign prostatic hyperplasia (9-10%), hypercholesterolemia (7-9%), diabetes (4-8%), osteoarthritis (5-8%). Cardiac disorders (by SOC and preferred term) were fairly evenly distributed across groups (19-22%). This was lower compared to trials 1222.11/1222.12, but similar to trial 1222.13.

In general, baseline medications were also similar between groups. Inhaled steroids were the most frequently used baseline medication (48-55%). Approximately 25-26% of patients were on tiotropium at baseline. During treatment, medication use was also

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similar between groups, however, IV/IM steroid use was more frequent in the placebo (8.9%) compared to the olodaterol and formoterol groups (6-7%).

Reviewer Comment

The patients' demographic and baseline data were similar across groups and typical of a COPD trial population. This data was similar to the previously reviewed 48-week COPD trials.

Compliance

Based on eDiary entries, compliance was high across groups ranging from 97-98%. Greater than 97% of patients in each group took their medication 80-100% of the time.

Efficacy

Co-primary endpoints:

The spirometric co-primary endpoints for this trial were FEV1 AUC (0-3 hours) response and trough FEV1 response after 24 weeks of treatment. Both doses demonstrated statistically significant differences from placebo for both co-primary endpoints. The 10mcg dose of olodaterol had numerically greater treatment compared to the 5mcg dose. The results of the sponsor's analysis are summarized in Table 90.

Table 90. Trial 1222.14. Co-primary endpoints FEV1 AUC (0-3 hours) response and trough FEV1 response at week 24 (day 169)

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|--------------------------------------|---------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | -0.013 (0.014) | | | -0.055 (0.014) | | |
| Olodaterol 5 mcg | 0.116 (0.014) | 0.129 (0.019) | <0.0001 | -0.003 (0.014) | 0.053 (0.019) | 0.0055 |
| Olodaterol 10 mcg | 0.140 (0.014) | 0.154 (0.019) | <0.0001 | 0.014 (0.014) | 0.069 (0.019) | 0.0003 |
| Formoterol | 0.137 (0.014) | 0.150 (0.019) | <0.0001 | -0.13 (0.014) | 0.042 (0.019) | 0.0270 |

Source: Trial 1222.14 CSR; tables 11.4.1.1.1:1 and 11.4.1.1.2:1; pp 94 and 96.

When comparing the co-primary endpoints between patients in the tiotropium strata to non-tiotropium strata, the treatment difference from placebo was of lesser or similar magnitude in the non-tiotropium strata. The comparisons of olodaterol to placebo all had p-values <0.05 for both FEV1 AUC (0-3 hours) response and trough FEV1 response. Analysis of the formoterol treatment effect on the spirometric co-primary endpoints was similar, except that when comparing trough FEV1 response in tiotropium strata, there was no statistical difference from placebo. It should be noted that these comparisons were not corrected for multiplicity and were conducted on subsets not powered to show treatment differences between groups. These results are summarized in Table 91

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Table 91. Trial 1222.14. Sponsor analysis by strata for spirometric co-primary endpoints

| Treatment Group | Tiotropium Strata | | | Non-tiotropium Strata | | |
|-----------------|--------------------------------------|------------------------|---------|--------------------------------------|------------------------|---------|
| | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.010 (0.027) | | | -0.009 (0.016) | | |
| Olo 5 mcg | 0.143 (0.027) | 0.152 (0.038) | <0.0001 | 0.112 (0.016) | 0.122 (0.022) | <0.0001 |
| Olo10 mcg | 0.139 (0.027) | 0.149 (0.038) | <0.0001 | 0.146 (0.016) | 0.155 (0.022) | <0.0001 |
| Formoterol | 0.125 (0.027) | 0.135 (0.038) | 0.0004 | 0.146 (0.016) | 0.155 (0.155) | <0.0001 |
| | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.056 (0.027) | | | -0.047 (0.016) | | |
| Olo 5 mcg | 0.015 (0.027) | 0.071 (0.038) | 0.0596 | 0.000 (0.015) | 0.047 (0.022) | 0.0326 |
| Olo 10 mcg | 0.015 (0.026) | 0.071 (0.037) | 0.0576 | 0.022 (0.015) | 0.069 (0.022) | 0.0018 |
| Formoterol | -0.021 (0.027) | 0.035 (0.038) | 0.3462 | -0.002 (0.015) | 0.045 (0.022) | 0.0424 |

Source: Trial 1222.14 CSR; Tables 11.4.1.1:2 &11.4.1.2:2; pp 95 and 97

For the third co-primary endpoint of Mahler TDI, at 24 weeks, no group demonstrated statistically significant improvements compared to placebo. This was true for the both the total score and individual component scores.

Reviewer Comment:

For the spirometric co-primary endpoints of FEV1 AUC (0-3 hours) and trough FEV1 response at 24 weeks, both doses demonstrated a statistically significant difference from placebo. The treatment effect for olodaterol 10mcg and olodaterol 5mcg were similar. The treatment effect was lesser in magnitude compared to trial 1222.13, and more similar to 1222.12. In the by strata analysis, the difference from placebo for olodaterol was less/similar for both co-primary endpoints for the non-tiotropium strata versus the tiotropium strata. This is contrast to the by strata results in trials 1222.11 and 1222.12. It should also be noted that the treatment effect even in the non-tiotropium strata is modest and less than other LABAs. For the third co-primary endpoint of Mahler TDI score, there was no significant difference from placebo, however the sponsor had pre-specified that analysis would be performed on the pooled data with 1222.13.

Key Secondary Endpoints

Although the sponsor planned to pool data for analysis the key secondary endpoints, in this report, they also provided analysis for data from this trial only. The combined analysis will be discussed in section 6 Review of Efficacy. For the key secondary endpoint of SGRQ at week 24, both olodaterol groups demonstrated a statistically significant difference from placebo (Olo 5mcg=-3.2, p=0.0197; Olo 10mcg=-3.5, p=0.0094). This difference, while statistically significant, did not meet the MCID of -4 for SGRQ. The difference from placebo in SGRQ for formoterol was not statistically significant and even smaller in magnitude.

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Comparisons to formoterol

For the spirometric co-primary endpoints, comparisons were also made between olodaterol groups to formoterol. As with the SGRQ, the sponsor planned to pool data for this analysis. However, in this report, they also provided analysis for data from this trial only. When comparing FEV1 AUC (0-3 hours) response at 24 weeks between olodaterol groups to formoterol, there were no statistically significant differences. Numerical differences between the olodaterol 5 and 10mcg doses to formoterol were -0.021L and 0.003L, respectively. When comparing trough FEV1 response at 24 weeks between olodaterol groups and formoterol, there were also no statistically significant differences. Numerical differences between the olodaterol 5 and 10mcg doses to formoterol were 0.011L and 0.027L, respectively.

Other secondary endpoints

For the following endpoints, there was no protection for type 1 error; therefore, the analysis was considered descriptive by the sponsor.

Spirometric Secondary Endpoints:

For the secondary endpoint of FEV1 AUC (0-3 hours) response after 48 weeks (337 days) of treatment, the olodaterol 10mcg, olodaterol 5mcg, and formoterol dose groups had differences from placebo of 0.141L, 0.118L, and 0.129L (p-values <0.0001), respectively. At days 1, 43, 85, 169, and 337, the results were similar, all with p-values <0.0001. The magnitude for the differences from placebo during these time points for the olodaterol 5mcg group were 0.149, 0.172, 0.145, 0.129, and 0.118L, respectively. For olodaterol 10mcg, the differences from placebo at the same time points were 0.171, 0.192, 0.175, 0.154, 0.141, respectively. For formoterol, the results for the same time points were 0.152, 0.184, 0.170, 0.150, and 0.129L, respectively. These results are represented graphically in Figure 21

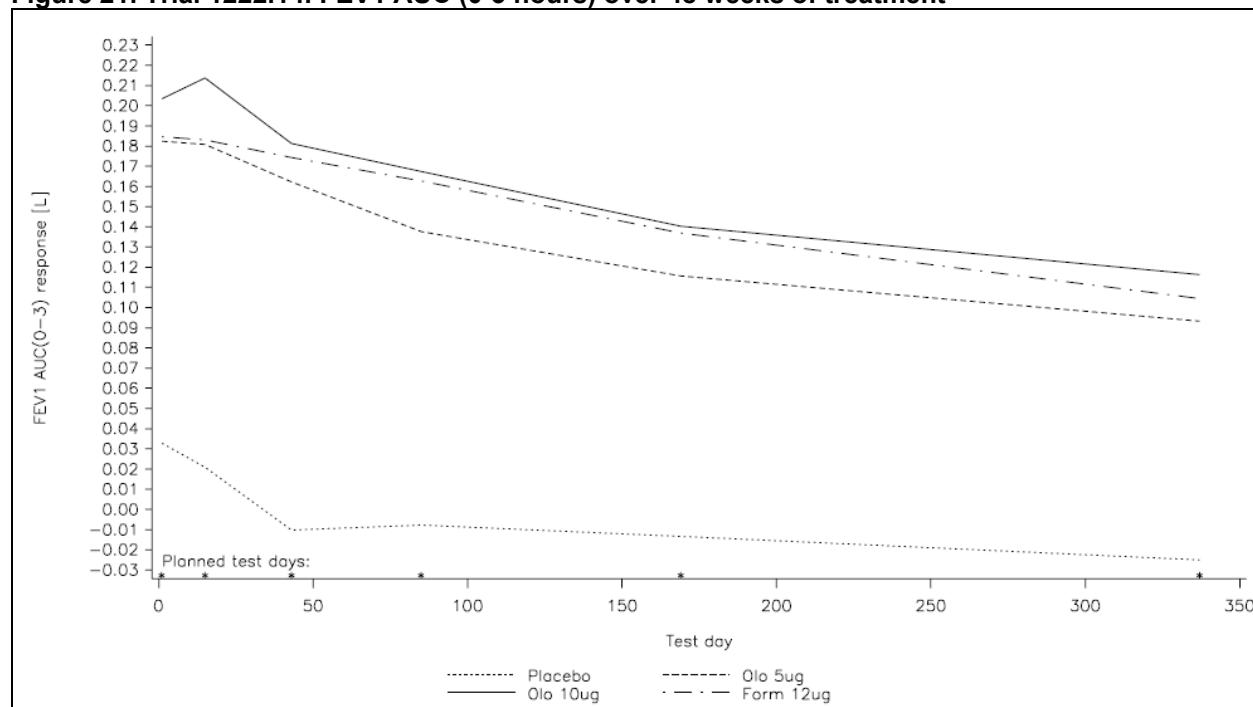
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Figure 21. Trial 1222.14. FEV1 AUC (0-3 hours) over 48 weeks of treatment



source: Trial 1222.14 CSR; figure 15.2.1.1.2:1; pp 267

For the secondary endpoint of trough FEV1 response over the 48 week period, both olodaterol doses demonstrated an increase in response compared to placebo at key trial time points (days 15, 43, 85, 169, and 337). The mean differences from placebo in liters for olodaterol 5mcg were 0.069, 0.084, 0.059, 0.053, 0.044L at the key study time points of day 15, 43, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.119, 0.104, 0.093, 0.069, and 0.059L, respectively. For formoterol, the differences from placebo were 0.049, 0.070, 0.042, 0.036L, respectively. P-values for all treatment groups at these time points ranged between <0.0001 and 0.0664. Note that the p-value of 0.0664 was from the comparison to placebo at day 337. The difference for the olodaterol to placebo comparisons range from <0.0001 to 0.027. These data are represented graphically in Figure 22.

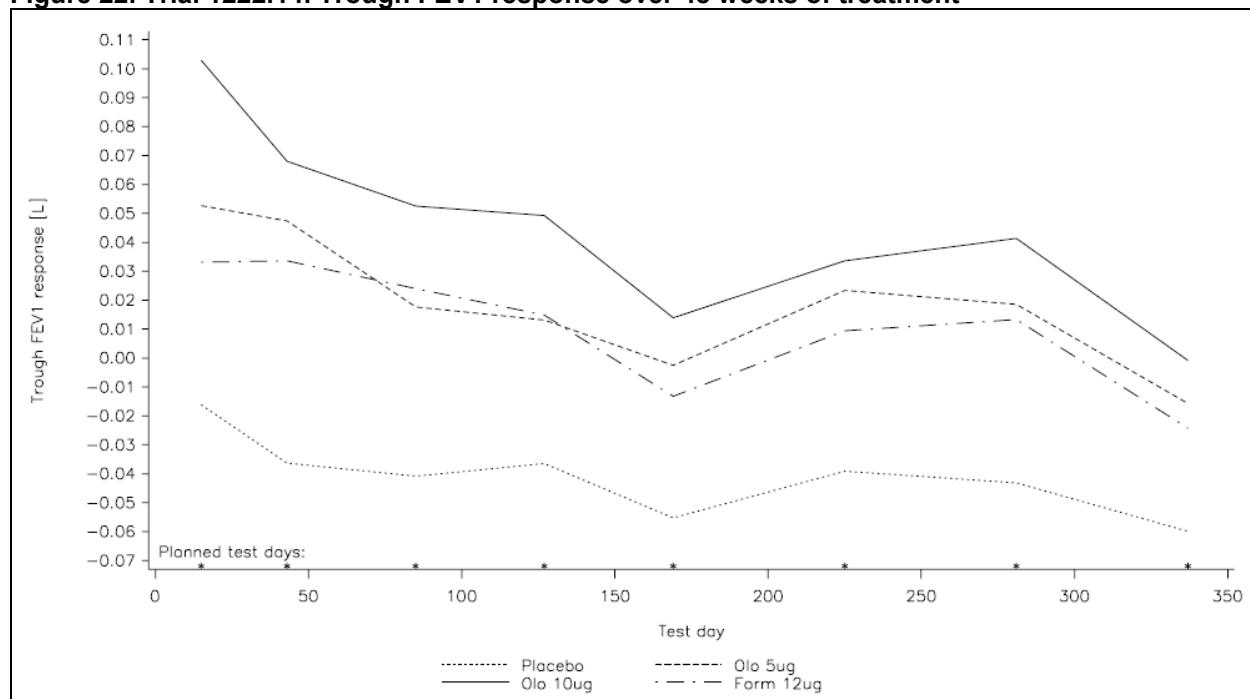
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Figure 22. Trial 1222.14. Trough FEV1 response over 48 weeks of treatment



Source: Trial 1222.14 CSR; figure 15.2.1.3:1; pp 274

For the secondary endpoint FEV1 peak (0-3) response compared to placebo, the mean differences from placebo in liters for olodaterol 5mcg were 0.149, 0.141, 0.123, and 0.112L, respectively, at days 1, 85, 169, and 337, respectively. For the olodaterol 10mcg group, the differences from placebo in liters at the same time points were 0.171, 0.168, 0.151, and 0.126L, respectively. For the formoterol group, the differences from placebo in liters at the same time points were 0.149, 0.164, 0.143, and 0.118L, respectively. P-values for both olodaterol doses and formoterol at all time points were <0.0001.

The difference from placebo in FEV1 response for the olodaterol 5mcg group at 5, 15, 30, 60, 120, and 180 minutes post-dose on Day 1 were 0.102, 0.136, 0.135, 0.157, 0.158, and 0.161L, respectively. For olodaterol 10mcg, the differences from placebo were 0.113, 0.149, 0.154, 0.178, 0.183, and 0.184L, respectively. For formoterol the differences from placebo were 0.128, 0.155, 0.154, 0.159, 0.155, and 0.150L, respectively. All p-values were <0.0001. This is represented graphically in Figure 23.

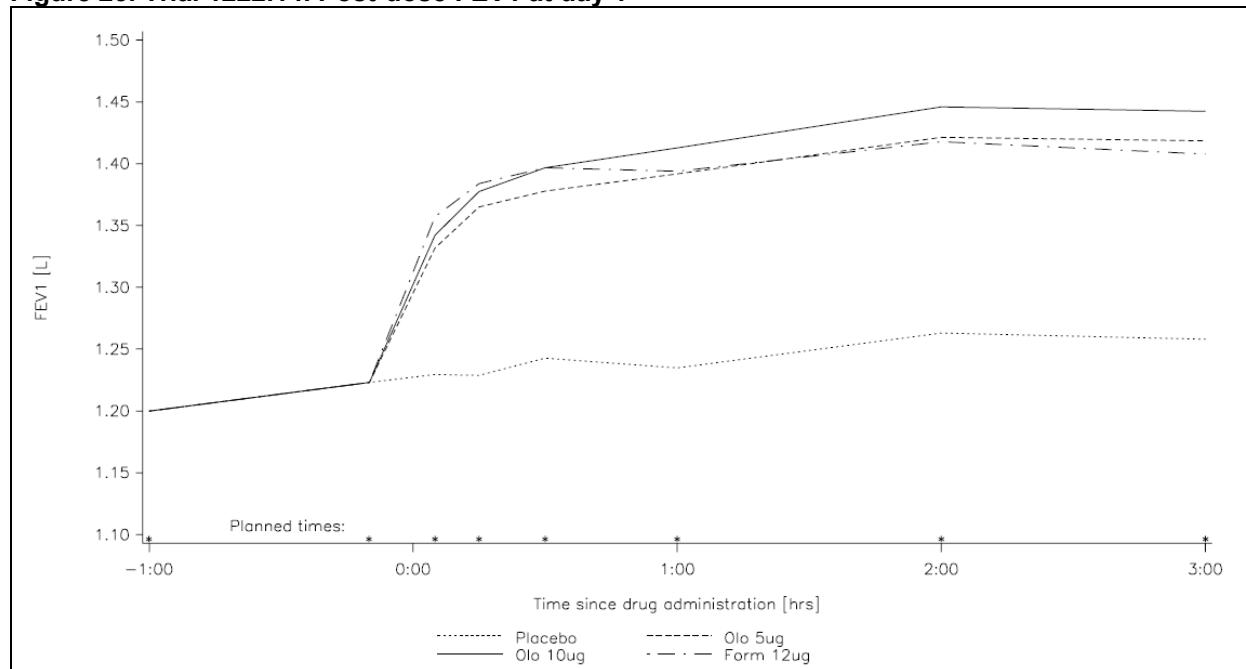
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Figure 23. Trial 1222.14. Post-dose FEV1 at day 1



Source: Trial 1222.14 CSR; figure 15.2.1.1:1; pp 228

Sensitivity analysis using unadjusted means (original analysis plan for trials 1222.11 and 1222.12) for the FEV1-related endpoints also demonstrated similar results.

The results for the FVC-related secondary endpoints demonstrated similar trends with the results for the analogous FEV1-related secondary endpoints. For the trough FVC response at 24 weeks, the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.066L ($p=0.0718$), 0.063L ($p=0.0863$), and 0.038L ($p=0.2982$), respectively]. Similar trends were seen at all other time points, however p-values <0.05 were only seen for all three groups at weeks 6 and 12 (days 43 and 85).

For the FVC AUC (0-3 hours) response at 24 weeks, the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.199L, 0.213L, and 0.241L (all p-values <0.0001), respectively]. Similar trends were seen at all other time points

For the FVC AUC (0-3 hours) response at 24 weeks (day 169), the olodaterol 5mcg, olodaterol 10mcg, and formoterol groups demonstrated improvements compared to placebo [0.199L, 0.213L, and 0.241, respectively, $p<0.0001$]. The findings were similar at all time points.

With regard to FVC peak (0-3) response, at 24 weeks (day 169), olodaterol 5mcg, olodaterol 10mcg, and formoterol all demonstrated improvements compared to placebo

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[0.182L ($p<0.0001$), 0.180L ($p<0.0001$), and 0.207L ($p<0.0001$), respectively]. Results were similar at days 1, 43, 85, and 337.

For weekly mean values from morning PEFR, both olodaterol groups demonstrated improvements from placebo. The magnitude of mean differences from placebo at key study time points (Week 1, 12, 24, and 48) was 11.3, 11.8, 13.7, and 15.2 L/min, respectively, for olodaterol 5mcg; 25.2, 22.1, 20.9 and 22.2L/min, respectively, for olodaterol 10mcg; and 16.2, 14.1, 14.2, and 13.2L/min, respectively, for formoterol. For these time points, the p-values were between 0.0057 to <0.0001 . Results were similar for evening PEFR.

Reviewer Comment

The results for the secondary endpoints related to FEV1 and FVC were supportive of a bronchodilatory effect for olodaterol compared to placebo. As with the primary endpoint, there was no consistent incremental benefit for the 10mcg dose over the 5mcg dose with regard to FEV1 related secondary endpoints. Over the 48 week treatment period, spirometric responses for the olodaterol groups compared to placebo generally appeared to decrease as time progressed (days 1, 43, 85, 169, and 337), implying that overtime the treatment effect may wane. This is generally consistent with the other 48 week COPD trials. Additionally, when comparing the treatment effect between the 6 and 12 week (days 43 and 85) timepoints, the treatment effects decreased.. Based on the results of this trial, it appears that over time the treatment effect of olodaterol at either dose may wane.

Non-spirometric secondary endpoints:

For the secondary endpoint of weekly mean daily rescue medication use over the 48 week treatment period, both olodaterol dose groups demonstrated less rescue medication use compared to placebo. For olodaterol 10mcg, weekly mean rescue medication use was decreased compared to placebo every week for the 48 week treatment period (0.408-0.911 fewer puffs/day, p-values range from 0.0008 to 0.05). For olodaterol 5mcg, a similar trend was seen; however, it was not as statistically robust, with p-values >0.05 for the majority of measurements.

The results for the secondary endpoints of daytime and night-time rescue medication use over the 48 week treatment period were similar. At each weekly time point, the mean daytime reduction for olodaterol 10mcg ranged from 0.114 to 0.365 fewer puffs/day compared to placebo. P-values varied widely, however after 24 weeks of treatment, most p-values were <0.05 . For the olodaterol 5mcg, the difference from placebo were less compared to olodaterol 10mcg and p-values were never <0.05 . Results for the formoterol group were similar to olodaterol 5mcg. Results for nighttime rescue medication were similar, though the magnitude effect was greater and p-values smaller.

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The number and time to first COPD exacerbation were also evaluated as secondary endpoints. For time to first COPD exacerbation, moderate COPD exacerbation, and first COPD exacerbation leading to hospitalization, there were no statistically significant differences between olodaterol and placebo groups. There was a trend for a treatment effect (Table 92), as demonstrated by hazard ratios <1. There was also no statistically significant difference with respect to number of exacerbations between groups. However, there was a trend towards fewer exacerbations in the olodaterol groups

Table 92. Trial 1222.14. Hazard ratio (HR) for time to first exacerbation

| Exacerbation | Treatment | Hazard ratio (SE) compared to placebo | p-values |
|-----------------|------------------|---------------------------------------|----------|
| Any | Olo 5mcg | 0.80 (0.13) | 0.19 |
| | Olo 10mcg | 0.87 (0.14) | 0.41 |
| | Formoterol 12mcg | 0.92 (0.15) | 0.64 |
| Hospitalization | Olo 5mcg | 0.69 (0.25) | 0.29 |
| | Olo 10mcg | 0.94 (0.32) | 0.86 |
| | Formoterol 12mcg | 0.80 (0.28) | 0.55 |
| Moderate | Olo 5mcg | 0.81 (0.15) | 0.25 |
| | Olo 10mcg | 0.79 (0.14) | 0.20 |
| | Formoterol 12mcg | 0.90 (0.16) | 0.58 |

Source: Trial 1222.14 CSR; table 15.2.4:1; pg 505

PK data

The geometric mean concentration 10 minutes after inhalation was 1.8 fold higher in olodaterol 10mcg versus olodaterol 5mcg. Serum concentrations were also slightly higher in Asians compared to Whites. There was also no evidence of a relationship between oldaterol serum levels and serum potassium levels. It should be noted that 31 (3.6 %) out of the 855 plasma samples from placebo patients had detectable levels of olodaterol. In addition 22 (4.8%) of 457 samples taken from olodaterol patients taken prior to first trial drug administration also had detectable olodaterol levels.

Reviewer comment

The detection of olodaterol in patients who were not exposed to olodaterol is concerning. However, the overall numbers were small and this would likely dilute treatment effects rather than accentuate them. As such, this does not affect efficacy conclusions.

Safety

Exposure

A total of 934 patients received at least one dose of trial drug. Mean exposure was higher in the olodaterol groups and formoterol group (302-309 days) compared to placebo (291 days). The difference is likely related to the higher number of discontinuations in the placebo group compared to the olodaterol groups. Patient exposure is summarized Table 93.

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Table 93. Trial 1222.14. Patient exposure

| | Placebo | Olo 5mcg | Olo 10mcg | Formoterol | Total |
|----------------------------------|------------|------------|------------|------------|------------|
| Extent of exposure (days) | | | | | |
| N | 235 | 232 | 234 | 233 | 934 |
| Mean | 291.4 | 308.5 | 306.6 | 302.4 | 302.2 |
| SD | 96.5 | 75.5 | 80.5 | 89.7 | 86.1 |
| Min | 2 | 5 | 7 | 1 | 1 |
| Median | 337 | 337 | 337 | 337 | 337 |
| Max | 363 | 367 | 371 | 398 | 398 |
| Extent of exposure [N(%)] | | | | | |
| <=15 days | 3 (1.3) | 1 (0.4) | 3 (1.3) | 3 (1.3) | 10 (1.1) |
| 16 - 43 days | 7 (3.0) | 1 (0.4) | 6 (2.6) | 8 (3.4) | 22 (2.4) |
| 44 - 85 days | 10 (4.3) | 8 (3.4) | 4 (1.7) | 8 (3.4) | 30 (3.2) |
| 86 - 127 days | 8 (3.4) | 5 (2.2) | 2 (0.9) | 3 (1.3) | 18 (1.9) |
| 128 - 169 days | 4 (1.7) | 9 (3.9) | 4 (1.7) | 6 (2.6) | 23 (2.5) |
| 170 - 225 days | 10 (4.3) | 3 (1.3) | 11 (4.7) | 1 (0.4) | 25 (2.7) |
| 226 - 281 days | 7 (3.0) | 7 (3.0) | 4 (1.7) | 7 (3.0) | 25 (2.7) |
| 282-337 days | 117 (49.8) | 119 (51.3) | 132 (56.4) | 118 (50.6) | 486 (52.0) |
| >=338 days | 69 (29.4) | 79 (34.1) | 68 (29.1) | 79 (33.9) | 295 (31.6) |

Source: Trial 1222.14 CSR; table 12.1:1; pg117

Deaths

Of the 934 patients who received treatment, 25 patients died on treatment [Olo 5mcg=7 (3%), Olo 10mcg=6 (2.5%), Formoterol=6 (2.6%), and placebo=6 (2.6%)]. Patient deaths are summarized in Table 94.

Table 94. Trial 1222.14. Deaths during on treatment period and during off-treatment/solicited vital status follow-up

| Period | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol N(%) |
|-------------------------------------|-----------------|------------------|-------------------|--------------------|
| Total | 9 (3.9) | 9 (3.9) | 7 (2.9) | 7 (3) |
| On treatment | 6 (2.6) | 7 (3) | 6 (2.5) | 6 (2.6) |
| Solicited vital status follow-up | 3 (1.3) | 2 (0.9) | 1 (0.4) | 1 (0.4) |

Source. Trial 1222.14 CSR; table 12.3.1:1 and 12.3.1:2; pp 123 and 124.

Overall, the most frequent cause of death was COPD exacerbation, followed by sudden cardiac death. Of the 7 patients in the olodaterol 5mcg group that died during the treatment period, the causes of death were cardiorespiratory arrest, COPD, sudden cardiac death, atrial fibrillation/cardiac failure/dyspnea/peripheral edema, respiratory failure, hepatic neoplasm, and COPD/malnutrition. As per MAC, the causes of death were sudden cardiac death, COPD exacerbation, sudden cardiac death, COPD exacerbation, COPD exacerbation, hepatic carcinoma, and COPD exacerbation. For the olodaterol 10mcg group, the causes of death were congestive cardiac failure, lung metastases, lung neoplasm, laryngeal cancer, COPD, and death. The MAC assessment was in agreement, except for the 'death', where they assessed the cause as unknown.

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For the formoterol group, the causes of death were cardiac arrest, COPD, death, anaphylactic shock (arthropod sting), pneumonia/sepsis/multi-organ failure, arrhythmia. Per MAC, the causes of death were COPD exacerbation, COPD exacerbation, sudden cardiac death, arthropod bite, COPD exacerbation, and sudden cardiac death. In the placebo group, the causes of death were cardiorespiratory arrest, cardiac failure, death, COPD, COPD, and cerebrovascular accident. Per MAC, the causes of death were sudden death, unknown, unknown, COPD exacerbation, COPD exacerbation, and cerebrovascular accident.

Six additional patients died during the post-treatment period (placebo=3, Olo 5mcg=2, Olo 10mcg=1). For the placebo group, the causes of death were septic shock, myocardial infarction (MI), and traffic accident. The MAC assessment agreed with the traffic accident, however assigned septic shock and MI as deep venous thrombosis and sudden cardiac death, respectively. The causes of death in the olodaterol 5mcg group were pneumonia/sepsis/cardiorespiratory arrest/multiorgan failure and acute myocardial infarction. Per MAC the causes of death were COPD exacerbation and sudden death. In the olodaterol 10mcg group, the cause of death was pancreatic carcinoma. This was in agreement with MAC. One death occurred beyond the planned observation period. This occurred in a patient receiving formoterol; the cause of death was aspiration pneumonia. Per MAC the cause of death was asphyxiation.

SAEs

One-hundred-fifty-nine (159) patients experienced SAEs (placebo=20.4%, Olo 5mcg=14.7%, Olo 10mcg=17.5%, and Foradil=15.5%). The most common SAEs were COPD exacerbation (7.2%), pneumonia (1.6%), dyspnea (0.5%), atrial fibrillation (0.4%), pulmonary embolism (0.4%), and respiratory failure (0.4%). There were no imbalances between groups with regard to SAEs based on SOC. However, based on PT, pneumonia was more frequent in olodaterol 10mcg compared to all other groups. Table 95 summarizes SAEs. This table includes PTs that occurred in ≥ 2 patients. Additionally, if a PT that occurred in < 2 patients was similar to a PT that occurred in ≥ 2 patients, that PT was also listed in the SAE table (e.g. cardiac failure, cardiac failure acute, and cardiac failure congestive).

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Table 95. Trial 1222.14. Serious adverse events

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol |
|------------------------------------|-----------------|------------------|-------------------|------------|
| Total patients | 235(100.0) | 232(100.0) | 234(100.0) | 233(100.0) |
| Total SAEs | 48 (20.4) | 34 (14.7) | 41 (17.5) | 36 (15.5) |
| Infections Infestations | 9 (3.8) | 8 (3.4) | 8 (3.4) | 6 (2.6) |
| Pneumonia | 2 (0.9) | 2 (0.9) | 7 (3.0) | 4 (1.7) |
| Lobar pneumonia | 0 | 0 | 0 | 1 (0.4) |
| Bronchitis | 2 (0.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Infective exacerbation of COPD | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Neoplasms benign and malignant | 3 (1.3) | 4 (1.7) | 6 (2.6) | 2 (0.9) |
| Bladder cancer | 1 (0.4) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Lung adenocarcinoma | 0 (0.0) | 0 (0.0) | 1 (0.4) | 1 (0.4) |
| Prostate Cancer | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Immune system disorder | 0 | 0 | 0 | 1 (0.4) |
| Metabolism and nutrition | 0 | 1 (0.4) | 2 (0.9) | 0 |
| Psychiatric disorder | 2 (0.9) | 0 | 0 | 0 |
| Nervous system disorder | 6 (2.6) | 2 (0.9) | 0 | 0 |
| Transient ischemic attack | 2 (0.9) | 0 | 0 | 0 |
| Eye disorders | 1 (0.4) | 0 | 0 | 0 |
| Ear and labyrinth disorder | 0 | 1 (0.4) | 0 | 0 |
| Cardiac disorders | 10 (4.3) | 6 (2.6) | 6 (2.6) | 3 (1.3) |
| Atrial fibrillation | 2 (0.9) | 2 (0.9) | 0 (0.0) | 0 (0.0) |
| Angina unstable | 1 (0.4) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Cardiac failure | 0 (0.0) | 2 (0.9) | 0 (0.0) | 0 (0.0) |
| Cardiac failure acute | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Cardiac failure congestive | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Acute myocardial infarction | 0 (0.0) | 0 (0.0) | 3 (1.3) | 0 (0.0) |
| Myocardial infarction | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Myocardial ischemia | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Vascular disorders | 4 (1.7) | 2 (0.9) | 1 (0.4) | 1 (0.4) |
| Deep vein thrombosis | 1 (0.4) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Hypovolemic shock | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Respiratory, thoracic, mediastinal | 23 (9.8) | 16 (6.9) | 22 (9.4) | 22 (9.4) |
| COPD | 18 (7.7) | 14 (6.0) | 17 (7.3) | 18 (7.7) |
| Pulmonary embolism | 0 (0.0) | 0 (0.0) | 3 (1.3) | 1 (0.4) |
| Respiratory failure | 3 (1.3) | 1 (0.4) | 0 (0.0) | 0 (0.0) |
| Acute respiratory failure | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dyspnea | 1 (0.4) | 1 (0.4) | 1 (0.4) | 2 (0.9) |
| Pneumothorax | 1 (0.4) | 0 (0.0) | 1 (0.4) | 1 (0.4) |
| Gastrointestinal disorders | 0 (0.0) | 1 (0.4) | 3 (1.3) | 3 (1.3) |
| Abdominal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| Diarrhea | 0 (0.0) | 0 (0.0) | 1 (0.4) | 1 (0.4) |
| Hepatobiliary disorder | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Skin and subcutaneous | 0 | 1 (0.4) | 0 | 0 |
| Musculoskeletal disorder | 1 (0.4) | 0 | 2 (0.9) | 3 (1.3) |
| Back pain | 0 | 0 | 2 (0.9) | 0 |
| Intervertebral disk protrusion | 1 (0.4) | 0 | 0 | 2 (0.9) |
| Renal and urinary disorders | 1 (0.4) | 1 (0.4) | 0 | 1 (0.4) |
| Renal Failure | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Reproductive disorders | 0 | 1 (0.4) | 0 | 1 (0.4) |
| General disorders | 3 (1.3) | 4 (1.7) | 3 (1.3) | 3 (1.3) |
| Chest pain | 0 (0.0) | 1 (0.4) | 1 (0.4) | 0 (0.0) |
| Death | 1 (0.4) | 0 (0.0) | 1 (0.4) | 1 (0.4) |
| Sudden cardiac death | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) |

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| | | | | |
|---|---------|---------|---------|---------|
| Injury, poisoning, and procedural complications | 4 (1.7) | 1 (0.4) | 4 (1.7) | 3 (1.3) |
| Road Traffic accident | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Surgical and medical procedures | 0 | 0 | 1 (0.4) | 1 (0.4) |

Source: Trial 1222.14 CSR; table 15.3.2.1:6; pp 543-549

Discontinuations due to adverse events

Sixty-seven patients (7.2%) withdrew due to AEs. This occurred more frequently in the placebo (8.1%) group compared to the olodaterol 10mcg (6.8%) and olodaterol 5mcg (6.5%) groups. The most common AE leading to discontinuation was COPD. This was more common in the olodaterol and formoterol groups compared to placebo. A summary of all AEs by SOC leading to discontinuation can be found in Table 96. Additionally, if a PT that occurred in <2 patients was similar to a PT that occurred in ≥2 patients, that PT was also listed in the SAE table (e.g. respiratory failure and acute respiratory failure).

Table 96. Trial 1222.14. TEAEs leading to discontinuation

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Fomoterol N(%) |
|---|-----------------|------------------|-------------------|-------------------|
| Total patients | 225 (100) | 227 (100) | 225 (100) | 227 (100) |
| Total AEs leading to discontinuation | 19 (8.1) | 15 (6.5) | 16 (6.8) | 17 (7.3) |
| Infections Infestations | 3 (1.3) | 2 (0.9) | 0 | 3 (1.3) |
| Pneumonia | 0 | 0 | 0 | 2 (0.9) |
| Neoplasms benign and malignant | 1 (0.4) | 2 (0.9) | 4 (1.7) | 1 (0.4) |
| Lung neoplasm | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Bladder cancer | 1 (0.4) | 0 | 1 (0.4) | 0 |
| Immune system | 0 | 0 | 0 | 1 (0.4) |
| Metabolism and nutrition | 0 | 1 (0.4) | 0 | 0 |
| Nervous system disorder | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Eye disorders | 0 | 1 (0.4) | 0 | 0 |
| Ear and labyrinth disorder | 0 | 1 (0.4) | 0 | 0 |
| Cardiac disorders | 3 (1.3) | 3 (1.3) | 5 (2.1) | 3 (1.3) |
| Acute myocardial infarction | 0 | 0 | 2 (0.9) | 0 |
| Atrial fibrillation | 0 | 1 (0.4) | 1 (0.4) | 0 |
| Vascular disorders | 3 (1.3) | 0 | 0 | 0 |
| Respiratory, thoracic, mediastinal | 7 (3) | 7 (3) | 7 (3) | 11 (4.7) |
| COPD | 4 (1.7) | 5 (2.2) | 6 (2.6) | 7 (3) |
| Dyspnea | 1 (0.4) | 1 (0.4) | 0 | 2 (0.9) |
| Acute respiratory failure | 1 (0.4) | 0 | 0 | 0 |
| Respiratory failure | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Gastrointestinal disorder | 1 (0.4) | 0 | 0 | 0 |
| Hepatobiliary disorder | 1 (0.4) | 0 | 0 | 0 |
| Musculoskeletal disorder | 1 (0.4) | 0 | 0 | 0 |
| Reproductive System | | | | |
| Renal and urinary disorders | 1 (0.4) | 0 | 0 | 1 (0.4) |
| Acute renal failure | 1 (0.4) | 0 | 0 | 1 (0.4) |
| General disorders | 1 (0.4) | 3 (1.3) | 1 (0.4) | 3 (1.3) |
| Chest pain | 0 | 1 (0.4) | 0 | 1 (0.4) |
| Injury, poisoning, and procedural complications | 1 (0.4) | 0 | 0 | 1 (0.4) |

Source: Trial 1222.14; table 15.3.2.1:5; pp 539-542

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Reviewer comment:

With regard to deaths, there was no apparent imbalance. However, compared to trials 1222.11, 1222.12, and 1222.13, there were more deaths in this trial. With regard to overall SAEs, by SOC there were no imbalances. With regard to AEs leading to discontinuation, there were no imbalances based on SOC. However, there were more discontinuations due to COPD exacerbations in olodaterol 10mcg than the other treatment groups. This was not seen in any of the other 48 week trials, and the numbers are small. This may be a chance occurrence.

Common TEAEs

The most common TEAEs (>3%) based on preferred term were COPD, nasopharyngitis, and URI, and cough. COPD, cough, and URI were most commonly reported in the placebo group. Nasopharyngitis was most commonly reported in olodaterol 5mcg. Common TEAEs are summarized in Table 97.

Table 97. Trial 1222.14. Common TEAEs ($\geq 3\%$)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol N(%) |
|---------------------------------------|-----------------|------------------|-------------------|--------------------|
| Number of patients | 235 (100) | 232 (100) | 234 (100) | 233 (100.) |
| Total with adverse events | 173 (73.6) | 169 (72.8) | 169 (72.2) | 169 (72.5) |
| Respiratory, thoracic and mediastinal | 102 (43.4) | 77 (33.2) | 88 (37.6) | 99 (42.5) |
| COPD | 69 (29.4) | 54 (23.3) | 65 (27.8) | 69 (29.6) |
| Cough | 16 (6.8) | 6 (2.6) | 12 (5.1) | 14 (6.0) |
| Dyspnea | 11 (4.7) | 11 (4.7) | 4 (1.7) | 19 (8.2) |
| Infections and infestations | 83 (35.3) | 100 (43.1) | 89 (38.0) | 78 (33.5) |
| Nasopharyngitis | 22(9.4) | 37(15.9) | 28 (12.0) | 23 (9.9) |
| Upper respiratory tract infection | 19(8.1) | 14 (6.0) | 15 (6.4) | 21 (9.0) |
| Bronchitis | 9 (3.8) | 13 (5.6) | 10 (4.3) | 8 (3.4) |
| Pneumonia | 7 (3.0) | 6 (2.6) | 12 (5.1) | 9 (3.9) |
| Musculoskeletal disorders | 29 (12.3) | 29 (12.5) | 37 (15.8) | 35 (15.0) |
| Back pain | 9 (3.8) | 10 (4.3) | 7 (3.0) | 9 (3.9) |
| Myalgia | 1 (0.4) | 4 (1.7) | 8 (3.4) | 2 (0.9) |
| Gastrointestinal disorders | 27 (11.5) | 33 (14.2) | 34 (14.5) | 25 (10.7) |
| Diarrhea | 5 (2.1) | 9 (3.9) | 9 (3.8) | 4 (1.7) |
| General disorders and | 26 (11.1) | 25 (10.8) | 25 (10.7) | 28 (12.0) |
| Pyrexia | 8 (3.4) | 6 (2.6) | 13 (5.6) | 9 (3.9) |
| Nervous system disorders | 24 (10.2) | 17 (7.3) | 17 (7.3) | 20 (8.6) |
| Headache | 10 (4.3) | 10 (4.3) | 11 (4.7) | 9 (3.9) |

Source: Trial 1222.14 CSR; table 12.2.2.2:1; pg 120

Reviewer Comment:

The common TEAEs seen in this trial were typical of a LABA development program. Unlike in trial 1222.12 and similar to 1222.11, and similar to 1222.14 the infections and infestation SOC did not demonstrate a dose response. However AEs in that SOC occurred more frequently in olodaterol groups compared to placebo.

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Labs:

Based on mean lab values, there were no notable changes in lab values. With regard to CPK, mean changes from baseline were -13 U/L, 6 U/L, 23 U/L and -276 U/L for the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups. Similar numbers of patients in the olodaterol groups also had normal CPK levels at baseline and above normal maximum values (placebo=2%, Olo 5mcg=5.6%, Olo 10mcg=9.5%, and formoterol=14.8%).

When examining glucose and potassium, the percentage of patients per group who had normal baseline values and elevated maximum values were similar between groups. There were also no mean differences in serum glucose from baseline compared to end of treatment. When comparing mean difference from placebo in serum potassium (at day 43 and 85 at 1 and 3 hours post-dose) statistically significant decreases were only seen in the olodaterol 10mcg and formoterol groups compared to placebo ($p=0.0223$ and 0.0398, respectively). However, the magnitude of the difference is likely not clinically significant and ranged from 0.089 and 0.080 mM/L.

When examining potentially clinically significant changes in lab values as defined by the sponsor, numbers were generally similar between groups. Notably, potentially clinically significant decreases in potassium were marginally more frequent in placebo (0.9%) compared to olodaterol (0-0.04%) and formoterol (0.5%) groups. The same was true for potentially clinically significant increases in glucose (2.8% versus 1.8-2.3%).

Vital signs:

With regard to SBP, there were no significant differences between groups based on change in mean values or shifts from normal to high or normal to low. When using maximum on-treatment values to assess for marked increases in patients with a normal baseline, marked increases in SBP were more common in the olodaterol (Olo 5mcg=2.2%, Olo 10mcg=1.7%) and formoterol (2.6%) groups compared to placebo (0.9%). With regard to DBP there were no significant differences between groups based on change in mean values, shifts from normal to low, or shifts from normal to high. Marked shifts in DBP were more frequent in placebo patients compared to olodaterol and formoterol. For pulse rate, there were no significant differences between groups based on change in mean values or shifts from normal to high. However, more patients in the olodaterol groups had decreases in pulse compared to placebo (Olo 5mcg=11.3%, Olo 10mcg=8.6%, placebo=9.9%, formoterol=5.2%).

ECG

ECGs were assessed as mean changes from baseline, mean changes exceeding a pre-specified threshold (450, >480, or >500ms in QTc interval), mean changes exceeding categorized change (>30ms or >60ms in QTc interval), notable changes, and frequency of ECG abnormalities. Notable changes were defined as in trial 1222.11.

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Based on these parameters, there were no notable changes from baseline. When analyzing the QTcF based on threshold values (>450ms, >480ms, and >500ms), no imbalances were identified, nor was there any evidence of dose response. However, during the entire treatment period, there were 8 reported increases of QTcF of >500ms, and none were in the placebo group (Olo 10mcg=7, Olo 5mcg=1, formoterol=0). When analyzing the QTcF based on categorized change (>30ms or >60ms), the overall numbers of patients experiencing a >30 or >60 ms change were small for all time points. During the entire treatment period, there were only 23 reported increases of QTcF of >60ms (placebo=3, Olo 5mcg=5, Olo 10mcg=3, Formoterol=12). Reports of increases >30ms were more frequent; however, there was neither a clear dose-dependent nor time-dependent effect. No patients discontinued based on ECG findings.

Holter monitoring

With regard to supraventricular couplets, change from baseline at days 85, 169, 281, and 337 were variable within groups. Within groups, there were no apparent time-related trends. Between groups, there were also no consistent differences.

The results for supraventricular tachycardia runs was also variable when comparing change from baseline at day 85, 169, 281, and 337. Within groups, there were no apparent time-related trends, nor were there consistent differences between groups at each time point.

With regard to ventricular couplets, at all time points the mean number of ventricular couplets increased compared to baseline versus for the olodaterol 5mcg. This is in contrast to trial 1222.13, where the opposite was observed. For olodaterol 10mcg, at all time points the mean number of ventricular couplets decreased compared to baseline. With regard to ventricular runs, the differences between groups were minimal, and the mean change from baseline in the number of runs in each group was small.

Based on shift table analysis of ventricular premature beats (VPB) and supraventricular premature beats (SVPB), most patients had similar numbers of SVPBs when comparing baseline values to last value on treatment.

Reviewer Comment:

With regard to vital signs, ECG, and holter data, no significant imbalances were seen. Notably, the olodaterol groups did not appear to have an increased frequency of QTcF prolongation as was implied in some of the asthma dose ranging trials. However, the pooled ECG and holter data from the 48 week trials will be analyzed in the combined safety section.

Overall Reviewer Comment on trial 1222.14

Based on the sponsor analysis of the primary endpoints, both doses of olodaterol are effective bronchodilators. As with the other 48 week COPD trials, the 10 mcg dose of olodaterol offers no added benefit compared to the 5 mcg dose. Also similar to the other

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48 week trials, the difference from placebo with respect to trough FEV1, is relatively small; however, this trial allowed for the use of all background COPD medications (e.g tiotropium) except for LABAs. The treatment response in the non-tiotropium strata tended to be smaller/similar compared to the tiotropium-treated strata. With regard to maintenance of effect, the treatment effect with respect to trough FEV1 decreased over time. There appears to be no effect of olodaterol on exacerbations and some mild improvement in rescue medication use. With regard to safety, the deaths were fairly well balanced, as were overall SAEs.

5.3.12 Trial 1222.37 (COPD Exercise Trial)

Administrative Information

- **Study title:** Randomised, double-blind, placebo-controlled, 3-way cross-over study to determine the effect of 6 weeks treatment of olodaterol 5mcg and olodaterol 10mcg delivered by the Respimat Inhaler on exercise endurance time during constant work rate cycle ergometry in patients with COPD
- **Study dates:** 1/23/10-4/16/11
- **Study sites:** Australia (4), Austria (2), Canada (3), France (3), Germany (4)
- **Study report date:** 3/28/12

Objectives

Primary Objective

- To compare the effects of olodaterol versus placebo on constant work rate exercise tolerance after 6 weeks of treatment in patients with COPD.

Secondary Objectives

- To compare the effects of olodaterol to placebo on lung hyperinflation (based on inspiratory capacity) during constants work rate exercise in patients with COPD
- To compare the effects of olodaterol versus placebo on the intensity of breathing discomfort experienced during constant work rate exercise in patients with COPD (Borg scale)

Trial design and conduct

Overview

This was a multi-center, multi-national, randomized, double-blind, 3-way cross-over trial in moderate to severe COPD patients. The three 6-week treatment arms included placebo, olodaterol 5mcg, and olodaterol 10mcg. Between each treatment period, there was a 2-week washout period. Following the initial screening visit (visit 1), patients entered the 2 week run-in period. At visit 2, a baseline constant work rate exercise (CWRE) test was performed. At visit 3 (day 1), patients were randomized into their treatment sequence, and treatment period 1 began. They returned to clinic after 6 weeks (visit 4) of treatment for repeat testing. After visit 6 and a 2 week washout period, patients returned to clinic for the next treatment period. For treatment periods 2 and 3, there were also 2 clinic visits, one for initiation of therapy and baseline assessments (5 and 7), and a second visit (6 and 8) for repeat assessments and exercise testing. A

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follow-up visit occurred approximately 2 weeks after the last clinic visit. The trial schedule is summarized in Figure 24. The assessments performed at each visit are summarized in Table 98. Note that while patients were tested for reversibility, reversibility did not affect inclusion or exclusion from this trial.

Figure 24. Trial 1222.37. Trial schematic

| | Screening/Baseline | | | Treatment Period | | | | | | Follow-up |
|-------------------|--------------------|-----|----|------------------|----|----------|----|----------|-----|-----------|
| | | | | Period 1 | | Period 2 | | Period 3 | | |
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Week of treatment | - | - | - | 0 | 6 | 0 | 6 | 0 | 6 | - |
| Day of treatment | - | - | - | 1 | 43 | 1 | 43 | 1 | 43 | - |
| Week (cumulative) | | -2 | -1 | 0 | 6 | 8 | 14 | 16 | 22 | 24 |
| Day (cumulative) | | -14 | -7 | 1 | 43 | 57 | 99 | 113 | 155 | V8+14 |

Source: trial 1222.37 CSR; appendix 16.1.1 (module 5.3.5.1.4); pg6

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Table 98. Trial 1222.37. Assessment schedule

| Visit | Screening | | | Treatment Period ¹ | | Follow-up |
|--|----------------|-----------------|----------|-------------------------------|-----------------|----------------|
| | 0 | 1 | 2 | 3, 5, 7 | 4, 6, 8 | |
| Week of treatment | - | - | - | 0 | 6 | V8 + 2 weeks |
| Day of treatment | - | -14 | -7 to -2 | 1 | 43 + 7 | V8 + 14 + 7 |
| Time Window (days) | | | | | | |
| Informed consent, subject information | X ² | | | | | |
| Demographics | | X | | | | |
| Medical History | | X | | | | |
| COPD Characteristics | | X | | | | |
| Smoking status | | X | | X | | |
| In-/Exclusion Criteria | | X | | X | | |
| Physical examination | | X | | | X ³ | |
| Laboratory tests | | X | | | X ³ | |
| Pregnancy testing ⁴ | | X | | X | | X |
| Pharmacogenetics | | | | X (Visit 3) | | |
| 12-lead ECG ⁵ | | X | | X | X ³ | |
| Training in use of Respimat® inhaler | | X | | X ⁶ | | |
| Randomization | | | | X (Visit 3) | | |
| Dispense trial medication | | | | X | | |
| Dispense rescue medication | X ⁷ | X | | X | X | |
| Administer trial medication at clinic | | | | X | X | |
| Collect trial medication | | | | | X ⁸ | |
| Issue patient diary | | X | | X | X | |
| Collect patient diary | | | | X | X | |
| Incremental Cycle Ergometry, | | X | | | | |
| Constant Work Rate Cycle Ergometry | X ⁹ | X ¹⁰ | | | X ¹¹ | |
| Breathing / leg discomfort during exercise (Borg Category-Ratio Scale) | | X | X | | X | |
| Inspiratory Capacity (IC) during exercise | | X ¹² | X | | X | |
| Body Plethysmography (FRC, IC, TLC) | | | | X ¹³ | X ¹³ | |
| Spirometry (FEV ₁ , FVC, PEF) | | X ¹⁴ | | X ¹⁵ | X ¹⁵ | |
| Vital signs (seated) ¹⁶ | | X | | X | X | |
| Adverse events | X | X | | X | X | X |
| Concomitant therapy | X | X | | X | X | X |
| Compliance check | X | X | | X | X | |
| Drug accountability | | | | | X | |
| Trial medication termination | | | | | X | |
| Trial completion | | | | | | X |

1. In this cross-over design, each treatment period (period 1, period 2, period 3) will follow the same flow chart: Procedures during Visits 3, 5, & 7 and 4, 6, & 8 will be identical
2. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions
3. To be completed whenever trial participation ends
4. Women of child-bearing potential: serum pregnancy test at Visit 1; urine pregnancy test at Visits 3, 5, 7, 9
5. 12-lead ECG recording at Screening (Visit 1). In addition, 12-lead ECG recording will be performed pre-dose and at 40 minutes post dose at Visits 3-9
6. The patient will be instructed in the use of the Respimat inhaler, but the patient should not inhale from the placebo inhaler at this visit
7. Rescue medication is supplied at visit 0 where applicable
8. Last dose of trial medication for respective treatment period will be the morning dose on Day 43. All medication is collected after this dosing
9. Training constant work rate cycle ergometry at 75%Wcap (may be performed between Visit 1 and Visit 2, with at least 2 days between training test and baseline test)
10. Baseline constant work rate cycle ergometry at 75%Wcap
11. Constant work rate cycle ergometry at 75%Wcap, 2 hr post-morning dose (+15 minutes)
12. Inspiratory capacity measurements taken during training constant work rate cycle ergometry test only.

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13. Pre-morning dose body plethysmography ("body box"): 30 mins prior to morning dose of study medication
Post-morning dose body plethysmography ("body box"): 1 hr post-dose
14. Pre- and post-bronchodilator (400 mcg salbutamol (albuterol))
15. Pre-morning dose spiroometry: 30 mins prior to inhalation of morning dose of study medication (after body box) Post-morning dose spirometry: 1 hr post-morning dose (after body box)
16. Immediately prior to body plethysmography

Source: trial 1222.37 CSR; appendix 16.1.1 (module 5.3.5.1.4); pg6

Trial Population

The trial consisted of 151 randomized GOLD II-IV COPD patients. They were randomized using an IVRS system.

Key Inclusion Criteria

See trial 1222.13 (section 5.3.9)

Key Exclusion Criteria

Same as trial 1222.13, with the addition of patients with an endurance time of ≥ 25 minutes during the training (visit 1) or baseline constant work rate cycle ergometry at visit 2. Patients were also excluded from the trial if they had contraindications to exercise testing (see below)

Enrollment Cautions

See trial 1222.13 (section 5.3.9)

Contraindications to exercise

1. unstable angina
2. uncontrolled arrhythmias causing symptoms or hemodynamic compromise
3. active endocarditis
4. acute myocarditis or pericarditis
5. symptomatic severe aortic stenosis
6. uncontrolled heart failure
7. acute non-cardiac disorder that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)
8. thrombosis of lower extremities
9. left main coronary stenosis or its equivalent
10. moderate stenotic valvular heart disease
11. electrolyte abnormalities
12. severe untreated arterial hypertension (>200 mmHg systolic, >120 mmHg diastolic)
13. significant pulmonary hypertension
14. tachyarrhythmias or bradyarrhythmias
15. hypertrophic cardiomyopathy
16. mental impairment leading to inability to cooperate
17. high-degree atrioventricular block

Patients were also withdrawn from the trial if they experienced a COPD exacerbation or were judged by the investigator to require tiotropium during the treatment period

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Treatments

Treatment Groups

Olodaterol 5mcg qD (2 actuations of 2.5mcg/actuation)

Olodaterol 10mcg qD (2 actuations of 5mcg/actuation)

Placebo

All were administered using the Respimat inhaler.

Concomitant/Restricted Medications:

Patients were allowed to take ICS, xanthines, and short-acting anticholinergics during the trial. However, LABAs and tiotropium were not permitted. Medications taken by the patient within 3 months of the screening visit were recorded in the eCRF. All medications used during the trial were also recorded in the eCRF. Use of SABAs was allowed as necessary; however, if a patient required SABA treatment during exercise testing, the testing was stopped. Temporary increases in the dose or addition of oral steroids and theophylline were allowed, but if increased use occurred within 7 days prior to a clinic visit, the visit was postponed (up to 14 days). The use of antibiotics was not restricted, although clinic visits were postponed for at least 2 days, but not more than 7 days. Medications limitations are summarized in Table 99.

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Table 99. Trial 1222.37. Prohibited and restricted medications

| Drug Class | Sub-class | Prior to Trial | Trial period | | | |
|-------------------------------------|---|---------------------|-----------------|------------------|----------------|------------------|
| | | | Baseline Period | Treatment Period | Washout Period | Follow up Period |
| Corticosteroids | Inhaled corticosteroids ¹ | permitted | permitted | permitted | permitted | permitted |
| | Oral corticosteroids ¹ [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent)] | permitted | permitted | permitted | permitted | permitted |
| Beta-adrenergics / Beta-blockers | Inhaled short-acting beta-adrenergics | rescue | rescue | rescue | rescue | rescue |
| | Inhaled long-acting beta-adrenergics ² | permitted (washout) | not permitted | study medication | not permitted | permitted |
| | Oral beta-adrenergics | not permitted | not permitted | not permitted | not permitted | not permitted |
| | Beta blockers ¹ | permitted | permitted | permitted | permitted | permitted |
| Anticholinergics ³ | Short-acting anticholinergics (inhalation aerosol and nasal spray) | permitted | permitted | permitted | permitted | permitted |
| | Long-acting anticholinergics ⁴ | permitted (washout) | not permitted | not permitted | not permitted | permitted |
| Miscellaneous | Other investigational drugs ⁵ | permitted (washout) | not permitted | not permitted | not permitted | not permitted |
| | Oral cromolyn sodium / nedocromil sodium ⁶ | permitted | permitted | permitted | permitted | permitted |
| | Antihistamines, antileukotrienes ⁶ | permitted | permitted | permitted | permitted | permitted |
| | Methylxanthines ⁷ | permitted | permitted | permitted | permitted | permitted |
| | Mucolytics ¹ | permitted | permitted | permitted | permitted | permitted |

1 if stabilized for at least six weeks prior to Visit 1

2 at least a 48-hour washout of long-acting beta-adrenergics prior to Visit 1

3 short acting anticholinergic agents not to be taken within 8 hours prior to clinic visits

4 washout of at least 1 week prior to visit 1 and 3 week prior to visit 3

5 washout of at least one month or 6 half lives

6 only allowed if prescribed for conditions other than asthma

7 at least a 24-hour washout of short-acting (BID or more frequent administration) theophylline preparations prior to all clinic visits; least a 48-hour washout of long-acting (QD administration) theophylline preparation prior to all clinic visits

Source: Trial 1222.37 protocol and amendments; table 4.2.2:1;pg 35

Reviewer Comment:

The objective and data generated may be problematic as exercise endurance testing can be dependent on multiple non-disease/non-treatment-related factors such as patient motivation, administering staff, and patient effort. The trial length may also be an issue as COPD is a chronic disease and studies should ideally be designed to show a sustained effect over time. A 6-week treatment period trial is not sufficient to show duration of effect. The inclusion/exclusion criteria were appropriate for a COPD trial and should have captured typical COPD patients. With regard to the enrollment cautions, while not exclusion criteria, these cautions may have discouraged investigators from enrolling patients who were more likely to have adverse events known to be associated with LABAs. It should also be noted, that in contrast to the 48-week COPD trials, LAMAs were prohibited. As such, one may expect that trough FEV1 and other spirometric parameters change from baseline may be greater in comparison.

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Efficacy Parameters

Primary endpoint

- Endurance time during constant rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wcap) after 6 weeks of treatment.
 - Wcap was defined as maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at visit 1

The endurance time (ET) after each six week treatment period (visit 4, 6, and 8) was compared to the baseline values at visit 2. Testing was performed 2 hours post-dosing.

In order to minimize variability in exercise test performance (both incremental cycle ergometry and constant work rate ergometry) between sites, the sponsor attempted control for physiological, biomechanical, and psychological factors that could have affected performance.

To control for physiological factors, the sponsor encouraged patients not to eat within 2 hours of exercise testing and to maintain adequate hydration. The labs where the testing was performed also maintained temperature and humidity sufficient to keep patients comfortable. Patients were encouraged to stay well-rested prior to testing and to avoid strenuous activity the morning of testing. Patients were also asked to avoid strenuous activities to which they were not accustomed for 2-3 days prior to testing visit to avoid muscle soreness.

To control for biomechanical factors, the equipment was adjusted to the patients' comfort and the setting determined at baseline was maintained for subsequent testing.

To control for psychological factors, external motivational cues were controlled across subjects and across sites. Visual cues regarding time were also kept away from the patients' view. Verbal encouragement was also limited to one member of the team who was blinded to the results of the lung function tests. Additionally, the tone of encouragement was to be 'enthusiastic and supportive,' but not 'overbearing, overly loud or coercive.' External incentives for performance were also prohibited. Research staff also explained to patients that there was no specific time limit with any of the testing and that patients were to continue to exercise for as long as they could. Research staff also minimized distraction and familiarized patients with the testing and what to expect. Patients were also encouraged to wear appropriate clothing.

Key Secondary endpoints

- Inspiratory capacity (IC) at isotime during constant work rate cycle ergometry to symptom limitation at 75% Wcap
- Intensity of breathing discomfort (Borg Category-Ratio Scale) at isotime during constant work rate cycle ergometry to symptom limitation at 75% Wcap

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- Isotime was defined as the endurance time of the constant work rate exercise test of shortest duration from visits 2, 4, 6, and 8

The Borg Category-Ratio Scale was used to rate the intensity of discomfort with patient's breathing and discomfort in patients legs. The Borg scale is rated 0-10. The definition of the numerical scores is provided in Table 100. The scale was administered to the patient by blinded research staff. During assessments, patients were asked to put their finger on the number that best described their discomfort.

Table 100. Trial 1222.37 Borg Category-Ratio Scale

| Score | Description |
|-------|--------------------------------------|
| 10 | Maximal |
| 9 | Very, very severe (almost maximal) |
| 8 | |
| 7 | Very severe |
| 6 | |
| 5 | Severe |
| 4 | Somewhat severe |
| 3 | Moderate |
| 2 | Slight |
| 1 | Very slight |
| 0.5 | Very, very, slight (just noticeable) |
| 0 | Nothing at all |

Source: Trial 1222.37 protocol and amendments; Table 10.4; pg 86

Other secondary endpoints

- FRC, IC, TLC (trough, 1 hour post-dose)
- FEV1, FVC, PEF (trough, 1 hour post-dose)
- IC during constant work rate cycle ergometry to symptom limitation at 75% Wcap: pre-exercise, every 2 minutes during exercise and at end exercise
- Intensity of breathing discomfort and leg discomfort (Borg Scale) during constant work rate cycle ergometry to symptom limitation at 75% Wcap: pre-exercise, every 2 minutes during exercise and at end exercise
- Locus of symptom limitation (breathing discomfort, leg discomfort, breathing and leg discomfort, other) during constant work rate cycle ergometry to symptom limitation at 75% Wcap
- SaO₂, VO₂, VCO₂, Ti, Te, Ve, Vt, breathing frequency (f) during constant work rate cycle ergometry to symptom limitation at 75% Wcap (measured breath-by-breath; recorded as 15 second averages)

Note that trough parameters were measured 30 minutes prior to dosing and were not the mean of 2 values (parameters at -45 and -15 minutes) as in the 48 week COPD trials.

Safety parameters

Monitored safety parameters included the following:

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- Pulse rate, blood pressure in conjunction with spirometry
- Heart rate, blood pressure in conjunction with exercise
- ECG (at rest and during exercise)
- All adverse events

Compliance

Compliance was determined based on daily diary entries.

Ethics:

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol.

Reviewer comment

The safety and compliance parameters are acceptable. The primary and secondary efficacy parameters related to exercise testing may be problematic. In the clinical trial setting, results from exercise testing can be difficult to interpret and apply to the general population. There are multiple non-disease related factors that can confound the results. The sponsor acknowledges this and attempted to control for them; however, given the confounding factors, it is unclear if they can be controlled. The most problematic confounding factors are psychological. Although the sponsor stated that verbal motivation would be 'enthusiastic and supportive', rather than 'overbearing, overly loud, or coercive', it is unclear how they differed and how the sponsor ensured that each site interpreted them similarly. Additionally, while the sponsor attempted to normalize for external motivational cues, one cannot normalize for internal motivation cues.

Additionally, it is not clear if 6 weeks is sufficient to characterize the durability of the effect of a LABA (or any other COPD drug) on exercise testing results.

Use of the Borg scale is also problematic. The Borg scale was not developed specifically for clinical trials and results can be difficult to interpret in terms of clinical significance. As primary evidence of efficacy and support for a label claim, this scale would be insufficient. However, as supportive evidence, the Borg scale may be acceptable.

Statistical Analysis

Sample Size

Based on BI's previous experience, the standard deviation of within-subject treatment difference for endurance time on a log10 scale was assumed to be approximately 0.181 seconds. As such, in order detect a 15% difference in endurance time (ET) with 90% power (type 1 error rate 0.05) then a sample size of 102 patients was required.

Therefore, BI planned to randomize 150 patients with the assumption of a 20% drop-out rate.

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Missing Data

There was no imputation for endurance times; if rescue medications were administered during exercise visits, then any recorded data afterward was set to missing. If there was missing spirometric data on visits 3, 5, and 7 (beginning of each 6 week treatment period), values were not imputed. If patients required rescue medications during clinic visits 4, 6, and 8 (end of each 6 week treatment period), then PFTs at the time of rescue were considered missing and values were imputed using the least favorable prior observation. If the entire visit was missing, because a patient discontinued due to worsening disease, then data was imputed by worst observation carried forward for the previous visit. If post-dose data was missing, pre-dose data was used for imputation; however if no pre-dose data was available, then the post-dose value was considered missing.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients who received study drug and had baseline data and any evaluable post-dosing data for the primary endpoint. The per protocol set (PPS) consisted of all FAS minus patients with important protocol deviations. The safety population was made up of all treated patients.

Efficacy Analysis

In order to protect against type 1 error, analysis of the primary endpoint was performed in a hierachal manner. The first comparison was between olodaterol 10mcg and placebo. If that result was significant, the olodaterol 5mcg was compared to placebo. If the first comparison failed, the second comparison was considered exploratory/descriptive. Analysis of the key secondary endpoints was performed in a similar manner. For analysis of the other secondary endpoints, there was no protection against type 1 error, nor alpha corrections for multiple comparisons.

Results

Protocol Amendments

There was a single local amendment (Germany) submitted on 1/14/2010 which clarified blood pressure monitoring during exercise testing. Subgroup analyses based on baseline ET (quartiles) and baseline locus of symptom limitation were also added.

Protocol violations

A total of 32 (21.2%) of the total 151 randomized patients had important protocol violations. The sponsor prospectively defined an important protocol violation as a deviation that could potentially affect the interpretation of the efficacy or safety data. Of the 32 important protocol violations, 24 had violations that were deemed by the sponsor to potentially affect efficacy. The most common violation was improper washout of medication, occurring in 7.9% of patients. As there was a greater than 10% difference between the FAS and PPS, sensitivity analysis was performed on the PPS.

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Disposition

Of the 201 enrolled patients, 151 were randomized and received at least one dose of medication. Of these, 133 (88.1%) completed all 3 treatment periods. The most common reason for discontinuations was AEs. Discontinuations were similar between treatment periods. Patient disposition and analysis populations are summarized in Table 101. It should also be noted that patients were allowed to withdraw between or during treatment periods, and were given the option of continuing in the next treatment period. Patients were also discontinued per protocol if they had a COPD exacerbation or required initiation of tiotropium during the treatment period. Note that in the analyses of the various endpoints, the 'N' was often lower than the FAS. This was due to missing, non-imputed data (i.e. data that was assigned as missing due to the analysis plan).

Table 101. Trial 1222.37. Patient disposition and analysis sets

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Total N(%) |
|---------------------------|-----------------|------------------|-------------------|---------------|
| Treated Set | 143 (100) | 147 (100) | 143 (100) | 151 (100)* |
| Full Analysis Set (FAS)** | 140 (97.9) | 145 (98.6) | 142 (99.3) | 147 (97.4) |
| Per Protocol Set (PPS)** | 119 (83.2) | 121 (82.3) | 120 (83.9) | 123 (81.5) |
| Completed | 137 (95.8) | 139 (94.6) | 140 (97.9) | 133 (88.1)*** |
| Premature discontinuation | 6 (4.2) | 8 (5.44) | 3 (2.1) | |
| Adverse events | 4 (2.8) | 4 (2.7) | 2 (1.4) | |
| AE study disease worse | 2 (1.4) | 1 (0.7) | 0 | |
| AE-other disease worse | 0 | 1 (0.7) | 0 | |
| AE-other | 2 (1.4) | 2 (1.4) | 2 (1.4) | |
| Non-compliance | 1 (0.7) | 1 (0.7) | 0 | |
| Consent withdrawn | 1 (0.7) | 0 | 0 | |
| Other | 0 | 3 (2.0) | 1 (0.7) | |

*completed at least one treatment

**calculated by the medical reviewer from ADSL dataset (5.3.5.1.25.3.1)

***completed all treatment periods

Source: Trial 1222.37 CSR; tables 10.1:1 and 11.1:1; pp 60 and 63

Demographics

The majority of the patients in this trial were white (100%) males (77%) with a mean age of 60.6 years. Most were ex-smokers (55.6%) with a 45.3 year pack history. The average duration of COPD diagnosis was 6.4 years. Most patients were GOLD II (66.2%) or GOLD III (28.5%). Average baseline FEV1 % predicted was 48.5%, and FEV1/FVC ratio was 46.2. Mean reversibility based on FEV1 was 15.7%.

Mean baseline exercise mean endurance time (visit 2) was 478.2 seconds. Note that this was the arithmetic mean. The geometric mean was 414 seconds. The reasons for stopping exercise were breathing discomfort (37.1%), leg and breathing discomfort (34.4%), and leg discomfort (26.5%). Mean baseline IC was decreased by 13% at the end of exercise (2L) compared to at rest (2.3L).

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Reviewer Comment

The patients' demographic and baseline data were generally typical for a COPD trial population. However, the racial homogeneity may affect the generalizability to the U.S. COPD population. Note that due to the imputation/missing data rules, the FAS during each treatment period did not necessarily equal the number of patients analyzed for in each treatment period for each endpoint. However, in general, the difference was minor and similar between treatment periods; and therefore not likely to significantly affect the analysis.

Compliance

Patient compliance based on patient diaries was >99% across all treatment periods.

Efficacy

Primary endpoint

The primary endpoint was endurance time after 6 weeks of therapy. Following 6 weeks of treatment, the ETs for olodaterol 10mcg (422 seconds) and olodaterol 5mcg (421 seconds) were greater than placebo (370 seconds) by approximately 1 minute. The common baseline ET was 414 seconds (geometric mean). There was no difference between olodaterol groups. These results are summarized in Table 102.

Table 102. Trial 1222.37. Primary endpoint. Endurance time after 6 weeks of treatment

| Treatment | N | Treatment mean (SE)[seconds] | Ratio to placebo | |
|-----------|-----|---------------------------------|------------------|---------|
| | | | Mean (SE) | p-value |
| Placebo | 136 | 369.8 (11.9) | | |
| Olo 5mcg | 140 | 421.6 (13.6) | 1.14 (0.04) | 0.0002 |
| Olo 10mcg | 136 | 420.7 (13.6) | 1.138 (0.04) | 0.0003 |

Source: Trial 1222.37 CSR; table 11.4.1.1:1; pg 71

A sensitivity analysis was also performed on the PPS and the results were similar. However, the overall magnitude of effect was lower, but the ratio to placebo was higher. The PPS consisted of 116, 118, and 117 placebo, olodaterol 5mcg and olodaterol 10mcg patients, respectively.

The sponsor also performed subgroup analysis based on baseline ET and locus of symptom limitation. Patients with the largest increase in ET were those in the lowest quartile baseline ET. Patients in the highest quartile baseline ET had the least benefit. With regard to locus of symptom limitation, patients who baseline limitation was due to breathing discomfort alone had the greatest improvement in ET after treatment. The smallest increase was seen in patients whose limitation primarily stemmed from leg discomfort alone.

Reviewer comment:

Based on the primary endpoint, both doses of olodaterol improve ET compared to placebo; however, the clinical significance of approximately 1 minute improvement is unclear. Additionally, it is unclear how durable this improvement is given the short

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duration of this trial. The results for the subgroup analysis based on locus of symptom limitation are not surprising given that olodaterol is a bronchodilator. It is also not surprising that those with the longest baseline ETs benefited the least.

Secondary Endpoints

Key secondary endpoints

The first key secondary endpoint was mean IC at isotime following 6 weeks of olodaterol. For both olodaterol 5mcg and olodaterol 10 mcg there was a statistically significant difference from placebo (0.182L and 0.174L, respectively). The sponsor also reported IC pre-exercise and post-exercise ('other' secondary endpoints). For both, ICs were greater in the olodaterol groups. These results are summarized in Table 103. Note that the key secondary endpoint is highlighted in grey.

Table 103. Trial 1222.37. Inspiratory capacity at isotime (key secondary endpoint), pre-exercise, and post-exercise after 6 weeks of treatment

| Time point | Treatment | N | Treatment mean IC (SE) [L] | Difference from placebo | |
|--------------|-----------|-----|-------------------------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Pre-exercise | Placebo | 134 | 2.220 (0.032) | | |
| | Olo 5mcg | 139 | 2.478 (0.032) | 0.258 (0.034) | <0.0001 |
| | Olo 10mcg | 133 | 2.513 (0.032) | 0.294 (0.035) | <0.0001 |
| Isotime | Placebo | 136 | 1.917 (0.038) | | |
| | Olo 5mcg | 140 | 2.099 (0.038) | 0.182 (0.036) | <0.0001 |
| | Olo 10mcg | 135 | 2.091 (0.038) | 0.174 (0.036) | <0.0001 |
| End-exercise | Placebo | 136 | 1.887 (0.035) | | |
| | Olo 5mcg | 140 | 2.067 (0.035) | 0.180 (0.037) | <0.0001 |
| | Olo 10mcg | 135 | 2.024 (0.035) | 0.137 (0.037) | 0.0003 |

Source: Trial 1222.37 CSR; table 11.4.1.2.1:1; pg73

The second key secondary endpoint was intensity of breathing discomfort as measured by Borg Category Ratio Scale (BCRS) score at isotime after 6 weeks of treatment. The sponsor also analyzed the same variable at the pre-exercise and end exercise time point as 'other secondary endpoints'. At isotime, both olodaterol groups demonstrated decreases in BCRS scores compared to placebo, however for the other time points, a statistically significant difference was only seen for olodaterol 5mcg at pre-exercise. The results are summarized in Table 104. Note that the key secondary endpoint is highlighted in grey.

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Table 104. Trial 1222.37. BCRS score at pre-exercise, isotime (key secondary endpoint), and end-exercise after 6 week fo treatment

| Time point | Treatment | N | BCRS | Difference from placebo | |
|--------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Pre-exercise | Placebo | 136 | 0.288 (0.041) | | |
| | Olo 5mcg | 140 | 0.185 (0.040) | -0.103 (0.051) | 0.0447 |
| | Olo 10mcg | 135 | 0.224 (0.041) | -0.064 (0.052) | 0.2132 |
| Isotime | Placebo | 136 | 5.870 (0.185) | | |
| | Olo 5mcg | 140 | 5.104 (0.182) | -0.766 (0.223) | 0.0007 |
| | Olo 10mcg | 136 | 5.235 (0.185) | -0.634 (0.225) | 0.0051 |
| End-exercise | Placebo | 136 | 6.978 (0.143) | | |
| | Olo 5mcg | 140 | 6.890 (0.141) | -0.088 (0.154) | 0.5698 |
| | Olo 10mcg | 136 | 7.234 (0.143) | 0.256 (0.155) | 0.1003 |

Source: Trial 1222.37 CSR; table 15.2.2.3:1; pg172

Reviewer comments:

Based on the key secondary endpoints, both doses of olodaterol appear have increased ICs and improved BCRS scores at isotime. Based on the IC findings, both olodaterol doses may improve hyperinflation, at rest, during exercise (isotime), and at end exercise. Based on BCRS findings, both olodaterol decreased intensity of breathing discomfort during exercise, and the 5mcg dose decreased discomfort pre-exercise. However, the clinical significance of these improvements is unclear.

Other secondary endpoints

Box plethysmography

The FRC following 6 weeks of treatment was smaller for the olodaterol groups compared to placebo when performed one hour after dosing; however, when performed 30 minutes prior to dosing (trough), there were no statistically significant differences from placebo. This is in contrast to the findings 1 hour post-dose. These results are summarized in Table 105.

Table 105. Trial 1222.37. Secondary endpoint. Trough and 1-hour post-dose FRC after 6 weeks of treatment

| Time point | Treatment | N | FRC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 134 | 4.977 (0.062) | | |
| | Olo 5mcg | 139 | 4.855 (0.061) | -0.122 (0.069) | 0.0784 |
| | Olo 10mcg | 134 | 4.862 (0.062) | -0.115 (0.070) | 0.1013 |
| 1:00 | Placebo | 134 | 4.950 (0.064) | | |
| | Olo 5mcg | 139 | 4.740 (0.063) | -0.210 (0.066) | 0.0015 |
| | Olo 10mcg | 134 | 4.577 (0.064) | -0.373 (0.066) | <.0001 |

Source: Trial 1222.37 CSR; table 15.2.4.1:1; pg 179

The IC at rest following 6 weeks of treatment was smaller for the olodaterol groups compared to placebo when performed 30 minutes prior to and one hour after dosing. These results are summarized in Table 106.

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Table 106. Trial 1222.37. Secondary endpoint. Trough and 1-hour post-dose IC after 6 weeks of treatment

| Time point | Treatment | N | IC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 135 | 2.170 (0.040) | | |
| | Olo 5mcg | 140 | 2.289 (0.040) | 0.119 (0.034) | 0.0005 |
| | Olo 10mcg | 134 | 2.262 (0.040) | 0.092 (0.034) | 0.0073 |
| 1:00 | Placebo | 135 | 2.221 (0.040) | | |
| | Olo 5mcg | 140 | 2.427 (0.040) | 0.206 (0.035) | <.0001 |
| | Olo 10mcg | 134 | 2.437 (0.040) | 0.216 (0.036) | <.0001 |

Source: Trial 1222.37 CSR; table 15.2.4.1:3; pg181

For TLC following 6 weeks of treatment, there were no differences when comparing placebo treatment period to olodaterol period, except for TLC 1-hour post-dose for olodaterol 10mcg. These results are summarized Table 107.

Table 107. Trial 1222.37. Secondary endpoint. Trough and 1-hour post-dose TLC after 6 weeks of treatment

| Time point | Treatment | N | TLC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 135 | 7.142 (0.064) | | |
| | Olo 5mcg | 140 | 7.148 (0.063) | 0.006 (0.062) | 0.9239 |
| | Olo 10mcg | 134 | 7.121 (0.064) | -0.021 (0.062) | 0.7368 |
| 1:00 | Placebo | 135 | 7.156 (0.066) | | |
| | Olo 5mcg | 140 | 7.142 (0.066) | -0.014 (0.067) | 0.8302 |
| | Olo 10mcg | 134 | 6.997 (0.067) | -0.159 (0.068) | 0.0202 |

Source: Trial 1222.37 CSR; table 15.2.4.1; pg181

Spirometry

For the secondary endpoints of FEV1, FVC, and PEFR response, 30 minutes prior to dosing (trough), responses were greater during the olodaterol treatment periods compared to placebo periods. These results are summarized in Table 108. A similar result was demonstrated when analyzing the same variables 1 hour post dose; however, the magnitude of effect was approximately double.

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Table 108. Trial 1222.37. Trough FEV1, trough FVC, and trough PEFR response after 6 weeks of treatment

| Endpoint | Treatment | N | Mean value | Difference from placebo | |
|----------|-----------|-----|----------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| tFEV1 | Placebo | 136 | 1.475 (0.017) | | |
| | Olo 5mcg | 137 | 1.564 (0.017) | 0.089 (0.017) | <0.0001 |
| | Olo 10mcg | 137 | 1.576 (0.017) | 0.101 (0.017) | <0.0001 |
| tFVC | Placebo | 135 | 3.212 (0.037) | | |
| | Olo 5mcg | 136 | 3.319 (0.037) | 0.107 (0.031) | 0.0006 |
| | Olo 10mcg | 136 | 3.310 (0.037) | 0.098 (0.031) | 0.0017 |
| tPEFR | Placebo | 136 | 4.374 (0.059) | | |
| | Olo 5mcg | 137 | 4.692 (0.059) | 0.318 (0.056) | <0.0001 |
| | Olo 10mcg | 137 | 4.677 (0.059) | 0.303 (0.056) | <0.0001 |

Source: Trial 1222.37 CSR; tables 11.4.1.3.2:1, 11.4.1.3.2:2, 11.4.1.3.2:3; pp 77-78

With regard to intensity of leg discomfort, after 6 weeks of treatment, at pre-exercise and end of exercise, olodaterol had no effect. At isotime, only the during the olodaterol 5mcg treatment period was leg discomfort decreased compared to placebo (difference from placebo=-0.466, p-value=0.04). The olodaterol 10mcg dose did not have a statistically significant effect.

Reviewer comment

Of these above endpoints, only the IC was consistently different from placebo during the trough and 1 hour post dose time point, indicating that olodaterol may decrease lung hyperinflation at rest. For FRC, which is also a measure of hyperinflation, differences from placebo were only statistically significant at the 1-hour post-dose time point, but not at trough. This implies that while olodaterol may improve FRC, its effect is transient and does not span the dosing interval. Alternatively, FRC may not be as sensitive as IC at detecting hyperinflation. There was effect on TLC, though this is not surprising as TLC is derived from FRC+IC. With regard to the FEV1/FVC/PEFR related endpoints, these are consistent with the data from the 48-week trials.

Safety

Exposure

One-hundred-fifty-one (151) patients received at least one dose of olodaterol. When broken down by treatment period, 147 patients received olodaterol 5mcg, 143 patients received olodaterol 10mcg, and 143 patients received placebo. Mean exposure across treatment periods was similar and ranged from 45-46 days.

Deaths and SAEs

There were no deaths reported in this trial. Nine patients had SAEs, three during each treatment period. Only COPD exacerbation occurred in more than one patient. During the placebo treatment period, the SAEs were COPD exacerbation (n=2) and coronary artery occlusion. In one of the patients (37200) who experienced a COPD exacerbation, trial medication had been stopped the day prior to the exacerbation. In the other patient

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(37222) who experienced a COPD exacerbation, trial medication was continued. It is unclear why patient 37222 was not discontinued from the trial as exacerbation was a withdrawal criterion. During the olodaterol 5mcg treatment period, the SAEs were COPD exacerbation, diabetic nephropathy, and fibula fracture. The patients reporting fracture and COPD exacerbation both discontinued. During the olodaterol 10mcg treatment period, the SAEs were atrial fibrillation and COPD exacerbation (n=2). One patient with a COPD exacerbation discontinued. All patients, except for the patient with atrial fibrillation, recovered.

Ten patients discontinued due to TEAEs. This was more common in the placebo (n=4) and olodaterol 5mcg (n=4) compared to olodaterol 10mcg (n=2). Aside from COPD exacerbation, all were isolated events.

Treatment Emergent AEs

TEAEs were defined as those that occurred after the first dose and up to 12 days after the last dose. The most common TEAEs were COPD, dyspnea, and nasopharyngitis. None of the three demonstrated a dose response. Based on preferred term, insomnia, headache, and diarrhea demonstrated a dose response. Common TEAEs ($\geq 2\%$) are summarized in Table 109.

Table 109. Trial 1222.37. Common TEAEs ($\geq 2\%$)

| System organ class/ Preferred term | Placebo N (%) | Olodaterol 5ug N (%) | Olodaterol 10ug N (%) | Total N (%) |
|---|------------------|-------------------------|--------------------------|----------------|
| Number of subjects | 143 (100.0) | 147 (100.0) | 143 (100.0) | 151 (100.0) |
| Total with adverse events | 38 (26.6) | 49 (33.3) | 42 (29.4) | 79 (52.3) |
| Infections and infestations | | | | |
| Nasopharyngitis | 4 (2.8) | 3 (2.0) | 1 (0.7) | 7 (4.6) |
| Bronchitis | 2 (1.4) | 1 (0.7) | 0 (0.0) | 3 (2.0) |
| Herpes zoster | 2 (1.4) | 0 (0.0) | 1 (0.7) | 3 (2.0) |
| Respiratory tract infection bacterial | 1 (0.7) | 0 (0.0) | 2 (1.4) | 3 (2.0) |
| Psychiatric disorders | | | | |
| Insomnia | 0 (0.0) | 2 (1.4) | 3 (2.1) | 5 (3.3) |
| Nervous system disorders | | | | |
| Headache | 1 (0.7) | 4 (2.7) | 2 (1.4) | 5 (3.3) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Chronic obstructive pulmonary disease | 10 (7.0) | 11 (7.5) | 7 (4.9) | 23 (15.2) |
| Dyspnoea | 3 (2.1) | 4 (2.7) | 2 (1.4) | 9 (6.0) |
| Cough | 2 (1.4) | 1 (0.7) | 3 (2.1) | 6 (4.0) |
| Oropharyngeal pain | 1 (0.7) | 0 (0.0) | 3 (2.1) | 3 (2.0) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 0 (0.0) | 2 (1.4) | 2 (1.4) | 4 (2.6) |

Source: Trial 1222.37 CSR; table 12.2.2.2:1; pg 86

Labs:

Based on shift tables, in general, hematologic and chemistry lab values were stable from baseline to end of treatment. However, for non-fasting glucose, during the olodaterol 5mcg treatment period, a higher percentage of patients shifted from normal to high (8.9%) versus placebo (4.4%) and olodaterol 10mcg (3.4%), when comparing baseline to maximum value. Changes in serum potassium levels were similar between treatment periods based on shift table analysis. No AEs related to lab values were reported.

Vitals signs

The number of patients with changes in blood pressures or pulse rates was similar between treatment groups. Based on shift table analysis for SBP, DBP, and pulse rate, there did not appear to be any dose-related effects. New or worsening of ECG changes were not noted.

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Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well-tolerated. The SAEs and AEs noted were typical of a COPD trial. The lab changes were minimal.

5.3.13 Trial 1222.38 (COPD Exercise Trial)

Administrative Information

- **Study title:** Randomised, double-blind, placebo-controlled, 3-way cross-over study to determine the effect of 6 weeks treatment of olodaterol 5mcg and olodaterol 10 mcg delivered by the Respimat Inhaler on exercise endurance time during constant work rate cycle ergometry in patients with COPD
- **Study dates:** 1/27/10-4/05/11
- **Study sites:** Austria (2), Belgium (4), Canada (4), Germany (6), Russia (3)
- **Report Date:** 3/20/12

Trial 1222.38 was identical in design to trial 1222.37.

Results

Protocol violations

A total of 22 (14.0%) of the total 157 randomized patients had important protocol deviations (same definition as in trial 1222.37). Of these, 15 had violations that the sponsor deemed to have potentially affected efficacy. Deviations included use of prohibited medications (n=5), not meeting inclusion criteria (n=3), primary endpoint recorded outside of specified window (n=3), medication taken outside of window (n=3), and non-compliance [only 1 puff daily (n=1)]. These patients were excluded from the PPS.

Disposition

Of the 204 enrolled patients, 157 were randomized and received at least one dose of medication. Of the randomized patients, 133 (84.7%) completed all treatment periods. The most common reason for discontinuations was AEs. Discontinuations were similar between treatment periods, though somewhat more frequent in the olodaterol groups. Patient disposition and analysis populations are summarized in Table 110. It should be noted that, as in trial 1222.37, patients were allowed to withdraw between or during treatment periods, and were given the option of continuing in the next treatment period. Note that in the analyses of the various endpoints, the 'N' was often lower than the FAS. This was due to missing, non-imputed data (i.e. data that was assigned as missing due to the analysis plan).

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Table 110. Trial 1222.38. Patient disposition and analysis sets

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Total N(%) |
|---------------------------|-----------------|------------------|-------------------|---------------|
| Treated Set | 149 (100) | 150 (100) | 147 (100) | 157 (100)* |
| Full Analysis Set (FAS)** | 148 (99.3) | 149 (99.3) | 146 (99.3) | 154 (98.1) |
| Per Protocol Set (PPS)** | 134 (90.0) | 135 (90.0) | 133 (90.5) | 139 (88.5) |
| Completed | 144 (96.6) | 142 (94.7) | 138 (93.9) | 133 (84.7)*** |
| Premature discontinuation | 5 (3.36) | 5 (5.33) | 9 (6.1) | |
| Adverse events | 3 (2) | 8 (5.3) | 5 (3.4) | |
| AE study disease worse | 1 (0.7) | 1 (0.7) | 2 (1.4) | |
| AE-other disease worse | 1 (0.7) | 2 (1.3) | 0 | |
| AE-other | 1 (0.7) | 5 (3.33) | 3 (2.0) | |
| Non-compliance | 1 (0.7) | 0 | 1 (0.7) | |
| Lost to follow-up | 1 (0.7) | 0 | 0 | |
| Consent withdrawn | 0 | 0 | 1 (0.7) | |
| Other | 0 | 0 | 2 (1.4) | |

*completed at least one treatment

**calculated by the medical reviewer from ADSL dataset (5.3.5.1.25.3.1)

***completed all treatment periods

Source: Trial 1222.38 CSR; tables 10.1:1 and 11.1:1; pp 60 and 63

Demographics

The majority of the patients in this trial were white (98.7%) males (73.9%) with a mean age of 60.6 years. Most were ex-smokers (58.6%) with a 50 pack-year history. The average duration of COPD diagnosis was 7.1 years. Most patients were GOLD II (70.7%) or GOLD III (26.1%). Average baseline FEV1 % predicted was 51.6%, and FEV1/FVC ratio was 48.7%. Mean reversibility based on FEV1 was 10.8%.

Mean baseline exercise mean endurance time (visit 2) was 415.5 seconds. Note that this was the arithmetic mean. The geometric mean was 374 seconds. The reasons for stopping were breathing discomfort (52.9%), leg and breathing discomfort (26.8%), and leg discomfort (17.2%). Mean baseline IC was decreased by 10.4% at the end of exercise (2L) compared to at rest (2.3L).

Reviewer Comment

The patients' demographic and baseline data were generally typical for a COPD trial population. However, the racial homogeneity may affect the generalizability to the U.S. COPD population. Compared to the population in trial 1222.37, this population had similar baseline FEV1, but decreased reversibility and decreased ET.

As with trial 1222.37, due to the imputation/missing data rules, the FAS during each treatment period did not necessarily equal the number of patients analyzed for in each treatment period for each endpoint. In general, the difference was minor and similar between treatment periods, and therefore not likely to significantly affect analysis.

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Primary endpoint

The primary endpoint was ET after 6 weeks of therapy. Following 6 weeks of treatment, the ETs for olodaterol 10mcg (392 seconds) and olodaterol 5mcg (396 seconds) were greater than placebo (354 seconds) by approximately 40 seconds. The common baseline geometric ET was 374 seconds. There was no difference between olodaterol groups. These results are summarized in Table 111.

Table 111. Trial 1222.38. Primary endpoint. Endurance time after 6 weeks of treatment

| Treatment | N | Treatment mean (SE)[seconds] | Ratio to placebo | |
|-----------|-----|---------------------------------|------------------|---------|
| | | | Mean (SE) | p-value |
| Placebo | 146 | 354.3 (12.1) | | |
| Olo 5mcg | 141 | 396.3 (13.7) | 1.12 (0.04) | 0.0018 |
| Olo 10mcg | 140 | 391.5 (13.6) | 1.11 (0.04) | 0.0050 |

Source: Trial 1222.38 CSR; table 11.4.1.1:1; pg71

A sensitivity analysis was also performed in the PPS and the results were similar. The PPS consisted of 132, 130, and 127 placebo, olodaterol 5mcg and olodaterol 10mcg patients, respectively.

The sponsor also performed subgroup analysis based on baseline ET and locus of symptom limitation. Patients with the largest increase in ET were those in the lowest quartile baseline ET. Patients in the highest quartile baseline ET had the least benefit. With regard to locus of symptom limitation, patients whose baseline limitation was due to breathing discomfort alone had the greatest improvement in ET after treatment. Across all loci of symptom limitation, there were no differences in change in ET.

Reviewer comment:

Based on the primary endpoint, both doses of olodaterol improved ET compared to placebo; however, the clinical significance of an approximately 40 second improvement is unclear. These results are consistent with trial 1222.38.

Secondary Endpoints

Key secondary endpoints

The first key secondary endpoint was mean IC at isotime following 6 weeks of olodaterol. For both olodaterol 5mcg and olodaterol 10mcg there was a statistically significant difference from placebo (0.084L and 0.166L, respectively). The sponsor also reported IC pre-exercise and post-exercise ('other' secondary endpoints). For both, ICs were greater in the olodaterol groups. These results are summarized in Table 112Note that the key secondary endpoint is highlighted in grey.

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Table 112. Trial 1222.38. Inspiratory capacity at isotime (key secondary endpoint), pre-exercise, and post-exercise after 6 weeks of treatment

| Time point | Treatment | N | Treatment mean IC (SE) [L] | Difference from placebo | |
|--------------|------------------|-----|-------------------------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Pre-exercise | Placebo | 146 | 2.273 (0.036) | | |
| | Olo 5mcg | 141 | 2.437 (0.036) | 0.164 (0.036) | <0.0001 |
| | Olo 10mcg | 138 | 2.468 (0.037) | 0.195 (0.036) | <0.0001 |
| Isotime | Placebo | 146 | 2.162 (0.039) | | |
| | Oladaterol 5mcg | 141 | 2.246 (0.039) | 0.084 (0.035) | 0.0155 |
| | Oladaterol 10mcg | 139 | 2.328 (0.039) | 0.166 (0.034) | <0.0001 |
| End-exercise | Placebo | 146 | 2.158 (0.039) | | |
| | Oladaterol 5mcg | 141 | 2.236 (0.040) | 0.078 (0.034) | 0.0245 |
| | Oladaterol 10mcg | 139 | 2.330 (0.040) | 0.172 (0.034) | <0.0001 |

Source: Trial 1222.38 CSR; table 11.4.1.2.1:1; pg73

The second key secondary endpoint was intensity of breathing discomfort as measured by Borg Category Ratio Scale (BCRS) score at isotime after 6 weeks of treatment. The sponsor also analyzed the same variable at the pre-exercise and end exercise time point as 'other secondary endpoints'. The only time point where the difference from placebo was statistically significant was for olodaterol 10mcg at end-exercise. At all other time points, olodaterol did not demonstrate a statistically significant difference from placebo, although there was a numerical improvement over placebo. These results are summarized in Table 113. Note that the key secondary endpoint is highlighted in grey.

Table 113. Trial 1222.38. BCRS score at pre-exercise, isotime (key secondary endpoint), and end-exercise after 6 weeks of treatment.

| Time point | Treatment | N | BCRS | Difference from placebo | |
|--------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Pre-exercise | Placebo | 146 | 0.389 (0.062) | | |
| | Olo 5mcg | 141 | 0.315 (0.063) | -0.074 (0.07) | 0.30 |
| | Olo 10mcg | 140 | 0.364 (0.064) | -0.025 (0.07) | 0.07 |
| Isotime | Placebo | 146 | 5.585 (0.177) | | |
| | Olo 5mcg | 141 | 5.250 (0.180) | -0.336 (0.21) | 0.12 |
| | Olo 10mcg | 140 | 5.520 (0.181) | -0.066 (0.21) | 0.76 |
| End-exercise | Placebo | 146 | 7.010 (0.13) | | |
| | Olo 5mcg | 141 | 7.101 (0.13) | 0.091 (0.15) | 0.5313 |
| | Olo 10mcg | 140 | 7.351 (0.13) | 0.341 (0.15) | 0.02 |

Source: Trial 1222.38 CSR; table 11.4.1.2.2:1; pg74

Reviewer comments:

Both doses of olodaterol appeared to have increased ICs at isotime. For BCRS, neither dose demonstrated a difference from placebo. This is in contrast to trial 1222.37, where a difference was seen for both parameters. Given the subjectivity of the BCRS measurement, it is not necessarily surprising that the results are inconsistent.

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Other secondary endpoints

Box plethysmography

The FRC following 6 weeks of treatment was smaller for the olodaterol groups compared to placebo when performed one hour after dosing. These differences were all statistically significant except for olodaterol 5mcg at trough. These results are summarized in Table 114.

Table 114. Trial 1222.38. Secondary endpoint. Trough and 1-hour post-dose FRC after 6 weeks of treatment

| Time point | Treatment | N | FRC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 147 | 4.842 (0.062) | | |
| | Olo 5mcg | 145 | 4.757 (0.063) | -0.086 (0.053) | 0.1048 |
| | Olo 10mcg | 141 | 4.723 (0.063) | -0.120 (0.053) | 0.0246 |
| 1:00 | Placebo | 147 | 4.770 (0.065) | | |
| | Olo 5mcg | 145 | 4.557 (0.065) | -0.213 (0.053) | <0.0001 |
| | Olo 10mcg | 141 | 4.557 (0.065) | -0.187 (0.054) | 0.0005 |

Source: Trial 1222.38 CSR; table 15.2.4.1:1; pg 179

For all olodaterol doses and time points, the ICs following 6 weeks of treatment were larger compared to placebo. These results are summarized in Table 115.

Table 115. Trial 1222.38. Secondary endpoint. Trough and 1-hour post-dose IC after 6 weeks of treatment

| Time point | Treatment | N | IC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 147 | 2.463 (0.041) | | |
| | Olo 5mcg | 146 | 2.613 (0.041) | 0.150 (0.040) | 0.0002 |
| | Olo 10mcg | 142 | 2.618 (0.042) | 0.154 (0.040) | 0.0001 |
| 1:00 | Placebo | 147 | 2.493 (0.040) | | |
| | Olo 5mcg | 146 | 2.725 (0.040) | 0.232 (0.036) | <0.0001 |
| | Olo 10mcg | 142 | 2.696 (0.040) | 0.203 (0.036) | <0.0001 |

Source: Trial 1222.38 CSR; table 15.2.4.1:3; pg181

For TLC following 6 weeks of treatment there were no differences when comparing placebo treatment period to olodaterol periods. These results are summarized Table 116.

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Table 116. Trial 1222.38. Secondary endpoint. Trough and 1-hour post-dose TLC after 6 weeks of treatment

| Time point | Treatment | N | TLC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| Trough | Placebo | 147 | 7.311 (0.067) | | |
| | Olo 5mcg | 146 | 7.368 (0.067) | 0.057 (0.056) | 0.3109 |
| | Olo 10mcg | 142 | 7.340 (0.068) | 0.029 (0.056) | 0.6080 |
| 1:00 | Placebo | 147 | 7.262 (0.069) | | |
| | Olo 5mcg | 146 | 7.285 (0.069) | 0.023 (0.056) | 0.6809 |
| | Olo 10mcg | 142 | 7.272 (0.069) | 0.010 (0.056) | 0.8580 |

Source: Trial 1222.38 CSR; table 15.2.4.1:5; pg183

Spirometry

For the secondary endpoints of FEV1, FVC, and PEFR response, 30 minutes prior to dosing (trough), responses were greater during the olodaterol treatment periods compared to placebo periods. These results are summarized in Table 117. A similar result was demonstrated when analyzing the same variables 1 hour post-dose; however, the magnitude of effect was approximately double.

Table 117. Trial 1222.38. Trough FEV1, trough FVC, and trough PEFR response after 6 weeks of treatment

| Endpoint | Treatment | N | Mean value | Difference from placebo | |
|----------|------------------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| FEV1 | Placebo | 146 | 1.520 (0.024) | | |
| | Olo 5mcg | 143 | 1.630 (0.025) | 0.110 (0.019) | <0.0001 |
| | Olo 10mcg | 139 | 1.630 (0.025) | 0.110 (0.019) | <0.0001 |
| FVC | Placebo | 146 | 3.103 (0.039) | | |
| | Olodaterol 5mcg | 143 | 3.222 (0.040) | 0.119 (0.036) | 0.0013 |
| | Olodaterol 10mcg | 139 | 3.222 (0.040) | 0.119 (0.037) | 0.0013 |
| PEFR | Placebo | 146 | 4.258 (0.081) | | |
| | Olodaterol 5mcg | 143 | 4.539 (0.081) | 0.281 (0.063) | <.0001 |
| | Olodaterol 10mcg | 139 | 4.549 (0.082) | 0.291 (0.063) | <.0001 |

source: Trial 1222.38 CSR; tables 11.4.1.3.2:1, 11.4.1.3.2:2, 11.4.1.3.2:3; pp 77-78

With regard to leg discomfort, for olodaterol 10mcg, after 6 weeks of treatment, leg discomfort scores increased (worsened) compared to placebo at both isotime and end-exercise. The reasons for this change are unclear. There were no other differences between olodaterol groups and placebo.

Reviewer comment

These box plethysmography and spirometric endpoint results are generally consistent with trial 1222.37. Of these above endpoints, only the IC was consistently different from placebo during the trough and 1 hour post dose time point, indicating that olodaterol may decrease lung hyperinflation even at rest. For FRC, another measure of hyperinflation, differences from placebo were only statistically significant at both trough and 1 hour post-dose for olodaterol 10mcg. For olodaterol 5mcg there was only a

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statistically significant effect at the 1 hour post-dose time point, but not at trough. This implies that while olodaterol 5mcg may improve FRC, its effect is transient and does not span the dosing interval. Alternatively, FRC may be less sensitive at detecting lung hyperinflation compared to IC. There was no consistent effect on TLC, though this is not surprising as TLC is derived from FRC+IC. These results are consistent with trial 1222.37. With regard to the FEV1/FVC/PEFR-related endpoints, these are consistent with the data from the 48-week trials.

Safety

Exposure:

One-hundred-fifty-seven (157) patients received at least one dose of olodaterol. When broken down by treatment period, 150 patients received olodaterol 5mcg, 147 patients received olodaterol 10mcg, and 149 patients received placebo. Mean exposure across treatment periods was similar and ranged from 45-46 days.

Deaths and SAEs:

There was one death (patient 38240) reported in this trial. The death occurred during the patient's first treatment period which was olodaterol 10mcg. The patient died within 5 days of treatment initiation. The cause of death is unknown, and the research staff only became aware of the death due to a newspaper obituary. The death was confirmed with the patient's primary physician.

Fourteen patients had SAEs; 3 during the placebo period, 8 during the olodaterol 5mcg period, and 3 during the olodaterol 10mcg period. Two patients experienced COPD exacerbations, and the rest were isolated. SAEs of note included a cerebrovascular accident that occurred during washout of olodaterol 5mcg, and atrial fibrillation (patient 38470) that occurred during the olodaterol 5mcg treatment period. The patient with atrial fibrillation discontinued, and the SAE resolved. All patients recovered except the patient who died.

Three patients discontinued due to TEAE; 1 during the placebo period (COPD) and 2 during the olodaterol 5mcg period (COPD and atrial fibrillation).

Treatment Emergent AEs

TEAEs were defined as in trial 1222.37. The most common TEAEs were COPD and nasopharyngitis. TEAEs were generally balanced among treatment groups. Common TEAEs ($\geq 2\%$) are summarized in Table 118.

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Table 118. Trial 1222.38. Common TEAEs ($\geq 2\%$)

| System organ class/ Preferred term | Placebo N (%) | Olodaterol 5 μ g N (%) | Olodaterol 10 μ g N (%) | Total ^a N (%) |
|--|------------------|-------------------------------|--------------------------------|-----------------------------|
| Number of subjects | 149 (100.0) | 150 (100.0) | 147 (100.0) | 157 (100.0) |
| Total with adverse events | 34 (22.8) | 42 (28.0) | 31 (21.1) | 73 (46.5) |
| <i>Respiratory, thoracic and mediastinal disorders</i> | 16 (10.7) | 12 (8.0) | 7 (4.8) | 32 (20.4) |
| Chronic obstructive pulmonary disease | 10 (6.7) | 9 (6.0) | 4 (2.7) | 21 (12.7) |
| <i>Infections and infestations</i> | 7 (4.7) | 7 (4.7) | 12 (8.2) | 24 (15.3) |
| Nasopharyngitis | 3 (2.0) | 2 (1.3) | 7 (4.8) | 12 (7.6) |
| Bronchitis | 1 (0.7) | 2 (1.3) | 1 (0.7) | 4 (2.5) |

Source: Trial 1222.38 CSR; table 12.2.2.2:1; pg85

Labs

Based on shift tables, in general, hematologic and chemistry lab values were stable from baseline to end of treatment. No AEs related to lab values were reported.

Vitals signs

Based on shift table analysis, the number of patients with changes in blood pressures or pulse rates was similar between treatment periods. ECG changes were also similar between treatment periods.

Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well-tolerated. Given the cross-over design and the dearth of information on the single death, it is impossible to assign causality. The SAEs and AEs noted were typical of a COPD trial.

5.3.14 Trial 1222.24 (COPD 6 Week Treatment Period Trial)

Administrative Information

- **Study title:** Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to determine the 24-hour FEV1-time profiles of orally inhaled olodaterol (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]), administered once daily with the Respimat Inhaler, and orally inhaled formoterol (12 mcg), administered twice daily Inhaler, after 6 weeks of treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 6/28/2009-4/30/2010
- **Study sites:** U.S. (11)
- **Study report date:** 3/22/11

Objectives/Rationale

- To determine the 24-hour FEV1-time profile of olodaterol inhalation solution after 6 weeks of treatment
- To compare the 24-hour FEV1-time profile of olodaterol inhalation solution to formoterol

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Study Design and Conduct

Overview

This was a randomized double-blind, double-dummy, placebo controlled 4-way cross-over trial to characterize the 24-hour FEV1 time profiles of olodaterol (5mcg and 10mcg once daily) and formoterol (12mcg BID). Each of the four treatment periods lasted 6 weeks, and periods were separated by a 2 week washout period. At visit 0, consent was obtained and washout of prohibited medications began. Rescue medications (albuterol) and a symptom diary were also dispensed. At visit 1, eligibility, compliance, and appropriate washout were confirmed. Baseline spirometry was also obtained. After visit 1, patients entered a 2 week run-in phase. At visit 2 (or visits 5, 8, and 11 for the other treatment periods), PFTs were performed at 1 hour and at 10 minutes prior to morning dose of medication. Post-dose PFTs were performed at 30 minutes, 1, 2, and 3 hours. Test medication was also dispensed. At visit 3, (week 3 of treatment) (or visits 6, 9, and 12 for other treatment periods), test medication was dispensed, but PFTs were not performed. At visit 4, (after 6 weeks of treatment)(visits 7, 10, and 13 for other treatment periods), 24 hour post-dose spirometry was performed. Two weeks after the last treatment period, the patients were seen for their final follow-up visit. The trial schedule is summarized in Table 119. The assessments performed at each visit are summarized in Table 120. Note that while patients were tested for reversibility, that did not affect inclusion or exclusion from this trial.

Table 119. Trial 1222.24. Trial schematic

| | Screening* | | Treatment Period | | | | | | | | | | | | Follow-up |
|-------------------|------------|------------|------------------|----|----|----------|----|----|----------|-----|-----|----------|-----|-----|-----------|
| | | | Period 1 | | | Period 2 | | | Period 3 | | | Period 4 | | | |
| Visit | 0 | 1* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14/EOT |
| Week of treatment | - | - | 0 | 3 | 6 | 0 | 3 | 6 | 0 | 3 | 6 | 0 | 3 | 6 | - |
| Day of treatment | - | - | 1 | 22 | 43 | 1 | 22 | 43 | 1 | 22 | 43 | 1 | 22 | 43 | - |
| Week (cumulative) | | -6 | 0 | 3 | 6 | 8 | 11 | 14 | 16 | 19 | 22 | 24 | 27 | 30 | 32 |
| Day (cumulative) | | -42 to -14 | 1 | 22 | 43 | 57 | 78 | 99 | 113 | 134 | 155 | 169 | 190 | 211 | V13+14 |

* Visit 0 represents the consent date. The screening visit could occur from Day -42 to Day -14, but must include a two week baseline period prior to randomization of the cohort.

source: Trial 1222.24 (protocol and amendments); pp 6

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Table 120. Trial 1222.24. Assessment schedule

| | Screening | | Treatment Period ¹ | | | Follow-up ⁴ |
|--|----------------|-----------------|-------------------------------|-----------------|--------------------|-----------------------------------|
| | Visit | 0 1 | 2, 5, 8, 11 | 3, 6, 9, 12 | 4, 7, 10, 13 | |
| Week of treatment | - | - | 0 | 3 | 6 | 2 weeks post randomized treatment |
| Day of treatment | - | -42 to -14 | 1 | 22 (±3 days) | 43/44 ² | (±3 days) |
| Informed consent and subject information | X ³ | | | | | |
| Demographics | | X | | | | |
| Medical history | | X | | | | |
| Smoking status | X | X | | | | |
| In-/Exclusion criteria | X | | | | | |
| Physical examination | X | | | X ⁴ | | |
| Laboratory tests (fasting) | X | | | X ⁴ | | |
| Pregnancy testing ⁵ | X | X | | | X | |
| 12-lead ECG ⁶ | X | X | | X ⁴ | | |
| Training in use of Respimat [®] and Aerolizer [®] inhalers | X | X ⁷ | X ⁷ | X ⁷ | | |
| Randomisation | | | X | | | |
| Dispense trial medication | | | X | X | | |
| Dispense rescue medication (pm) | X | X | X | X | | |
| Administer trial medication | | | X | | X | |
| Collect trial medication | | | | X | X ⁸ | X |
| Issue patient diary | X | X | X | | | |
| Collect patient diary | | X | X | X | | |
| PFTs (FEV ₁ /FVC) | X ⁹ | X ¹⁰ | | X ¹¹ | | |
| Vital signs (seated) ¹² | X | X | | X | | |
| Adverse events | X | X | X | X | X | |
| Concomitant therapy | X | X | X | X | X | |
| Compliance check | | | X | X | | |
| Drug accountability | | X | X | X | | |
| Trial medication termination | | | | X | | |
| Trial completion | | | | | | X |

1 In this cross-over design, each treatment period (Period 1, Period 2, Period 3, Period 4) will follow the same flow chart.

- procedures during Visits 2, 5, 8, 11 will be identical
- procedures during Visits 3, 6, 9, 12 will be identical
- procedures during Visits 4, 7, 10, 13 will be identical

2 Final visit of each treatment period (Visits 4, 7, 10, 13) requires the patient to remain in the clinic for an overnight stay in order to complete the 24 hour PFTs; the days refer to the first and second day of each clinic visit

3 All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions

4 To be completed whenever trial participation ends

5 Women of child-bearing potential: serum pregnancy test at Visit 1; urine pregnancy test at Visits 2, 5, 8, 11, 14

6 12-lead ECG recording in all patients at Screening Visit (Visit 1). In addition, 12-lead ECG recording will be performed pre-dose and at 40 minutes post dose in all patients at the first visit of each treatment period (Visits 2, 5, 8 and 11) and the last visit of each treatment period (Visits 4, 7, 10 and 13)

7 Patient again will be instructed in the use of the Respimat[®] inhaler, but the patient should not inhale from the placebo inhaler at this visit

8 Last dose of trial medication for respective treatment period will be evening dose (Foradil[®] / Foradil[®] Placebo) on the first day of the last clinic visit (i.e., Day 43); all medication is collected after this evening dose

9 Pre- and post-bronchodilator (400 µg salbutamol (albuterol))

10 Pre-morning dose PFT: 1 hr, and 10 mins prior to inhalation of morning dose of study medication

Post-morning dose PFTs: 30 mins, 1, 2, and 3 hrs post-morning dose

11 Pre-morning dose PFT: 30 mins prior to inhalation of morning dose of study medication

Post-morning dose PFTs: 30 mins, 1, 2, 3, 4, 6, 8, 10 hrs and 11 hrs 50 mins post-morning dose

Evening dose: 12 hours post-morning dose

Post-evening dose PFTs: 30 mins, 1, 2, 10, 11 hrs and 11 hrs 50 mins post-evening dose

12 In conjunction with pulmonary function testing (up to 3 hrs post-morning dose)

source: Trial 1222.24 (protocol and amendments); pp 7-8

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Trial Population

The trial population consisted of 99 randomized COPD patients. They were randomized using IVRS.

Key inclusion/exclusion criteria and enrollment cautions:

See trial 1222.11 (section 5.3).

Treatments

Treatment Groups

Olodaterol 5mcg qD (2 actuations of 2.5mcg/actuation) via Respimat

Olodaterol 10mcg qD (2 actuations of 5mcg/actuation) via Respimat

Formoterol 12 mcg BID via the Aerolizer

Placebo via Respimat

Placebo via Aerolizer

Concomitant/Restricted Medications:

Medications taken by the patient within 3 months of the screening visit were recorded in the eCRF. All medications used during the trial were also recorded in the eCRF. Use of SABAs were allowed as necessary, however, if a patient required SABA treatment during 24 hour PFTs, the testing was continued when possible. Temporary increases in the dose or addition of oral steroids and theophylline were allowed, however, PFTs could not be performed within 7 days of the last dose. PFTs could be postponed up to 14 days. The use of antibiotics was not restricted. However, PFTs would have been postponed for at least 2 days, but not more than 7 days. Medication limitations are summarized in Table 121.

Table 121. Trial 1222.24. Restricted/Prohibited Medications

| Drug Class | Sub-class | Prior to study | Study Period | | |
|------------------|---|----------------|-----------------|------------------|------------------|
| | | | Baseline Period | Treatment Period | Follow up Period |
| Corticosteroids | Inhaled corticosteroids ¹ | permitted | permitted | permitted | permitted |
| | Oral corticosteroids [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent)] | permitted | permitted | permitted | permitted |
| Beta-adrenergics | Inhaled short-acting beta-adrenergics | permitted | rescue | rescue | rescue |
| | Inhaled long-acting beta-adrenergics ² | permitted | not permitted | study drug | permitted |
| | Oral beta-adrenergics | not permitted | not permitted | not permitted | not permitted |
| | Beta blockers ¹ | permitted | permitted | permitted | permitted |

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| | | | | | |
|-------------------------------|--|---------------|---------------|---------------|---------------|
| Anticholinergics ³ | Short-acting anticholinergics ³ (inhalation aerosol and nasal spray) | permitted | permitted | permitted | permitted |
| | Long-acting anticholinergics ⁴ | permitted | permitted | permitted | permitted |
| Miscellaneous | Other investigational drugs ⁵ | not permitted | not permitted | not permitted | not permitted |
| | Cromolyn sodium/nedocromil sodium ⁶ | permitted | permitted | permitted | permitted |
| | Antihistamines, antileukotrienes ⁶ | permitted | permitted | permitted | permitted |
| | Methylxanthines ⁷ | permitted | permitted | permitted | permitted |
| | Mucolytics ¹ | permitted | permitted | permitted | permitted |

1. if stabilized for six weeks prior to Visit 1
2. at least a 48-hour washout of long-acting beta-adrenergics such as salmeterol and formoterol prior to Visit 2
3. specific time restrictions detailed in protocol for all PFT days
4. at least 3 week washout prior to Visit 2 (baseline 24 hour FEV₁-time profile)
5. washout of at least one month or six half lives (whichever is greater)
6. only allowed if prescribed for conditions other than asthma
7. at least a 24-hour washout of short-acting (bid or more frequent administration) theophylline preparations prior to Visit 1; at least a 48-hour washout of long-acting (QD administration) theophylline preparation prior to Visit 1

source: Trial 1222.24 CSR; table 9.4.2.2:1; pp42

Efficacy Parameters

Primary Endpoint

The co-primary endpoints were FEV₁ AUC (0-12 hours) and FEV₁ AUC (12-24 hours) response after 6 weeks of treatment compared between olodaterol groups and placebo. 'Response' and 'AUC' were defined as in trial 1222.11 (see section 5.3). Baseline for all treatment periods was defined as pre-dose spirometry at visit 2 (mean of -1 hour and - 10 minute).

Secondary Endpoints

Secondary endpoints were as follows:

1. FEV₁ AUC (0-12 hours) and FEV₁ AUC (12-24 hours) response after 6 weeks of treatment compared between olodaterol groups and formoterol.
2. FEV₁ AUC (0-24 hours) response, FEV₁ AUC (0-3 hours) response, peak FEV₁ response and trough FEV₁ response after 6 weeks of treatment
3. FVC AUC (0-24 hours) response, FVC AUC (0-3 hours) response, peak FVC response and trough FVC response after 6 weeks of treatment
4. Individual FEV₁ and FVC measurements at each time points over 24 hours after 6 weeks of treatment

Safety parameters:

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Monitored safety parameters will include AEs, vital signs, clinical labs, urinalysis, and ECG.

Compliance

Compliance was determined based on eDiary entries and in a subset of patients, returned medications.

Reviewer comment

The trial design was generally reasonable for a phase 3 COPD trial meant to characterize the 24-hour FEV1 profile of a once daily LABA. However, it should be noted that the in the 12-24 post-dosing period, there is an 8 hour gap in FEV1 data (hours 14-22). Additionally, spirometry was assessed after only 6 weeks of treatment. Based on the data from the 48 week COPD trials, it is unclear if 24 hour spirometry from the 6 week time point is representative of the later time points (i.e. 12 and 24 weeks). In 3 of the 4 forty-eight week trials, between week 6 and week 12, the FEV1 AUC (0-3 hours) response and trough FEV1 response decreased in magnitude, though was fairly similar when taking the whole 48 weeks into consideration. The inclusion/exclusion criteria were also appropriate for a COPD trial.

Ethics:

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

Based on BI's previous experience, the standard deviations for FEV1 AUC (0-12 hours) was estimated to be 160mL and for FEV1 AUC (12-24 hours) were 140mL. BI estimated that a total of 80 patients/treatment period would yield 90% power to detect a 60mL FEV1 AUC (0-12 hours) with a one-sided alpha of 0.025.

Missing Data

Missing data was imputed by the available data from the patient at that visit.

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients who received study drug and had baseline data and at least one evaluable post-dosing data for the first co-primary endpoint. The per protocol set (PPS) consisted of all FAS minus patients with important protocol violations. The safety population was made up of all treated patients.

Efficacy Analysis

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The co-primary endpoints were analyzed in a hierachal manner, with subsequent statistical comparisons only being performed when the previous comparison demonstrated superiority of olodaterol to placebo. If the previous comparison did not demonstrate a statistically significant difference, then the subsequent analyses were considered descriptive. The first co-primary endpoint [FEV1 AUC (0-12 hours) response] was compared between Olo 10mcg and placebo, followed by a comparison of the second co-primary endpoints [FEV1 AUC (12-24 hours) response] for Olo 10mcg and placebo. Similar comparisons of Olo 5mcg to placebo followed.

Secondary endpoints were not analyzed in a hierachal manner, nor were p-values corrected for multiplicity.

Results:

Protocol amendments

There was a single protocol amendment (8/07/2009) increasing the pre-PFT anticholinergic washout from 24 to 48 hours.

Protocol Violations

A total of 3 patients (3%) had important protocol violations. One patient did not have appropriate washout of beta-agonists, and for 2 patients the randomization order was not followed due to human error. For both these patients, the error occurred during the first 3 weeks of the 3rd treatment period. A patient meant for placebo was given Olo 5mcg, and a patient meant for Olo 5mcg was given placebo. Both patients were given the appropriate trial medication in the second 3 weeks of the treatment period. These two patients were analyzed according to their intended treatment allocation. Note that as there were so few important protocol deviations, analysis on the PPS was not performed.

Patient Disposition

A total of 99 patients were randomized, of these 96 were included in the FAS. Ninety-three (93), 92, 91, and 90 in the Olo 5mcg, Olo 10mcg, and formoterol periods, respectively were included in the six week efficacy analysis. These numbers excluded those from the FAS who had missing non-imputable data. Eighty-nine (89) patients completed all 4 treatment periods. For individual treatment periods, 94, 92, 91, and 90 patients completed the placebo, Olo 5mcg, Olo 10mcg, and formoterol periods. Dropout during each treatment period was similar and ranged from 1-3%. The most common reason for discontinuation was AEs.

Demographics

The patients in this trial were predominantly white (93.9%) males (52.5%) with an average age of 61.8 years. The average smoking pack year history was 54.9 years and most were current smokers (60.6%). Average duration of COPD diagnosis was 7.4 years. Baseline FEV1 % predicted was 44.9% with an FEV1/FVC ratio of 49.6. Average

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post-bronchodilator change was 15%. Most patients were GOLD II (51.5%) or GOLD III (39.4%).

Reviewer comments:

The protocol violations and patient discontinuations were low and did not likely affect interpretation. Patient demographics were fairly typical of a COPD trial.

Compliance

Based on patient diaries, overall treatment compliance was high at 99.7%.

Efficacy

Co-primary endpoints

For the co-primary endpoints of FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment, Olo 10mcg demonstrated a statistically significant difference from placebo. The same was true for Olo 5mcg. The formoterol group also demonstrated a statistically significant difference from placebo. The results are summarized in Table 122.

Table 122. Trial 1222.24. Co-primary endpoints. FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment

| Treatment Group | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (12-24 hours) Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|------------------------------------|------------------------|---------|-------------------------------------|------------------------|---------|
| Placebo | -0.060 (0.020) | | | -0.123 (0.021) | | |
| Olodaterol 5 mcg | 0.088 (0.021) | 0.148 (0.018) | <0.0001 | -0.014 (0.022) | 0.109 (0.019) | <0.0001 |
| Olodaterol 10 mcg | 0.088 (0.021) | 0.148 (0.018) | <0.0001 | 0.004 (0.022) | 0.127 (0.019) | <0.0001 |
| Formoterol | 0.081 (0.021) | 0.141 (0.018) | <0.0001 | 0.049 (0.022) | 0.172 (0.019) | <0.0001 |

source: Trial 1222.24 CSR; table 11.4.1.1:1; pp 67

This data is represented graphically in Figure 25.

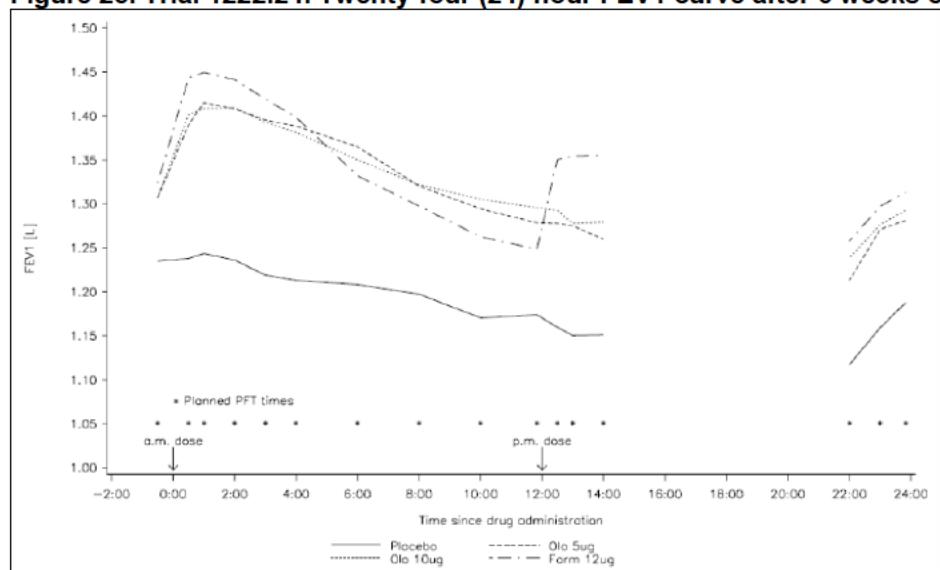
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Figure 25. Trial 1222.24. Twenty-four (24) hour FEV1 curve after 6 weeks of treatment



source: trial 1222.24 CSR; figure 11.4.1:1; pp66

When comparing the co-primary endpoints between olodaterol groups and formoterol, there were no statistically significant differences. For the secondary endpoint of FEV1 AUC (0-24 hours) after 6 weeks of treatment, all groups demonstrated a statistically significant difference from placebo (Olo 5mcg=0.128L, Olo 10mcg=0.137L, and formoterol=0.156L; $p<0.0001$). Additionally, there was no statistically significant difference between olodaterol groups and formoterol.

For the secondary endpoints of FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment, both olodaterol groups demonstrated statistically significant improvement compared to placebo. This is summarized in Table 123.

Table 123. Trial 1222.24. FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|-----------------------------------|------------------------|---------|---------------------------|------------------------|---------|
| Placebo | -0.030 (0.020) | | | -0.093 (0.023) | | |
| Olodaterol 5 mcg | 0.134 (0.021) | 0.164 (0.019) | <0.0001 | 0.012 (0.024) | 0.106 (0.021) | <0.0001 |
| Olodaterol 10 mcg | 0.135 (0.021) | 0.164 (0.019) | <0.0001 | 0.020 (0.024) | 0.113 (0.021) | <0.0001 |
| Formoterol | 0.168 (0.021) | 0.198 (0.019) | <0.0001 | 0.040 (0.024) | 0.133 (0.021) | <0.0001 |

source: Trial 1222.24 CSR; tables 11.4.1.2.3:1 & 11.4.1.2.5:1; pp 70 & 71

Similar results were demonstrated for the other secondary endpoints.

Reviewer comment:

Based on the co-primary endpoints, both doses of olodaterol have a statistically significant treatment effect compared to placebo over the 24 hours. This is further

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supported by the FEV1 AUC (0-24 hours), FEV1 AUC (0-3 hours), and trough FEV1 response data. Note that compared to the 48 week COPD trials, in this trial the FEV1 AUC (0-3 hours) and trough FEV1 response difference from placebo was of greater magnitude.

Safety

Exposure

A total of 99 patients received at least one dose of trial medication. In each treatment period, 92-96 patients received at least one dose. Across treatment periods, mean exposure was approximately 43 days. Approximately 93-99% of patients received 23-43 days of trial medication during each treatment period.

Deaths and SAEs

There was one death in this trial. This occurred 17 days into the patient's Olo 5mcg treatment period (period 2). The patient was 63 years old and had a history of congestive heart failure, hypertension, and COPD (diagnosed for 1 year 8 months). This patient had received placebo in her previous treatment period. She had complaints of shortness of breath and when EMS arrived, she was without spontaneous respirations. In the ER, she had pulseless electrical activity with intermittent asystole. ACLS was initiated, but the patient did not respond. The cause of death was assigned as cardio-pulmonary arrest.

There were a total of 9 patients with SAEs. COPD exacerbation occurred in 3 patients (during Olo 5mcg, formoterol, and placebo periods) and myocardial infarction in 2 patients (during Olo 10mcg and formoterol periods). Otherwise, SAEs were isolated. All patients recovered, except the patient that died.

Five patients discontinued due to AEs. During the Olo 5mcg period, the 3 discontinuations were due to cardio-pulmonary arrest (fatal), lower limb fracture, and nausea. During the placebo the discontinuation was due to a cerebrovascular accident. During the formoterol period, the discontinuation was due to myocardial infarction.

Common Adverse Events

Adverse events occurring at a frequency of $\geq 2\%$ are summarized in Table 124. No dose responses were seen based on SOC or PT.

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Table 124. Trial 1222.24. Common TEAEs ($\geq 2\%$)

| System Organ Class/ Preferred Term | Placebo N (%) | Olodaterol 5 µg qd N (%) | Olodaterol 10 µg qd N (%) | Foradil® 12 µg bid N (%) | Total N (%) |
|---|------------------|--------------------------------|---------------------------------|--------------------------------|----------------|
| Number of patients | 96 (100.0) | 95 (100.0) | 92 (100.0) | 93 (100.0) | 99 (100.0) |
| Total with adverse events | 25 (26.0) | 22 (23.2) | 20 (21.7) | 17 (18.3) | 49 (49.5) |
| Infections and infestations | | | | | |
| Bronchitis | 0 (0.0) | 3 (3.2) | 2 (2.2) | 2 (2.2) | 6 (6.1) |
| Upper respiratory tract infection | 0 (0.0) | 1 (1.1) | 2 (2.2) | 2 (2.2) | 4 (4.0) |
| Urinary tract infection | 1 (1.0) | 0 (0.0) | 2 (2.2) | 0 (0.0) | 2 (2.0) |
| Nasopharyngitis | 1 (1.0) | 0 (0.0) | 1 (1.1) | 0 (0.0) | 2 (2.0) |
| Immune system disorders | | | | | |
| Seasonal allergy | 0 (0.0) | 1 (1.1) | 1 (1.1) | 0 (0.0) | 2 (2.0) |
| Metabolism and nutrition Disorders | | | | | |
| Hyperglycaemia | 1 (1.0) | 0 (0.0) | 1 (1.1) | 0 (0.0) | 2 (2.0) |
| Psychiatric disorders | | | | | |
| Insomnia | 0 (0.0) | 1 (1.1) | 0 (0.0) | 1 (1.1) | 2 (2.0) |
| Nervous system disorders | | | | | |
| Headache | 1 (1.0) | 1 (1.1) | 4 (4.3) | 2 (2.2) | 6 (6.1) |
| Dizziness | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 2 (2.0) |
| Cardiac disorders | | | | | |
| Myocardial infarction | 0 (0.0) | 0 (0.0) | 1 (1.1) | 1 (1.1) | 2 (2.0) |
| Vascular disorders | | | | | |
| Hypertension | 3 (3.1) | 1 (1.1) | 0 (0.0) | 1 (1.1) | 5 (5.1) |
| Respiratory, thoracic and mediastinal disorders | | | | | |
| Chronic obstructive pulmonary disease | 6 (6.3) | 5 (5.3) | 1 (1.1) | 4 (4.3) | 14 (14.1) |
| Cough | 1 (1.0) | 2 (2.1) | 0 (0.0) | 0 (0.0) | 3 (3.0) |
| Respiratory tract congestion | 2 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.0) |
| Gastrointestinal disorders | | | | | |
| Nausea | 2 (2.1) | 1 (1.1) | 0 (0.0) | 0 (0.0) | 3 (3.0) |
| Diarrhoea | 0 (0.0) | 0 (0.0) | 2 (2.2) | 0 (0.0) | 2 (2.0) |

source: Trial 1222.24 CSR; table 12.2.2.2:1; pp79

Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well tolerated. The SAEs and AEs noted were typical of a COPD trial. With regard to the single death, it is difficult to attribute causality to olodaterol due to the patient's presentation and medical history.

5.3.15 Trial 1222.25 (COPD 6 Week Treatment Period Trial)

Administrative Information

- Study title:** Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to determine the 24-hour FEV1-time profiles of orally inhaled olodaterol (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]), administered once daily with the Respimat Inhaler, and orally inhaled formoterol (12 mcg), administered twice daily Inhaler, after 6 weeks of treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)
- Study dates:** 7/09/2009-4/28/2010
- Study sites:** U.S. (13)
- Study report date:** 4/25/11

Trial Design

This trial was identical to 1222.25 in design. See section 5.3

Results:

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Protocol amendments

There was a single protocol amendment (8/07/2009) increasing the pre-PFT anticholinergic washout from 24 to 48 hours.

Protocol Violations

A total of 6 patients (6%) had an important protocol violation. One patient did not have appropriate washout of a long acting anticholinergic agent. One patient was randomized despite an FEV1/FVC ratio >0.7. One patient was randomized with an upper respiratory tract infection. Two patients had study drug administration outside of the allowed time window. In two patients the randomization order was not followed due to human error. For one of the patient, it made no difference as the patient received the appropriate treatment (placebo Respimat), despite the error. In the other patient, the patient received formoterol placebo, rather than formoterol active. These two patients were analyzed according to their intended treatment allocation. Note that as there were so few important protocol deviations, analysis on the PPS was not performed.

Patient Disposition

A total of 100 patients were randomized and 97 were included in the FAS. Ninety-one (91), 92, 90, and 90 in the placebo, Olo 5mcg, Olo 10mcg, and formoterol periods, respectively, were included in the six week efficacy analysis. These numbers excluded those from the FAS who had missing non-imputable data. Eighty two (82) completed all 4 treatment periods. For individual treatment periods, 91, 92, 89, and 88 patients completed the placebo, Olo 5mcg, Olo 10mcg, and formoterol periods, respectively. Drop-out was lowest during the Olo 5mcg (1%) treatment period. Drop-out during the placebo period was 3.2%. For Olo 10mcg and formoterol, it was 6.3% and 5.4% respectively. The most common reason for discontinuation was AEs. Drop-out rate due to AEs was 3.2% for placebo, Olo 10mcg, and formoterol patients. For Olo 5mcg, it was 1%.

Demographics

The patients in this trial were predominantly white (91%) males (54%) with an average age of 63.5 years. The average smoking pack year history was 51.2 years and most were ex-smokers (57%). Average duration of COPD diagnosis was 9.4 years. Baseline FEV1 % predicted was 46% with an FEV1/FVC ratio of 48.7. Average post-bronchodilator change was 18%. Most patients were GOLD II (56%) or GOLD III (39%).

Reviewer comments:

Overall the number of protocol violations was small and not likely to affect interpretation. The drop-out rate was higher for this trial compared to 1222.24, and was not as evenly distributed across groups; however, the rate was still relatively low. Patient demographics were fairly typical of a COPD trial.

Compliance

Based on patient diaries, overall treatment compliance was high at 99.5%.

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Efficacy

Co-primary endpoints

For the co-primary endpoints of FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment, Olo 10mcg demonstrated a statistically significant difference from placebo. The same is true for Olo 5mcg. The formoterol group also demonstrated a statistically significant difference from placebo. The results are summarized in Table 125.

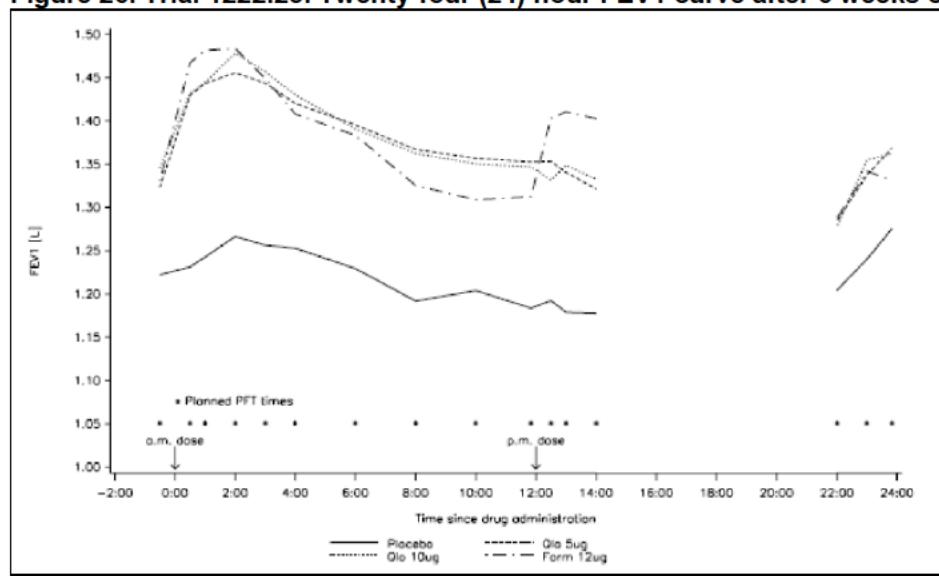
Table 125. Trial 1222.25. Co-primary endpoints. FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment

| Treatment Group | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|---------------------------------------|---------------------------|---------|---------------------------------------|---------------------------|---------|
| Placebo | -0.022 (0.024) | | | -0.048 (0.025) | | |
| Olodaterol 5 mcg | 0.150 (0.024) | 0.172 (0.017) | <0.0001 | 0.069 (0.025) | 0.118(0.018) | <0.0001 |
| Olodaterol 10 mcg | 0.152 (0.024) | 0.174 (0.017) | <0.0001 | 0.072 (0.025) | 0.120 (0.018) | <0.0001 |
| Formoterol | 0.136 (0.024) | 0.158 (0.017) | <0.0001 | 0.107 (0.025) | 0.155 (0.018) | <0.0001 |

source: Trial 1222.25 CSR; table 11.4.1.1:1; pp 65

This data is represented graphically in Figure 26.

Figure 26. Trial 1222.25. Twenty-four (24) hour FEV1 curve after 6 weeks of treatment



source: trial 1222.25 CSR; figure 11.4.1:1; pp64

When comparing the co-primary endpoints between olodaterol groups and formoterol, there were no statistically significant differences, except when comparing Olo 5mcg to formoterol for FEV1 AUC (12-24 hours). The treatment difference was -0.037 (Olo 5mcg-formoterol, p-value=0.04). For the secondary endpoint of FEV1 AUC (0-24 hours)

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after 6 weeks of treatment, all groups demonstrated a statistically significant difference from placebo (Olo 5mcg=0.145L, Olo 10mcg=0.147L, and formoterol=0.156L; p<0.0001). Additionally, there was no statistically significant difference between olodaterol groups and formoterol.

For the secondary endpoints of FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment, both olodaterol groups demonstrated statistically significant improvement compared to placebo. This is summarized in Table 126.

Table 126. Trial 1222.25. FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-------------------|--------------------------------------|---------------------------|---------|------------------------------|---------------------------|---------|
| Placebo | 0.004 (0.024) | | | 0.012 (0.030) | | |
| Olodaterol 5 mcg | 0.190 (0.025) | 0.186 (0.019) | <0.0001 | 0.109 (0.030) | 0.097 (0.026) | <0.0001 |
| Olodaterol 10 mcg | 0.202 (0.025) | 0.198 (0.019) | <0.0001 | 0.115 (0.030) | 0.103 (0.026) | <0.0001 |
| Formoterol | 0.217 (0.025) | 0.213 (0.019) | <0.0001 | 0.093 (0.030) | 0.080 (0.026) | <0.0001 |

source: Trial 1222.25 CSR; tables 11.4.1.2.3:1 & 11.4.1.2.5:1; pp 68 & 69

Similar results were demonstrated for the other secondary endpoints.

Reviewer comment:

Based on the co-primary endpoints, both doses of olodaterol have a statistically significant treatment effect compared to placebo over the 24 hours. This is further supported by the FEV1 AUC (0-24 hours), FEV1 AUC (0-3 hours), and trough FEV1 response data. Note that as with trial 1222.24, compared to the 48 week COPD trials, the FEV1 AUC (0-3 hours) and trough FEV1 response difference from placebo was of greater magnitude. It should also be noted that for FEV1 AUC (12-24 hours), the formoterol difference from placebo was greater than that for both olodaterol doses. This is likely related to the BID dosing of formoterol. However, for the overall 24 hour period, the treatment effect is similar in magnitude.

Safety

Exposure

A total of 100 patients received at least one dose of trial medication. In each treatment period, 93-95 patients received at least one dose. Across treatment periods, mean exposure was approximately 43 days. Approximately 87-89% of patients received 23-43 days of trial medication during each treatment period.

Deaths and SAEs

There was one death in this trial. This occurred 24 days into the patient's Olo 10mcg treatment period (period 2). The patient was 80 years old and had a history of COPD, benign prostatic hyperplasia, memory loss, GERD, and hypokalemia. This patient had received formoterol in his previous treatment period. The patient died in his sleep.

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Following autopsy, the cause of death was assigned as respiratory failure secondary to COPD.

There were a total of 14 patients with SAEs. COPD exacerbation occurred in 4 patients [during Olo 10mcg, formoterol (x2), and placebo periods]. Otherwise, SAEs were isolated.

Nine patient discontinued due to AEs. During the Olo 5mcg period, one patient discontinued due to pneumothorax. During the placebo period, 2 patients discontinued due to COPD and one due to pelvic fracture status-post fall. During the Olo 10mcg period, the 3 discontinuations were due to congestive cardiac failure, COPD and respiratory failure (fatal). During the formoterol period, discontinuations were due to COPD and angioedema.

Common Adverse Events

Adverse events occurring at a frequency of $\geq 2\%$ are summarized in Table 127. No dose responses were seen based on SOC or PT.

Table 127. Trial 1222.25. Common TEAEs ($\geq 2\%$)

| System Organ Class/ Preferred Term | Placebo N (%) | Oladaterol 5 µg qd N (%) | Oladaterol 10µg qd N (%) | Foradil® 12 µg bid N (%) | Total N (%) |
|---------------------------------------|------------------|--------------------------------|--------------------------------|--------------------------------|----------------|
| Number of patients | 94(100.0) | 93(100.0) | 95(100.0) | 93(100.0) | 100(100.0) |
| Total with adverse events | 35(37.2) | 39(41.9) | 44(46.3) | 32(34.4) | 80(80.0) |
| Chronic obstructive pulmonary disease | 6 (6.4) | 5 (5.4) | 8 (8.4) | 4 (4.3) | 21 (21.0) |
| Upper respiratory tract infection | 4 (4.3) | 4 (4.3) | 5 (5.3) | 5 (5.4) | 15 (15.0) |
| Cough | 0 (0.0) | 4 (4.3) | 1 (1.1) | 4 (4.3) | 9 (9.0) |
| Bronchitis | 3 (3.2) | 4 (4.3) | 2 (2.1) | 2 (2.2) | 8 (8.0) |
| Sinusitis | 2 (2.1) | 1 (1.1) | 3 (3.2) | 3 (3.2) | 8 (8.0) |
| Urinary tract infection | 3 (3.2) | 0 (0.0) | 2 (2.1) | 2 (2.2) | 7 (7.0) |
| Muscle spasms | 1 (1.1) | 1 (1.1) | 1 (1.1) | 2 (2.2) | 5 (5.0) |
| Chest pain | 2 (2.1) | 1 (1.1) | 2 (2.1) | 0 (0.0) | 5 (5.0) |
| Hypertension | 0 (0.0) | 2 (2.2) | 0 (0.0) | 2 (2.2) | 4 (4.0) |
| Oedema peripheral | 0 (0.0) | 0 (0.0) | 2 (2.1) | 2 (2.2) | 4 (4.0) |
| Tooth abscess | 0 (0.0) | 3 (3.2) | 0 (0.0) | 0 (0.0) | 3 (3.0) |
| Acute sinusitis | 0 (0.0) | 1 (1.1) | 2 (2.1) | 0 (0.0) | 3 (3.0) |
| Oral candidiasis | 2 (2.1) | 1 (1.1) | 1 (1.1) | 0 (0.0) | 3 (3.0) |
| Pneumonia | 0 (0.0) | 0 (0.0) | 2 (2.1) | 1 (1.1) | 3 (3.0) |
| Dysphonia | 1 (1.1) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 3 (3.0) |
| Epistaxis | 0 (0.0) | 0 (0.0) | 1 (1.1) | 2 (2.2) | 3 (3.0) |
| Diarrhoea | 1 (1.1) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 3 (3.0) |
| Fall | 2 (2.1) | 1 (1.1) | 0 (0.0) | 0 (0.0) | 3 (3.0) |
| Cellulitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.2) | 2 (2.0) |
| Wheezing | 0 (0.0) | 2 (2.2) | 0 (0.0) | 0 (0.0) | 2 (2.0) |
| Arthralgia | 0 (0.0) | 2 (2.2) | 0 (0.0) | 0 (0.0) | 2 (2.0) |
| Chest discomfort | 2 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.0) |

source: Trial 1222.25 CSR; table 12.2.2.2:1; pp78

Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well tolerated. The SAEs and AEs noted were typical of a COPD trial. with regard to the single death, it is difficult to attribute causality to olodaterol due to the patient's presentation and medical history, and that this was the patient's second treatment period.

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5.3.16 Trial 1222.39 (COPD 6 Week Treatment Period Trial)

Administrative Information

- **Study title:** Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to determine the 24-hour FEV1-time profiles of orally inhaled olodaterol (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]), administered once daily with the Respimat Inhaler, and orally inhaled tiotropium (18 mcg), administered once daily Inhaler, after 6 weeks of treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 1/08/2010-1/12/2011
- **Study sites:** Belgium (3), Denmark (3), Germany (3), Hungary (6),
- **Study report date:** 1/11/2012

Trial Design

This trial was similar in design to 1222.24/25 in design. However, rather than using the active comparator formoterol, this trial used tiotropium 18mcg daily. Tiotropium and one of the double dummy placebos was administered via the Handihaler device. Long acting anticholinergics were also washed out prior to a starting trial medication. Additionally, the washout period was 21 days rather than 14 days (as in trials 1222.24/25). During each treatment period, there was also only a visit at beginning of treatment and after 6 weeks of treatment. There was no 3 week visit as in trials 1222.24/25. Also, for the 24 hour post-dose spirometry, spirometry was not performed at hour 14, otherwise time points for spirometry were the same.

Reviewer comment

It is likely that the sponsor increased the washout period compared to trials 1222.24/25 as tiotropium has a longer half life compared to formoterol. As with the previously reviewed cross-over trials, interpretation of safety data will still difficult. Removal of the 14 hour post-dose spirometric measurement leaves a 10 hour gap in the 12-24 post period, potentially making use of these curves in label problematic.

Results:

Protocol amendments

There was a single protocol amendment (12/02/2010) which changed the definition of 'response' for primary and secondary endpoints. Note that this change made it consistent with the definition used in trials 1222.24/25.

Protocol Violations

A total of 6 patients (5.6%) had an important protocol violation. One patient did not have appropriate washout of a short acting beta agonist. One patient received study medication for significantly longer than the planned duration. One patient had primary endpoint data recorded outside of the specified time window. One patient discontinued serevent prior to signing informed consent. Another patient discontinued tiotropium prior to signing consent, and one patient did not have pre and post PFTs performed at visit 1.

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Note that as there were so few important protocol deviations, analysis on the PPS was not performed.

Patient Disposition

A total of 108 patients were randomized and 104 were included in the FAS. Ninety-one (91) patients completed all 4 treatment periods. For individual treatment periods, 98, 98, 98, and 96 patients completed the entire placebo, Olo 5mcg, Olo 10mcg, and tiotropium periods, respectively. The most common reason for discontinuation was AEs. This was highest during the placebo (3%) and tiotropium (3%) treatment periods. Discontinuation due to AEs was 1% for both olodaterol dose treatment periods.

Demographics

The patients in this trial were predominantly white (100%) males (76.9%) with an average age of 61.7 years. The average smoking pack year history was 41.5 years and most were ex-smokers (57.4%). Average duration of COPD diagnosis was 9.4 years. Baseline FEV1 % predicted was 50.4% with an FEV1/FVC ratio of 46.5. Average post-bronchodilator change was 18%. Most patients were GOLD II (63.9%) or GOLD III (29.6%).

Reviewer comments:

The protocol amendment was reasonable and makes comparisons to trials 1222.24/25 easier. Overall the number of protocol violations was small and not likely to affect interpretation. The drop-out rate was evenly distributed across groups. Patient demographics were fairly typical of a COPD trial.

It should be noted that all efficacy analysis was performed in the FAS population where appropriate endpoint data was available. For different endpoints, due to imputation rules, the numbers analyzed in each treatment period may have slightly differed. However, the numbers of patients with missing or non-imputable data was small and similar across treatment periods in individual endpoints.

Compliance

Based on patient diaries, mean treatment compliance across treatment periods ranged from 99.3-99.7%.

Efficacy

Co-primary endpoints

For the co-primary endpoints of FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment, Olo 10mcg demonstrated a statistically significant difference from placebo. The same is true for Olo 5mcg. The tiotropium group also demonstrated a statistically significant difference from placebo. The results are summarized in Table 128.

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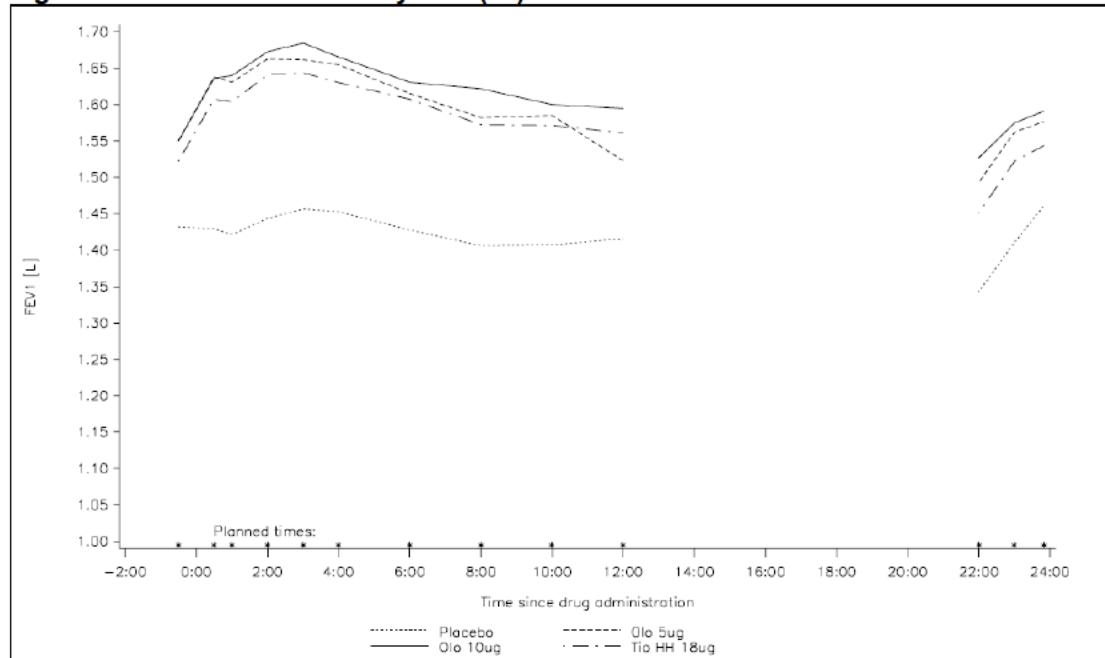
Table 128. Trial 1222.39. Co-primary endpoints. FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment

| Treatment Group | N | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|-----|---------------------------------------|------------------------|---------|---------------------------------------|------------------------|---------|
| Placebo | 99 | -0.054 (0.020) | | | -0.095 (0.021) | | |
| Olo 5 mcg | 100 | 0.131 (0.020) | 0.185 (0.020) | <0.0001 | 0.036 (0.021) | 0.131 (0.021) | <0.0001 |
| Olo 10 mcg | 99 | 0.152 (0.020) | 0.207 (0.020) | <0.0001 | 0.082 (0.021) | 0.178 (0.021) | <0.0001 |
| Tiotropium | 99 | 0.119 (0.020) | 0.173 (0.020) | <0.0001 | 0.027 (0.021) | 0.123 (0.021) | <0.0001 |

source: Trial 1222.39 CSR; table 11.4.1.1:1; pp 67

This data is represented graphically in Figure 27.

Figure 27. Trial 1222.39. Twenty-four (24) hour FEV1 curve after 6 weeks of treatment



source: trial 1222.39 CSR; figure 15.2.1.2:1; pp 149

Sensitivity analysis using only observed cases (no imputation also had similar results) demonstrated similar results. For the secondary endpoint of FEV1 AUC (0-24 hours) after 6 weeks of treatment, all groups demonstrated a statistically significant difference from placebo (Olo 5mcg=0.158L, Olo 10mcg=0.192L, and formoterol=0.148L; p<0.0001). Additionally, there was no statistically significant difference between olodaterol groups and tiotropium.

For the secondary endpoints of FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment, both olodaterol groups demonstrated statistically significant improvement compared to placebo. This is summarized in Table 129.

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Table 129. Trial 1222.39. FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment

| Treatment Group | N | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|-----|-----------------------------------|------------------------|---------|---------------------------|------------------------|---------|
| Placebo | 99 | -0.45 (0.019) | | | -0.043 (0.02) | | |
| Olo 5 mcg | 100 | 0.161 (0.019) | 0.206 (0.019) | <0.0001 | 0.090 (0.020) | 0.133 (0.019) | <0.0001 |
| Olo 10 mcg | 99 | 0.170 (0.019) | 0.215 (0.018) | <0.0001 | 0.104 (0.02) | 0.147 (0.019) | <0.0001 |
| Formoterol | 99 | 0.137 (0.019) | 0.182 (0.019) | <0.0001 | 0.054 (0.020) | 0.097 (0.019) | <0.0001 |

source: Trial 1222.39 CSR; tables 11.4.1.2.3:2 & 11.4.1.2.4:2; pp 70 & 71

Similar results were demonstrated for the other secondary endpoints.

Reviewer comment:

Based on the co-primary endpoints, both doses of olodaterol have a statistically significant treatment effect compared to placebo over the 24 hours. This is further supported by the FEV1 AUC (0-24 hours), FEV1 AUC (0-3 hours), and trough FEV1 response data. Note that as with trials 1222.24/25, compared to the 48 week COPD trials, the FEV1 AUC (0-3 hours) and trough FEV1 response difference from placebo was of much greater magnitude. This may be related to the prohibition of tiotropium during treatment periods in this trial, in contrast to the 48 week trials. The 24-hour FEV1 profile of both doses of olodaterol is also visually similar to tiotropium.

Safety

Exposure

A total of 108 patients received at least one dose of trial medication. In each treatment period, 101-102 patients received at least one dose trial medication. Across treatment periods, mean exposure was approximately 43 days.

Deaths and SAEs

There were no deaths in this trial. There were a total of 10 patients with SAEs. All SAEs were isolated. All patients recovered, except for one who was diagnosed with lung neoplasm.

Eight patients discontinued due to AEs. During the Olo 5mcg period, one patient discontinued due to COPD. During the placebo period, 2 patients discontinued due to COPD and one due to bronchitis. During the Olo 10mcg period, one patient discontinued due to arthralgia. During the tiotropium period, discontinuations were due to COPD, chills and angina pectoris.

Common Adverse Events

Adverse events occurring at a frequency of $\geq 2\%$ are summarized in Table 130. No dose responses were seen based on SOC or PT.

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Table 130. Trial 1222.39. Common TEAEs ($\geq 2\%$)

| Preferred Term | Placebo N (%) | Olodaterol 5 µg N (%) | Olodaterol 10 µg N (%) | Tiotropium 18 µg N (%) | Total N (%) |
|---------------------------------------|------------------|-----------------------------|------------------------------|------------------------------|----------------|
| Number of patients | 102 (100.0) | 101 (100.0) | 101 (100.0) | 101 (100.0) | 108 (100.0) |
| Total with adverse events | 35 (34.3) | 32 (31.7) | 34 (33.7) | 35 (34.7) | 72 (66.7) |
| Nasopharyngitis | 8 (7.8) | 6 (5.9) | 4 (4.0) | 7 (6.9) | 21 (19.4) |
| Chronic obstructive pulmonary disease | 4 (3.9) | 8 (7.9) | 2 (2.0) | 4 (4.0) | 15 (13.9) |
| Dyspnoea | 2 (2.0) | 1 (1.0) | 2 (2.0) | 2 (2.0) | 7 (6.5) |
| Cough | 2 (2.0) | 0 | 3 (3.0) | 1 (1.0) | 6 (5.6) |
| Back pain | 1 (1.0) | 2 (2.0) | 0 | 1 (1.0) | 4 (3.7) |
| Headache | 2 (2.0) | 3 (3.0) | 1 (1.0) | 2 (2.0) | 4 (3.7) |
| Epistaxis | 2 (2.0) | 0 | 1 (1.0) | 2 (2.0) | 3 (2.8) |
| Gastrointestinal disorder | 0 | 2 (2.0) | 1 (1.0) | 0 | 3 (2.8) |
| Hypertension | 1 (1.0) | 1 (1.0) | 2 (2.0) | 0 | 3 (2.8) |
| Pharyngitis | 1 (1.0) | 0 | 2 (2.0) | 1 (1.0) | 3 (2.8) |
| Sputum increased | 1 (1.0) | 1 (1.0) | 2 (2.0) | 0 | 3 (2.8) |
| Syncope | 1 (1.0) | 0 | 1 (1.0) | 1 (1.0) | 3 (2.8) |
| Upper respiratory tract infection | 0 | 2 (2.0) | 0 | 1 (1.0) | 3 (2.8) |
| Vomiting | 0 | 0 | 1 (1.0) | 2 (2.0) | 3 (2.8) |

source: Trial 1222.39 CSR; table 12.2.2.2:1; pp80

Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well tolerated. The SAEs were all isolated and the AEs noted were typical of a COPD trial.

5.3.17 Trial 1222.40 (COPD 6 Week Treatment Period Trial)

Administrative Information

- Study title:** Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to determine the 24-hour FEV1-time profiles of orally inhaled olodaterol (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]), administered once daily with the Respimat Inhaler, and orally inhaled tiotropium (18 mcg), administered once daily Inhaler, after 6 weeks of treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)
- Study dates:** 1/12/2010-1/10/2011
- Study sites:** Netherlands (3), U.S. (3), Norway (3), Germany (3)
- Study report date:** 1/11/2012

Trial Design

This trial was identical in design to 1222.39.

Results:

Protocol amendments

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There was a single protocol amendment (12/02/2010) which changed the definition of 'response' for primary and secondary endpoints. Note that this change made it consistent with the definition used in trials 1222.24/25/39.

Protocol Violations

A total of 12 patients (9.8%) had an important protocol violation. Eight patients received study medication for significantly longer than the planned duration. One patient was unable to comply with medication restrictions prior to randomization, one patient used a prohibited medication (LABA), one patient only received trial medication from the Handihaler during the first treatment period (i.e. none using Respimat device), and one patient signed consent only after stopping Spiriva. Note that as there were so few important protocol deviations (<10%), analysis on the PPS was not performed.

Patient Disposition

A total of 122 patients were randomized and 121 were included in the FAS. Ninety-six (96) patients completed all 4 treatment periods. For individual treatment periods, 103, 106, 104, and 111 patients completed the placebo, Olo 5mcg, Olo 10mcg, and tiotropium periods, respectively. The most common reason for discontinuation was AEs. This was highest during the placebo (5.45%) and Olo 10mcg (6.2%) treatment periods. Discontinuation due to AEs was 0.86% for the Olo 5mcg treatment period and 0.88% for the tiotropium treatment period.

Demographics

The patients in this trial were predominantly white (99.2%) males (61.5%) with an average age of 62.7 years. The average smoking pack year history was 47.4 years and most were current smokers (54.1%). Average duration of COPD diagnosis was 9.3 years. Baseline FEV1 % predicted was 42.5% with an FEV1/FVC ratio of 43.4. Average post-bronchodilator change was 18%. Most patients were GOLD II (51.6%) or GOLD III (39.3%).

Reviewer comments:

The protocol amendment was reasonable and makes comparisons to trials 1222.24/25/39 easier. Overall the number of protocol violations was small and not likely to affect interpretation. The drop-out rate was fairly similar between placebo and olodaterol treatment periods, however, during the tiotropium and Olo 5mcg treatment periods fewer patients discontinued compared to placebo (and Olo 10mcg). This may imply that tiotropium and Olo 5mcg have a treatment effect compared to placebo. However, as Olo 10mcg had a similar discontinuation rate as placebo, this observation may have nothing to do with efficacy. Patient demographics were fairly typical of a COPD trial. However, compared to trial 1222.39, these patients had lower mean FEV1 and more were GOLD III.

As with trial 1222.39, all efficacy analysis was performed in the FAS population where appropriate endpoint data was available. For different endpoints, due to imputation

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rules, the numbers analyzed in each treatment period may have slightly differed. However, the numbers of patients with missing or non-imputable data was small and similar across treatment periods in individual endpoints.

Compliance

Based on patient diaries, mean treatment compliance across treatment periods ranged from 99.5-99.9%.

Efficacy

Co-primary endpoints

For the co-primary endpoints of FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment, Olo 10mcg demonstrated a statistically significant difference from placebo. The same is true for Olo 5mcg. The tiotropium group also demonstrated a statistically significant difference from placebo. The results are summarized in Table 128.

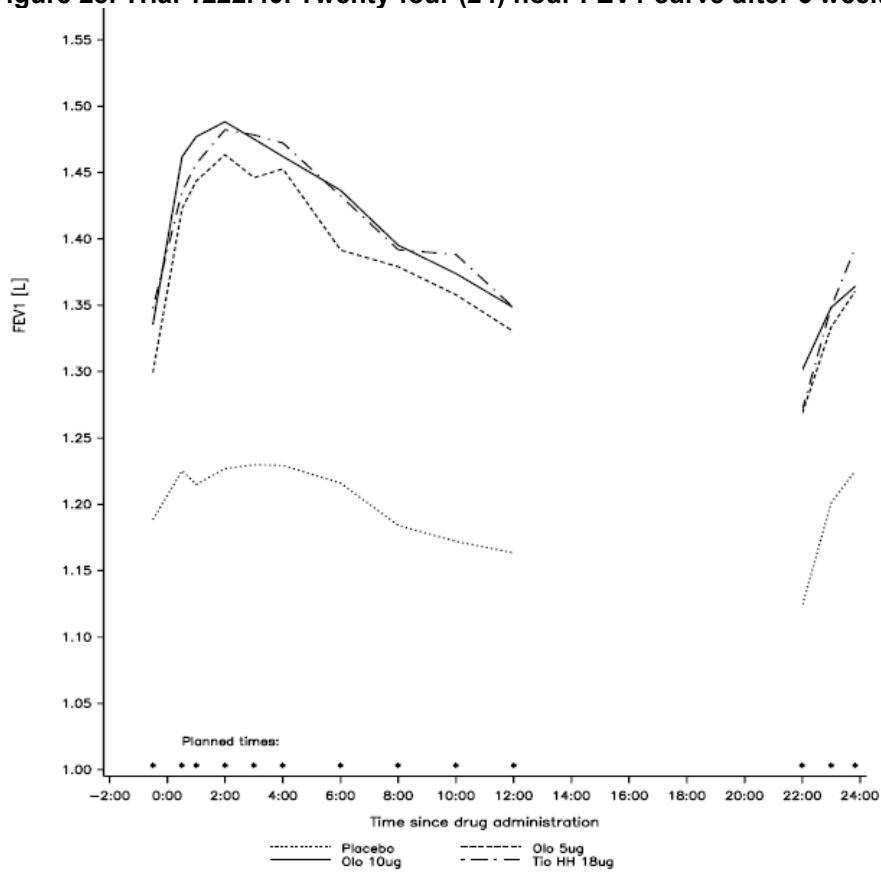
Table 131. Trial 1222.40. Co-primary endpoints. FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response after 6 weeks of treatment

| Treatment Group | N | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|-----|---------------------------------------|------------------------|---------|---------------------------------------|------------------------|---------|
| Placebo | 105 | -0.008 (0.019) | | | -0.059 (0.018) | | |
| Olo 5 mcg | 115 | 0.189 (0.019) | 0.197 (0.017) | <0.0001 | 0.094 (0.018) | 0.153 (0.018) | <0.0001 |
| Olo 10 mcg | 106 | 0.213 (0.019) | 0.221 (0.018) | <0.0001 | 0.111 (0.018) | 0.170 (0.018) | <0.0001 |
| Tiotropium | 112 | 0.213 (0.019) | 0.221 (0.017) | <0.0001 | 0.105 (0.018) | 0.164 (0.018) | <0.0001 |

source: Trial 1222.40 CSR; table 11.4.1.1:1; pp 72

This data is represented graphically in Figure 28.

Figure 28. Trial 1222.40. Twenty-four (24) hour FEV1 curve after 6 weeks of treatment



source: trial 1222.40 CSR; figure 11.4.1:1; pp 71

Sensitivity analysis using only observed cases (no imputation also had similar results). For the secondary endpoint of FEV1 AUC (0-24 hours) after 6 weeks of treatment, all groups demonstrated a statistically significant difference from placebo (Olo 5mcg=0.175L, Olo 10mcg=0.191L, and tiotropium=0.192; p<0.0001). Additionally, there was no statistically significant difference between olodaterol groups and tiotropium.

For the secondary endpoints of FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment, both olodaterol groups demonstrated statistically significant improvement compared to placebo. This is summarized in Table 132.

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Table 132. Trial 1222.40. FEV1 AUC (0-3 hours) response and trough FEV1 response after 6 weeks of treatment

| Treatment Group | N | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|-----|-----------------------------------|------------------------|---------|---------------------------|------------------------|---------|
| Placebo | 105 | 0.011 (0.020) | | | 0.003 (0.019) | | |
| Olo 5 mcg | 115 | 0.225 (0.019) | 0.214 (0.019) | <0.0001 | 0.137 (0.019) | 0.134 (0.019) | <0.0001 |
| Olo 10 mcg | 106 | 0.255 (0.020) | 0.245 (0.019) | <0.0001 | 0.146 (0.019) | 0.143 (0.019) | <0.0001 |
| Formoterol | 112 | 0.246 (0.019) | 0.235 (0.019) | <0.0001 | 0.158 (0.019) | 0.158 (0.019) | <0.0001 |

source: Trial 1222.40 CSR; tables 11.4.1.2.3:2 & 11.4.1.2.5:1; pp 75 and 76

Similar results were demonstrated for the other secondary endpoints.

Reviewer comment:

Based on the co-primary endpoints, both doses of olodaterol have a statistically significant treatment effect compared to placebo over the 24 hours. This is further supported by the FEV1 AUC (0-24 hours), FEV1 AUC (0-3 hours), and trough FEV1 response data. Note that as with trials 1222.24/25/39, compared to the 48 week COPD trials, the FEV1 AUC (0-3 hours) and trough FEV1 response difference from placebo was of greater magnitude. In this trial, this may be partially related to the prohibition of concomitant use tiotropium during non-tiotropium treatment periods, in contrast to the 48 week trials. The 24-hour FEV1 profile of both doses of olodaterol is also visually similar to tiotropium.

Safety

Exposure

A total of 122 patients received at least one dose of trial medication. During treatment each period, 110-116 patients received at least one dose trial medication. Across treatment periods, mean exposure was 42-43 days.

Deaths and SAEs

There were no deaths in this trial. There were a total of 17 patients with SAEs. During the placebo, Olo 5mcg, Olo 10mcg, and tiotropium treatment period, 2, 0, 4, and 1 patient(s), respectively, reported the SAE of COPD exacerbation. Otherwise all SAEs were isolated events.

Sixteen patients discontinued due to AEs. During the Olo 5mcg period, one patient discontinued due to nausea and another due to colon cancer. During the placebo period, discontinuations were due to COPD (x3), renal impairment, anemia, and displaced fracture. During the Olo 10mcg period, discontinuations were due to COPD (x2), neuroendocrine tumor, atrial fibrillation (x2), and increased creatinine. During the tiotropium period, discontinuations were due to COPD, backpain, and rheumatoid arthritis.

Common Adverse Events

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Adverse events occurring at a frequency of $\geq 2\%$ are summarized in Table 133. Dose responses were demonstrated with respect to total AEs, and in the SOC infections and infestations and cardiac disorders. Based on PT, a dose response was seen for atrial fibrillation and cystitis.

Table 133. Trial 1222.40. Common TEAEs ($\geq 2\%$)

| System organ class/ Preferred term | Placebo N(%) | Olodaterol 5ug N(%) | Olodaterol 10ug N(%) | Tiotropium 18ug N(%) | Total N(%) |
|--|-----------------|---------------------------|----------------------------|----------------------------|---------------|
| Number of patients | 109(100.0) | 115(100.0) | 113(100.0) | 113(100.0) | 122(100.0) |
| Total with adverse events | 37(33.9) | 41(35.7) | 44(38.9) | 38(33.6) | 84(68.9) |
| Infections and infestations | 9(8.3) | 18(15.7) | 18(15.9) | 9(8.0) | 42(34.4) |
| Nasopharyngitis | 4(3.7) | 8(7.0) | 4(3.5) | 4(3.5) | 18(14.8) |
| Urinary tract infection | 0(0.0) | 0(0.0) | 4(3.5) | 1(0.9) | 5(4.1) |
| Cystitis | 0(0.0) | 2(1.7) | 3(2.7) | 1(0.9) | 4(3.3) |
| Bronchitis | 0(0.0) | 1(0.9) | 0(0.0) | 2(1.8) | 3(2.5) |
| Respiratory tract infection | 2(1.8) | 1(0.9) | 2(1.8) | 0(0.0) | 3(2.5) |
| Upper respiratory tract infection | 0(0.0) | 2(1.7) | 1(0.9) | 0(0.0) | 3(2.5) |
| Metabolism and nutrition disorders | 2(1.8) | 1(0.9) | 2(1.8) | 2(1.8) | 6(4.9) |
| Diabetes mellitus | 1(0.9) | 1(0.9) | 0(0.0) | 1(0.9) | 3(2.5) |
| Nervous system disorders | 2(1.8) | 2(1.7) | 1(0.9) | 1(0.9) | 6(4.9) |
| Headache | 2(1.8) | 1(0.9) | 1(0.9) | 1(0.9) | 5(4.1) |
| Eye disorders | 1(0.9) | 0(0.0) | 2(1.8) | 3(2.7) | 6(4.9) |
| Cataract | 0(0.0) | 0(0.0) | 0(0.0) | 3(2.7) | 3(2.5) |
| Cardiac disorders | 1(0.9) | 3(2.6) | 6(5.3) | 1(0.9) | 10(8.2) |
| Palpitations | 0(0.0) | 0(0.0) | 3(2.7) | 0(0.0) | 3(2.5) |
| Atrial fibrillation | 0(0.0) | 1(0.9) | 2(1.8) | 0(0.0) | 3(2.5) |
| Vascular disorders | 1(0.9) | 1(0.9) | 2(1.8) | 3(2.7) | 6(4.9) |
| Hypertension | 1(0.9) | 1(0.9) | 0(0.0) | 2(1.8) | 4(3.3) |
| Respiratory, thoracic and mediastinal disorders | 14(12.8) | 14(12.2) | 15(13.3) | 10(8.8) | 39(32.0) |
| Chronic obstructive pulmonary disease | 6(5.5) | 6(5.2) | 7(6.2) | 2(1.8) | 18(14.8) |
| Cough | 4(3.7) | 1(0.9) | 4(3.5) | 4(3.5) | 11(9.0) |
| Dyspnoea | 3(2.8) | 4(3.5) | 3(2.7) | 4(3.5) | 11(9.0) |
| Rhinorrhoea | 2(1.8) | 2(1.7) | 0(0.0) | 0(0.0) | 4(3.3) |
| Gastrointestinal disorders | 8(7.3) | 4(3.5) | 1(0.9) | 4(3.5) | 15(12.3) |
| Nausea | 3(2.8) | 2(1.7) | 1(0.9) | 0(0.0) | 5(4.1) |
| Vomiting | 2(1.8) | 0(0.0) | 0(0.0) | 1(0.9) | 3(2.5) |
| Musculoskeletal and connective tissue disorders | 5(4.6) | 2(1.7) | 1(0.9) | 4(3.5) | 12(9.8) |
| Back pain | 2(1.8) | 0(0.0) | 0(0.0) | 2(1.8) | 4(3.3) |
| General disorders and administration site conditions | 3(2.8) | 6(5.2) | 5(4.4) | 4(3.5) | 16(13.1) |
| Oedema peripheral | 0(0.0) | 1(0.9) | 3(2.7) | 0(0.0) | 3(2.5) |
| Condition aggravated | 0(0.0) | 2(1.7) | 1(0.9) | 0(0.0) | 3(2.5) |

source: Trial 1222.40 CSR; table 12.2.2.2:1; pp86

Reviewer comments

As this was a cross-over trial, it is difficult to interpret safety data. However, overall, olodaterol was fairly well tolerated. The SAEs and AEs noted were typical of a COPD trial. However, the dose response seen in the cardiac disorder SOC is concerning, especially as it appears to be driven by the PT atrial fibrillation. However, given that the total number of atrial fibrillation events is very small (3 patients total) and that this was a cross-over trial, it is difficult to attribute this to olodaterol. It should be noted that atrial fibrillation was not reported in any of the 48 week COPD trials as a common AE. The

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presence of a potential cardiac safety signal was carefully analyzed in the summary of safety (section 7).

6 Review of Efficacy

Efficacy Summary

The proposed indication for the product Olodaterol inhalation solution (Olo) for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The proposed dose is 5mcg (2 actuations of 2.5mcg) once daily inhaled via the Respimat device once daily. In their development program the sponsor explored higher doses of olodaterol, however, no significant benefit to increased dosing was seen. In addition to the proposed indication, the sponsor included label claims for increased exercise tolerance and decreased lung hyperinflation. These claims would be unique to this product class. No other LABAs carry these claims.

Support for efficacy is derived primarily from the four parallel group 48-week COPD trials, two of which were conducted primarily in the United States (US) and two of which were conducted primarily in Europe (EU). These trials shared the same spirometric co-primary endpoints of forced expiratory volume in 1 second (FEV1) AUC (0-3 hours) response and trough FEV1. The two US trials (1222.11 and 1222.12) were 3-arm trials which assessed the co-primary endpoints after 12 weeks of treatment. The two EU trials (1222.13 and 1222.14) were 4-arm trials including the active comparator formoterol and assessed the co-primary endpoints after 24 weeks. Trials 1222.13 and 1222.14 also included a third non-spirometric co-primary endpoint of Mahler Transitional Dyspnea Index (TDI) score assessed at 24 weeks and the key secondary endpoint of the Saint George's Respiratory Questionnaire (SGRQ).

Bronchodilator effects

In three (1222.11, 1222.13, and 1222.14) of the four 48 week COPD trials, olodaterol 5mcg demonstrated significant improvements in both spirometric co-primary endpoints. For trial 1222.12, results were only statistically significant for FEV1 AUC (0-3 hours) response, but not trough FEV1 response when using the protocol-specified analysis. The difference from placebo for FEV1 AUC (0-3 hours) response in trials 1222.11, 1222.12, 1222.13, and 1222.14 were 0.164, 0.134, 0.151, and 0.129L (all p-values <0.0001), respectively. For trough FEV1 response, the differences from placebo were 0.084 (p=0.0002), 0.033 (p>0.05), 0.078 (p=0.0002), and 0.053L (p=0.006), respectively. Based on these results, the effect size was relatively modest with respect to trough FEV1. However, this may have been in part related to concomitant medications, as patients were allowed to continue on all maintenance COPD medications, except for LABAs. In these trials approximately 20-25% of patients were on tiotropium as background therapy. When the sponsor performed a stratified analysis

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based on baseline tiotropium usage, the difference between strata was not statistically significant. In the 6-week trials 1222.39 and 1222.40 in which LAMAs were prohibited as background therapy, the treatment effect of olodaterol 5mcg on trough FEV1 after 6 weeks of treatment was higher at 0.133 and 0.134L, respectively ($p<0.0001$). It should also be noted that in trials 1222.13 and 1222.14 the treatment effect of olodaterol 5mcg was similar to the active comparator fomoterol.

Efficacy was further supported by the spirometric secondary endpoints in these trials. These secondary endpoints included FEV1 AUC (0-3 hours) response at days 1, 43, 85, 169, and 337; and trough FEV1 response at days 15, 43, 85, 169, and 337. At all time points and across all the 48 week trials, olodaterol 5mcg demonstrated a statistically significant improvement compared to placebo. The magnitude of the treatment effect at these time points was similar to that of the co-primary endpoints. It is of note that secondary endpoint analyses were not corrected for multiple comparisons. In distinction to the spirometric endpoints, olodaterol 5mcg had no statistically significant effect on Mahler TDI scores. With regard to SGRQ, while there were statistically significant differences between olodaterol 5mcg and placebo, the differences were consistently less than the minimal clinically important difference (MCID) of 4.

Overall, based on the totality of the data, olodaterol 5mcg appears to have a clinically significant effect on bronchodilation. Although the magnitude of the treatment effect is somewhat modest in the 48-week trials, this may be related to the baseline COPD medications allowed in those trials. Whether or not this modest treatment effect in the setting of other baseline medications is sufficient to warrant a bronchodilator claim for olodaterol will be a topic of discussion at the PADAC meeting. The outcome of the discussion may affect the clinical recommendation.

Effects on exercise tolerance

To support their labeling claims for increased exercise tolerance, increased inspiratory capacity (IC) at rest and at end exercise, and reduced lung hyperinflation based on decreased functional residual capacity (FRC), the sponsor submitted the results from trials 1222.37 and 1222.38. These were 6-week treatment period cross-over trials with a primary endpoint of exercise endurance time (ET) during constant workrate cycle ergometry (CWRCE) at 75% maximal workload after 6 weeks of treatment. Maximal workload was determined using incremental cycle ergometry performed prior to receiving any trial medication. Key secondary endpoints included IC and intensity of breathing discomfort at isotime. Isotime was defined as ET. CWRCE was performed 2 hours after trial medication was administered.

ET after 6 weeks of olodaterol 5mcg was statistically significantly greater than after 6 weeks of placebo. The treatment difference was 12-14% or 40-50 seconds across the two trials [baseline 374-414 seconds (geometric mean)]. ICs were also increased at isotime and at rest (trough and 1 hour post-dose) after receiving olodaterol 5mcg compared to placebo. Statistically significant differences for breathing discomfort as

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measured by the Borg Category Ratio Scale (BCRS) were only reported in trial 1222.37 and not 1222.38. This lack of replication implies that olodaterol does not improve breathing discomfort. For FRC, while it was statistically significantly decreased 1 hour post dose when comparing olodaterol 5mcg to placebo, this was not the case for the trough value. These data imply that the olodaterol 5mcg effect on FRC was not durable over the dosing interval. The clinical significance of the effect of olodaterol 5mcg on exercise tolerance and lung hyperinflation will be a topic for discussion at the PADAC meeting. The outcome of the discussion may affect product labeling.

6.1 COPD

Olodaterol is proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The proposed dose is 5mcg inhaled via the Respimat inhaler once daily.

6.1.1 Methods

Support for efficacy is derived primarily from the four parallel group 48-week COPD trials, two of which were conducted primarily in the United States (US) and two of which were conducted primarily in Europe (EU). These trials shared the same spirometric co-primary endpoints of FEV1 AUC (0-3 hours) response and trough FEV1. The two US trials (1222.11 and 1222.12) were 3 arm trials which assessed the co-primary endpoints after 12 weeks of treatment. The two EU trials (1222.13 and 1222.14) were four arm trials including the active comparator formoterol and assessed the co-primary endpoints after 24 weeks. Trials 1222.13 and 1222.14 also included a third non-spirometric co-primary endpoint of Mahler TDI score assessed at 24 weeks and the key secondary endpoint of SGRQ.

These 4 trials were adequately designed to assess for efficacy. However, the statistical analysis plans for trials 1222.11 and 1222.12 were modified post-database lock/unblinding. As such, the modified analysis was not used to evaluate for efficacy, but rather the protocol pre-specified analysis. The individual 48 week COPD trials are reviewed in depth in section 5.3 Discussion of Individual Studies/Clinical Trials.

To support their label claims for increased exercise tolerance, increased inspiratory capacity (IC) at rest and at end exercise, and reduced lung hyperinflation based on functional residual capacity (FRC), the sponsor submitted the results from trials 1222.37 and 1222.38. These were 6-week treatment period, cross-over trials with a primary endpoint of exercise endurance time (ET) during constant workrate cycle ergometry (CWRCE) at 75% maximal workload after 6 weeks of treatment. Maximal workload was determined using incremental cycle ergometry performed prior to receiving any trial medication. Key secondary endpoints included IC and intensity of breathing discomfort at isotime as measured by Borg Category Ratio Scale (BCRS). Isotime was defined as

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ET. CWRCE was performed 2 hours after trial medication was administered. The individual exercise endurance trials were reviewed in depth in section 5.3 Discussion of Individual Studies/Clinical Trials. Analysis of these trials is also summarized in section 6.1.6 Other Endpoints.

To support the labeling claims regarding 24-hour serial spirometry, the sponsor also submitted four 6 week treatment period cross-over trials in patients with COPD (1222.25, 1222.26, 1222.39, 1222.40). Trials 1222.25 and 1222.26 were replicate trials and included formoterol as an active comparator. Trials 1222.39 and 1222.40 were also replicate trials and included tiotropium as an active comparator. Twenty-four hour serial spirometry was assessed following each 6 week treatment period. The co-primary endpoints were FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 6 weeks of treatment. This is potentially an issue, as it is unclear if the treatment effect at 6 weeks is representative of the effect at 12 and 24 weeks. These trials were individually reviewed briefly in section 5.3 Analysis of these trials is also summarized in section 6.1.6 Other Endpoints.

6.1.2 Demographics

Patient demographics for the 48-week and 6-week treatment period crossover trials are described individually in section Table 134. Demographic information for the pooled 48 weeks trials (1222.11, 1222.12, 1222.13, and 1222.14) is summarized in Table 134. Between trials, the demographic data was similar.

Table 134. Forty-eight (48) week trials. Pooled patient demographics

| | Placebo | Olo 5 mcg | Olo 10 mcg | Formoterol 12 mcg | Total |
|------------------------------|------------|------------|------------|-------------------|-------------|
| Number of patients | 885 | 876 | 883 | 460 | 3104 |
| Gender [N (%)] | | | | | |
| Male | 679 (76.7) | 666 (76.0) | 661 (74.9) | 371 (80.7) | 2377 (76.6) |
| Female | 206 (23.3) | 210 (24.0) | 222 (25.1) | 89 (19.3) | 727 (23.4) |
| Age [years] | | | | | |
| Mean | 64.3 | 64.0 | 64.2 | 64.9 | 64.3 |
| SD | 8.3 | 8.7 | 8.9 | 8.4 | 8.6 |
| Race [N (%)] | | | | | |
| White | 584 (66.0) | 577 (65.9) | 584 (66.1) | 317 (68.9) | 2062 (66.4) |
| Black/African Amer. | 11 (1.2) | 13 (1.5) | 13 (1.5) | 2 (0.4) | 39 (1.3) |
| Asian | 285 (32.2) | 281 (32.1) | 284 (32.2) | 140 (30.4) | 990 (31.9) |
| Amer.Ind./Alaska Nat. | 3 (0.3) | 2 (0.2) | 1 (0.1) | 1 (0.2) | 7 (0.2) |
| Hawaiian/Pacif. Islander | 2 (0.2) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 5 (0.2) |
| Missing | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Smoking history [N (%)] | | | | | |
| Ex smoker | 549 (62.0) | 547 (62.4) | 557 (63.1) | 305 (66.3) | 1958 (63.1) |
| Currently smokers | 336 (38.0) | 329 (37.6) | 326 (36.9) | 155 (33.7) | 1146 (36.9) |
| Smoking history – pack years | | | | | |
| Mean | 45.8 | 46.6 | 46.6 | 45.1 | 46.1 |
| SD | 25.0 | 27.6 | 32.3 | 26.0 | 28.1 |

Source: SCS; table 1.3.1:1; pg 33

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In the 6 week treatment period crossover trials the patient populations were ≥90% white. Otherwise, the demographic data were generally similar to the 48-week trials.

6.1.3 Subject Disposition

Patient disposition for the 48-week and 6-week treatment period crossover trials are described individually in section 5.3. For the pooled 48-week trials (1222.11, 1222.12, 1222.13, and 1222.14) a total of 3104 patients were randomized and received at least one dose of trial medication. Of these, 3070 patients were included in the full analysis set (patients with sufficient data to perform the primary analysis), and 2544 patients completed the entire trial. Patient disposition is summarized in Table 135.

Table 135. Forty-eight (48) week trials. Pooled patient disposition

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total N(%) |
|-----------------------------|-----------------|------------------|-------------------|--------------------------|---------------|
| Treated Set | 885 (100) | 876 (100) | 883 (100) | 460 (100) | 3104 (100) |
| Full Analysis Set (FAS) | 873 (98.6) | 865 (98.7) | 877 (99.3) | 455 (98.9) | 3070 (98.9) |
| Per Protocol Set (PPS) | 848 (95.8) | 844 (96.4) | 854 (96.7) | 433 (94.1) | 2979 (96.0) |
| Completed | 686 (77.5) | 744 (84.9) | 737 (83.5) | 377 (82.0) | 2544 (82.0) |
| Prematurely discontinued | 199 (22.5) | 132 (15.1) | 146 (16.5) | 83 (18.0) | 560 (18.0) |
| Adverse event: | 78 (8.8) | 59 (6.7) | 67 (7.6) | 36 (7.8) | 240 (7.7) |
| COPD worsening | 33 (3.7) | 27 (3.1) | 14 (1.6) | 13 (2.8) | 87 (2.8) |
| Other disease worsening | 18 (0.8) | 6 (0.7) | 8 (0.9) | 3 (0.6) | 35 (1.1) |
| Other | 7 (4.3) | 26 (3.0) | 45 (5.1) | 20 (4.4) | 98 (3.2) |
| Lack of Efficacy | 40 (4.5) | 12 (1.4) | 7 (0.8) | 5 (1.1) | 64 (2.1) |
| Noncompliance with protocol | 6 (0.7) | 8 (0.9) | 4 (0.5) | 5 (1.1) | 23 (0.7) |
| Lost to follow-up | 7 (0.8) | 6 (0.7) | 11 (1.3) | 3 (0.7) | 27 (0.9) |
| Consent withdrawn | 50 (5.7) | 30 (3.4) | 38 (4.3) | 27 (5.9) | 145 (4.7) |
| Other | 18 (2.0) | 17 (1.9) | 19 (2.2) | 7 (1.5) | 61 (2.0) |

Source: SCS; table 1.2.4.1:1; pg30

For the pooled 48-week data, the placebo group had more premature discontinuations compared to both olodaterol doses and formoterol. This imbalance was seen across all reasons for discontinuation. However, it was the most marked in the 'lack of efficacy' and 'consent withdrawn' category. For 'consent withdrawn' the most common reasons were related to patient preference and patient relocation/scheduling. The discontinuations due to lack of efficacy appeared to follow an inverse dose response, implying that olodaterol had a clinically significant treatment effect. Discontinuations due to AEs are discussed in section 7.3.3 Dropouts and/or Discontinuations.

Patient disposition for the 6 week treatment period cross-over trials can be found in section 5.3. For the exercise trials (1222.37 and 1222.38), approximately 84-88% of patients completed all 3 periods of the trial.

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6.1.4 Analysis of Primary Endpoint(s)

All four 48-week trials (1222.11, 1222.12, 1222.13, and 1222.14) shared two spirometric co-primary endpoints, which were trough FEV1 response and FEV1 AUC (0-3 hours) response. Trough FEV1 was defined as the mean of the FEV1 obtained at 1 hour and 10 minutes prior to daily trial medication. FEV1 AUC (0-3 hours) was defined as area under the curve from 0 to 3 hours post-dose using the trapezoid rule, divided by the time duration. Response for both parameters was defined as change from baseline. For trials 1222.11 and 1222.12, the co-primary endpoints were assessed after 12 weeks of treatment, whereas in trials 1222.13 and 1222.14 the co-primary endpoints were assessed after 24 weeks of treatment. Both spirometric co-primary endpoints are appropriate and are commonly used in COPD trials. The trough FEV1 is meant to demonstrate persistence of effect throughout the dosing interval and the FEV1 AUC (0-3 hours) is meant to characterize initial effect. The 12 and 24-week time points are also appropriate as per COPD Guidance for Industry. Results for the spirometric co-primary endpoints are summarized in Table 136. Note that for trials 1222.11 and 1222.12, results shown are for the pre-specified analysis, not the post-hoc analysis. Also note that the post-hoc analysis for trials 1222.11 and 1222.12 were the same as the pre-specified analysis for trials 1222.13 and 1222.14. For trial 1222.11 and 1222.12, the results at week 24 were similar to the results at week 12, and vice versa for 1222.13 and 1222.14.

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Table 136. Forty-eight (48) week trials. Trough FEV1 and FEV1 AUC (0-3 hours) response (pre-specified analysis)

| Treatment Group | FEV AUC (0-3 hours) Response (SE) | Diff from placebo (SE) | p-value | Trough FEV1 Response (SE) | Diff from placebo (SE) | p-value |
|-----------------------------|-----------------------------------|------------------------|---------|---------------------------|------------------------|---------|
| 1222.11 | | | | | | |
| After 12 weeks of treatment | | | | | | |
| Placebo | 0.002 (0.016) | | | -0.032 (0.016) | | |
| Olo 5mcg | 0.167 (0.016) | 0.164(0.023) | <0.0001 | 0.052 (0.016) | 0.084(0.023) | 0.0002 |
| Olo 10mcg | 0.157 (0.016) | 0.155(0.022) | <0.0001 | 0.048 (0.015) | 0.080(0.022) | 0.0003 |
| 1222.12 | | | | | | |
| After 12 weeks of treatment | | | | | | |
| Placebo | 0.021 (0.016) | | | 0.005 (0.17) | | |
| Olo 5mcg | 0.155 (0.016) | 0.134 (0.022) | <0.0001 | 0.038 (0.017) | 0.033 (0.024) | 0.1624 |
| Olo 10mcg | 0.151 (0.016) | 0.130 (0.022) | <0.0001 | 0.049 (0.016) | 0.045 (0.023) | 0.0563 |
| 1222.13 | | | | | | |
| After 24 weeks of treatment | | | | | | |
| Placebo | -0.009 (0.016) | | | -0.056 (0.015) | | |
| Olo 5mcg | 0.142 (0.015) | 0.151 (0.021) | <0.0001 | 0.021 (0.015) | 0.078 (0.021) | 0.0002 |
| Olo 10mcg | 0.156 (0.015) | 0.165 (0.021) | <0.0001 | 0.028 (0.015) | 0.085 (0.021) | <0.0001 |
| Formoterol | 0.168 (0.015) | 0.177 (0.021) | <0.0001 | -0.002 (0.015) | 0.054 (0.021) | 0.0088 |
| 1222.14 | | | | | | |
| After 24 weeks of treatment | | | | | | |
| Placebo | -0.013 (0.014) | | | -0.055 (0.014) | | |
| Olo 5mcg | 0.116 (0.014) | 0.129 (0.019) | <0.0001 | -0.003 (0.014) | 0.053 (0.019) | 0.0055 |
| Olo 10mcg | 0.140 (0.014) | 0.154 (0.019) | <0.0001 | 0.014 (0.014) | 0.069 (0.019) | 0.0003 |
| Formoterol | 0.137 (0.014) | 0.150 (0.019) | <0.0001 | -0.13 (0.014) | 0.042 (0.019) | 0.0270 |

Source:

Trial 1222.11 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2:16 and 6.1.1.2:14;pp 527 & 689

Trial 1222.12 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2.16 and 6.1.1.2.14; pp 549 & 711

Trial 1222.13 CSR; tables 11.4.1.1.1:1 and 11.4.1.1.2:1; pp 96 and 98

Trial 1222.14 CSR; tables 11.4.1.1.1:1 and 11.4.1.1.2:1; pp 94 and 96.

For the co-primary endpoint of FEV1 AUC (0-3 hours) response, both olodaterol doses demonstrated statistically significant improvements compared to placebo across all trials. This improvement versus placebo was similar in magnitude to the improvement seen in the formoterol group, and ranged from 129 to 151 mL for the olodaterol 5mcg dose group. For trough FEV1 response, in trials 1222.11, 1222.13, and 1222.14, both olodaterol doses consistently demonstrated a statistically significant difference from placebo, ranging from 53 to 84 mL for the olodaterol 5mcg dose group. In trials 1222.13 and 1222.14, the difference from placebo was greater in magnitude than for the active comparator formoterol. In contrast to the other 3 trials, in trial 1222.12, the difference from placebo for both olodaterol doses was small in magnitude (33-45 mL) and not statistically significant for trough FEV1. Note that in the sponsor's *post-hoc* analysis of trial 1222.12, the treatment effect for both doses was larger and statistically significant for both co-primary endpoints (the treatment effect was also larger in magnitude in the *post-hoc* analysis of trial 1222.11). Although both olodaterol doses demonstrated a treatment effect based on the spirometric co-primary endpoints in 3 of 4 trials, there was little incremental benefit to the 10mcg dose over the 5mcg dose.

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Despite the statistical significance for most of the FEV1 AUC (0-3 hours) and trough FEV1 response data, it should be noted that the treatment effect based on trough FEV1 response was modest. This may be partially due to the fact that trial patients were allowed to continue COPD background therapy, such as LAMAs (i.e. tiotropium) and ICS. Approximately 20-25% of the treated patients were on tiotropium at baseline across the 48-week trials across treatment groups.

Due to potential dilution of effect, the sponsor also performed a stratified analysis based on baseline tiotropium use. In the trial protocols, randomization was stratified based on baseline tiotropium use. This stratified analysis was exploratory in nature and did not correct for multiple comparisons. For the FEV1 AUC (0-3 hours) endpoint, both the tiotropium and non-tiotropium strata demonstrated a statistically significant difference from placebo in all trials. For the trough FEV1 endpoint, in the non-tiotropium strata, all olodaterol groups demonstrated a statistically significant difference from placebo; however the results were mixed for the tiotropium strata. In trial 1222.11, the tiotropium strata for both olodaterol doses did not demonstrate a statistically significant difference from placebo. This was also true for the 10mcg olodaterol dose in trial 1222.13. For both endpoints, in most cases, the difference from placebo was numerically larger in the non-tiotropium strata compared to the tiotropium strata, except for olodaterol 5mcg in trials 1222.13 and 1222.14. These results are summarized in Table 137.

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Table 137. Forty-eight (48) week trials. By strata analysis of co-primary endpoints difference from placebo

| Treatment Group | FEV AUC (0-3 hours) Response | | Trough FEV1 Response | |
|-----------------|------------------------------|-----------------------|---------------------------|------------------------------------|
| | Tiotropium Strata | Non-tiotropium Strata | Tiotropium Strata | Non-tiotropium Strata |
| | Diff from placebo (SE)[L] | | Diff from placebo (SE)[L] | |
| 1222.11 | | | | After 12 weeks of treatment |
| Olo 5mcg | 0.150 (0.040) | 0.179 (0.022) | 0.072 (0.040)* | 0.096 (0.021) |
| Olo 10mcg | 0.113 (0.039) | 0.196 (0.022) | 0.041 (0.039)* | 0.119 (0.021) |
| 1222.12 | | | | After 12 weeks of treatment |
| Olo 5mcg | 0.107 (0.040) | 0.161 (0.019) | 0.011 (0.043) | 0.056 (0.021) |
| Olo 10mcg | 0.107 (0.039) | 0.152 (0.019) | 0.039 (0.042) | 0.050 (0.021) |
| 1222.13 | | | | After 24 weeks of treatment |
| Olo 5mcg | 0.159 (0.041) | 0.148 (0.024) | 0.093 (0.040) | 0.072 (0.024) |
| Olo 10mcg | 0.099 (0.042) | 0.188 (0.024) | 0.042 (0.041)* | 0.099 (0.024) |
| Formoterol | 0.142 (0.042) | 0.189 (0.024) | 0.034 (0.042)* | 0.062 (0.024) |
| 1222.14 | | | | After 24 weeks of treatment |
| Olo 5mcg | 0.152 (0.038) | 0.122 (0.022) | 0.071 (0.038) | 0.047 (0.022) |
| Olo 10mcg | 0.149 (0.038) | 0.155 (0.022) | 0.071 (0.037) | 0.069 (0.022) |
| Formoterol | 0.135 (0.038) | 0.155 (0.155) | 0.035 (0.038)* | 0.045 (0.022) |

*p-values > 0.05 for comparison to placebo. Otherwise p-values were < 0.05

Source:

Trial 1222.11 CSR; Tables 11.4.1.1:2 &11.4.1.1:; pp 87 and 88

Trial 1222.12 CSR; Tables 11.4.1.1:2 &11.4.1.1:4; pp 89 and 90

Trial 1222.13 CSR; Tables 11.4.1.1:2 &11.4.1.2:2; pp 97 and 99

Trial 1222.14 CSR; Tables 11.4.1.1:2 &11.4.1.2:2; pp 95 and 97

While, in general, the treatment effect was larger in the non-tiotropium strata compared to the tiotropium strata, the 95% confidence intervals (not shown) were widely overlapping. In addition, when the FDA statistical reviewer analyzed the by strata treatment effect after 12 weeks of treatment in trials 1222.13 and 1222.14, the results demonstrated a greater benefit in the tiotropium strata compared to the non-tiotropium strata. This was consistent with the 24 week by strata analysis. Given the mixed results, it cannot be definitively concluded that baseline tiotropium use alters olodaterol's treatment effect. These data suggest that olodaterol has a beneficial bronchodilator effect when given either with or without tiotropium, although the observed treatment effect may be larger when not given on a background of tiotropium. Given this, caution is warranted in comparing treatment effects across trials from other COPD development programs in which background medication use was not permitted.

Compared to trials 1222.11 and 1222.12, trials 1222.13 and 1222.14 had an additional co-primary endpoint which was Mahler TDI. Fundamental weaknesses of the Mahler Baseline Dyspnea Index/Transitional Dyspnea Index (TDI), as discussed in the September 6, 2002 PADAC meeting, preclude use of this instrument to support a dyspnea claim in the US. This endpoint was likely included for registration in Europe.

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Per the pre-specified analysis plan, the results from these 2 trials were pooled for analysis. Based on the combined analysis, there was no statistically significant improvement for either olodaterol dose compared to placebo. This was consistent with the results from the individual trials. A responder analysis was also performed (responder defined as a Mahler TDI focal score ≥ 1). In trial 1222.13, there were minimal differences between percent responders when comparing olodaterol groups (Olo 5mcg=59.4%, Olo 10mcg=59.4%) to placebo (55.7%). Results were similar for trial 1222.14 (Olo 5mcg=51.6%, Olo 10mcg=53.6%, placebo=49.3%).

Based on the spirometric co-primary endpoints from the majority of the 48 week trials, both olodaterol doses have a statistically significant bronchodilatory effect compared to placebo. The 10mcg dose demonstrates minimal incremental benefit over the 5mcg dose, and for both doses, the olodaterol treatment effect is modest. While the bronchodilatory effect is a statistically significant, whether the effect is clinically significant is a matter for discussion at the PADAC.

Based on pooled and individual trial analysis of TDI, olodaterol does not improve dyspnea. Note that as olodaterol did not demonstrate a treatment effect based on TDI and because TDI was a co-primary endpoint for trials 1222.13 and 1222.14 using a hierarchical approach to control for Type I error, analysis of all secondary endpoints for trials 1222.13 and 1222.14 are descriptive only.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints

In order to support the proposed indication, the 48 week COPD trials had multiple shared secondary endpoints. However, only trials 1222.13 and 1222.14 had key secondary endpoints. These were as follows:

- Trough FEV1 response after 24 weeks of therapy in olodaterol groups versus formoterol
- FEV1 AUC (0-3 hours) response after 24 weeks of therapy in olodaterol groups versus formoterol.
- Total SGRQ after 24 weeks of therapy in placebo versus olodaterol groups versus formoterol

The applicant is not seeking a claim for superiority or equivalence to formoterol. Results comparing trough FEV1 and FEV1 AUC (0-3 hours) between olodaterol and formoterol will not be discussed (see individual trial reviews, section 5.3). Results comparing total SGRQ data between placebo and olodaterol groups will be discussed as the sponsor proposes a claim that olodaterol 5 mcg significantly improves SGRQ total score as compared to placebo. The SGRQ label claim is relatively novel, as only one US product (indacaterol maleate) for COPD includes information regarding SGRQ in the product

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label. As discussed in the March 8, 2011 PADAC meeting for indacaterol maleate, the MCID for mean change from baseline compared to placebo is -4.

Based on the sponsor analysis, olodaterol 10mcg had a statistically significant improvement in SGRQ score in trials 1222.13 and 1222.14, as well as in the combined analysis. However, the improvement was consistently less than 4, the MCID. For olodaterol 5mcg, a statistically significant improvement was seen in the combined analysis and in trial 1222.13, but not 1222.14. As with the higher olodaterol dose, the improvement seen in SGRQ was also consistently less than 4. Formoterol did not demonstrate a statistically significant improvement in either individual trial, or the combined analysis. These results are summarized in Table 138.

Table 138. SGRQ score after 24 weeks of treatment

| Treatment Group | SGRQ mean score (SE) | Diff from placebo (SE) | 95% CI | p-value |
|-----------------|----------------------|------------------------|------------------|---------|
| 1222.13 | | | | |
| Placebo | 41.068 (1.038) | | | |
| Olo 5mcg | 38.627 (0.995) | -2.442 (1.401) | (-5.190, 0.307) | 0.0816 |
| Olo 10mcg | 37.674 (0.998) | -3.394 (1.400) | (-6.141, -0.648) | 0.0155 |
| Formoterol | 40.116 (0.994) | -0.952 (1.396) | (-3.691, 1.787) | 0.4954 |
| 1222.14 | | | | |
| Placebo | 42.120 (0.995) | | | |
| Olo 5mcg | 38.970 (0.965) | -3.150 (1.349) | (-5.796, -0.503) | 0.0197 |
| Olo 10mcg | 38.597 (0.969) | -3.524 (1.354) | (-6.180, -0.867) | 0.0094 |
| Formoterol | 40.704 (0.984) | -1.416 (1.365) | (-4.093, 1.261) | 0.2995 |
| Combined | | | | |
| Placebo | 41.639 (0.718) | | | |
| Olo 5mcg | 38.794 (0.693) | -2.846 (0.972) | (-4.751, -0.940) | 0.0034 |
| Olo 10mcg | 38.205 (0.695) | -3.434 (0.973) | (-5.343, -1.525) | 0.0004 |
| Formoterol | 40.391 (0.699) | -1.248 (0.976) | (-3.161, 0.665) | 0.2009 |

Source: SCE; table 3.2.2.2:1; pg149

Although statistical significance was demonstrated in some cases, these analyses could only be considered descriptive as no effect was seen for the co-primary endpoint of TDI. Additionally, and more importantly, the MCID was never reached in any of the analyses. As such, the improvements seen in the SGRQ are not considered to be clinically significant.

Other secondary endpoints

The 48-week trials shared multiple secondary spirometric and non-spirometric endpoints. Notable spirometric endpoints included trough FEV1 response, FEV1 AUC (0-3 hours) response, and peak FEV1 0-3 hours after dosing at various time points over the 48-week treatment period. Spirometric endpoints also assessed for onset of action (FEV1 response at 5, 15, 30, 60, 120, and 180 minutes after dosing on day 1). Trials 1222.11 and 1222.12 also included FEV1 AUC (0-12 hours) response in a subset of

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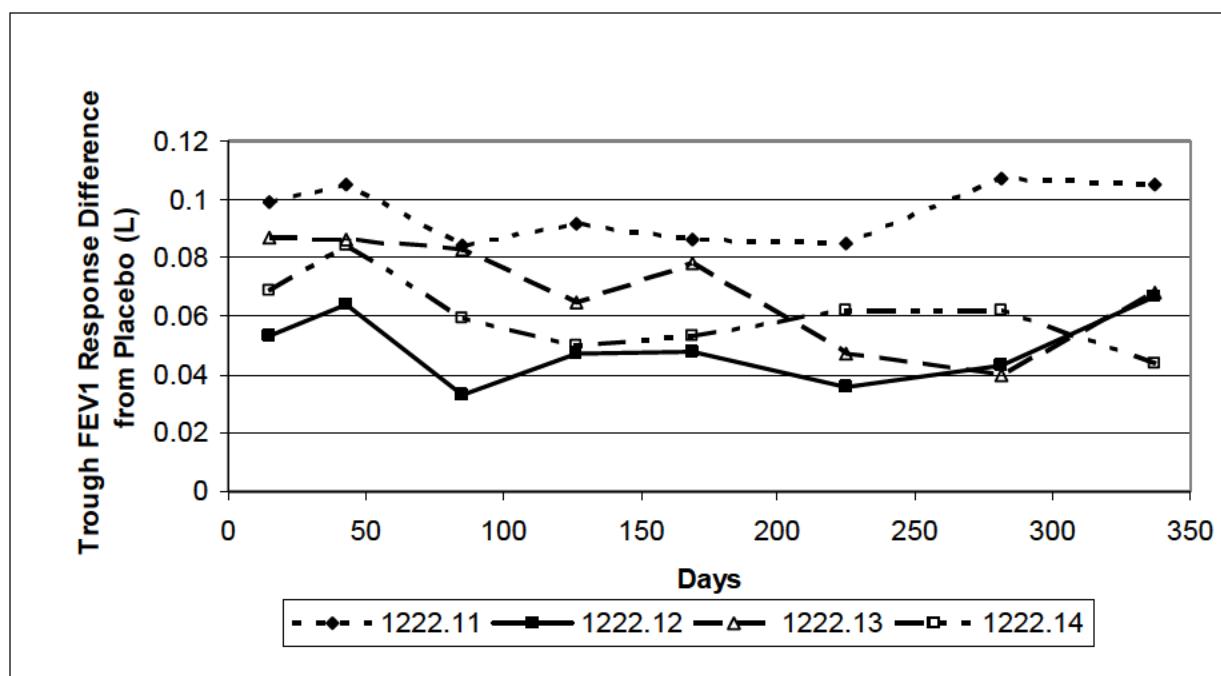
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patients at week 12. There were also corresponding FVC-related endpoints. Other non-spirometric secondary endpoints included rescue medication use and exacerbation-related outcomes. Note that for all secondary endpoint analyses, no corrections were made for type 1 error.

Spirometric secondary endpoints

In order to support maintenance of effect, the sponsor analyzed difference from placebo for both trough FEV₁ response and FEV₁ AUC (0-3 hours) response over the course of the 48-week trials. Both parameters demonstrated some point-to-point variability over the 48-week time course. Both trials 1222.13 and 1222.14 demonstrated a slight downward trend. In trials 1222.11 and 1222.12, the treatment effect appeared more stable. Between weeks 6 (day 43) and 12 (day 85), in 3 out of the 4 trials, the treatment effect consistently decreased for both trough FEV₁ response and FEV₁ AUC (0-3 hours) response, although the treatment effect increased after day 85. The results for the difference from placebo for olodaterol 5mcg for each trial are summarized graphically in Figure 29 for trough FEV₁ response and Figure 30 for FEV₁ AUC (0-3 hours) response. Note that FEV₁ AUC (0-3 hours) assessments were performed less frequently compared to trough FEV₁ assessments.

Figure 29. Trough FEV₁ response difference from placebo for the 5mcg olodaterol dose in each 48 week trial



source:

Trial 1222.11 CSR; appendix 16.1.9.2(module 5.3.5.1.12); table 6.1.1.3.14; pg 689

Trial 1222.12 CSR; appendix 16.1.9.2(module 5.3.5.1.12); table 6.1.1.2.14; pg 711

Trial 1222.13 CSR; table 15.2.1.1.3:1; pg 280

Trial 1222.14 CSR; table 15.2.1.1.3:1; pg 275

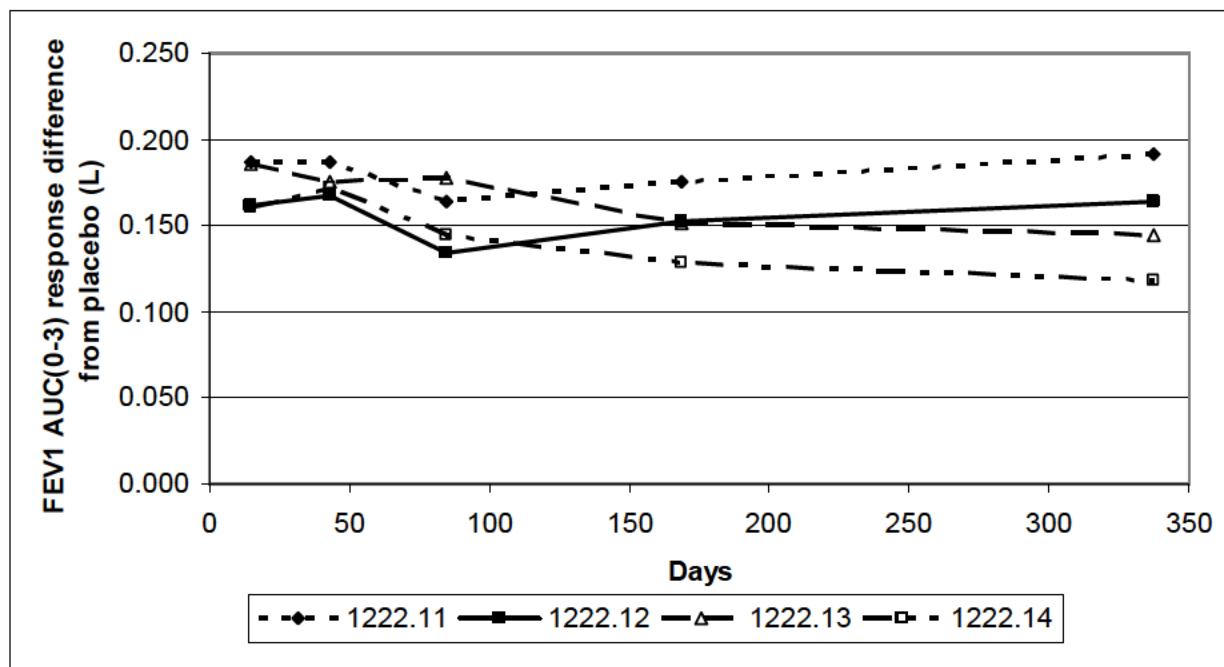
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Figure 30. FEV1 AUC (0-3 hours) response difference from placebo for the 5mcg olodaterol dose in each 48 week trial



source:

Trial 1222.11 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2.16; pg 527

Trial 1222.12 CSR; appendix 16.1.9.2(module 5.3.5.1.12); tables 6.1.1.2.16; pp 549

Trial 1222.13 CSR; table 15.2.1.1.2:1; pg 273

Trial 1222.14 CSR; table 15.2.1.1.2:1; pg 268

Results for the 10mcg dose were generally similar.

In trials 1222.11 and 1222.12, a subset of patients received 12 hour post-dose spirometry after 12 weeks of treatment. For these patients, FEV1 AUC (0-12 hours) response was compared between olodaterol groups and placebo. In both trials, olodaterol 10mcg and olodaterol 5mcg demonstrated statistically significant improvements from placebo (not corrected for multiple comparisons). In trial 1222.11, the difference from placebo in FEV1 AUC (0-12 hours) was 0.173L and 0.169L for olodaterol 10mcg and olodaterol 5mcg, respectively. For trial 1222.12, the differences from placebo were 0.089L and 0.110L, respectively. Results for each time point in the 12-hour post-dose period are summarized graphically in Figure 31 and Figure 32.

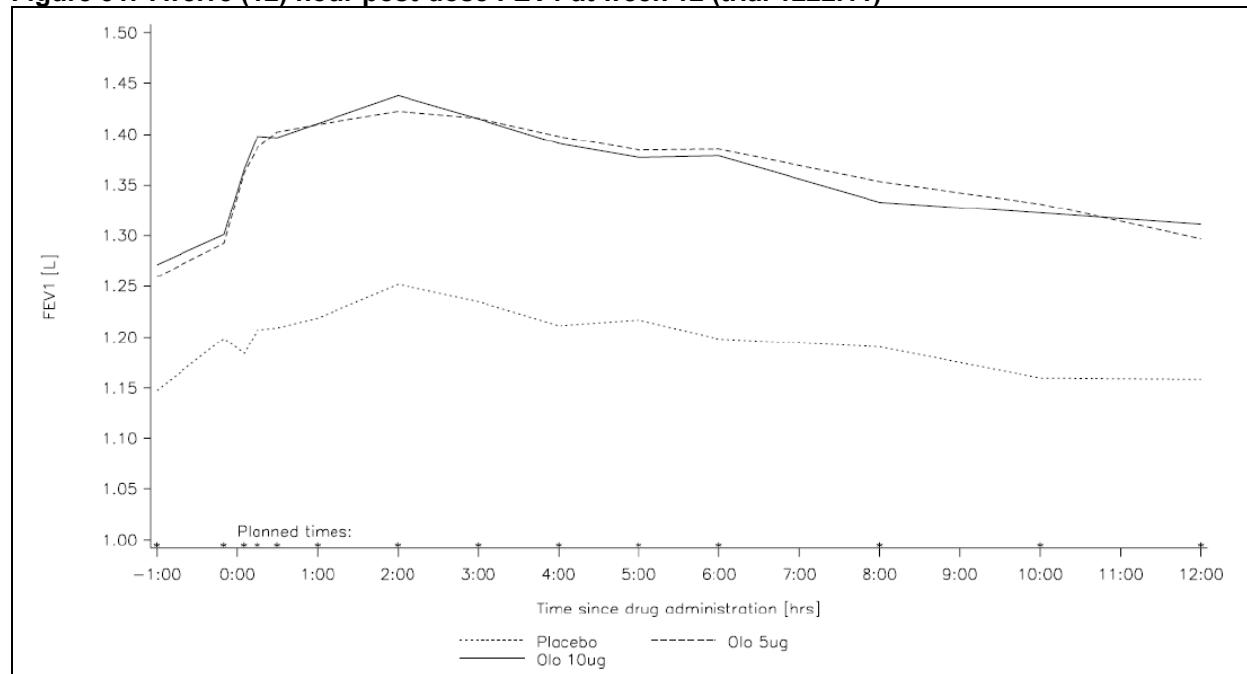
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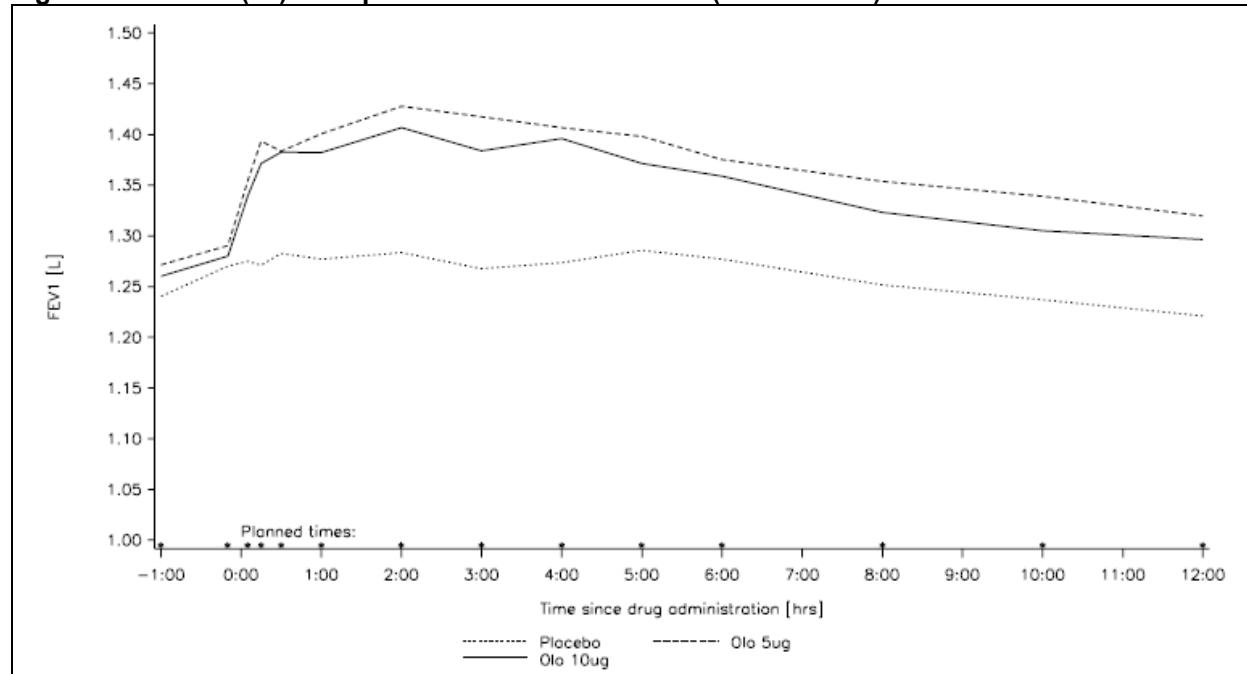
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Figure 31. Twelve (12) hour post-dose FEV1 at week 12 (trial 1222.11)



Source: Trial 1222.11 CSR; figure 11.4.1:2; pg 85

Figure 32. Twelve (12) hour post-dose FEV1 at week 12 (trial 1222.12)



Source: Trial 1222.12 CSR; figure 15.2.1.1:3; pg229

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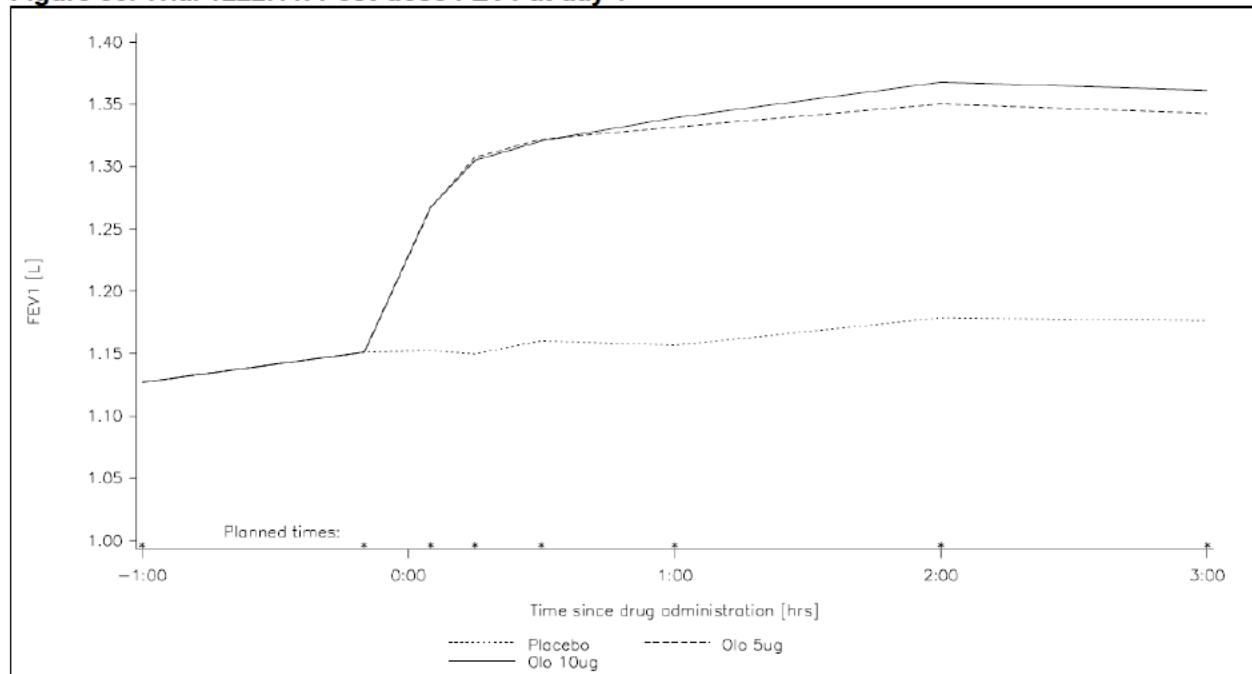
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The treatment effect based on difference from placebo was less in trial 1222.12 compared to 1222.11. This is likely related to the higher FEV1s seen in placebo patients in trial 1222.12 compared to 1222.11.

The sponsor also performed spirometry at day 1 at 5, 15, 30, 60, 120, and 180 minutes post dose. For these timepoints, in all trials, for both olodaterol doses, the FEV1 response difference from placebo was statistically significant. Rapid increases were seen at the 5, 15, and 30 minute timepoints, after which the increases plateaued. Results from trial 1222.11 are shown in Figure 33. This is representative of the results from trials 1222.12, 1222.13, and 1222.14.

Figure 33. Trial 1222.11. Post-dose FEV1 at day 1



Source: Trial 1222.11 CSR; figure 15.2.1.1.1:1; pg212

Improvements in morning PEFR were also seen in all 48-week trials when measured at weeks 1, 12, 24 and 48. For the 5mcg dose, the differences from placebo ranged from 13.3-15.9L/min. For the 10mcg dose, the differences from placebo ranged from 17.6-22.5 L/min (p-values<0.0001 for both doses). Evening PEFR demonstrated similar results.

FVC data was generally consistent with FEV1 and PEFR data (see individual trial reviews in section 5.3).

Non-spirometric endpoints

The sponsor also explored multiple exacerbation-related endpoints. Neither dose of olodaterol demonstrated a statistically significant treatment effect with regard to any

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exacerbation-related endpoints. However, in trials 1222.11 and 1222.14, there was a numerical trend towards increased time to first exacerbation and decreased number of exacerbations.

Rescue medication use was generally lower in the olodaterol groups compared to placebo, both in individual trials and in the combined dataset. In trials 1222.11 and 1222.12, the weekly mean daily rescue medication use was lower in both olodaterol dose groups compared to placebo. In trial 1222.11, at weeks 1, 12, 24, and 48, the difference from placebo ranged from 0.51 to 1.1 puffs per day for olodaterol 5mcg and from 0.56 to 1.5 puffs per day for olodaterol 10mcg. In trial 1222.12, at weeks 1, 12, 24, and 48, the difference from placebo ranged from 0.59 to 0.85 puffs per day for olodaterol 5mcg and from 0.6 to 1.2 puffs per day for olodaterol 10mcg. Similar results were seen for trial 1222.13. However, in trial 1222.14, while the olodaterol 10mcg dose consistently demonstrated statistically significant decreases in rescue medication, the 5mcg dose did not.

Summary of secondary endpoints

Results for the secondary spirometric endpoints are consistent with the spirometric co-primary endpoints. Based on the secondary spirometric endpoints, both doses of olodaterol have a bronchodilator effect. This effect is also maintained in the 12 hour post-dosing interval. In the 48 week COPD trials, there is no data regarding the 12-24 hour time interval. The time to onset is fairly rapid occurring within 5-30 minutes post-dosing and plateauing thereafter. Again consistent with the co-primary endpoints, there appeared to be minimal incremental benefit to the 10mcg dose versus the 5mcg dose. Overall, spirometric secondary endpoints are supportive of the proposed indication. Results for the non-spirometric endpoint of rescue medication use are also supportive of the proposed indication and consistent with what would be expected given the spirometric results.

6.1.6 Other Endpoints

Exercise Endurance Trials (1222.37 and 1222.38)

In addition to the 48 week trials, BI also performed replicate trials (1222.37 and 1222.38) to support the label claim of increased exercise tolerance. This is based on the trials' primary endpoint of endurance time (ET) during constant workrate cycle ergometry (CWRCE) to symptom limitation when performed at 75% maximal work capacity. These trials were also meant to support additional label claims of increased inspiratory capacity at rest and during exercise, and reduced lung hyperinflation based on decreased FRC.

Label claims related to increased exercise tolerance and exercise testing are entirely novel for LABAs indicated to treat COPD. This is in part due to the multiple issues in the interpretation of exercise data in the setting of a clinical trial. These issues include, but are not limited to, the following: 1) multiple non-disease related factors can influence

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exercise tolerance, confounding results; 2) lack of agreed upon MCID for ET; and 3) unknown minimum trial duration required to demonstrate a durable effect on ET. Interpretation of results should keep these limitations in mind.

In the trial designs, the sponsor attempted to minimize variability due to non-disease related factors. This was done by giving test sites guidelines under which the testing was to be performed. Test sites were told to encourage patients to maintain adequate hydration, refrain from eating within 2 hours of testing, and avoid strenuous activity prior to testing. Exercise lab temperature and humidity was also maintained to keep patients comfortable. The exercise equipment was also adjusted to the patients' comfort at baseline testing. These settings were maintained for all subsequent testing. To control for motivational factors, verbal encouragement was performed by a single member of the research team. Encouragement was 'enthusiastic and supportive,' but not 'overbearing, overly loud or coercive.' Visual cues regarding time were also kept away from patients. It is unclear how well the guidelines were adhered to between sites and if they would have indeed controlled for non-disease related variability in testing. The sponsor did not address the lack of MCID nor justify the treatment period duration in their protocols nor application.

Baseline demographic data were generally similar between trials 1222.37/38 and the 48 week COPD trials, except for a larger proportion of Caucasians and males in the exercise trials. Note that LAMAs were prohibited in these trials in distinction to the 48 week trials. It should also be noted that the difference from placebo in 'trough' FEV1 response after at 6 weeks was generally higher in these trials [Olo 5mcg range: 0.089-0.110L; Olo 10mcg range=0.101-0.110L (see Table 108 and Table 117)], compared to the 6 week data in the 48 week trials (Olo 5mcg range=0.064-0.105L, Olo 10mcg range=0.076-0.104L, pre-specified analysis). This is not entirely surprising given the numerical trends seen when comparing the tiotropium strata to non-tiotropium strata from the 48 week COPD trials. These differences should be taken into account when considering the generalizability of the exercise endurance data to the whole COPD population. Note that trough was defined as FEV1 taken at 23:30 post-dose.

Primary endpoint

The primary endpoint for these trials was ET at 75% maximal work load after 6 weeks of treatment. ET was assessed 2 hours after the morning medication dose. After 6 weeks of treatment with olodaterol 5mcg or olodaterol 10mcg, the ET was statistically significantly greater than after 6 weeks of treatment with placebo. The difference was approximately 11-14% (40-50 seconds). These results are summarized in Table 139.

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Table 139. Endurance time after 6 weeks of treatment in trials 1222.37 and 1222.38

| Treatment | Endurance time mean(SE)[seconds] | Ratio to placebo | |
|-----------|-------------------------------------|------------------|---------|
| | | Mean (SE) | p-value |
| 1222.37 | | | |
| Placebo | 369.8 (11.9) | | |
| Olo 5mcg | 421.6 (13.6) | 1.14 (0.04) | 0.0002 |
| Olo 10mcg | 420.7 (13.6) | 1.14 (0.04) | 0.0003 |
| 1222.38 | | | |
| Placebo | 354.3 (12.1) | | |
| Olo 5mcg | 396.3 (13.7) | 1.12 (0.04) | 0.0018 |
| Olo 10mcg | 391.5 (13.6) | 1.11 (0.04) | 0.0050 |

Source:

Trial 1222.37 CSR; table 11.4.1.1:1; pg 71

Trial 1222.38 CSR; table 11.4.1.1:1; pg 71

While there was a statistically significant increase in ET in the treatment arms at both doses, the clinical significance is unclear, as there is no established MCID. However, studies by Puente-Maestu *et al* (2009) and Laviolette *et al* (2008) have attempted to determine an MCID following pulmonary rehabilitation. In the Puente-Maestu *et al* study, COPD patients underwent pulmonary rehabilitation for 8 weeks followed by CWRCE (75% maximal workload based on baseline incremental cycle ergometry). Patients also rated perceived exercise tolerance. Study results demonstrated that for a patient to report perceived exercise tolerance as "slightly better," ET had to improve by 34% (95% CI 29-39%) or 101 seconds (96% CI 86-116s) from baseline. The Laviolette *et al* study demonstrated similar results. In the Laviolette *et al* study, CWRCE was performed at 80% maximal work load and the pulmonary rehabilitation program ranged from 6-12 weeks. This study demonstrated that in order for a patient to have an improvement in SGRQ of ≥ 4 , an improvement in endurance time of 153 seconds (95% CI 93-213s) was required. While these studies have generated MCIDs, it should be noted that they have not been universally accepted or validated. However, the results imply that a 40-50 second increase in ET compared to placebo is modest (or of questionable clinical significance).

Direct cross trial comparisons to literature studies cannot be made, due to differences in design, population, exact testing protocols, etc. However, to provide context for the improvements in ET seen in the olodaterol development program, review of similar studies from the literature is of some utility. Although the literature studies reviewed below used various treatment lengths (3-6 weeks), the results were remarkably consistent. O'Donnell *et al* (2006), Maltais *et al* (2011), and O'Donnell *et al* (2011) studied the effect of fluticasone/salmeterol (250/50mcg), aclidinium (200mcg), and indacaterol (300mcg) on ET, respectively. Improvements in ET compared to placebo following treatment ranged from 111-132 seconds. The O'Donnell *et al* (2006) study also examined the effect of salmeterol, which increased ET by 86 seconds compared to placebo.

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An additional factor to consider is the duration of the trial. Given that COPD is a chronic disease, a sustained effect over time is important. It is unclear if a 6-week treatment period is sufficient to demonstrate durability of effect.

It should also be noted that CWRCE was performed 2 hours after trial medication. It is unclear if the statistically significant effect would have been sustained throughout the duration of the dosing interval.

While there was a statistically significant improvement in ET, it appears to be modest. This is consistent with the modest improvements seen in the trough FEV₁ in the 48 week COPD trials. Whether or not the modest improvement in ET is clinically significant, durable over time, and warrants inclusion in the label, is a topic for discussion at the PADAC meeting.

Key secondary endpoints

The first key secondary endpoint for these trials was IC at isotime after 6 weeks of treatment. Isotime was defined as the ET. Increases in IC would indicate a decrease in dynamic hyperinflation, which is characteristic of COPD. For both doses and in both trials, IC was increased compared to placebo at isotime. These results are summarized in Table 140.

Table 140. IC at isotime for trials 1222.37 and 1222.38

| Treatment | Inspiratory capacity, mean (SE)[L] | Difference from placebo | |
|-----------|------------------------------------|-------------------------|---------|
| | | Mean (SE) | p-value |
| 1222.37 | | | |
| Placebo | 1.917 (0.038) | | |
| Olo 5mcg | 2.099 (0.038) | 0.182 (0.036) | <0.0001 |
| Olo 10mcg | 2.091 (0.038) | 0.174 (0.036) | <0.0001 |
| 1222.38 | | | |
| Placebo | 2.162 (0.039) | | |
| Olo 5mcg | 2.246 (0.039) | 0.084 (0.035) | 0.0155 |
| Olo 10mcg | 2.328 (0.039) | 0.166 (0.034) | <0.0001 |

Source:

Trial 1222.37 CSR; table 11.4.1.2.1:1; pg 73

Trial 1222.38 CSR; table 11.4.1.2.1:1; pg 73

The increased IC at isotime implies that olodaterol may decrease dynamic hyperinflation during exercise. However, as with ET, the clinical significance of an 84-182mL increase in IC is unclear. Additionally, it is unclear if this effect would have been maintained for a longer duration over time or over the entire dosing interval.

The second key secondary endpoint was intensity of breathing discomfort based on the Borg Category Ratio Scale (BCRS) at isotime. The Borg scale is rated 0-10. The definition of the numerical scores is provided in Table 100. During assessments,

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patients were asked to put their finger on the number that best described their discomfort (0=none at all, 10=maximal). This scale was not specifically developed for use in clinical trials and its attributes in the longitudinal interventional setting have not been fully elucidated [FDA Guidance for Industry COPD:Developing Drugs for Treatment (2007)]. At isotime, a statistically significant decrease in breathing intensity was seen in olodaterol groups compared to placebo in trial 1222.37, but not 1222.38. These results are summarized in Table 141.

Table 141. Intensity of breathing discomfort at isotime (BCRS) for trials 1222.37 and 1222.38

| Treatment | BCRS | Difference from placebo | |
|-----------|---------------|-------------------------|---------|
| | | Mean (SE) | p-value |
| 1222.37 | | | |
| Placebo | 5.870 (0.185) | | |
| Olo 5mcg | 5.104 (0.182) | -0.766 (0.223) | 0.0007 |
| Olo 10mcg | 5.235 (0.185) | -0.634 (0.225) | 0.0051 |
| 1222.38 | | | |
| Placebo | 5.585 (0.177) | | |
| Olo 5mcg | 5.250 (0.180) | -0.336 (0.21) | 0.12 |
| Olo 10mcg | 5.520 (0.181) | -0.066 (0.21) | 0.76 |

Source:

Trial 1222.37 CSR; table 15.2.2.3:1; pg172

Trial 1222.38 CSR; table 11.4.1.2.2:1; pg74

The lack of concordance between trials may indicate lack of efficacy with respect to this endpoint, or limitations of the instrument, or both. Regardless of the reason, given the lack of concordance between trials, this endpoint is not supportive of efficacy.

Other secondary endpoints

Other secondary endpoints included FRC, IC, and TLC at trough and 1-hour post-dose after 6 weeks of treatment. FRC and IC were measured, and TLC was derived (FRC + largest IC). Note that statistical analyses for other secondary endpoints were not performed in a hierachal manner nor were p-values corrected for multiplicity.

Decreases in these endpoints would imply decreased air trapping and decreased hyperinflation at rest. For olodaterol 5mcg, there was no statistically significant decrease in trough FRC; however, a statistically significant decrease was seen 1-hour post-dose. Results for the 10mcg dose were similar, except that in one of the two trials (1222.38), the decrease in trough FRC was statistically significant. These results are summarized in Table 142.

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Table 142. FRC 30 minutes pre-dose (trough) and 1 hour post dose after 6 weeks of treatment

| Time point | Treatment | N | FRC (SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| 1222.37 | | | | | |
| Trough | Placebo | 134 | 4.977 (0.062) | | |
| | Olo 5mcg | 139 | 4.855 (0.061) | -0.122 (0.069) | 0.0784 |
| | Olo 10mcg | 134 | 4.862 (0.062) | -0.115 (0.070) | 0.1013 |
| 1:00 | Placebo | 134 | 4.950 (0.064) | | |
| | Olo 5mcg | 139 | 4.740 (0.063) | -0.210 (0.066) | 0.0015 |
| | Olo 10mcg | 134 | 4.577 (0.064) | -0.373 (0.066) | <.0001 |
| 1222.38 | | | | | |
| Trough | Placebo | 147 | 4.842 (0.062) | | |
| | Olo 5mcg | 145 | 4.757 (0.063) | -0.086 (0.053) | 0.1048 |
| | Olo 10mcg | 141 | 4.723 (0.063) | -0.120 (0.053) | 0.0246 |
| 1:00 | Placebo | 147 | 4.770 (0.065) | | |
| | Olo 5mcg | 145 | 4.557 (0.065) | -0.213 (0.053) | <0.0001 |
| | Olo 10mcg | 141 | 4.557 (0.065) | -0.187 (0.054) | 0.0005 |

Source:

Trial 1222.37 CSR; table 15.2.4.1:1; pg 179

Trial 1222.38 CSR; table 15.2.4.1:1; pg 179

The FRC data implies that while olodaterol may transiently decrease resting hyperinflation, this effect is not sustained throughout the 24-hour dosing regimen. As olodaterol is meant to be used as a daily maintenance COPD medication, transient non-durable effects may not be relevant. These results also imply that while olodaterol may increase ET 2 hours after dosing, this effect may not persist over the dosing interval.

For the secondary endpoint of trough IC and 1-hour post-dose IC, for both olodaterol doses, there were statistically significant increases in IC compared to placebo. As compared to the FRC data, the IC data imply that olodaterol may decrease hyperinflation in a durable manner. These results are summarized in Table 143.

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Table 143. IC 30 minutes pre-dose (trough) and 1 hour post dose after 6 weeks of treatment

| Time point | Treatment | N | IC(SE) [L] | Difference from placebo | |
|------------|-----------|-----|---------------|-------------------------|---------|
| | | | | Mean (SE) | p-value |
| 1222.37 | | | | | |
| Trough | Placebo | 135 | 2.170 (0.040) | | |
| | Olo 5mcg | 140 | 2.289 (0.040) | 0.119 (0.034) | 0.0005 |
| | Olo 10mcg | 134 | 2.262 (0.040) | 0.092 (0.034) | 0.0073 |
| 1:00 | Placebo | 135 | 2.221 (0.040) | | |
| | Olo 5mcg | 140 | 2.427 (0.040) | 0.206 (0.035) | <.0001 |
| | Olo 10mcg | 134 | 2.437 (0.040) | 0.216 (0.036) | <.0001 |
| 1222.38 | | | | | |
| Trough | Placebo | 147 | 2.463 (0.041) | | |
| | Olo 5mcg | 146 | 2.613 (0.041) | 0.150 (0.040) | 0.0002 |
| | Olo 10mcg | 142 | 2.618 (0.042) | 0.154 (0.040) | 0.0001 |
| 1:00 | Placebo | 147 | 2.493 (0.040) | | |
| | Olo 5mcg | 146 | 2.725 (0.040) | 0.232 (0.036) | <0.0001 |
| | Olo 10mcg | 142 | 2.696 (0.040) | 0.203 (0.036) | <0.0001 |

Source:

Trial 1222.37 CSR; table 15.2.4.1:3; pg181

Trial 1222.38 CSR; table 15.2.4.1:3; pg181

With regard to trough and 1-hour post-dose TLC, there were no statistically significant differences between olodaterol groups and placebo. This is not surprising as TLC was derived from the sum of FRC and largest IC, rather than directly measured.

Summary of exercise trials

The results of trials 1222.37 and 1222.38 demonstrated that both doses of olodaterol increased ET and IC (at isotime) compared to placebo. Consistent with 48-week COPD trial data, there was no incremental benefit with the higher olodaterol dose. Although statistically significant improvements were seen, the clinical significance of these improvements is unclear. This is due to limitations inherent to the assay itself and the timing of the exercise testing. Limitations of the assay include the fact that multiple non-disease factors can affect results and the lack of agreed upon MCID. It is also unclear if assessing ET after 6 weeks is sufficient to demonstrate durability of effect. Further exercise testing was performed 2 hours after trial drug administration. FRC data implied the olodaterol treatment effect on hyperinflation may not be durable over the duration of the dosing period. As such, while there was some improvement in IC and ET in exercise testing performed 2 hours after dosing, it is unclear if this would have been sustained throughout the dosing period. If improvements in ET are not sustained over the dosing period, or at least through a substantial portion of it, the clinical relevance of improvements in ET and IC are questionable.

24 hour spirometry

Trials 1222.24, 1222.25, 1222.39, and 1222.40 were meant to characterize the treatment effect of olodaterol over the 24 hour dosing interval. The co-primary endpoints

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for these trials were FEV1 AUC (0-12 hours) and FEV AUC (12-24 hours) response following a 6-week treatment period. Trials 1222.24 and 1222.25 included a 2-week washout period between treatment periods and trials 1222.39 and 1222.40 included a 3 week washout period. The difference in washout periods was due to the active comparator. In trials 1222.24 and 1222.25, the active comparator was formoterol and for 1222.39 and 1222.40, the active comparator was tiotropium. Note that in trials 1222.24 and 1222.25, patients were allowed on background COPD therapy including ICS and LAMA. However, in trials 1222.39 and 1222.40, patients were prohibited from taking LAMA due to the active comparator. For both co-primary endpoints in all 4 trials, both olodaterol groups demonstrated statistically significant improvement compared to placebo. These results are summarized in Table 144.

Table 144. Co-primary endpoints trials 1222.24, 1222.25, 1222.39 and 1222.40

| Treatment Group | FEV AUC (0-12 hours) Response (SE) | Diff from placebo (SE) | p-value | FEV AUC (12-24 hours) Response (SE) | Diff from placebo (SE) | p-value |
|-----------------|------------------------------------|------------------------|---------|-------------------------------------|------------------------|---------|
| 1222.24 | | | | | | |
| Placebo | -0.060 (0.020) | | | -0.123 (0.021) | | |
| Olo 5mcg | 0.088 (0.021) | 0.148 (0.018) | <0.0001 | -0.014 (0.022) | 0.109 (0.019) | <0.0001 |
| Olo 10mcg | 0.088 (0.021) | 0.148 (0.018) | <0.0001 | 0.004 (0.022) | 0.127 (0.019) | <0.0001 |
| Formoterol | 0.081 (0.021) | 0.141 (0.018) | <0.0001 | 0.049 (0.022) | 0.172 (0.019) | <0.0001 |
| 1222.25 | | | | | | |
| Placebo | -0.022 (0.024) | | | -0.048 (0.025) | | |
| Olo 5mcg | 0.150 (0.024) | 0.172 (0.017) | <0.0001 | 0.069 (0.025) | 0.118(0.018) | <0.0001 |
| Olo 10mcg | 0.152 (0.024) | 0.174 (0.017) | <0.0001 | 0.072 (0.025) | 0.120 (0.018) | <0.0001 |
| Formoterol | 0.136 (0.024) | 0.158 (0.017) | <0.0001 | 0.107 (0.025) | 0.155 (0.018) | <0.0001 |
| 1222.39 | | | | | | |
| Placebo | -0.054 (0.020) | | | -0.095 (0.021) | | |
| Olo 5mcg | 0.131 (0.020) | 0.185 (0.020) | <0.0001 | 0.036 (0.021) | 0.131 (0.021) | <0.0001 |
| Olo 10mcg | 0.152 (0.020) | 0.207 (0.020) | <0.0001 | 0.082 (0.021) | 0.178 (0.021) | <0.0001 |
| Tiotropium | 0.119 (0.020) | 0.173 (0.020) | <0.0001 | 0.027 (0.021) | 0.123 (0.021) | <0.0001 |
| 1222.40 | | | | | | |
| Placebo | -0.008 (0.019) | | | -0.059 (0.018) | | |
| Olo 5mcg | 0.189 (0.019) | 0.197 (0.017) | <0.0001 | 0.094 (0.018) | 0.153 (0.018) | <0.0001 |
| Olo 10mcg | 0.213 (0.019) | 0.221 (0.018) | <0.0001 | 0.111 (0.018) | 0.170 (0.018) | <0.0001 |
| Tiotropium | 0.213 (0.019) | 0.221 (0.017) | <0.0001 | 0.105 (0.018) | 0.164 (0.018) | <0.0001 |

Source:

Trial 1222.24 CSR; table 11.4.1.1:1; pp 67

Trial 1222.25 CSR; table 11.4.1.1:1; pp 65

Trial 1222.39 CSR; table 11.4.1.1:1; pp 67

Trial 1222.40 CSR; table 11.4.1.1:1; pp 72

Graphical representations of this data can be found in Figure 25, Figure 26, Figure 27, and Figure 28. For both doses for both co-primary endpoints, olodaterol demonstrated statistically significant improvements compared to placebo. For FEV1 AUC (0-12 hours), the treatment effects for both olodaterol doses were on par with the active comparators.

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For the FEV1 AUC (12-24 hours), both olodaterol doses had treatments effects that were generally numerically similar to tiotropium. However, when comparing olodaterol to formoterol, the treatment effect was generally numerically lower. This is not necessarily surprising given that formoterol is dosed BID versus olodaterol qD. It should also be noted that although FEV1 AUC (12-24 hours) were generated, for trials 1222.24 and 1222.25, there were no spirometric measurements from post-dose hours 14-22; and for trials 1222.39 and 1222.40, there were no measurement from post-dose hours 12-22.

Overall data from these trials demonstrate a statistically significant treatment effect over the entire 24-hour dosing interval. However, whether or not this data is applicable to later time points (i.e. 12 and 24 weeks) and appropriate for inclusion in the label is questionable. In the 48-week COPD trials, in the majority of trials, the treatment effect was numerically greater at 6 weeks versus 12 or 24 weeks. As such, the results from these 6 week treatment period cross-over trials may not accurately reflect the 24-hour spirometry at later time points.

6.1.7 Subpopulations

The sponsor performed multiple subgroup analyses using the co-primary endpoints of FEV1 AUC (0-3 hours) and trough FEV1 for trials 1222.11, 1222.12, 1222.13, and 1222.14; and SGRQ for trials 1222.13 and 1222.14. The subgroups were based on demographic and baseline parameters. With regard to baseline demographic parameters, there were no significant differences between subgroups. Notably the spirometric treatment effect in the 48-week COPD trials was similar between U.S.[595 patients (19%)], European [936 patients (30%)], Asian [983 patients (32%)], and 'rest of the world' patients [590 patients (19%)]. There were also no differences based on tiotropium, ICS, LABA, SAMA, or xanthine use, nor differences based on age ≥ 65 years. There were also no statistically significant differences in treatment effect based on baseline respiratory parameters. Although no statistically significant differences were noted, there was a trend for an increased spirometric treatment effect in patients with lesser disease severity, higher baseline FEV1, and those who were reversible following albuterol use ($\geq 12\%$). These trends are not necessarily surprising as olodaterol is a long-acting bronchodilator. For Asian patients and those using xanthines, there was also a trend for a decreased treatment effect.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This NDA proposes to market a single dose strength for olodaterol which is 5mcg once daily. Multiple dose ranging trials in COPD and asthma were performed using daily doses from 2-20mcg with dose regimens from qD to BID. There were 3 COPD dose ranging trials (1222.3, 1222.5, and 1222.26) and 4 asthma dose ranging trials (1222.4, 1222.6, 1222.27 and 1222.29). These were reviewed in section 5.3. Trial 1222.3 demonstrated that a single olodaterol dose from 2-20mcg resulted in statistically significant improvements in FEV1 in COPD patients. Trial 1222.5 demonstrated that

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after 4 weeks of once daily treatment with olodaterol at doses ranging from 2-20mcg, patients with COPD had statistically significant improvements in FEV1. In both trials 1222.3 and 1222.5, the incremental benefit of increasing doses was marginal after 10mcg. Additionally, the largest increase in treatment benefit occurred between the 2 and 5mcg doses. These results implied that the optimum total daily dose was between 5 and 10mcg. Trial 1222.26 was meant to determine optimum dosing regimen comparing once daily (qD) to twice daily (BID). Results from this trial were mixed. When comparing qD and BID for the 10mcg total daily dose, BID dosing appeared to have an increased treatment benefit. However when comparing 2mcg BID to 5mcg qD (the sponsor did not have 2.5 mcg formulation at the time of this trial), the once daily dosing appeared superior. Given this lack of clarity and the need to very clearly delineate dosing for LABAs, FDA recommended further dose ranging in asthmatics.

The asthma dose ranging trials included trials 1222.4, 1222.6, 1222.27, and 1222.29. Trial 1222.4 demonstrated that a single dose of olodaterol at doses ranging from 2-20mcg increased PC₂₀ in a dose-dependent manner. Trial 1222.6 demonstrated that after 4 weeks of once daily treatment with olodaterol at doses ranging from 2-20mcg, asthmatics had numerical improvements in FEV1; statistical significance was only apparent at 20mcg. A clear dose response was also not seen in this trial. Trial 1222.27 demonstrated that following 4 weeks of treatment with doses ranging 2-20mcg once daily, asthmatics had statistically significant improvements in FEV1. In this trial, similar to 1222.4, there was a clear dose response. Also similar to trial 1222.4, the incremental benefit decreased with increasing dose; however, this was not as marked compared to the COPD dose ranging trials. In both trials, the largest incremental benefit was seen between the 2 and 5mcg doses, and was smallest between the 10-20mcg doses. As such, the optimum daily dose, as with the COPD trials appeared to be between 5 and 10mcg daily. Trial 1222.29 was meant to determine the optimum dosing interval in the asthmatic population by comparing the 5mcg and 10mcg total daily dose when given qD versus BID. For both total daily doses, BID dosing appeared to have a small numerical increased treatment benefit compared to qD. However, the difference was modest.

Based on the COPD and asthma dose-ranging trials, the optimum total daily dose for olodaterol was clearly 5-10mcg. However, the optimum dosing interval was not as clear. In the asthma trials, BID dosing appeared superior to qD dosing; and in the COPD trials the results were mixed. However, when examining the totality of the dose regimen trial data (COPD and asthma), the differences between qD and BID dosing were modest. As such, either regimen and either total daily dose was considered reasonable to carry forward into phase 3.

In the 48-week COPD trials, the sponsor studied 5mcg and 10mcg qD. Consistent with the dose ranging trial, there was little incremental benefit to the 10mcg dosing. As such, the proposed dose of 5mcg qD is appropriate.

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6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Overall, for the 48 week treatment period, olodaterol 5mcg remained effective (see Figure 29 and Figure 30). However, there was some evidence that the treatment effect was greatest during the first 6 weeks of treatment, and waned to some degree thereafter.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety information for olodaterol 5mcg comes primarily from the 48-week COPD trials. In the 48-week trials, 876 patients were exposed to olodaterol 5mcg and 883 to olodaterol 10mcg for a total of 1,759 exposed patients. An additional 1594 COPD patients were exposed to olodaterol in shorter-term trials, for a total of 3353 COPD patients exposed for any duration during the olodaterol program. Of these patients, 1014 patients were exposed to olodaterol for ≥48 weeks (≥ 337 days). Five-hundred-twelve (512) asthmatic patients were also exposed to oldodaterol during the development program.

There were a total of 53 on-treatment deaths in the 48-week trials. These were relatively evenly split between treatment groups (placebo=1.5%, Olo 5mcg=1.5%, Olo 10mcg=1.9%, and formoterol=2.2%). Based on adjudicated data, the most frequent cause of death was COPD exacerbation as expected in this patient population.

Serious adverse events (SAEs) were also evenly balanced among treatment groups, with 16.4% of placebo patients, 15.8% of olodaterol 5mcg patients, 16.6% of olodaterol 10mcg patients, and 15.0% of formoterol patients experiencing an SAE in the 48 week trials. As expected in this patient population, the most common serious adverse events (SAE) were COPD exacerbation (5.8%), pneumonia (1.8%), all fractures (0.5%), and atrial fibrillation (0.5%). COPD exacerbations were evenly distributed across treatment groups. However, pneumonias were more common in the high-dose olodaterol (Olo) groups (Olo 5mcg=1.6%, Olo 10mcg=2.5%) compared to placebo (1.5%). The same was true of atrial fibrillation (placebo=0.3%, Olo 5mcg=0.6%, Olo 10mcg=0.6%).

The most common adverse [by preferred terms (PT)] leading to discontinuation were COPD exacerbation (2.2%), dyspnea (0.4%), pneumonia (0.3%), and atrial fibrillation (0.3%). There were not significant imbalances between groups. The most commonly reported treatment emergent adverse events (TEAEs) were COPD exacerbation (28.3%), nasopharyngitis (9.8%), upper respiratory infection (7.5%), dyspnea (3.9%),

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and bronchitis (3.8%). Of these, only nasopharyngitis was more commonly reported in both olodaterol groups compared to placebo. It should also be noted that there was a marked differential discontinuation in the placebo groups compared to olodaterol groups. Approximately 23% of placebo patients discontinued the 48-week trials early compared to 15-16% in the olodaterol groups. The most common reasons for discontinuation were adverse events (AEs) and lack of efficacy.

An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances. The sponsor's MACE analysis was also complemented by a cardiovascular assessment based on Standard MedDRA Queries (SMQs). Only in 2 SMQs were imbalances noted when comparing both olodaterol groups to placebo. Adverse events in the SMQ Cardiac arrhythmias sub- SMQ ventricular tachyarrhythmias occurred in 9 (1%), 17 (1.9%), and 12 (1.4%) in placebo, olodaterol 5mcg and olodaterol 10mcg, respectively. It should be noted that AEs in this SMQ occurred most frequently in the formoterol group [9 (2%)]. AEs in the SMQ Cardiac failure (narrow) occurred in 5 (0.6%), 11 (1.3%), and 7 (0.8%) in placebo, olodaterol 5mcg and olodaterol 10mcg, respectively. The noted imbalances were low in frequency, but consistent with the known potential cardiac effects of LABAs.

An adjudicated analysis of events leading to death, hospitalization, and intubation was also performed in the all COPD patients from the phase 2/3 trials, as well as all the asthma patients from the asthma dose-ranging trials. In the asthma population, there were no asthma-related deaths, hospitalizations, or intubations. There was single respiratory related event (pneumonia), which occurred in a patient who had received olodaterol 10mcg. The analysis of the COPD dataset did not reveal any significant imbalances nor any new safety signals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety information for olodaterol comes primarily from the 48-week COPD trials (1222.11, 1222.12, 1222.13, and 1222.14). Pooled safety data from these trials were reviewed in depth and are presented in this section. Safety data from 6 week treatment period cross-over trials (1222.24, 1222.25, 1222.37, 1222.38, 1222.39, 1222.40) were reviewed, however are not presented in depth in this section, as these trials had short treatment periods (6 weeks), were cross-over in design, and had varying washout periods. Safety data from the asthma dose ranging trials were also reviewed, but are also not presented in depth in this section, as these trials varied in design and length of treatment. However exposure data for the 6 week treatment period cross-over trials and asthma dose ranging trials are summarized in section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations. Safety data

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from these trials were consistent with data from the 48-week COPD trials and did not identify any new safety signals. Individual trial safety information can be found in section 5.3.

7.1.2 Categorization of Adverse Events

Adverse events were defined as any untoward medical occurrence, including the worsening of a pre-existing condition that occurred in conjunction with the use of trial drug. Serious AEs were defined as AEs that resulted in death, were immediately life-threatening, required hospitalization/prolongation of hospitalization, resulted in persistent or significant disability/incapacity, or were congenital birth defects. All verbatim terms reported by the investigator were coded using MedDRA version 14.1 for the Integrated Summary of Safety (ISS). However for adjudicated deaths, the MedDRA terms used in the original study report were used. The sponsor also grouped AEs based on Standardized MedDRA Queries (SMQ)(MedDRA 14.1) and BI defined pharmacovigilance (PV) endpoints.

The BI defined PV endpoints were created by grouping multiple MedDRA PTs by similar concepts, that did not necessarily correspond to SOCs or high level grouping terms (HLGTs). The PTs included in the PV endpoints were reviewed and were reasonable. Definitions are available in the SCS supplement [table 2.9.1, pp1061-1136 and response to clinical IR dated 11/13/2012 (stroke PV)]. PVs specifically referenced in this review include COPD exacerbation, COPD exacerbation (broad), upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), cough, pneumonia, pharyngitis, bronchitis, and stroke.

The COPD exacerbation PV is fairly limited and includes only the PTs COPD, infective exacerbation of COPD, and obstructive airways disease. The PV COPD exacerbation (broad) is much more expansive including PTs that could potentially overlap with COPD exacerbation such as bronchitis, increased bronchial secretions, sputum purulent, etc.. The URTI PV included PTs encompassing infections of the nose, sinuses, tonsils, pharynx, and larynx. The LRTI PV included PTs indicative of infections of lung and included abscesses, pneumonias by organism, pneumonia related terms, and bronchitis by organism. The cough PV was limited and included the PTs allergic cough, cough, productive cough. The pneumonia PV included the same pneumonia related PTs found in the LRTI PV. The bronchitis PV included similar bronchitis related PTs as in the LRTI PV. The stroke PV included an expansive list of PTs associated with thrombotic, embolic, occlusive, and hemorrhagic cerebrovascular events.

MACE analysis was also performed. MACE events were defined as fatal events in the cardiac disorder and vascular disorder SOCs; any events in the SMQ Ischemic heart disease sub-SMQ myocardial infarction (broad) and stroke PV; the PTs sudden death, cardiac death, and sudden cardiac death. Fatal MACE was defined similarly to MACE,

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however, included only fatalities associated with the SMQ Ischemic heart disease sub-SMQ myocardial infarction (broad) and the stroke PV.

Treatment emergent AEs (TEAEs) are the focus of the analysis in the ISS. TEAEs were defined as any AE with an onset occurring following the first dose of study drug until 12 days after last study drug intake. Trials with tiotropium as a comparator used a period of 21 days after last study drug intake. In cross-over trials, where the next treatment period started <12/21 days after the previous treatment period, the window was shortened to the start of the next treatment period. Post-treatment AEs were defined as those occurring >12 days (or >21 days) after the last dose of study drug and up to trial completion date.

Two separate adjudicated analysis of deaths and SAEs were also performed by two separate external adjudication committees; one of deaths and the other of SAEs. All causes of deaths occurring in trials 1222.11, 1222.12, 1222.13, and 1222.14 were reviewed by the mortality adjudication committee (MAC). In addition, a separate adjudication committee identified on treatment (i.e. treatment emergent) deaths, hospitalizations, and intubations (composite endpoint) as respiratory related or not. The events were further sub-classified into 4 categories: 1) asthma-related, 2) COPD-related, 3) pneumonia-related, 4) other respiratory-related events, or 5) non-respiratory. The adjudication committee analyzed the safety data based on categories 1-5 as a whole (total), categories 1-4 as a whole (respiratory related), and categories 1-3 as a whole (key respiratory events). SAEs that involved hospitalization and/or death were identified by BI. Intubations were identified by the adjudication committee.

Studies included in this analysis had treatment durations of >7day and which met the following criteria were included in the analysis:

- All blinded, parallel-arm, randomized, controlled trials that were conducted with olodaterol for the treatment of COPD or asthma
- All randomized, double-blind cross-over trials. Only the first crossover period and the washout period immediately following the first part of the crossover period of the trials were assessed.
- All trials of olodaterol combination products in which olodaterol was included as a monotherapy arm.

Five analysis populations were used in the analysis. These were as follows:

- All-treated safety population I- patients from COPD or asthma trials (active and placebo controlled) who took at least one dose.
- All-treated safety population II- patients from COPD or asthma placebo controlled only trials who took at least one dose.
- All-treated COPD safety population I- patients who took at least one dose in the COPD trials
- All-treated COPD safety population II- patients who took at least one dose in the placebo controlled COPD trials

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- All- treated asthma safety population- patients who took at least one dose in the asthma trials

Note that as the All-treated COPD safety population I and II were only minimally different as almost all trials were placebo controlled. As such, in the discussion of the adjudicated analysis, only the All-treated COPD safety population I will be discussed. Sub-group analysis of these safety populations were also performed based on various parameters including treatment period and reversibility.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For this application, evidence for safety is primarily derived from pooled data from the 48 week COPD trials (1222.11, 1222.12, 1222.13, and 1222.14). Safety data from these trials will be reviewed in depth in this section. Supportive safety data is derived from 6 week treatment period crossover trials (1222.24, 1222.25, 1222.37, 1222.38, 1222.39 and 1222.40) and asthma dose ranging trials. As these trials were of varying lengths with varying exposures, safety data from these trials were not pooled with the 48 week safety data, and are not presented in section 7 Review of Safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall the size of the database was adequate for this application. Including all phases of development, a total of 4,312 patients were exposed to at least one dose of olodaterol monotherapy. Of these, 3353 were COPD patients. Of the COPD patients, 3142 received olodaterol 5 or 10 mcg once daily in Phase 3 parallel group or crossover trials.

A total of 3104 patients were included in the 48-week trials. Of these patients, 1,759 patients were exposed to olodaterol. The extent of exposure for the 48-weeks trials was similar between treatment groups, with the lowest mean exposure time occurring in the placebo group and the highest in the olodaterol 5mcg group. The majority of patients were exposed to study drug between 282-337 days. Exposure by key analysis date demonstrated that generally similar numbers of patients were exposed to study drug for ≥ 85 , ≥ 169 , ≥ 330 , and ≥ 337 days. For each of these time points, exposure was the lowest in the placebo group. Exposure data for the 48 week trials is summarized in Table 145.

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Table 145. Exposure during 48 week trials

| | Placebo | Olo 5mcg | Olo 10mcg | Formoterol | Total |
|--|------------|------------|------------|------------|-------------|
| N (number of patients) | 885 | 876 | 883 | 460 | 3104 |
| Extent of exposure (days) | | | | | |
| Mean | 287.5 | 308.4 | 304.7 | 299.0 | 300.0 |
| SD | 104.0 | 78.4 | 84.8 | 93.1 | 90.6 |
| Min | 1 | 5 | 1 | 1 | 1 |
| Median | 337 | 337 | 337 | 337 | 337 |
| Max | 430 | 386 | 392 | 398 | 430 |
| Extent of exposure [N (%)] | | | | | |
| ≤ 15 days | 35 (4.0) | 6 (0.7) | 15 (1.7) | 11 (2.4) | 67 (2.2) |
| 16 – 43 days | 28 (3.2) | 11 (1.3) | 23 (2.6) | 14 (3.0) | 76 (2.4) |
| 44 – 85 days | 30 (3.4) | 28 (3.2) | 19 (2.2) | 18 (3.9) | 95 (3.1) |
| 86 – 127 days | 30 (3.4) | 23 (2.6) | 14 (1.6) | 5 (1.1) | 72 (2.3) |
| 128 – 169 days | 16 (1.8) | 18 (2.1) | 15 (1.7) | 9 (2.0) | 58 (1.9) |
| 170 – 225 days | 25 (2.8) | 17 (1.9) | 27 (3.1) | 6 (1.3) | 75 (2.4) |
| 226 – 281 days | 22 (2.5) | 16 (1.8) | 16 (1.8) | 12 (2.6) | 66 (2.1) |
| 282 – 337 days | 457 (51.6) | 492 (56.2) | 496 (56.2) | 248 (53.9) | 1693(54.5) |
| ≥ 338 days | 242 (27.3) | 265 (30.3) | 258 (29.2) | 137 (29.8) | 902 (29.1) |
| Extent of exposure based on key analysis dates | | | | | |
| ≥85 days (12 weeks) | 793 (89.6) | 833 (95.1) | 828 (93.8) | 420 (91.3) | 2874 (92.5) |
| ≥169 days (24 weeks) | 748 (84.5) | 792 (90.4) | 798 (90.4) | 403 (87.6) | 2741 (88.3) |
| ≥330 days (47 weeks) | 686 (77.5) | 741 (84.6) | 733 (83.0) | 376 (81.7) | 2536 (81.7) |
| ≥337 days (48 weeks) | 469 (53.0) | 504 (57.5) | 510 (57.8) | 259 (56.3) | 1742 (56.1) |

Source:

SCS; table 1.2.1.1:1; pg 25

SCS supplement; table 1.10; pg 690

For the 6 week treatment period crossover trial exposure data, a total of 737 patients were treated. The extent of exposure per treatment period was similar between groups based on mean exposure in days. Total exposure time to study treatments per patient was 147.4 days. These exposures are summarized in Table 146.

Table 146. Exposure during 6-week treatment period complete cross-over trials

| | Placebo | Olo 5mcg | Olo 10mcg | Tiotropium | Formoterol | Total |
|----------------------------|------------|------------|------------|------------|------------|------------|
| N (number of patients) | 694 | 702 | 691 | 214 | 186 | 737 |
| Extent of exposure [days] | | | | | | |
| Mean | 43.6 | 44.1 | 43.9 | 43.0 | 42.8 | 147.4 |
| SD | 4.6 | 5.5 | 5.1 | 2.6 | 3.1 | 34.8 |
| Min | 1 | 1 | 5 | 13 | 16 | 6 |
| Median | 43 | 43 | 43 | 43 | 43 | 167 |
| Max | 77 | 73 | 69 | 57 | 57 | 198 |
| Extent of exposure [N (%)] | | | | | | |
| 1 day | 1 (0.1) | 2 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 |
| 2 - 22 days | 6 (0.9) | 6 (0.9) | 5 (0.7) | 1 (0.5) | 2 (1.1) | 9 (1.2) |
| 23 – 43 days | 527 (75.9) | 525 (74.8) | 530 (76.7) | 187 (87.4) | 172 (92.5) | 16 (2.2) |
| > 43 days | 160 (23.1) | 169 (24.1) | 156 (22.6) | 26 (12.1) | 12 (6.5) | 712 (96.6) |

Source: SCS supplement; table 1.6; pg 684

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Note the total exposure column represents exposure during the entire trial (i.e. across multiple treatment periods).

As there is a known LABA safety signal in asthma, the sponsor also included an analysis of the pooled asthma dose ranging data in the Summary of Clinical Safety. As the asthma dose ranging trials varied in treatment length and included single dose, multiple dose, parallel group, and cross-over trials, it is difficult to compare exposure data. However, exposure based on mean days is summarized in Table 147.

Table 147. Exposure in asthma dose ranging trials

| | PBO | Olo 2mcg qD | Olo 2.5mcg BID | Olo 5mcg qD | Olo 5mcg BID | Olo 10mcg qD | Olo 20mcg qD | Formoterol | Total |
|-------------------------------|----------------|-------------------|----------------------|-------------------|--------------------|--------------------|--------------------|----------------|----------------|
| Number of patients [N (%)] | 409 (100.0) | 210 (100.0) | 101 (100.0) | 319 (100.0) | 101 (100.0) | 319 (100.0) | 214 (100.0) | 125 (100.0) | 731 (100.0) |
| Extent of exposure [days] | | | | | | | | | |
| Mean | 24.3 | 25.4 | 22.8 | 25.0 | 22.8 | 24.7 | 25.6 | 29.5 | 61.4 |
| SD | 7.7 | 9.9 | 2.6 | 9.2 | 2.0 | 9.0 | 10.2 | 3.1 | 38.2 |
| Min | 1.0 | 1.0 | 5.0 | 1.0 | 17.0 | 1.0 | 1.0 | 15.0 | 1.0 |
| Median | 25.0 | 29.0 | 22.0 | 28.0 | 22.0 | 28.0 | 29.0 | 29.0 | 66.0 |
| Max | 44.0 | 44.0 | 29.0 | 70.0 | 30.0 | 57.0 | 42.0 | 42.0 | 150.0 |

Source: SCS; table 1.2.2:1; pg 28

Note that as with the COPD exposure data from the 6 week treatment period cross over trial, the total exposure column represents exposure during the entire trial (i.e. across multiple treatment periods in cross over trials).

7.2.2 Explorations for Dose Response

The phase 3 trials evaluated two proposed doses of olodaterol. Additionally, the dose ranging trials (see section 5.3) explored multiple doses (2-20mcg total daily dose). This allowed for an assessment of dose related safety. Details of this analysis can be found in section 7.5.1 Dose Dependency for Adverse Events.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Clinical laboratory testing was performed as per tables in the individual trials reviewed in section 5.3. Normal ranges and definitions for potentially clinically significant lab abnormalities were defined as in sponsor's response (submitted 10/14/12) to the FDAs information request sent on 9/28/12. The normal ranges and criteria defining potentially clinically significant values were reasonable.

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7.2.5 Metabolic, Clearance, and Interaction Workup

Specific studies examining drug metabolism, clearance, and potential for interaction were performed by the sponsor. Additionally, in the development program, patients were allowed on background COPD therapy. Subgroup analyses were performed based on background medications.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The pivotal trials incorporated monitoring for toxicities associated with LABAs, evaluating for specific AEs/pharmacovigilance(PV) endpoints/standard MedDRA queries (SMQs), and monitoring laboratory, vital sign, and ECG parameters for adrenergic cardiac and metabolic effects. Details of these analyses are found in 7.3.5 Submission Specific Primary Safety Concerns and under the laboratory and vital sign subheadings.

7.3 Major Safety Results

7.3.1 Deaths

In the 48-week trials, deaths were grouped into 4 categories; on treatment, post-treatment, post-study (within vital status follow-up), and post-study (outside of vital status follow-up). On-treatment was defined as events with onset anytime after the first dose of trial medication until 12 days after the last dose. Post-treatment was defined as events with onset greater than 12 days after last dose until trial completion date (48 weeks). Post-study (within vital status follow up) was defined as event with onset after trial completion, but within the vital status follow-up period (48 weeks+14 days). Post-study (outside of vital status follow-up) was defined as events with an onset after the vital status follow-up period (>48 weeks+14 days). This review will focus on the on-treatment deaths, post-treatment deaths, and post-study deaths (within vital status follow-up). Vital status follow up is important for these trials given the greater number of discontinuations in the placebo group compared to the active treatment groups.

In the 48-week COPD trials, there were a total of 53 on-treatment deaths. The most frequent causes of death were COPD (n=10), acute respiratory failure/respiratory failure (n=8), and pneumonia (n=7), which were generally balanced between the olodaterol groups and placebo [placebo=13 (1.5%), Olo 10mcg=13 (1.5%), and Olo 10mcg=17 (1.9%)]. Based on SOC, infections and infestations and neoplasms both demonstrated an imbalance. For infections and infestations, this was driven by the preferred term pneumonia. However, the overall numbers were very small as were the differences between the placebo [1(0.1%)] and olodaterol groups [Olo 5mcg=2(0.2%), Olo 10mcg=3(0.3%)]. For neoplasms, the imbalance was not driven by a single preferred term (PT); however, most the neoplasms in the olodaterol groups leading to the imbalance were lung-related (i.e. lung adenocarcinoma, small cell lung cancer, lung

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neoplasm malignant, and metastases to lung). However, as with the imbalance in the infections and infestation SOC, the overall numbers for deaths related to neoplasms SOC were small [placebo=0, Olo 5mcg=2 (0.2%), Olo 10mcg=7 (0.8%)].

COPD exacerbation as a cause of death was similar across treatments. Deaths attributed to the cardiac disorder SOC were also relatively balanced between olodaterol groups and placebo, and were highest in the formoterol group. The pooled mortality data for the 48 week trials are summarized in Table 148.

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Table 148. Forty-eight (48) week trials. On treatment deaths (investigator assigned)

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol N(%) | Total N(%) |
|--|-----------------|------------------|-------------------|--------------------|---------------|
| Number of patients | 885 (100) | 876 (100) | 883 (100) | 460 (100) | 3104 (100) |
| Total deaths | 13 (1.5) | 13 (1.5) | 17 (1.9) | 10 (2.2) | 53 (1.7) |
| Infections and infestations | 1 (0.1) | 3 (0.3) | 4 (0.5) | 1 (0.2) | 9 (0.3) |
| Pneumonia | 1 (0.1) | 2 (0.2) | 3 (0.3) | 1 (0.2) | 7 (0.2) |
| Sepsis | 0 | 0 | 0 | 1 (0.2) | 1 (0.0) |
| Lung infection | 0 | 1 (0.1) | 0 | 0 | 1 (0.0) |
| Pneumonia legionella | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) |
| Neoplasms benign, malignant and unspecified | 0 (0.0) | 2 (0.2) | 7 (0.8) | 1 (0.2) | 10 (0.3) |
| Lung adenocarcinoma | 0 | 0 | 1 (0.1) | 1 (0.2) | 2 (0.1) |
| Small cell lung cancer stage unspecified | 0 | 0 | 2 (0.2) | 0 | 2 |
| Lung neoplasm malignant | 0 | 1 (0.1) | 1 (0.1) | 0 | 2 (0.1) |
| Hepatic neoplasm malignant | 0 | 1 (0.1) | 0 | 0 | 1 (0.03) |
| Laryngeal cancer | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| Metastases to lung | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) |
| Esophageal squamous cell carcinoma | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| Immune system disorders | 0 | 0 | 0 | 1 (0.2) | 1 (0.03) |
| Anaphylactic shock | 0 | 0 | 0 | 1 (0.2) | 1 (0.03) |
| Metabolism and nutrition disorders | 0 | 1 (0.1) | 0 | 0 | 1 (0.03) |
| Malnutrition | 0 | 1 (0.1) | 0 | 0 | 1 (0.03) |
| Psychiatric disorders | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| Completed suicide | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| Nervous system disorders | 1 (0.1) | 0 | 0 | 0 | 1 (0.03) |
| Cerebrovascular accident | 1 (0.1) | 0 | 0 | 0 | 1 (0.03) |
| Cardiac disorders | 3 (0.3) | 2 (0.2) | 1 (0.1) | 3 (0.7) | 9 (0.3) |
| Arrhythmia | 0 | 0 | 0 | 1 (0.2) | 1 (0.0) |
| Atrial fibrillation | 0 | 1 (0.1) | 0 | 0 | 1 (0.0) |
| Cardiac arrest | 0 | 0 | 0 | 1 (0.2) | 1 (0.0) |
| Cardio-respiratory arrest | 1 (0.1) | 1 (0.1) | 0 | 0 | 2 (0.1) |
| Myocardial infarction | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Cardiac failure acute | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) |
| Cardiac failure congestive | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) |
| Cardiac failure | 0 | 1 (0.1) | 0 | 1 (0.2) | 2 (0.1) |
| Vascular disorders | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Aortic aneurysm rupture | 0 | 0 | 0 | 1 (0.2) | 1 (0.0) |
| Aortic aneurysm | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) |
| Respiratory, thoracic and mediastinal disorders | 4 (0.5) | 8 (0.9) | 3 (0.3) | 2 (0.4) | 17 (0.5) |
| COPD | 4 (0.5) | 4 (0.4) | 1 (0.1) | 1 (0.2) | 10 (0.3) |
| Acute respiratory failure | 1 (0.1) | 2 (0.2) | 1 (0.1) | 0 | 4 (0.1) |
| Respiratory failure | 1 (0.1) | 2 (0.2) | 1 (0.1) | 0 | 4 (0.1) |
| Dyspnea | 0 | 1 (0.1) | 0 | 1 (0.2) | 2 (0.1) |
| Congenital, familial and genetic disorders | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| Tracheo-esophageal fistula | 0 | 0 | 1 (0.1) | 0 | 1 (0.03) |
| General disorders and administration site conditions | 3 (0.3) | 2 (0.2) | 2 (0.2) | 3 (0.7) | 10 (0.3) |
| Death | 2 (0.2) | 0 | 1 (0.1) | 1 (0.2) | 4 (0.1) |
| Sudden death | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Sudden cardiac death | 0 | 1 (0.1) | 1 (0.1) | 0 | 2 (0.1) |
| Multi-organ failure | 0 | 0 | 0 | 1 (0.2) | 1 (0.0) |
| Edema peripheral | 0 | 1 (0.1) | 0 | 0 | 1 (0.03) |
| Injury, poisoning and procedural complications | 0 | 0 | 0 | 1 (0.2) | 1 (0.3) |
| Arthropod sting | 0 | 0 | 0 | 1 (0.2) | 1 (0.3) |

Source: SCS; Table 2.1.3.2.1:1; pp 64-65

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After the on-treatment period, there were an additional 23 deaths. Of the 23 deaths, two occurred after the vital status follow-up period. The remaining 21 deaths occurred within the vital status follow-up period. The causes of death were generally consistent with the on-treatment deaths. There were 10, 6, 4, and 3 deaths in the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups, respectively. These additional deaths did not result in any new imbalances.

All deaths were also reviewed by a mortality adjudication committee (MAC). On review of the patient narratives, the agency believes the MAC assignments to be more correct. In general, where there were disagreements, the investigator tended to assign cause of death to the terminal cause, whereas the MAC assigned based on root cause (e.g. respiratory failure versus COPD exacerbation). Based on the adjudicated analysis, many of the causes of death attributed to respiratory failure were reassigned to COPD exacerbation (Table 149). Note that compared to Table 150, in Table 149 in the olodaterol 5mcg group, pneumonia was not listed as a cause of death. This is likely because in two patients (11836 and 114631), the investigator assigned the primary cause of death as COPD; however, in the CRFs, the AE pneumonia was also listed as contributory for the deaths.

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Table 149. Forty-eight (48) week trials. Patients with AEs leading to death with onset during the treatment period (Investigator versus MAC cause of death)

| Trial/Patient ID | Age/ Gender | Time to death | Time to D/C | Cause of death (MAC) | Investigator assigned cause of death |
|------------------|----------------|---------------------|----------------|--------------------------------------|--|
| Placebo | | | | | |
| 1222.11/3719 | 71/M | 36 | 36 | Aortic aneurysm | Aortic aneurysm |
| 1222.12/7015 | 81/M | 101 | 43 | COPD exacerbation | Pneumonia |
| 1222.13/ 12118 | 84/M | 140 | 156* | Unknown cause | Cardio-respiratory arrest |
| 1222.13/ 11288 | 55/M | 63 | 63 | Sudden cardiac death | Death |
| 1222.13/12162 | 76/M | 178 | 177 | Sudden death (> 1 hr and < 24 hr) | Acute respiratory failure / COPD |
| 1222.13/11561 | 67/M | 225 | 224 | Sudden cardiac death | Sudden death |
| 1222.13/11463^ | 68/M | 281 | 280 | COPD exacerbation | Myocardial infarction |
| 1222.14/13661 | 64/M | 202 | 202 | Sudden death >1hr and <24 hr | COPD, Respiratory Failure |
| 1222.14/13649 | 71/M | 235 | 234 | Unknown cause of death | Cardiac failure acute |
| 1222.14/13695 | 64/M | 146 | 146 | Unknown cause of death | Death |
| 1222.14/14248 | 70/M | 244 | 242 | COPD exacerbation | COPD |
| 1222.14/14434 | 70/M | 189 | 178 | COPD exacerbation | COPD |
| 1222.14/14647 | 74/M | 214 | 208 | Cerebrovascular accident | Cerebrovascular accident |
| Olo 5mcg | | | | | |
| 1222.11/4079 | 58/M | 208 | 198 | COPD exacerbation | Lung infection |
| 1222.11/3431 | 73/F | 77 | 69 | COPD exacerbation | Acute respiratory failure |
| 1222.11/4037 | 57/M | 179 | 178 | COPD exacerbation | Respiratory failure |
| 1222.13/11112 | 73/M | 259 | 147 | Lung cancer | Lung neoplasm malignant |
| 1222.13/11532 | 50/M | 129 | 110 | COPD exacerbation | Acute respiratory failure/COPD |
| 1222.13/ 11836 | 55/F | 262 | 231 | COPD exacerbation | COPD |
| 1222.14/13157 | 74/M | 165 | 165 | Sudden cardiac death | Cardio-respiratory arrest |
| 1222.14/13225 | 69/M | 137 | 133 | COPD exacerbation | COPD |
| 1222.14/13406 | 59/M | 21 | 21 | Sudden cardiac death | Sudden cardiac death |
| 1222.14/13277 | 80/F | 145 | 144 | COPD exacerbation | Atrial fibrillation, cardiac failure, dyspnea, edema peripheral |
| 1222.14/14438 | 69/M | 113 | 103 | COPD exacerbation | Respiratory Failure |
| 1222.14/14512 | 60/M | 249 | 168 | Hepatic carcinoma | Hepatic neoplasm malignant |
| 1222.14/14631** | 68/M | 236 | 217 | COPD exacerbation | COPD, malnutrition |
| Olo 10mcg | | | | | |
| 1222.11/3621 | 70/M | 383 | 118 | Lung cancer | Small cell lung cancer |
| 1222.12/6379 | 49/M | 357 | 328 | COPD exacerbation | Respiratory failure |
| 1222.12/6671 | 63/M | 194 | 194 | Unknown | Sudden cardiac death |
| 1222.12/6910 | 57/M | 92 | 7 | Lung cancer | Small cell lung cancer stage unspecified |
| 1222.12/7365 | 84/M | 184 | 172 | Pneumonia | Pneumonia legionella |
| 1222.13/10996 | 58/M | 279 | 276 | COPD exacerbation | Pneumonia / |
| | | | | | Acute respiratory failure |
| 1222.13/11707 | 74/M | 131 | 130 | COPD exacerbation | Pneumonia |
| 1222.13/11845 | 71/M | 247 | 247 | Pneumonia | Pneumonia |
| 1222.13/11606 | 56/M | 326 | 307 | Lung cancer | Lung adenocarcinoma |
| 1222.13/11217 | 64/M | 242 | 214 | Esophageal carcinoma | Esophageal squamous cell carcinoma/tracheo- esophageal fistula |
| 1222.13/10307 | 52/M | 40 | 39 | Suicide | Completed suicide |

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| | | | | | |
|-------------------|------|-----|-----|-----------------------------|---|
| 1222.14/13029 | 87/M | 246 | 191 | Congestive heart failure | Cardiac failure congestive |
| 1222.14/13346 | 73/M | 311 | 172 | Bladder carcinoma | Metastases to lung |
| 1222.14/13736 | 63/F | 164 | 131 | Lung cancer | Lung neoplasm malignant |
| 1222.14/14245 | 70/M | 203 | 193 | Laryngeal carcinoma | Laryngeal cancer |
| 1222.14/14253 | 65/M | 241 | 241 | COPD exacerbation | COPD |
| 1222.14/14306 | 43/M | 238 | 238 | Unknown cause of death | Death |
| Formoterol | | | | | |
| 1222.13/11862 | 75/M | 20 | 19 | Unknown cause | Cardiac failure |
| 1222.13/11323 | 60/M | 90 | 90 | Sudden cardiac death | Sudden death |
| 1222.13/10855 | 71/M | 240 | 62 | Lung cancer | Lung adenocarcinoma |
| 1222.13/11943 | 68/M | 228 | 227 | Ruptured abdominal aneurysm | Aortic aneurysm rupture |
| 1222.14/13772 | 75/M | 60 | 59 | COPD exacerbation | Cardiac Arrest/ dyspnea |
| 1222.14/14099 | 66/M | 5 | 5 | COPD exacerbation | COPD |
| 1222.14/14310 | 59/M | 261 | 260 | Sudden cardiac death | Death |
| 1222.14/14517 | 47/M | 27 | 25 | Arthropod bite | Anaphylactic shock, arthropod sting |
| 1222.14/14642 | 57/M | 79 | 74 | COPD exacerbation | Pneumonia, sepsis, multi- organ failure |
| 1222.14/14662 | 51/M | 165 | 164 | Sudden cardiac death | Arrhythmia/myocardial infarction |

^aOnset of fatal event myocardial infarction one day after termination from trial

*Clerical error

**The terminal event leading to this patient's death (investigator assigned) was pneumonia which occurred during the post-study period. However, the underlying cause of death was COPD exacerbation, which occurred during the on-treatment period. For accounting purposes, the death was assigned as on-treatment.

Source: SCS; table 2.1.3.2.1:2; pp 67-68

For on-treatment deaths, based on MAC analysis, the most common causes of death were COPD (n=20), sudden cardiac death (n=7), unknown (n=6), and lung cancer (n=6). There was a slight imbalance with regard to COPD as a cause of death. For the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups, there were 4 (0.5%), 9 (1%), 4 (0.5%), and 3 (0.7%) deaths due to COPD exacerbation, respectively. There was also a slight imbalance with regard to lung cancer deaths [placebo=0, Olo 5mcg=1 (0.1%), Olo 10mcg=4 (0.5%)], as was noted in the non-adjudicated analysis. Sudden cardiac deaths and unknown deaths were no more frequent in olodaterol groups compared to placebo. The adjudicated causes of death on-treatment are summarized in Table 150.

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Table 150. Forty-eight (48) week trials. Adjudicated on-treatment deaths

| Cause of death | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol N(%) | Total N(%) |
|------------------------------------|-----------------|------------------|-------------------|--------------------|---------------|
| Number of patients | 885 (100) | 876 (100) | 883 (100) | 460 (100) | 3104 (100) |
| Total deaths | 13 (1.5) | 13 (1.5) | 17 (1.9) | 10 (2.2) | 53 (1.7) |
| COPD exacerbation | 4 (0.45) | 9 (1.03) | 4 (0.45) | 3 (0.65) | 20 (0.64) |
| Sudden cardiac death | 2 (0.23) | 2 (0.23) | 0 (0) | 3 (0.65) | 7 (0.23) |
| Unknown | 3 (0.34) | 0 (0) | 2 (0.23) | 1 (0.22) | 6 (0.19) |
| Lung cancer | 0 | 1 (0.11) | 4 (0.45) | 1 (0.22) | 6 (0.19) |
| Sudden death | 2 (0.23) | 0 | 0 | 0 | 2 (0.06) |
| Pneumonia | 0 | 0 | 2 (0.23) | 0 | 2 (0.06) |
| Aortic Aneurysm | 1 (0.11) | 0 | 0 | 0 | 1 (0.03) |
| Cerebrovascular events | 1 (0.11) | 0 | 0 | 0 | 1 (0.03) |
| Hepatic carcinoma | 0 | 1 (0.11) | 0 | 0 | 1 (0.03) |
| Esophageal carcinoma | 0 | 0 | 1 (0.11) | 0 | 1 (0.03) |
| Laryngeal carcinoma | 0 | 0 | 1 (0.11) | 0 | 1 (0.03) |
| Bladder carcinoma | 0 | 0 | 1 (0.11) | 0 | 1 (0.03) |
| Congestive heart failure | 0 | 0 | 1 (0.11) | 0 | 1 (0.03) |
| Suicide | 0 | 0 | 1 (0.11) | 0 | 1 (0.03) |
| Ruptured abdominal aortic aneurysm | 0 | 0 | 0 | 1 (0.22) | 1 (0.03) |
| Arthropod bite (anaphylaxis) | 0 | 0 | 0 | 1 (0.22) | 1 (0.03) |

Source: SCS; table 2.1.3.2.1:2, pp 67-68

During the post-treatment period, there were an additional 10, 7, 4, and 3 deaths in the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups, respectively. Based on MAC assessment; 0, 4 (0.5%), 0, and 1 (0.2%) deaths were due to COPD exacerbations in the placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol groups, respectively. Combining these two periods, the imbalance between olodaterol 5mcg [13 (1.5%)] and placebo [4 (0.5%)] appeared to be heightened. However, after reviewing the SAE narratives, this is likely not the case. Of the 4 additional COPD-related deaths, only 1 was likely relevant. The death of patient 1222.11/4047 occurred 232 days after the last dose, and is therefore unlikely to be related to olodaterol. For patient 1222.13/12054, the death occurred approximately 1 month after discontinuation from the trial. This patient was discontinued due to overdosing of olodaterol 5mcg. In the 2 months prior to discontinuation, this patient had taken 2-3 times the protocol specified dose. As such, this patient's exposure was likely equivalent to 10-15mcg of olodaterol daily, rather than 5mcg. Therefore, it is appropriate from a reporting standpoint, but may be misleading to include this death in the olodaterol 5mcg group. The death of patient 1222.14/14631, while listed in the post-treatment/post-study death table (SCS, table 2.1.3.2.1:3; pp 70), was actually already counted as an on-treatment death, as the onset of one of the AEs contributing to death occurred during the treatment period (see footnote to Table 149)

The small imbalance between placebo and olodaterol 5mcg group for COPD exacerbation-related deaths is concerning. However is it puzzling that the olodaterol 10mcg group had fewer deaths due to COPD exacerbation as compared to olodaterol 5mcg. One would expect that if the deaths were solely drug-related that there would either be a dose effect, or parity between olodaterol groups. Additionally, when

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examining SAEs and common AEs related with the PT COPD exacerbation, this imbalance was not seen (see sections 7.3.2 Nonfatal Serious Adverse Events and 7.4.1 Common Adverse Events). This further supports the assertion that the imbalance in deaths due to COPD exacerbations was not solely related to olodaterol exposure.

7.3.2 Nonfatal Serious Adverse Events

In the 48-week trials, there were 499 (16.1%) patients with on-treatment SAEs. These were balanced across groups. The most common SAEs by preferred term were by far COPD exacerbation (5.8%) and pneumonia (1.8%). SAEs were most commonly reported in the respiratory, thoracic, and mediastinal SOC; followed by the infections and infestations SOC. Within infections and infestations, the preferred term 'pneumonia' was more common in olodaterol 10mcg (2.5%) compared to placebo (1.5%); however, this was not the case for olodaterol 5mcg (1.6%) nor formoterol (1.5%). Within the respiratory, thoracic, and mediastinal SOC, the preferred term 'pulmonary embolism' demonstrated a mild imbalance, with a frequency of 0 in placebo group, 0.1% in olodaterol 5mcg, and 0.5% in olodaterol 10mcg. COPD exacerbation was also more frequent in the olodaterol 10mcg (6.8%) compared to placebo (6%). This was not the case for either olodaterol 5mcg (4.7%) nor formoterol (5.9%).

Three SOCs demonstrated an imbalance in both olodaterol doses compared to placebo: neoplasm benign, malignant, and unspecified; musculoskeletal and connective tissues disorders; and injury, poisonings, and procedural complications. For the SOC musculoskeletal and connective tissue disorders, the most common preferred term was 'back pain', which was more common in olodaterol 10mcg (0.5%) compared to placebo (0) and olodaterol 5mcg (0.1%). For the SOC injury, poisoning, and procedural complications, the most common preferred term was fall, which also followed a dose response. The imbalance seen in the musculoskeletal and connective disorder and injury, poisoning, and procedural complications SOC are unlikely to be related to olodaterol. On review of the SAE narratives, most of the preferred terms in the musculoskeletal and connective tissue SOC were related to a recent injury or exacerbation of existing disease. With regard to the injury, poisoning, and procedural complications SOC, based on review of the narratives, no events were clearly associated with dizziness, syncope, presyncope, hypotension, arrhythmia, chest pain, or palpitations. Most falls and fractures were related to environmental conditions. As such, it is unlikely that these events were directly related to or precipitated by olodaterol. Additionally, these imbalances were small in magnitude.

Similar to the imbalance seen in deaths related to the SOC neoplasms benign, malignant, and unspecified, the imbalance seen in SAEs for the same SOC did not appear to be driven by a single PT. However, it did appear to be driven by the high level group term (HLGT) of respiratory and mediastinal neoplasms malignant and unspecified [placebo=2 (0.2%), Olo 5mcg=4 (0.5%), Olo 10mcg=7 (0.8%), formoterol=4 (0.9%)]. The imbalance seen for the SOC neoplasms benign, malignant and unspecified is of

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unclear significance. Given the latency period of lung cancers, it is unlikely that olodaterol was directly causative. However, it is theoretically possible that olodaterol may have unmasked the cancers. Given the small numbers and a patient population prone to lung-related cancers; this imbalance, like the imbalance seen in deaths, is likely due to chance.

The SAEs are summarized in Table 151.

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Table 151. Forty-eight (48) week trials. On treatment SAEs that occurred in ≥2 patients

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol (N%) |
|---|-----------------|------------------|-------------------|--------------------|
| Number of patients | 885 (100) | 876 (100) | 883 (100) | 460 (100) |
| Total with SAEs | 145 (16.4) | 138 (15.8) | 147 (16.6) | 69 (15) |
| Infections and infestations | | | | |
| Pneumonia | 13 (1.5) | 14 (1.6) | 22 (2.5) | 7 (1.5) |
| Infective exacerbation of COPD | 4 (0.5) | 2 (0.2) | 1 (0.1) | 2 (0.4) |
| Gastroenteritis | 3 (0.3) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Urinary tract infection | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) |
| Bronchitis | 2 (0.2) | 0 (0.0) | 1 (0.1) | 1 (0.2) |
| Lobar pneumonia | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.2) |
| Lung infection | 1 (0.1) | 1 (0.1) | 2 (0.2) | 0 (0.0) |
| 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) |
| Prostate cancer | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.4) |
| Small cell lung cancer stage unspecified | 0 (0.0) | 0 (0.0) | 3 (0.3) | 0 (0.0) |
| Basal cell carcinoma | 2 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| Bladder cancer | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Lung adenocarcinoma | 1 (0.1) | 2 (0.2) | 1 (0.1) | 1 (0.2) |
| Metabolism and nutrition disorders | | | | |
| Dehydration | 2 (0.2) | 3 (0.3) | 3 (0.3) | 0 (0.0) |
| Nervous system disorders | | | | |
| Cerebrovascular accident | 13 (1.5) | 10 (1.1) | 5 (0.6) | 0 (0.0) |
| Carotid artery stenosis | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dizziness | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| Syncope | 0 (0.0) | 1 (0.1) | 2 (0.2) | 0 (0.0) |
| Transient ischemic attack | 2 (0.2) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| Cardiac disorders | | | | |
| Atrial fibrillation | 26 (2.9) | 19 (2.2) | 17 (1.9) | 7 (1.5) |
| Atrial flutter* | 3 (0.3) | 5 (0.6) | 5 (0.6) | 1 (0.2) |
| Acute myocardial infarction | 0 | 1 (0.1) | 0 | 0 |
| Acute coronary syndrome | 2 (0.2) | 1 (0.1) | 4 (0.5) | 0 (0.0) |
| Cardiac failure | 3 (0.3) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Coronary artery disease | 0 (0.0) | 3 (0.3) | 1 (0.1) | 1 (0.2) |
| Coronary artery occlusion | 3 (0.3) | 3 (0.3) | 2 (0.2) | 0 (0.0) |
| Myocardial infarction | 3 (0.3) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Angina unstable | 3 (0.3) | 1 (0.1) | 0 (0.0) | 1 (0.2) |
| Cardiac failure congestive | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Vascular disorder | 8 (0.9) | 8 (0.9) | 5 (0.6) | 4 (0.9) |
| Aortic aneurysm | 1 (0.1) | 3 (0.3) | 0 (0.0) | 0 (0.0) |
| Deep vein thrombosis | 1 (0.1) | 1 (0.1) | 3 (0.3) | 0 (0.0) |
| Hypovolemic shock | 2 (0.2) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| COPD | 64 (7.2) | 48 (5.5) | 70 (7.9) | 31 (6.7) |
| Respiratory failure | 53 (6.0) | 41 (4.7) | 60 (6.8) | 27 (5.9) |
| Pneumothorax | 7 (0.8) | 2 (0.2) | 3 (0.3) | 0 (0.0) |
| Pulmonary embolism | 5 (0.6) | 2 (0.2) | 3 (0.3) | 1 (0.2) |
| Dyspnea | 0 (0.0) | 1 (0.1) | 4 (0.5) | 1 (0.2) |
| Acute respiratory failure | 3 (0.3) | 1 (0.1) | 1 (0.1) | 2 (0.4) |
| Hemoptysis | 0 (0.0) | 0 (0.0) | 2 (0.2) | 1 (0.2) |

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|--|----------|----------|----------|---------|
| Gastrointestinal disorders | 10 (1.1) | 5 (0.6) | 11 (1.2) | 5 (1.1) |
| Gastritis | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ileus | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Inguinal hernia | 2 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| Hepatobiliary disorders | 3 (0.3) | 1 (0.1) | 4 (0.5) | 0 (0.0) |
| Cholecystitis acute | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Musculoskeletal and connective tissue disorders | 3 (0.3) | 9 (1.0) | 11 (1.2) | 4 (0.9) |
| Back pain | 0 (0.0) | 1 (0.1) | 4 (0.5) | 0 (0.0) |
| Intervertebral disc protrusion | 1 (0.1) | 1 (0.1) | 2 (0.2) | 2 (0.4) |
| Intervertebral disc degeneration | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) |
| Reproductive system and breast disorders | 1 (0.1) | 1 (0.1) | 1 (0.1) | 2 (0.4) |
| Benign prostatic hyperplasia | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.4) |
| General disorders and administration site conditions | 7 (0.8) | 8 (0.9) | 7 (0.8) | 5 (1.1) |
| Chest pain | 1 (0.1) | 2 (0.2) | 1 (0.1) | 1 (0.2) |
| Death | 2 (0.2) | 0 (0.0) | 1 (0.1) | 1 (0.2) |
| Pyrexia | 1 (0.1) | 0 (0.0) | 2 (0.2) | 0 (0.0) |
| Injury, poisoning and procedural complications | 9 (1.0) | 12 (1.4) | 16 (1.8) | 5 (1.1) |
| Fall | 1 (0.1) | 2 (0.2) | 4 (0.5) | 0 (0.0) |
| Road traffic accident | 2 (0.2) | 1 (0.1) | 1 (0.1) | 2 (0.4) |
| All fractures** | 5 (0.6) | 5 (0.6) | 5 (0.6) | 1 (0.2) |
| Humerus fracture | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Joint dislocation | 0 (0.0) | 2 (0.2) | 2 (0.2) | 0 (0.0) |
| Tendon rupture | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

* included as PT was similar to another PT (atrial fibrillation)

**compiled by the reviewer. Included foot, hip, pelvic, femoral neck, femur, lower limb, patella, rib, fibula, and humerus fractures

Source: ISS; table 2.1.4.1.1:1; pg73

It should also be noted that for the cardiac disorder SOC, SAEs were balanced. However, when examining by high level group term, the group term 'heart failure' was more frequent in Olo 5mcg [8 (0.9%)] and Olo 10mcg [4 (0.5%)] compared to placebo [2 (0.2%)]. This was primarily driven by the preferred terms 'cardiac failure congestive' and 'cardiac failure'. The overall numbers are small, and do not follow a dose response, as such it is unclear if this imbalance is solely drug-related. For the high level group term 'cardiac arrhythmias', the numbers were balanced. However, the preferred term 'atrial fibrillation' was more common in olodaterol groups compared to placebo.

It is also notable that for the respiratory thoracic and mediastinal SOC, there was no imbalance in SAEs. This was also the case for the preferred term 'COPD exacerbation'. This is somewhat surprising as for adjudicated deaths, COPD exacerbation was more frequent in olodaterol 5mcg versus placebo. An adjudicated analysis of SAEs was also performed by the sponsor. The adjudicated SAE assignments were consistent with the investigator assignments.

7.3.3 Dropouts and/or Discontinuations

Patient disposition

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In the 48-week exposure group (trials 1222.11, 1222.12, 1222.13, and 1222.14), 4,220 patients were enrolled and 3,104 were randomized and treated. Approximately 82% of treated patients completed their trials. Across olodaterol and formoterol groups, similar percentages of patients completed the trials. Discontinuation was the highest in the placebo groups. The most common reason for discontinuation was AEs, followed by withdrawal of consent, and lack of efficacy. Discontinuation due to overall AEs was most common in the placebo group. This imbalance in discontinuation due to overall AEs was primarily driven by the placebo groups' increased frequency of withdrawal due to worsening COPD. Withdrawal due to lack of efficacy was also higher in the placebo group. It should also be noted that withdrawals due to lack of efficacy and AE 'COPD worse' followed an inverse dose response. This implies that olodaterol has a true treatment effect and is consistent with efficacy data reviewed in section 6 Review of Efficacy. It should also be noted the differential in discontinuations may exaggerate imbalances between placebo and olodaterol groups for safety findings as the sickest patients may have dropped out in the placebo groups. The patient disposition information is summarized in Table 152.

Table 152. Forty-eight (48) week trials. Pooled patient disposition

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total |
|------------------------------|-----------------|------------------|-------------------|-----------------------------|---------------|
| Treated | 885 (100.00) | 876 (100.00) | 883 (100.00) | 460 (100.00) | 3104 (100.00) |
| Completed | 686 (77.51) | 744 (84.93) | 737 (83.47) | 377 (81.96) | 2544 (81.96) |
| Premature discontinuation | 199 (22.49) | 132 (15.07) | 146 (16.53) | 83 (18.04) | 560 (18.04) |
| AE* | 78 (8.81) | 59 (6.74) | 67 (7.59) | 36 (7.83) | 240 (7.73) |
| AE COPD worse | 33 (3.73) | 27 (3.08) | 14 (1.59) | 13 (2.83) | 87 (2.80) |
| AE other disease worse | 7 (0.79) | 6 (0.68) | 8 (0.91) | 3 (0.65) | 24 (0.77) |
| AE other | 38 (4.29) | 26 (2.97) | 45 (5.10) | 20 (4.35) | 129 (4.16) |
| Lack of efficacy | 40 (4.52) | 12 (1.37) | 7 (0.79) | 5 (1.09) | 64 (2.06) |
| Non-compliant | 6 (0.68) | 8 (0.91) | 4 (0.45) | 5 (1.09) | 23 (0.74) |
| Lost to follow-up | 7 (0.79) | 6 (0.68) | 11 (1.25) | 3 (0.65) | 27 (0.87) |
| Consent withdrawn | 50 (5.65) | 30 (3.42) | 38 (4.30) | 27 (5.87) | 145 (4.67) |
| Other | 18 (2.03) | 17 (1.94) | 19 (2.15) | 7 (1.52) | 61 (1.97) |

*this includes AEs that were not considered treatment emergent, Table 153 summarizes discontinuations due to TEAEs

Source: SCS; table 1.2.4.1:1; pg30

Discontinuations related to TEAEs

In the pooled 48-week data, based on the sponsor's disposition table, a total of 240 patients withdrew due to AEs. Note that this included all AEs and not just TEAEs. Only 231 patients discontinued due to TEAEs. Overall discontinuations due to TEAEs were most common in the placebo group and least common in the olodaterol 5mcg group. The most common TEAE leading to discontinuation were in the respiratory thoracic and mediastinal disorders and cardiac disorders SOC. Both were more common in the

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placebo compared to olodateterol groups. The most common preferred terms leading to discontinuation were COPD exacerbation (2.2%), dyspnea (0.4%), pneumonia (0.3%), and atrial fibrillation (0.3%). These preferred terms did not demonstrate a significant imbalance. No dose responses were observed based on preferred terms or SOC. These results are summarized in Table 153.

Table 153. Forty-eight (48) week trials. Discontinuations dues TEAEs (≥ 2 patients)

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total N(%) |
|---|-----------------|------------------|-------------------|-----------------------------|---------------|
| Treated Patients | 885 (100.00) | 876 (100.00) | 883 (100.00) | 460 (100.00) | 3104 (100.00) |
| Total with AEs leading to discontinuation | 74 (8.4) | 54 (6.2) | 66 (7.5) | 36 (7.8) | 231 (7.4) |
| Infections and infestations | 8 (0.9) | 6 (0.7) | 7 (0.8) | 4 (0.9) | 25 (0.8) |
| Pneumonia | 3 (0.3) | 1 (0.1) | 4 (0.5) | 2 (0.4) | 10 (0.3) |
| Infective exacerbation of COPD | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 2 (0.1) |
| Lobar pneumonia | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Neoplasms benign, malignant, and unspecified | 5 (0.6) | 5 (0.6) | 12 (1.4) | 4 (0.9) | 26 (0.8) |
| Lung adenocarcinoma | 1 (0.1) | 2 (0.2) | 1 (0.1) | 1 (0.2) | 5 (0.2) |
| Lung neoplasm malignant | 0 (0.0) | 1 (0.0) | 2 (0.2) | 2 (0.4) | 5 (0.2) |
| Small cell lung cancer stage unspecified | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.1) |
| Bladder cancer | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Hepatic neoplasm malignant | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Immune system disorders | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.2) | 2 (0.1) |
| Psychiatric disorders | 0 (0.0) | 0 (0.0) | 4 (0.5) | 0 (0.0) | 4 (0.1) |
| Nervous system disorders | 4 (0.5) | 2 (0.2) | 1 (0.1) | 1 (0.2) | 8 (0.3) |
| Cerebrovascular accident | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Headache | 1 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.2) | 3 (0.1) |
| Eye disorders | 2 (0.2) | 1 (0.1) | 2 (0.2) | 2 (0.4) | 7 (0.2) |
| Cardiac disorders | 13 (1.5) | 10 (1.1) | 10 (1.1) | 7 (1.5) | 40 (1.3) |
| Acute myocardial infarction | 2 (0.2) | 1 (0.1) | 3 (0.3) | 0 (0.0) | 6 (0.2) |
| Atrial fibrillation | 3 (0.3) | 2 (0.2) | 2 (0.2) | 1 (0.2) | 8 (0.3) |
| Acute coronary syndrome | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Bundle branch block left | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Cardiac failure | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.2) | 2 (0.1) |
| Ventricular extrasystoles | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.2) | 3 (0.1) |
| Ventricular tachycardia | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Cardiac failure congestive | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Cardio-respiratory arrest | 1 (0.1) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Coronary artery disease | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Vascular disorders | 6 (0.7) | 2 (0.2) | 0 (0.0) | 1 (0.2) | 9 (0.3) |
| Hypertension | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| Aortic aneurysm | 1 (0.1) | 1 (0.1) | 0 | 0 | 2 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 32 (3.6) | 26 (3.0) | 23 (2.6) | 17 (3.7) | 98 (3.2) |
| COPD | 20 (2.3) | 18 (2.1) | 18 (2.0) | 12 (2.6) | 68 (2.2) |
| Dyspnea | 6 (0.7) | 4 (0.5) | 0 (0.0) | 2 (0.4) | 12 (0.4) |
| Respiratory failure | 3 (0.3) | 2 (0.2) | 2 (0.2) | 0 (0.0) | 7 (0.2) |
| Acute respiratory failure | 1 (0.1) | 2 (0.2) | 2 (0.2) | 0 (0.0) | 5 (0.2) |
| Cough | 2 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Pneumothorax | 2 (0.2) | 0 (0.0) | 1 (0.1) | 1 (0.2) | 4 (0.1) |
| Pulmonary embolism | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |

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| | | | | | |
|--|---------|---------|---------|---------|----------|
| Gastrointestinal disorders | 4(0.5) | 0(0.0) | 3(0.3) | 1(0.2) | 8 (0.3) |
| Hepatobiliary disorders | 2(0.2) | 0(0.0) | 1(0.1) | 0(0.0) | 3 (0.1) |
| Musculoskeletal and connective tissue disorders | 1(0.1) | 1(0.1) | 3(0.3) | 0(0.0) | 5 (0.2) |
| Muscle spasms | 1(0.1) | 0(0.0) | 1(0.1) | 0(0.0) | 2 (0.1) |
| Renal and urinary disorders | 1(0.1) | 0(0.0) | 1(0.1) | 1(0.2) | 3 (0.1) |
| Renal failure acute | 1(0.1) | 0(0.0) | 0(0.0) | 1(0.2) | 2 (0.1) |
| General disorders and administration site conditions | 4(0.5) | 6(0.7) | 3(0.3) | 5(1.1) | 18 (0.6) |
| Chest pain | 0(0.0) | 1(0.1) | 0(0.0) | 2(0.4) | 3 (0.1) |
| Death | 2(0.2) | 0(0.0) | 1(0.1) | 1(0.2) | 4 (0.1) |
| Edema peripheral | 0(0.0) | 2(0.2) | 0(0.0) | 0(0.0) | 2 (0.1) |
| Sudden death | 1(0.1) | 0(0.0) | 0(0.0) | 1(0.2) | 2 (0.1) |
| Sudden cardiac death | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Investigations | 3(0.3) | 2(0.2) | 3(0.3) | 1(0.2) | 9 (0.3) |
| Electrocardiogram QT prolonged | 0(0.0) | 1(0.1) | 1(0.1) | 1(0.2) | 3 (0.1) |
| Electrocardiogram T wave inversion | 1(0.1) | 0(0.0) | 0(0.0) | 1(0.2) | 2 (0.1) |
| Hepatic enzyme increased | 1(0.1) | 0(0.0) | 1(0.1) | 0(0.0) | 2 (0.1) |
| Injury, poisoning and procedural complications | 1(0.1) | 3(0.3) | 4(0.5) | 1(0.2) | 9 (0.3) |
| Contusion | 0(0.0) | 1(0.1) | 1(0.1) | 0(0.0) | 2 (0.1) |
| Road traffic accident | 1(0.1) | 1(0.1) | 1(0.1) | 0(0.0) | 3 (0.1) |

Source: ISS; table 2.1.5.1.1:1; pp78-79

7.3.4 Significant Adverse Events

Adverse events of interest for this product are discussed in Section 7.3.5. AEs leading to discontinuation are discussed in Section 7.3.3. Lab and ECG abnormalities are discussed in section 7.4.2 and 7.4.4, respectively.

7.3.5 Submission Specific Primary Safety Concerns

Due to specific safety concerns with LABAs, the sponsor conducted analyses using respiratory, cardiac, and beta-agonist class effect related pharmacovigilance (PV)/SMQ safety endpoints. A Major Adverse Cardiac Events (MACE) analysis and an adjudicated analysis of SAEs and deaths were also performed. The sponsor defined PV endpoints primarily consisted of PTs grouped by similar concepts, but that did not necessarily correspond to SOCs. The PTs included in the PV endpoints were reasonable. SMQs used were from MedDRA 14.1. See section 7.1.2 Categorization of Adverse Events for the definition of MACE, PV endpoints specifically discussed in this section, and the method of adjudication.

Respiratory

Respiratory related PV endpoints that were more frequent in olodaterol groups (either dose) compared to placebo groups included COPD exacerbation with pneumonia, COPD exacerbation, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), cough, pneumonia, pharyngitis, bronchitis, and sinusitis. In general the

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imbalances were minimal. None exhibited a dose response. These results are summarized in Table 154. Note that only the PTs with a frequency $\geq 2\%$ were listed under the PV endpoint.

Table 154. 48-week trials. PV endpoints that were more frequent in olodaterol groups compared to placebo and were $\geq 2\%$

| PV/PT | Placebo N (%) | Olo 5 mcg N (%) | Olo 10mcg N (%) | Formoterol N (%) | Total N (%) |
|---|------------------|--------------------|--------------------|---------------------|----------------|
| Number of patients | 885 (100.0) | 876 (100.0) | 883 (100.0) | 460 (100.0) | 3104 (100.0) |
| Total with adverse events related to respiratory system | 627 (70.8) | 622 (71.0) | 642 (72.7) | 318 (69.1) | 2209 (71.2) |
| COPD exacerbation (broad) with pneumonia #PV* | 298 (33.7) | 288 (32.9) | 308 (34.9) | 155 (33.7) | 1049 (33.8) |
| COPD | 255 (28.8) | 227 (25.9) | 266 (30.1) | 131 (28.5) | 879 (28.3) |
| Bronchitis | 32 (3.6) | 41 (4.7) | 31 (3.5) | 13 (2.8) | 117 (3.8) |
| Pneumonia | 24 (2.7) | 21 (2.4) | 35 (4.0) | 14 (3.0) | 95 (3.1) |
| COPD exacerbation (broad) #PV | 287 (32.4) | 279 (31.8) | 296 (33.5) | 146 (31.7) | 1008 (32.5) |
| COPD exacerbation #PV | 261 (29.5) | 231 (26.4) | 267 (30.2) | 134 (29.1) | 893 (28.8) |
| Upper respiratory tract infection #PV | 165 (18.6) | 198 (22.6) | 182 (20.6) | 89 (19.3) | 634 (20.4) |
| Nasopharyngitis | 68 (7.7) | 99 (11.3) | 91 (10.3) | 46 (10.0) | 304 (9.8) |
| Upper respiratory tract infection | 66 (7.5) | 72 (8.2) | 62 (7.0) | 32 (7.0) | 232 (7.5) |
| Sinusitis | 21 (2.4) | 8 (0.9) | 20 (2.3) | 1 (0.2) | 50 (1.6) |
| Pharyngitis #PV | 88 (9.9) | 118 (13.5) | 106 (12.0) | 52 (11.3) | 364 (11.7) |
| Nasopharyngitis | 68 (7.7) | 99 (11.3) | 91 (10.3) | 46 (10.0) | 304 (9.8) |
| Lower respiratory tract infection #PV | 69 (7.8) | 87 (9.9) | 86 (9.7) | 34 (7.4) | 276 (8.9) |
| Bronchitis | 32 (3.6) | 41 (4.7) | 31 (3.5) | 13 (2.8) | 117 (3.8) |
| Pneumonia | 24 (2.7) | 22 (2.5) | 35 (4.0) | 14 (3.0) | 95 (3.1) |
| Cough #PV | 37 (4.2) | 43 (4.9) | 40 (4.5) | 31 (6.7) | 151 (4.9) |
| Cough | 35 (4.0) | 37 (4.2) | 35 (4.0) | 27 (5.9) | 134 (4.3) |
| Bronchitis #PV | 34 (3.8) | 42 (4.8) | 31 (3.5) | 15 (3.3) | 122 (3.9) |
| Bronchitis | 32 (3.6) | 41 (4.7) | 31 (3.5) | 13 (2.8) | 117 (3.8) |
| Pneumonia #PV | 24 (2.7) | 25 (2.9) | 38 (4.3) | 15 (3.3) | 102 (3.3) |
| Pneumonia | 24 (2.7) | 22 (2.5) | 35 (4.0) | 14 (3.0) | 95 (3.1) |
| Sinusitis #PV | 28 (3.2) | 12 (1.4) | 32 (3.6) | 4 (0.9) | 76 (2.4) |
| Sinusitis | 21 (2.4) | 8 (0.9) | 20 (2.3) | 1 (0.2) | 50 (1.6) |

*COPD exacerbation (broad PV) + pneumonia PV

See SCS supplement table 2.8.1.1 for complete listing of PV endpoints and included PTs; pp 988-996.

Source: ISS; table 2.1.7.1:1; pg84

Of note, the pneumonia PV demonstrated an imbalance between both olodaterol groups and placebo, with a frequency of 2.7%, 2.9%, and 4.3% for placebo, olodaterol 5mcg, and olodaterol 10mcg, respectively. The difference between placebo and olodaterol 5mcg was marginal, in contrast to the difference between placebo and olodaterol 10mcg. This is consistent with pneumonia SAEs (section 7.3.2 Nonfatal Serious

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Adverse Events) and pneumonia common TEAEs (section 7.4.1 Common Adverse Events). This may indicate that development of pneumonia is potentially associated with olodaterol use. However, for the pneumonia SAEs, PV, and common TEAEs, the imbalance is consistently most marked when comparing olodaterol 10mcg to placebo. The difference between olodaterol 5mcg and placebo is marginal and not likely clinically significant.

Notably, there were no imbalances with respect to COPD exacerbation-related PV endpoints.

Cardiac Safety

Cardiac related SMQs and PV endpoints were also analyzed. Imbalances were noted in the SMQ cardiac arrhythmias sub-SMQs cardiac arrhythmia terms, tachyarrhythmias, and ventricular tachyarrhythmias. Note that there was significant overlap in the PTs used in these SMQs. In all three sub-SMQs, two out of the three most common PTs that demonstrated an imbalance between olodaterol and placebo (ventricular extrasystoles and ventricular tachycardia) were shared. Additional imbalances were noted in the SMQ cardiac failure and Torsades de pointes/QT prolongation and the sub-SMQ myocardial infarction (broad). Although these imbalances were noted, they were small in magnitude (relative risk <2) and only the sub-SMQs cardiac arrhythmia terms and tachyarrhythmia occurred in more than 2% of patients. No PTs within the SMQs were reported in ≥2% of any treatment group. Imbalances in cardiac related SMQs and PTs are not surprising given that cardiovascular adverse reactions are known class effect of LABAs. It should also be noted that no SMQ/sub-SMQs or PTs demonstrated a dose response, making it less likely that the small imbalances were solely drug-related. Data are summarized in Table 155. Analysis of cardiac related PV endpoints demonstrated similar results.

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Table 155. Cardiac SMQs which demonstrated imbalances between olodaterol groups and placebo

| SMQ/PT | Placebo N (%) | Olo 5 mcg N (%) | Olo 10mcg N (%) | Formoterol N (%) | Total N (%) |
|---|------------------|-----------------------|-----------------------|---------------------|-----------------|
| Number of patients | 885 (100.0) | 876 (100.0) | 883 (100.0) | 460 (100.0) | 3104 (100.0) |
| Total with adverse events | 627 (70.8) | 622 (71.0) | 642 (72.7) | 318 (69.1) | 2209 (71.2) |
| SMQ Cardiac arrhythmia sub-SMQ Cardiac arrhythmia terms | 37 (4.2) | 49 (5.6) | 39 (4.4) | 20 (4.3) | 145 (4.7) |
| SMQ Cardiac arrhythmias sub- SMQ Tachyarrhythmias | 30 (3.4) | 31 (3.5) | 26 (2.9) | 15 (3.3) | 102 (3.3) |
| SMQ Cardiac arrhythmias sub- SMQ ventricular tachyarrhythmias | 9 (1.0) | 17 (1.9) | 12 (1.4) | 9 (2.0) | 47 (1.5) |
| SMQ Ischaemic heart disease sub-SMQ Myocardial infarction (broad) | 9 (1.0) | 4 (0.5) | 12 (1.4) | 4 (0.9) | 29 (0.9) |
| SMQ Cardiac failure (narrow) | 5 (0.6) | 11 (1.3) | 7 (0.8) | 1 (0.2) | 24 (0.8) |
| SMQ Torsades de pointes/QT- prolongation (narrow) | 6 (0.7) | 11 (1.3) | 4 (0.5) | 5 (1.1) | 26 (0.8) |

Source: SCS supplement; table 2.8.2.1; pp 1004-1009

The Agency also reviewed all AEs in the cardiac disorder SOC by preferred term and high level group term. No imbalance was noted in overall cardiac AEs. High level group terms were also fairly balanced and no dose responses were observed. However, three high level group terms were more common in olodaterol 5mcg compared to both placebo and olodaterol 10mcg. The high level group term ‘cardiac arrhythmia’ was more frequent in olodaterol 5mcg (5.8%) compared to placebo (4.5%) and olodaterol 10mcg (4.6%). The HGLT heart failure also followed a similar pattern (placebo=0.6%, Olo 5mcg=1.1%, Olo 10mcg=0.8%). A similar pattern was seen for the HLGT cardiac valve disorders. This is largely consistent with the sponsor’s cardiac SMQ analysis. As with the cardiac SMQ data, the lack of dose response imply that the mild imbalance seen between the HLGTs is not solely related to olodaterol exposure. Overall, there does not appear to be a cardiac safety signal associated with olodaterol based on this analysis. However, this will continue to be monitored in the post-marketing period.

There were no imbalances noted in the sponsor’s MACE analysis (fatal and non-fatal events). Results of the MACE analysis are summarized in Table 156.

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Table 156. Forty-eight (48) week trials. MACE analysis

| | Placebo N (%) | Olo 5 mcg N (%) | Olo 10mcg N (%) | Formoterol N (%) | Total N (%) |
|---|------------------|-----------------------|-----------------------|---------------------|-----------------|
| Number of patients | 885 (100.0) | 876 (100.0) | 883 (100.0) | 460 (100.0) | 3104 (100.0) |
| Death | | | | | |
| Fatal AE | 13 (1.5) | 13 (1.5) | 17 (1.9) | 10 (2.2) | 53 (1.7) |
| Fatal MACE | | | | | |
| Cardiac disorder SOC (fatal) | 3 (0.3) | 2 (0.2) | 1 (0.1) | 3 (0.7) | 9 (0.3) |
| Vascular disorder SOC (fatal) | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| SMQ Ischemic heart disease sub-SMQ myocardial infarction (fatal) | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Stroke PV (fatal) | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) |
| Sudden death PT | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Cardiac death PT | 0 | 0 | 0 | 0 | 0 |
| Sudden cardiac death PT | 0 | 1 (0.1) | 1 (0.1) | 0 | 2 (0.1) |
| MACE | | | | | |
| Cardiac disorder SOC (fatal) | 3 (0.3) | 2 (0.2) | 1 (0.1) | 3 (0.7) | 9 (0.3) |
| Vascular disorder SOC (fatal) | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| SMQ Ischemic heart disease sub-SMQ myocardial infarction (any) | 9 (1.0) | 4 (0.5) | 12 (1.4) | 4 (0.9) | 29 (0.9) |
| Stroke PV (any) | 11 (1.2) | 3 (0.3) | 3 (0.3) | 1 (0.2) | 18 (0.6) |
| Sudden death PT | 1 (0.1) | 0 | 0 | 1 (0.2) | 2 (0.1) |
| Cardiac death PT | 0 | 0 | 0 | 0 | 0 |
| Sudden cardiac death PT | 0 | 1 (0.1) | 1 (0.1) | 0 | 2 (0.1) |

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

Adjudicated analysis-COPD

The sponsor also performed an adjudicated analysis of deaths and SAEs, specifically evaluating for respiratory-related causes. Deaths and SAEs were adjudicated as described in section 7.1.2 Categorization of Adverse Events. The analysis populations are summarized in Table 157. The All-treated COPD safety population I consisted of all COPD patients who received at least one dose of trial medication in trials >7 days in duration. In cross-over trials, only data from the first treatment period was analyzed. For these reasons, the total olodaterol exposure in the All-treated COPD safety population I (N=2868) does not equal the total olodaterol exposure in COPD patients in the olodaterol clinical development program (N=3353). Although the bulk of the patients in

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this safety population were derived from the 48 week COPD trials, this safety population also included patients from trials with shorter exposures (COPD dose ranging trials and 6 week treatment period cross-over trials). As deaths, SAEs and hospitalization are not common events and are more likely to occur in longer duration trials, inclusion of these shorter exposure trials may lead to an underestimate of these events with long-term use.

Table 157. All trials in olodaterol development program. Adjudicated safety data sets

| | Placebo | Olo 2mcg qD | Olo 2mcg BID | Olo 2.5mcg BID | Olo 5mcg qD | Olo 5mcg BID | Olo 10mcg qD | Olo 20mcg qD | Olo Total | Form 12mcg BID | Tio 18mcg qD |
|--------------------|---------|-------------------|--------------------|----------------------|-------------------|--------------------|--------------------|--------------------|--------------|----------------------|--------------------|
| All treated | 1409 | 258 | 11 | 34 | 1401 | 46 | 1457 | 173 | 3380 | 541 | 57 |
| All-treated COPD I | 1254 | 165 | 11 | 0 | 1273 | 12 | 1328 | 79 | 2868 | 508 | 57 |
| All-treated asthma | 155 | 93 | 0 | 34 | 128 | 34 | 129 | 94 | 512 | 33 | 0 |

source: SCS; table 2; pg148

With regard to asthma-related, pneumonia-related, other respiratory-related, and non-respiratory related deaths, there were no significant imbalances between olodaterol groups and placebo. However, there were imbalances when comparing olodaterol 5mcg to placebo in deaths related to key respiratory events (Olo 5mcg=0.7%, placebo=0.4%) and total respiratory events (Olo 5mcg=0.6%, placebo=0.4%). This was driven almost totally by COPD-related deaths [Olo 5mcg (0.6%) to placebo (0.3%)]. It should be noted that the overall numbers were small and an imbalance was not seen between placebo and olodaterol 10mcg. This implies that the imbalance may not be solely related to drug exposure and is more likely a chance occurrence. This imbalance in COPD related deaths was previously discussed in section 7.3.1 Deaths.

Hospitalizations related to total respiratory events, key respiratory events, and COPD-related events were more frequent in the placebo group compared to olodaterol 5mcg and olodaterol 10mcg. Hospitalizations related to asthma and pneumonia were similar in frequency between olodaterol and placebo groups. Hospitalizations due to other respiratory related events were more frequent in olodaterol 5mcg and olodaterol 10mcg (0.5% and 0.9%, respectively) compared to placebo (0.2%). The non-respiratory events were primarily related to neoplasms (see section 7.3.2 Nonfatal Serious Adverse Events for discussion of neoplasms). Intubations were rare (<1%) and were balanced between treatment groups.

As the combined dataset included exposures of various durations, the sponsor also conducted an exposure adjusted analysis of deaths. For deaths related to COPD, pneumonia, other respiratory events, non-respiratory events, and all events; the rate per 100 patient-years ranged from 0-1.67. In olodaterol 5mcg the rate ranged from 0.12-

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1.58. For olodaterol 10mcg the range was from 0.49-2.18. In almost all cases, the difference between olodaterol groups and placebo was small with 95% confidence intervals crossing zero. For other respiratory related deaths in the olodaterol 10mcg compared to placebo, the 95% confidence interval did not cross zero (0.075-1.146). It should be noted that the total number of events was small (N=5) and given the number of comparisons, this finding is of unclear significance.

Adjudicated Analysis-Asthmatics

As there is a known LABA safety signal in asthmatics, safety data from the asthma dose ranging trials was specifically analyzed by the adjudication committee. In the asthma safety population, there was a single respiratory-related hospitalization (pneumonia) that occurred in a patient receiving olodaterol 10mcg. One olodaterol 20mcg patient was reported to have a non-respiratory related event. There were no intubations and there were no deaths in the asthma safety population. Based on this analysis, no safety signal was evident; however, the overall exposure in the asthma population was small.

Beta2-adrenergic effects

The sponsor also analyzed AEs using multiple pharmacovigilance/SMQ endpoints which were potentially representative of beta2-adrenergic class effects. For the PVs, the grouped PTs were reasonable. The PV/SMQs with the highest frequency were the arthralgia/myalgia/muscle weakness PV and the accident and injuries SMQ. There were no clinically significant imbalances in the PV/SMQ analysis.

Bronchoconstriction

The sponsor also analyzed the data for respiratory events indicative of bronchoconstriction. These events included drops in FEV₁≥15%; rescue medication use within 30 minutes of test medication inhalation during a clinic visit; and cough, wheeze or dyspnea AE reported within 30 minutes of test medication inhalation during a clinic visit. Based on this analysis, olodaterol patients had a lower frequency of these events individually and in any combination. Use of olodaterol does not appear to be associated with paradoxical bronchoconstriction.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common TEAEs reported in the 48-week COPD trials were within the respiratory thoracic and mediastinal and infections and infestations SOC. The most common PTs were COPD exacerbation (28.3%), nasopharyngitis (9.8%), upper respiratory infection (7.5%), dyspnea (3.9%), and bronchitis (3.8%). No TEAEs based on SOC or PT demonstrated a dose response. However, several PTs were more common in both olodaterol groups compared to placebo. These included nasopharyngitis, urinary tract infection, back pain, and arthralgia. Of note, pneumonia

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was most common in olodaterol 10mcg and similar in frequency between olodaterol 5mcg and placebo, which is consistent with the SAE and pneumonia PV data (section 7.3.2 Nonfatal Serious Adverse Events and 7.3.5 Submission Specific Primary Safety Concerns). The common TEAE results are summarized in Table 158. Note that the cardiac disorder SOC is not included on this table as no cardiac disorder PTs occurred in ≥2% of the total population.

Table 158. TEAE reported in ≥2% of patients in the 48 week COPD trials

| SOC/PT | Placebo N(%) | Olo 5mcg N(%) | Olo 10mcg N(%) | Formoterol 12mcg N(%) | Total N(%) |
|--|-----------------|------------------|-------------------|-----------------------------|---------------|
| Number of patients | 885 (100.0) | 876 (100.0) | 883 (100.0) | 460 (100.0) | 3104 (100.0) |
| Total with AEs, N (%) | 627 (70.8) | 622 (71.0) | 642 (72.7) | 318 (69.1) | 2209 (71.2) |
| Infections and infestations | 292 (33.0) | 333 (38.0) | 317 (35.9) | 147 (32.0) | 1089 (35.1) |
| Nasopharyngitis | 68 (7.7) | 99 (11.3) | 91 (10.3) | 46 (10.0) | 304 (9.8) |
| Upper respiratory tract infection | 66 (7.5) | 72 (8.2) | 62 (7.0) | 32 (7.0) | 232 (7.5) |
| Bronchitis | 32 (3.6) | 41 (4.7) | 31 (3.5) | 13 (2.8) | 117 (3.8) |
| Pneumonia | 24 (2.7) | 22 (2.5) | 35 (4.0) | 14 (3.0) | 95 (3.1) |
| Urinary tract infection | 9 (1.0) | 22 (2.5) | 16 (1.8) | 5 (1.1) | 52 (1.7) |
| Influenza | 16 (1.8) | 16 (1.8) | 9 (1.0) | 11 (2.4) | 52 (1.7) |
| Sinusitis | 21 (2.4) | 8 (0.9) | 20 (2.3) | 1 (0.2) | 50 (1.6) |
| Gastroenteritis | 11 (1.2) | 10 (1.1) | 8 (0.9) | 10 (2.2) | 39 (1.3) |
| Nervous system disorders | 78 (8.8) | 71 (8.1) | 84 (9.5) | 31 (6.7) | 264 (8.5) |
| Headache | 32 (3.6) | 25 (2.9) | 30 (3.4) | 15 (3.3) | 102 (3.3) |
| Dizziness | 19 (2.1) | 20 (2.3) | 18 (2.0) | 7 (1.5) | 64 (2.1) |
| Vascular disorders | 47 (5.3) | 50 (5.7) | 45 (5.1) | 18 (3.9) | 160 (5.2) |
| Hypertension | 30 (3.4) | 23 (2.6) | 26 (2.9) | 8 (1.7) | 87 (2.8) |
| Respiratory, thoracic and mediastinal disorders | 370 (41.8) | 317 (36.2) | 352 (39.9) | 176 (38.3) | 1215 (39.1) |
| COPD | 255 (28.8) | 227 (25.9) | 266 (30.1) | 131 (28.5) | 879 (28.3) |
| Cough | 35 (4.0) | 37 (4.2) | 35 (4.0) | 27 (5.9) | 134 (4.3) |
| Dyspnea | 37 (4.2) | 35 (4.0) | 25 (2.8) | 25 (5.4) | 122 (3.9) |
| Gastrointestinal disorders | 123 (13.9) | 116 (13.2) | 120 (13.6) | 55 (12.0) | 414 (13.3) |
| Diarrhea | 22 (2.5) | 25 (2.9) | 22 (2.5) | 11 (2.4) | 80 (2.6) |
| Constipation | 15 (1.7) | 5 (0.6) | 19 (2.2) | 3 (0.7) | 42 (1.4) |
| Musculoskeletal and connective tissue disorders | 96 (10.8) | 121 (13.8) | 115 (13.0) | 67 (14.6) | 399 (12.9) |
| Back pain | 24 (2.7) | 31 (3.5) | 28 (3.2) | 18 (3.9) | 101 (3.3) |
| Muscle spasms | 11 (1.2) | 12 (1.4) | 8 (0.9) | 10 (2.2) | 41 (1.3) |
| Arthralgia | 7 (0.8) | 18 (2.1) | 14 (1.6) | 6 (1.3) | 45 (1.4) |
| General disorders and administration site conditions | 73 (8.2) | 71 (8.1) | 77 (8.7) | 42 (9.1) | 263 (8.5) |
| Chest Pain | 16 (1.8) | 11 (1.3) | 16 (1.8) | 13 (2.8) | 56 (1.8) |
| Pyrexia | 17 (1.9) | 12 (1.4) | 20 (2.3) | 12 (2.6) | 61 (2.0) |

Source: SCS; table 2.1.2.1.1:1; pg 54

Overall the common TEAEs reported were typical and expected in a LABA development program

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7.4.2 Laboratory Findings

Clinical laboratories were measured at week 0, 6, 12, 24, 48, and at the end of study visit. Labs were drawn at 1 and 3 hours post-dosing at the 6 and 12 week visits. At week 0, 24, and 48 fasting labs were drawn.

Chemistries and Hematology

In general, review of clinical laboratory findings did not identify any specific safety concerns. Mean changes from baseline to the last value on treatment were generally small and similar between groups. Shift table analysis also generally did not demonstrate any significant differences between groups. Possible clinically significant (PCS) lab changes were relatively infrequent and evenly distributed.

Notably for serum potassium levels, there were no differences in mean values from baseline to end of treatment between placebo and olodaterol groups. Shift table analysis also demonstrated no differences between groups. PCS lab changes were infrequent and similar in frequency across groups.

For serum glucose, there were no differences between groups based on mean changes and shift table analysis. However, PCS increases for serum glucose were slightly more common in olodaterol 5mcg (3.7%) compared to placebo (2.6%). This was not dose dependent (Olo 10mcg=2.8%).

For CPK, analysis based on mean serum concentrations and shift table consistently demonstrated differences between olodaterol groups to placebo. For serum CPK, there was a mean change between baseline and last value on treatment of 27 U/L (median 12U/L) for olodaterol 10mcg compared to -1 U/L (median 4 U/L) for olodaterol 5mcg and -22 U/L (median -8 U/L) for placebo. CPK levels at week 12 and 24 were also compared to baseline. The results were similar. Note that in these analyses, the change from baseline for the olodaterol groups was lesser in magnitude than for the formoterol group. Shift analysis also demonstrated differences in CPK when comparing baseline values to those at the end of trial. For the placebo group, 2.5% of patients shifted from a normal baseline to greater than the upper limits of normal. This is in contrast to olodaterol 5mcg and olodaterol 10mcg, where the frequencies were 6.7% and 8.7%. The frequency in formoterol patients (12.7%) was greater than both placebo and olodaterol groups. A similar shift analysis was performed comparing baseline CPK values to maximum during the trials. The results demonstrated a similar trend. For placebo, olodaterol 5mcg, olodaterol 10mcg, and formoterol, the frequencies were 8.2%, 14.1%, 17.7%, and 21.4%, respectively. Based on this data, olodaterol exposure clearly affects serum CPK levels in a dose dependent manner. However, the magnitude of this effect appears to be less than formoterol, an approved product. While the mean change from baseline was greater in the olodaterol groups compared to placebo, the mean change for olodaterol 5mcg was still negative. There is a clear relationship between olodaterol exposure and increased CPK levels. However, it should also be noted that only patients in the olodaterol 10cmg group (5) reported the AE of CPK

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elevated compared to 0 in placebo and olodaterol 5mcg groups. This implies that while CPK serum elevations are observed in a dose dependent manner, they are only clinically relevant at the 10mcg dose. As the sponsor's proposed dose is 5mcg, CPK elevations are likely not a significant safety issue. The sponsor also analyzed the AE frequency and distribution in the subset of patients who had shifts from normal baselines to values greater than or equal to the upper limit of normal (N=386); there were no notable differences from the overall population. This further supports the possibility that elevated CPKs are not a significant safety issue.

7.4.3 Vital Signs

Vital signs were monitored at all clinic visits in conjunction with pulmonary function testing. Based on mean values, there were small decreases in both systolic and diastolic blood pressures at the majority of post-baseline assessments. In general, the decreases were similar between groups. Similar results were seen with pulse rate. Marked changes in blood pressure and pulse rates, occurred with similar frequency between treatment groups. The results for marked changes are summarized in Table 159.

Table 159. 48-week trials. Marked changes in vital signs

| | Placebo N(%) | Olo 5mcg N(%) | Olo 10 mcg N(%) | Formoterol N(%) |
|--------------------|-----------------|------------------|--------------------|--------------------|
| Number of patients | 883 (100.0) | 871 (100.0) | 877 (100.0) | 457 (100.0) |
| Systolic BP | | | | |
| Increase | 211 (23.9) | 218 (25.0) | 232 (26.5) | 94 (20.6) |
| Decrease | 135 (15.3) | 163 (18.7) | 149 (17.0) | 54 (11.8) |
| Diastolic BP | | | | |
| Increase | 208 (23.6) | 184 (21.1) | 170 (19.4) | 92 (20.1) |
| Decrease | 174 (19.7) | 167 (19.2) | 175 (20.0) | 51 (11.2) |
| Pulse rate | | | | |
| Increase | 118 (13.4) | 115 (13.2) | 123 (14.0) | 60 (13.1) |
| Decrease | 117 (13.3) | 127 (14.6) | 128 (14.6) | 50 (10.9) |

Marked increase: SBP = 25 mmHg > baseline, DBP = >90 mmHg and >10 mmHg > baseline, Pulse = > 100 bpm if not at that level at baseline and >10 % above baseline.

Marked decrease: SBP = <100 mmHg if not at that level at baseline and >10 mmHg < baseline, DBP = <60 mmHg if not at that level at baseline and >10 mmHg < baseline, pulse = <60 bpm if not at that level at baseline and >10 bpm < baseline.

Source: SCS; table 4.1.1:1; pg100

7.4.4 Electrocardiograms (ECGs)

The sponsor conducted a thorough QT trial under IND 76,363 (trial 1222.8). This was a 6-way crossover trial including placebo, positive control (moxifloxacin), and multiple olodaterol doses (10mcg, 20mcg, 30mcg, and 50mcg). As per QT-interdisciplinary review team (QT-IRT) consult, the results demonstrated that olodaterol increased QTcF in a dose dependent manner. The maximum mean (95% upper confidence bound)

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difference in QTcF from placebo after baseline correction was 3.4 (7.1), 5.9 (9.6) ms, 7.4 (10.9) ms and 8.5 (12.4) ms following doses of 10, 20, 30 and 50 mcg, respectively. Therefore, at doses greater than 10mcg, QT prolongation was observed. The QT-IRT consult also stated that “Pre-dose QTc measurements in Phase 3 parallel group studies at weeks 6, 12, 24 and 48 are not suggestive of a delayed effect at the therapeutic dose.”

During the 48 week COPD trials, 12-lead ECG data was obtained on all participants. ECGs were performed at days 1, 43, 85, 169, and 337. Based on mean values, there were no significant changes from baseline in heart rate, PR interval, and QRS interval. Mean changes from baseline in QTcF were also similar between groups. When analyzing QTcF prolongation based on threshold values (prolongation >30msec or >60 msec), between groups at all assessed timepoints, the frequencies were low and similar. ECGs were also assessed for U-waves, ST segment, T-wave, rhythm, myocardial infarction, ECG conduction and morphological abnormalites. The percentage of patients with abnormalites was generally similar between treatment groups. Based on the ECGs, 23 AEs were reported. These AEs included QT prolongation, T-wave inversion, T-wave amplitude decreased, ST segment depression, abnormal ECG, PR prolongation, and abnormal T-wave. These AEs did not demonstrate a dose response and were fairly evenly spread between treatment groups. Note that ECG assessments were also performed in the phase 3 six week treatment period crossover trials. The results were consistent with the 48-week trials.

Twenty-four hour holter monitoring was also performed in a subset of patients (N=772) in the 48-week COPD trials at days 85, 169, 281, and 337. Based on mean values, there were no dose nor time related trends with regard to heart rate, supraventricular premature beats (SVPB), or ventricular premature beats (VPB). Shift table analysis demonstrated that, in the majority of patients across treatment groups, the number of SVPBs and VPBs at baseline was similar to the last test day. There did not appear to be a consistent trend for increased SVPBs or VPBs in olodaterol groups compared to placebo. The same was true for the formoterol group.

7.4.5 Special Safety Studies/Clinical Trials

not applicable

7.4.6 Immunogenicity

not applicable

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7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

For the SOC Neoplasms benign, malignant, and unspecified, there was suggestion of a possible dose response when analyzing death and SAEs. The neoplasms that drove this dose response were primarily lung related (see sections 7.3.1 Deaths and 7.3.2 Nonfatal Serious Adverse Events), and fell under the high level group term (HLGT) respiratory and mediastinal neoplasms malignant and unspecified. No single preferred term (PT) drove this observation. When examining all TEAEs, a similar dose response was noted, and was again driven by the same HLTG. Given the latency time for lung related neoplasms, it is unlikely that olodaterol could be directly causative of a lung related neoplasm. Additionally, the animal carcinogenicity studies did not demonstrate a lung related neoplasm signal. It should also be noted that while there was an imbalance, the frequency of events for olodaterol 5mcg was similar to/less than for formoterol. In addition the trial population, all of which have a significant smoking history, is prone to development of lung-related neoplasms, and that overall, these were not common events (<1%).

7.5.2 Time Dependency for Adverse Events

The sponsor did not perform a specific analysis of safety data for time dependency and adverse events. However, the safety profile from the 6 week treatment period crossover trials (trial 1222.24/25/39/40/37/38) and 48 week parallel group COPD trials were generally similar. The top three most common SOCs for all AEs were the same (infections and infestations, RTM, and musculoskeletal and connective tissue). Not surprisingly, there were more deaths and SAEs in the 48 week trials compared to the 6 week treatment period crossover trials. COPD exacerbations during treatment period were also more frequent in the 48-week versus 6-week crossover trials.

7.5.3 Drug-Demographic Interactions

The sponsor performed a variety of subgroup safety analyses based on baseline demographic information. There were no meaningful differences regarding the pattern/frequency of AEs based on sex and race. Based on age, SAEs were more frequent in the ≥65 year olds (19.4%) compared to <65 years olds (13.4%), but were balanced between treatment groups. Based on region, patterns and frequencies of AEs were generally similar between U.S., European, and Asian populations. However, the PT nasopharyngitis was much more frequent in Europe (17.6%) compared to the U.S. (3.9%) and Asia (7.7%). However, the pattern between treatment groups for each region was similar to the total population.

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7.5.4 Drug-Disease Interactions

Subgroup analyses based on baseline COPD disease severity demonstrated that patients with more severe COPD (GOLD criteria), reported similar numbers/frequencies of total AEs. However, the COPD exacerbation (broad) PV was reported more frequently in GOLD IV (42.6%) patients versus GOLD III (36.4%) and GOLD II (33.8%). Overall SAEs were also more common in GOLD IV compared to GOLD II or III. This is not surprising as one would expect that those with more severe disease would be more likely to experience SAEs.

The sponsor also analyzed the safety data for the subset of patients with a history of cardiac disease (N=2360). While AEs in the cardiac disorder SOC were more common compared to the total population, the distribution between treatment groups was similar and consistent with the total population.

Subgroup analysis was also performed based on presence or absence of diabetes and renal impairment. No effect was seen.

The sponsor also subgrouped based on reversibility of FEV1. Reversibility was defined as an increase in FEV1 of $\geq 12\%$ or 200mL following treatment with bronchodilators (albuterol). The total number of AEs was similar between subgroups, as was the pattern of distribution in general. SAEs were higher in the non-reversible subgroup (17.2%) compared to the reversible subgroup (13.7%). This is not necessarily surprising as non-reversible patients have fixed obstruction that is not likely as responsive to LABAs. Non-reversible olodaterol 10mcg patients also had increased frequency of pneumonia PV (4.9%) compared to placebo, olodaterol 5mcg, and formoterol (3%, 3.1%, and 4%, respectively). For the reversible subgroup, a similar trend was seen for olodaterol 10mcg, though not as marked (Olo 10mcg=3%, Olo 5mcg=2.3%, placebo=2.2%, and formoterol=1.9%). Findings were similar for the pneumonia PT. The adjudicated analysis also examined safety in the same subgroups. In the time to event analysis, patients with non-reversible FEV1 in the olodaterol 10mcg group had a HR of 2.29 (95% CI 1.01, 5.21) for the pneumonia related composite endpoint compared to placebo. However, this was not the case for the olodaterol 5mcg group. This is consistent with previously discussed pneumonia safety results where increased pneumonia and/or pneumonia-related endpoints were reported in the olodaterol 10mcg group compared to placebo, but not olodaterol 5mcg.

7.5.5 Drug-Drug Interactions

The sponsor performed 2 drug-drug interaction studies. Olodaterol is eliminated primarily via the CYP 2C9, as such, they performed trial 1222.48 to assess the effect of fluconazole (model inhibitor of CYP 2C9) on the bioavailability of inhaled olodaterol. Systemic exposure to fluconazole did not significantly affect the bioavailability of olodaterol. Trial 1237.3 compared the systemic exposure to olodaterol and tiotropium

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when given as a fixed dose inhaler versus when given as individual components. Neither drug significantly affected the other with regard to systemic exposure when given in combination.

In addition to drug-drug interaction studies, the sponsor performed multiple subgroup analyses based on background COPD medications. In general, for patients on baseline LAMAs, SAMA/LAMAs, ICS, LABAs, or xanthines, overall AEs were higher; however, the distribution of AEs were similar and no new safety signals were revealed. This increase in overall AEs is not surprising given that patients who were on baseline COPD maintenance medications were likely more symptomatic or had more severe disease.

The sponsor also performed subgroup analysis based on baseline LAMA use. Approximately 24% of the safety population was on a LAMA at baseline. Patients in the LAMA subgroup versus no LAMA subgroup were similar with respect to age (65.6 vs. 63.9), duration of COPD (7.7% vs. 7.2%), and pre-bronchodilator FEV1 (44.7% vs. 44%). Overall AEs were higher in the LAMA subgroup (79.2%) versus the no LAMA subgroup (70.9%). This increase was seen throughout all the SOCs and PTs, and was not driven by a single or group of PTs. This is not necessarily surprising as it is likely that patient on LAMAs at baseline were likely more symptomatic compared to patients not taking baseline LAMAs. Between treatment groups, frequencies of AEs were similar in the LAMA subgroup. In the LAMA subgroup, SAEs were most common in the olodaterol 5mcg group (22.2%) compared to placebo (16.7%), olodaterol 10mcg (17.8%), and formoterol (17.8%). The difference between the subgroups was driven by events in the infections and infestations; neoplasms, benign, malignant, and unspecified; and musculoskeletal and connective tissue disorders SOCs. In the no LAMA subgroup SAEs were less common in olodaterol 5mcg (14.5%) compared to placebo (17%) and olodaterol 10mcg (17%) and similar to formoterol (14.3%).

The sponsor performed a similar analysis subgrouping patients based on baseline SAMA/LAMA use. Results were largely similar to the LAMA subgroup analysis.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans. See non-clinical review for animal studies.

7.6.2 Human Reproduction and Pregnancy Data

No specific trials were conduct in pregnant women. There is no human data on exposure during pregnancy. In animal studies, olodaterol's the effects on fertility and

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prenatal development was assessed. No effects were noted at doses relevant to humans.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not-applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

It is expected that overdose with olodaterol would produce typical class effects for LABAs. This was confirmed in BI's clinical development program, in which they studied single inhaled doses up to 70mcg, multiple inhaled doses up to 30mcg, and single IV doses up to 25mcg. LABA class effects were generally noted with more frequency with increasing doses/exposure, though a dose effect was not consistently observed. In the thorough QT trial, a dose effect was also noted with QTcF prolongation. Significant prolongation was only noted at doses >10mcg. Potential for withdrawal and rebound were not formally assessed. Based on the low systemic bioavailability, withdrawal and rebound are not expected.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 120 day update. Data from that submission did not reveal any new issues not already commented on.

This medical officer also reviewed all AE PTs of which the exposure adjusted rate ratios (olandaterol:placebo) were ≥ 4 when comparing olodaterol groups to placebo. If rate ratios were not calculable (ie. because of zero cases in the placebo group), PTs were reviewed if ≥ 4 patients from olodaterol groups reported the event. Of the selected PTs, hematuria demonstrated the highest rate ratio; however, there was no dose response. These findings are of unclear clinical significance. There were 12 PTs whose frequency/rate ratio increased incrementally with increasing dose. These included atelectasis, acute sinusitis, colonic polyp, deep venous thrombosis, dermatitis contact, lung infection, pulmonary embolus, spinal osteoarthritis, tremor, vitamin D deficiency, and increase blood CPK. Lung infection have been previously discussed in the context of respiratory pharmacovigilance endpoints (section 7.3.5 Submission Specific Primary Safety Concerns). The increase blood CPK is consistent with the previously presented lab data. It should be noted that this was reported as an AE only in the olodaterol 10mcg group. With regard to tremors, the incremental increase with increasing dosing is not surprising given the known safety profile of LABAs. With regard to the remaining PTs, given the mechanism of action, the known LABA safety profile, the small overall numbers, and multiple comparisons performed, these imbalances are of unclear clinical significance. These data are summarized in Table 160.

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Table 160. AEs with rate ratios ≥ 4 (olodaterol:placebo) or greater than ≥ 4 events in olodaterol groups if zero events in placebo

| Preferred Term (PT) | Placebo N(%) | events/ 100pt years | Olo 5mcg N(%) | events/ 100 pt years | rate ratio | Olo 10mcg N(%) | events/ 100 pt years | rate ratio |
|-------------------------------------|-----------------|---------------------------|---------------------|----------------------------|---------------|-------------------|----------------------------|---------------|
| Acute sinusitis | 1 (0.1) | 0.14 | 1 (0.1) | 0.13 | 0.92 | 5 (0.6) | 0.65 | 4.74 |
| Atelectasis | 0 | 0 | 1 (0.1) | 0.13 | NC | 4 (0.5) | 0.52 | NC |
| Colonic polyp | 0 | 0 | 2 (0.2) | 0.26 | NC | 5 (0.6) | 0.65 | NC |
| CPK increased | 0 | 0 | 0 | 0 | NC | 6 (0.7) | 0.78 | NC |
| Deep vein thrombosis | 1 (0.1) | 0.14 | 2 (0.2) | 0.26 | 1.91 | 5 (0.6) | 0.65 | 4.76 |
| Dermatitis contact | 0 | 0 | 2 (0.2) | 0.26 | NC | 4 (0.5) | 0.52 | NC |
| Drug Hypersensitivity | 0 | 0 | 4 (0.5) | 0.52 | NC | 0 | 0 | NC |
| Ear Pain | 0 | 0 | 4 (0.5) | 0.52 | NC | 2(0.2) | 0.26 | NC |
| Hematuria | 1 (0.1) | 0.14 | 8 (0.9) | 1 | 7.68 | 7 (0.8) | 0.91 | 6.64 |
| Intervertebral disk degeneration | 0 | 0 | 5 (0.6) | 0.65 | NC | 0 | 0 | NC |
| Lung infection | 1 (0.1) | 0.14 | 5 (0.6) | 0.65 | 4.82 | 5 (0.6) | 0.65 | 4.84 |
| Prostatitis | 1 (0.1) | 0.14 | 5 (0.6) | 0.65 | 4.8 | 0 | 0 | NC |
| Pulmonary embolus | 0 | 0 | 1 (0.1) | 0.13 | NC | 4 (0.5) | 0.52 | NC |
| Skeletal injury | 1 (0.1) | 0.14 | 0 | 0 | NC | 5 (0.6) | 0.65 | 4.75 |
| Spinal osteoarthritis | 0 | 0 | 2 (0.2) | 0.26 | NC | 6 (0.7) | 0.78 | NC |
| Tremor | 1 (0.1) | 0.14 | 2 (0.2) | 0.26 | 1.88 | 5 (0.6) | 0.65 | 4.76 |
| Vitamin D deficiency | 0 | 0 | 1 (0.1) | 0.13 | NC | 4 (0.5) | 0.52 | NC |

NC= not calculable

Source:

SCS supplement; tables 2.11.3.1; pp1610-1631

SCS supplement; tables 2.11.3.3; pp1652-1674

8 Postmarket Experience

There is no postmarketing experience with this product.

9 Appendices

9.1 Literature Review/References

- 1) Laviolette L, Bourbeau J, Bernard S, Lacasse Y, Pepin V, Breton MJ, Baltzan M, Rouleau M, Maltais F. Assessing the impact of pulmonary rehabilitation on functional status in COPD. *Thorax*. 2008 Feb;63(2):115-21.
- 2) Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, Caracta C. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med*. 2011 Apr;105(4):580-7.
- 3) O'Donnell DE, Casaburi R, Vincken W, Puente-Maestu L, Swales J, Lawrence D, Kramer B; INABLE 1 study group. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. *Respir Med*. 2011 Jul;105(7):1030-6.
- 4) O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest*. 2006 Sep;130(3):647-56.
- 5) Puente-Maestu L, Villar F, de Miguel J, Stringer WW, Sanz P, Sanz ML, de Pedro JG, Martínez-Abad Y. Clinical relevance of constant power exercise duration changes in COPD. *Eur Respir J*. 2009 Aug;34(2):340-5.
- 6) FDA Guidance for Industry COPD:Developing Drugs for Treatment (2007). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf> (downloaded 12/12/2012).

9.2 Labeling Recommendations

Labeling negotiations have not begun at the time of this review. However the following issues with the clinical sections of the label have been identified:

- 1) [REDACTED] (b) (4)
- 2) [REDACTED] (b) (4)

3

(b) (4)

9.3 Advisory Committee Meeting

A Pulmonary-Allergy Drug Advisory Committee will be held on January 29, 2013 to discuss the safety, efficacy, and exercise related label claims of this new molecular entity.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H LIM
01/17/2013

THERESA M MICHELE
01/17/2013

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

| | |
|--|------------------------------|
| APPLICATION: NDA 203108 | TRADE NAME: None |
| APPLICANT/SPONSOR: Boehringer Ingelheim | USAN NAME: Olodaterol |
| MEDICAL OFFICER: Robert Lim, M.D. | |
| TEAM LEADER: Theresa M. Michele, M.D. | CATEGORY: LABA |
| DATE: 07/10/12 | ROUTE: Inhalation |

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| Document Date | CDER Stamp Date | Submission | Comments |
|----------------------|------------------------|-------------------|-----------------|
| 5/14/12 | 5/14/12 | NDA 203108, SD#1 | Initial NDA |

RELATED APPLICATIONS

| Document Date | Application Type | Comments |
|----------------------|-------------------------|-----------------|
| | | |

REVIEW SUMMARY:

Boehringer Ingelheim (BI) has submitted 505(b)(1) application for olodaterol solution for oral inhalation indicated for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema (NDA 203,108). It will be administered via the Respimat inhaler. The proposed dose is 5mcg once daily (2 puffs of 2.5mcg). This drug was developed under IND 76,362.

This clinical development program included 30 clinical trials. Twelve (12) were phase 1 trials and seven (7) were phase 2 trials. The phase 3 trials consisted of two sets of replicated 48 week safety and efficacy trials in patients with COPD (1222.11/1222.12 and 1222.13/1222.14), two sets of replicated 6 week serial spirometry trials in COPD patients (1222.24/1222.25 and 1222.39/1222.40), and one set of replicated exercise endurance trials (1222.37/1222.38). Doses used in the phase 3 trials were 5mcg and 10mcg daily based on phase 2 dose ranging trials in patients with COPD and asthma.

This submission is adequate to allow for clinical review. The submission is fileable.

OUTSTANDING ISSUES: comments provided for 74 day letter

RECOMMENDED REGULATORY ACTION

| | | |
|-------------------------|---|---------------------------|
| NDA/SUPPLEMENTS: | FILEABLE <input checked="" type="checkbox"/> | NOT FILEABLE _____ |
| | APPROVAL _____ | APPROVABLE _____ |
| OTHER ACTION: | COMMENTS FOR SPONSOR _____ | |

1. General Information

Boehringer Ingelheim (BI) has submitted a 505(b)(1) application for oral inhalation indicated for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema (NDA 203,108). It will be administered via the Respimat inhaler. The proposed dose is 5mcg once daily (2 puffs of 2.5mcg). This drug was developed under IND 76,362. Olodaterol is a novel long acting beta agonist (LABA) which, per sponsor analysis, requires only once daily dosing. BI plans to market this as a monoproduct; (b) (4)

2. Regulatory History

Prior to submission of this NDA, this product has been the subject of multiple regulatory proceedings (as IND 76,362), summarized below:

1/26/07: IND submission

- Safe to proceed
- Recommended serial spirometry during dose selection trials at day 1 and end of trial (b) (4)

7/17/08: EOP2 meeting 1. The major clinical points of discussion were as follows:

- The 5mcg and 10mcg doses are reasonable to carry forward; however, the optimum dosing interval has not been established.
- Co-primary endpoints of FEV1 AUC(0-3) and trough FEV1 at 12 weeks are reasonable to assess bronchodilator efficacy in phase 3.
- Phase 3 trials (1222.11 and 1222.12) should include a subset of patients with 24 hour serial spirometry to support the bronchodilator profile of olodaterol.
 - 8/19/08 submitted amended protocol:
 - Additional time points for post-dose serial spirometry for a subset of 240 patients in phase 3 trials 1222.11 and 1222.12 were added (out to 12 hours post-dose)
 - We agreed that this would allow for adequate description of FEV1 bronchodilator profile
- 24 hour serial spirometry data from 6 week trials would only be supportive if the treatment effect is similar at 6 weeks compared to 12 weeks [FEV1 AUC(0-3) and trough FEV1]
- Recommended adding COPD exacerbations as a additional secondary endpoint to phase 3 trials.

12/22/09: Advice request. Sponsor submitted data to support once daily dosing (trial 1222.26). Note T-con minutes (7/10) and review refer to it as 1222.6

- Once daily dosing not supported based on the COPD dose posology trial data
- Recommended determining optimum dose and dose regimen in asthmatics prior to proceeding to with COPD development program

7/19/11: Pre-NDA meeting request. Responses 9/28/11. The major points of discussion were as follows:

- Agreed with format of SCE and SES
- Include sub-group analysis using beta-agonist reversibility
- Include treatment by sub-group interaction analysis

- Submit all narratives for SAEs for phase 3 trials
- Include safety analysis for those with a cardiac history
- Include MACE analysis

3. Marketing History

This product has never been approved or marketed in the US or in any foreign countries.

4. Items Required for Filing

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h): 1.1.2
- Index : eCTD
- Summary 2.7 (clinical summary)
- Clinical technical section
 - Clinical study reports
 - Study reports 5.3.5.1
 - Reports of analyses of data from more than one study: 5.3.5.3
 - Integrated summary of efficacy 2.7.3
 - Integrated summary of safety 2.7.4
 - Good Clinical Practice: within the body of each CSR
 - Debarment certification: 1.3.3
 - Pediatric use: 1.9.1- Waiver
- Labeling: 1.14
- Case report forms: 5.3.5.1
- Financial disclosure 1.3.4

5. Development Program

This clinical development program includes 30 clinical trials. Twelve (12) were phase 1 trials and seven (7) were phase 2 trials. The phase 3 trials consisted of two sets of replicated 48 week safety and efficacy trials in patients with COPD (1222.11/1222.12 and 1222.13/1222.14), two sets of replicated 6 week serial spirometry trials in COPD patients (1222.24/1222.25 and 1222.39/1222.40), and one set of replicated exercise endurance trials (1222.37/1222.38).

Doses used in the phase 3 trials were 5mcg and 10mcg daily based on phase 2 dose ranging trials in patients with COPD and asthma. Trials pertinent to the proposed indication are summarized in the Table 1, in which trials conducted in an asthma population are shaded.

Table 1. Studies in Clinical Development Program

| Study | Objective | Design | Population | Ciclesonide Dose | Treatment Duration | Primary endpoint |
|----------------|----------------|---------------|--|---|--------------------|------------------|
| Phase 2 | | | | | | |
| 1222.3 | Dose range, PK | R, DB, PC, CO | COPD patients ≥40 years old N=36 | Olo 2 mcg x1 Olo 5 mcg x1 Olo 10 mcg x1 Olo 20 mcg x1 Pbo x 1 | single dose | Trough FEV1 |
| 1222.5 | Dose range | R, DB, PC, MC | COPD patients ≥40 years N=405 | Olo 2 mcg Olo 5 mcg Olo 10 mcg Olo 20 mcg | 4 weeks | Trough FEV1 |

| | | | | | | |
|---------|---------------|-------------------|------------------------------------|---|---------|---|
| | | | | Pbo | | |
| 1222.26 | Dose posology | R, DB, PC, CO | COPD patients ≥40 years N=47 | Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2 mcg BID Pbo | 3 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.6 | Dose range | R, DB, PC, MC | Asthma ≥18 years N=296 | Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Pbo | 4 weeks | Trough FEV1 |
| 1222.27 | Dose Range | R, DB, PC, AC, CO | Asthma 18-70 years N=198 | Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Foradil 12 mcg BID Pbo | 4 weeks | FEV1 AUC ₍₀₋₂₄₎ |
| 1222.29 | Dose posology | R, DB, PC, CO | Asthma 18-70 years N=180 | Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2.5 mcg BID Pbo | 3 weeks | FEV1 AUC ₍₀₋₂₄₎ |

Phase 3

| | | | | | | |
|---------|---------------------------|-------------------|----------------------------|--|----------|---|
| 1222.11 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=624 | Olo 5 mcg qD Olo 10 mcg qD | 48 weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 85 |
| 1222.12 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=642 | Olo 5 mcg qD Olo 10 mcg qD | 48 weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 85 |
| 1222.13 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=904 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID | 48 weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 169 |
| 1222.14 | Safety, Efficacy, PK | R, DB, PC, MC | COPD ≥40 years N=934 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID | 48 weeks | FEV1 AUC ₍₀₋₃₎ Trough FEV1 at day 169 |
| 1222.25 | 24 hour FEV1 time profile | R, BD, PC, AC, CO | COPD ≥40 years N=99 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.26 | 24 hour FEV1 time profile | R, BD, PC, AC, CO | COPD ≥40 years N=100 | Olo 5 mcg qD Olo 10 mcg qD Foradil 12 mcg BID Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.39 | 24 hour FEV1 time profile | R, BD, PC, AC, CO | COPD ≥40 years N=108 | Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.40 | 24 hour FEV1 time profile | R, BD, PC, AC, CO | COPD ≥40 years N=122 | Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo | 6 weeks | FEV1 AUC ₍₀₋₁₂₎ FEV1 AUC ₍₁₂₋₂₄₎ |
| 1222.37 | Exercise endurance | R, DB, PC, CO | COPD ≥40 years N=151 | Olo 5 mcg qD Olo 10 mcg qD Pbo | 6 weeks | Endurance time IC FRC |
| 1222.38 | Exercise | R, DB, | COPD | Olo 5 mcg qD | 6 weeks | Endurance time |

| | | | | | | |
|--|-----------|--------|--------------------|----------------------|--|-----------|
| | endurance | PC, CO | ≥40 years N=151 | Olo 10 mcg qD Pbo | | IC FRC |
|--|-----------|--------|--------------------|----------------------|--|-----------|

R=randomized, DB=double-blind, PC=placebo controlled, MC=multi-center, OL=open label, CO=cross-over, Olo=olodaterol

6. Clinical Studies

Only studies pertinent to the proposed indication will be reviewed below. All trials in Table 1, except for 1222.37 and 1222.38 will be reviewed in this document. Trials 1222.37 and 1222.38 were both exercise endurance trials. Claims related to exercise endurance trials have historically not been included in COPD label. Although these trials will not be reviewed in this filing document, they will be reviewed in the NDA review because the sponsor has included ^{(b) (4)} claims based on them.

Dose Ranging in COPD

6.1. Trial 1222.3

This was double-blind, randomized, placebo controlled, 5-way crossover, dose ranging in moderate to severe stable COPD patients. Each patient received a single dose of placebo, 2, 5, 10, and 20 mcg of Olo in a random sequence delivered via the Respimat inhaler. These doses were separated by a 14 day washout period. After each dose, serial PFTs were conducted over a 24 hour time period. The primary endpoint was difference from placebo in FEV1 at 24 hours after dosing. The study results for the primary endpoint are summarized in Table 2.

Table 2. Trial 1222.3. Primary Endpoint. FEV1 24 hours after dosing

| Treatment | N (total=36) | FEV1 [L] (SE) | Difference from placebo (95% CI) |
|------------|-----------------|---------------|-------------------------------------|
| Placebo | 35 | 0.916 (0.014) | — |
| Olo 2 mcg | 35 | 0.986 (0.014) | 0.070 (0.020) |
| Olo 5 mcg | 35 | 1.015 (0.014) | 0.099 (0.020) |
| Olo 10 mcg | 34 | 1.029 (0.014) | 0.113 (0.020) |
| Olo 20 mcg | 35 | 1.035 (0.014) | 0.119 (0.020) |

all p-values<0.0001 compared to placebo

Source: Trial 1222.3 CSR; Table 11.4.1.1:1; pp76

All doses demonstrated a statistically significant improvement compared to placebo, and in general there was a dose response.

6.2. Trial 1222.5

This was double-blind, randomized, placebo controlled, parallel group, dose-ranging trial in patients with moderate to severe stable COPD. Patients received 4 weeks of once daily olodaterol (2 mcg, 5 mcg, 10 mcg, and 20 mcg). The primary endpoint was trough FEV1 response after 4 weeks of treatment (change from baseline). The results for the primary endpoints are summarized in Table 3.

Table 3. Trial 1222.5. Primary Endpoint. Trough FEV1 response after 4 weeks.

| Treatment | N (total=405) | Trough FEV1 [L] Response (SE) | Difference from placebo (SE) |
|------------|------------------|----------------------------------|------------------------------|
| Placebo | 79 | -0.014 (0.021) | |
| Olo 2 mcg | 81 | 0.046 (0.021) | 0.061 (0.027) |
| Olo 5 mcg | 80 | 0.082 (0.021) | 0.097 (0.027) |
| Olo 10 mcg | 86 | 0.109 (0.021) | 0.123 (0.026) |
| Olo 20 mcg | 79 | 0.118 (0.021) | 0.132 (0.027) |

all p-values <0.05 compared to placebo

Source: Trial 1222.5 CSR; Table 11.4.1.1:1; pp81

All doses demonstrated a statistically significant benefit compared to placebo. These results also demonstrated a clear dose response.

6.3. Trial 1222.26

This was double-blind, randomized, 4-way crossover, dose interval trial in 47 patients with moderate to severe stable COPD. The objective of this trial was to determine optimum dosing interval (qD versus BID). Each treatment period lasted 3 weeks with no washout period between. The doses of olodaterol used were 2 mcg BID, 5 mcg BID, 5 mcg qD, and 10 mcg qD. There was no placebo group as patients were compared to their own baseline. The co-primary endpoints were FEV1 AUC(0-12) and FEV1 AUC(12-24) response after 3 weeks of treatment. The results for the co-primary endpoints are summarized in Table 4.

Table 4. Trial 1222.26. FEV1 AUC(0-12), (12-24), (0-24) response and trough FEV1 response after 3 weeks of treatment

| Interval | Treatment Group | FEV1 AUC (interval) |
|-------------|-----------------|------------------------|
| 0-12 hours | Olo 2 mcg BID | 0.155 (0.024) |
| | Olo 5 mcg qD | 0.209 (0.024) |
| | Olo 5 mcg BID | 0.189 (0.024) |
| | Olo 10 mcg qD | 0.204 (0.024) |
| 12-24 hours | Olo 2 mcg BID | 0.167 (0.022) |
| | Olo 5 mcg qD | 0.155 (0.022) |
| | Olo 5 mcg BID | 0.201 (0.022) |
| | Olo 10 mcg qD | 0.149 (0.022) |

Source: Trial 1222.26 CSR; Table 11.4.1.1:1; pp74

Based on this data, patients responded similarly to Olo 10mcg qD and 5mcg qD, which is consistent with the phase 3 trials. The treatment effect for Olo 5mcg BID was superior to Olo 10mcg qD based on FEV1 AUC(12-24). When comparing Olo 5mcg qD and 2mcg BID, the 5mcg dose was only superior for FEV1 AUC(0-12), but not FEV1 AUC (12-24).

Reviewer comment on COPD dose ranging trials:

Based on these trials, all tested doses of olodaterol demonstrated a significant bronchodilator effect. Additionally, there was, in general, a dose response. However, as doses were increased, the incremental benefit achieved from the higher dose decreased. This was most notable after the 5mcg dose. As such, 5mcg may be approaching the plateau of the dose response curve. With regard to dose interval, the once daily dosing appears equivalent/slightly less effective

compared to twice daily dosing. With regard to safety, olodaterol was fairly well tolerated in these trials.

Dose Ranging in Asthma

6.4. Trial 1222.6

This was a 4-week multi-center, randomized, double-blind placebo controlled, parallel group dose ranging trial in patients with asthma. Patients were randomized to receive either placebo or olodaterol at doses of 2, 5, 10, or 20 mcg once daily. The primary endpoint was trough FEV1 response after 4 weeks of treatment. For the primary endpoint, only the Olo 20 mcg group demonstrated a statistically significant improvement compared to placebo. The other olodaterol doses did demonstrate a trend for an effect; however, there was no evidence of a dose response.

6.5. Trial 1222.27

This was a multi-center, randomized, double-blind placebo controlled, active controlled, incomplete-crossover, dose ranging trial in patients with persistent asthma. Patients were randomized to receive a sequence of 4 out of a possible 6 treatments (Olo 2, 5, 10, 20 mcg qD, placebo, and Foradil 12mcg BID). Each treatment period was for 4 weeks. The primary endpoint was FEV1 AUC(0-24) response measured after 4 weeks of treatment. The results for the primary endpoint are summarized in Table 5.

Table 5. Trial 1222.27. Primary endpoint. FEV1 AUC(0-24) response after 4 weeks of treatment

| Treatment | N (total =198) | FEV1 AUC(0-24) [L] Response (SE) | Difference from placebo (SE) |
|------------|-------------------|-------------------------------------|------------------------------|
| Placebo | 122 | -0.004 (0.025) | |
| Olo 2 mcg | 119 | 0.135 (0.025) | 0.140 (0.022) |
| Olo 5 mcg | 126 | 0.178 (0.025) | 0.182 (0.021) |
| Olo 10 mcg | 121 | 0.201 (0.025) | 0.205 (0.022) |
| Olo 20 mcg | 119 | 0.225 (0.025) | 0.229 (0.022) |
| Foradil | 122 | 0.164 (0.025) | 0.169 (0.022) |

p-values <0.05 for comparisons to placebo

Source: Trial 1222.27 CSR; Table 11.4.1.1:1; pp93

All doses of olodaterol and Foradil demonstrated a statistically significant response with regard to the primary endpoint ($p<0.05$). There was also a clear dose response for olodaterol. All differences from placebo were statistically significant.

6.6. Trial 1222.29

This was double-blind, randomized, incomplete block, 3-way crossover, placebo controlled, dose interval trial in patients with moderate to severe persistent asthmatics. The objective of this trial was to determine optimum dosing interval (qD versus BID). Patients were randomized to 1 of 12 possible sequences in which they received either Olo 2.5mcg BID, Olo 5mcg qD, or placebo in a pre-determined order (6 possible sequences); or Olo 5mcg qD, Olo 10mcg qD, or placebo in a pre-determined sequence (6 possible sequences). The primary endpoint was FEV1 AUC(0-24) response after 3 weeks of treatment. These results are summarized in Table 6.

Table 6.Trial 1222.29. FEV1 AUC(0-24) response after 3 weeks of treatment

| Interval | Treatment Group | FEV1 AUC (interval) | Difference from placebo |
|------------|-----------------|------------------------|----------------------------|
| 0-24 hours | Placebo | 0.022 (0.020) | |
| | Olo 2.5 mcg BID | 0.213 (0.024) | 0.191 (0.020) |
| | Olo 5 mcg qD | 0.173 (0.024) | 0.150 (0.020) |
| | Olo 5 mcg BID | 0.250 (0.024) | 0.228 (0.020) |
| | Olo 10 mcg qD | 0.231 (0.024) | 0.209 (0.020) |

p-values<0.05 for all comparisons to placebo

Source: Trial 1222.29 CSR; Table 11.4.1.1:1; pp88

Based on the co-primary endpoints and the secondary endpoints (data not shown), all doses and dose regimens of olodaterol demonstrated a significant bronchodilatory effect compared to placebo. However, it is important to note that across all parameters, Olo 2.5mcg BID had a greater treatment effect than Olo 5mcg qD. A similar pattern can be seen when comparing Olo 5mcg BID to Olo 10mcg qD.

Reviewer Comment on asthma dose ranging trials:

Based on these trials, all doses of olodaterol demonstrated efficacy as a bronchodilator (except for trial 1222.6). There was also, in general, a dose response. As with some of the COPD dose ranging trials, while there was a dose response, the incremental benefit decreased with increasing doses. The greatest improvement were generally seen between the 2 and 5mcg olodaterol doses. As such, based on these trials, 5mcg may be the optimum total daily dose. With regard to dose interval, results from trial 1222.29 imply that olodaterol may be more optimally dosed BID, rather than qD. However, based on the totality of dosing data, the 5mcg total daily dose may be acceptable. With regard to safety, olodaterol was relatively well tolerated.

48 week Phase 3 COPD Trials

6.7. Trial 1222.11/1222.12

These were identically designed trials. They were multi-center, randomized, double-blind placebo controlled, 48 week trials to assess the safety and efficacy of two doses of olodaterol (5mcg qD and 10mcg qD) for the treatment of COPD. These COPD patients had FEV<80% predicted and were current smokers, or had at least a 10 year pack history. The co-primary endpoints were assessed at 12 weeks (day 85), the remainder of the trial was for collection of safety data. Patients were allowed to continue with inhaled corticosteroids and anticholinergics for the duration of the trial. At randomization patients were stratified based on tiotropium use. If a patient were started on tiotropium during the trial, they would be discontinued. The co-primary endpoints for this trial were FEV1 AUC(0-3) response and trough FEV1 response at week 12. The results are summarized in Table 7.

Table 7. Trial 1222.11/1222.12. Co-primary endpoints. FEV1 AUC(0-3) and trough FEV1 response at 12 weeks (day 85)

| Treatment Group | 1222.11 | | | 1222.12 | | |
|-----------------|--------------------------------------|------------------------------|---------|--------------------------------------|------------------------------|---------|
| | FEV AUC(0-3) [L] Response (SE) | Diff from placebo (SE) | p-value | FEV AUC(0-3) [L] Response (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.007 (0.014) | | | 0.008 (0.013) | | |
| Olodaterol 5 µg | 0.165 | 0.172 | <0.0001 | 0.159 | 0.151 | <0.0001 |

| | | | | | | |
|------------------|-----------------------------|------------------|---------|-----------------------------|------------------|---------|
| | (0.014) | (0.019) | | (0.013) | (0.017) | |
| Olodaterol 10 µg | 0.169 (0.014) | 0.176 (0.019) | <0.0001 | 0.152 (0.013) | 0.143 (0.017) | <0.0001 |
| | Trough FEV1 Response [L] | | | Trough FEV1 Response [L] | | |
| Placebo | -0.041 (0.014) | | | -0.003 (0.014) | | |
| Olodaterol 5 µg | 0.050 (0.014) | 0.091 (0.019) | <0.0001 | 0.044 (0.014) | 0.047 (0.019) | 0.0116 |
| Olodaterol 10 µg | 0.060 (0.014) | 0.101 (0.019) | <0.0001 | 0.045 (0.014) | 0.048 (0.019) | 0.0095 |

Source:

Trial 1222.11 CSR; Tables 11.4.1.1:1, 11.4.1.1:3; pp 86 & 87

Trial 1222.12 CSR; Tables 11.4.1.1:1, 11.4.1.1:3; pp 88 & 89

In both trials, for both co-primary endpoints, both doses of olodaterol were better than placebo alone. However, there was no significant incremental benefit for the higher olodaterol dose. Note that in these trials, the sponsor also analyzed the same endpoints at day 43 (week 6). For trial 1222.12, the treatment effect with respect to FEV1 AUC(0-3) and trough FEV1 was greater at 6 weeks compared to 12 weeks. This is in contrast to trial 1222.11, where the results were similar at both time points.

6.8. Trial 1222.13/1222.14

These identical trials were similar in design to trials 1222.11 and 1222.12. However, there was an additional co-primary end point of change from baseline in Mahler Transitional Dyspnea Indices. The co-primary endpoints were also assessed at week 24 (day 169) rather than week 12 (day 85). Additionally, this trial included Foradil as an active comparator. These trials also examined the SGRQ as a key secondary endpoint.

During trial 1222.13, BI performed 11 on-site audits. One site (2401, PI: Dr. De Salvo) had a compliance issue. This site randomized more patients than any other site in the four 48 week trials. The violation at Dr. De Salvo's site related to a single patient. On that patient's box of returned medication, none of which had been taken, there was a note that indicated that some medication should be removed. This note was left by a study nurse who is believed to have been terminated for other performance issues. This nurse had no role in the measurement of any primary efficacy endpoints in this trial.

The co-primary endpoints for this trial were FEV1 AUC(0-3) response, trough FEV1 response, and TDI response at week 24 (day 169). The sponsor only planned to analyze the TDI data combined with trial 1222.14, as such TDI data is not presented. The data are summarized Table 8.

Table 8. Trial 1222.13/1222.14. Co-primary endpoints. FEV1 AUC(0-3) and trough FEV1 response at week 24

| Treatment Group | Trial 1222.13 | | | Trial 1222.14 | | |
|-----------------|---|------------------------------|---------|---|---------------------------------|---------|
| | FEV AUC(0-3) Response [L] (SE) | Diff from placebo (SE) | p-value | FEV AUC(0-3) Response [L] (SE) | Diff from placebo (SE) | p-value |
| Placebo | -0.009 (0.016) | | | -0.013 (0.014) | | |

| | | | | | | |
|------------------|----------------------|------------------|---------|----------------------|------------------|---------|
| Olodaterol 5µg | 0.142 (0.015) | 0.151 (0.021) | <0.0001 | 0.116 (0.014) | 0.129 (0.019) | <0.0001 |
| Olodaterol 10µg | 0.156 (0.015) | 0.165 (0.021) | <0.0001 | 0.140 (0.014) | 0.154 (0.019) | <0.0001 |
| Foradil 12 µg | 0.168 (0.015) | 0.177 (0.021) | <0.0001 | 0.137 (0.014) | 0.150 (0.019) | <0.0001 |
| | Trough FEV1 Response | | | Trough FEV1 Response | | |
| Placebo | -0.056 (0.015) | | | -0.055 (0.014) | | |
| Olodaterol 5 µg | 0.021 (0.015) | 0.078 (0.021) | 0.0002 | -0.003 (0.014) | 0.053 (0.019) | 0.0055 |
| Olodaterol 10 µg | 0.028 (0.015) | 0.085 (0.021) | <0.0001 | 0.014 (0.014) | 0.069 (0.019) | 0.0003 |
| Foradil 12 µg | -0.002 (0.015) | 0.054 (0.021) | 0.0088 | -0.013 (0.014) | 0.042 (0.019) | 0.0270 |

Source:

Trial 1222.13 CSR; Tables 11.4.1.1:1, 11.4.1.1:3; pp 96 & 98

Trial 1222.14 CSR; Tables 11.4.1.1:1, 11.4.1.1:3; pp 94 & 96

For the co-primary endpoints of FEV AUC(0-3) response and trough FEV1 response, both doses of olodaterol were better than placebo alone. However, there was no significant incremental benefit for the higher olodaterol dose. Foradil also demonstrated a statistically significant treatment effect. Note that the sponsor also analyzed FEV1 AUC(0-3) and trough FEV1 response at week 6 and week 12 (day 43 and 85), as was analyzed in trials 1222.11 and 1222.12. The results for the olodaterol groups were similar at weeks 6 and 12.

With regard to the key secondary endpoint of SGRQ, for both trials, at day 169 both olodaterol doses demonstrated statistically significant improvement from baseline compared to placebo, however the magnitude was <4, the minimal clinically important difference (MCID). Foradil did not demonstrate any benefit with respect to SGRQ.

Reviewer Comments on 48 week trials:

Based on the co-primary endpoints, both doses of olodaterol are effective bronchodilators in COPD patients. However, there is no incremental benefit to the 10mcg dose compared to the 5mcg dose. When comparing results for the co-primary endpoints at the 6 and 12 weeks, the data were variable between trials. ^{(b) (4)}

The audit findings of the de Salvo site are concerning. In BI's phase 3 development program, Dr. de Salvo's site randomized the most patients. It is possible that more patients returned medicine data was affected as a result of the nurse's actions. Although she was not involved in collection of primary endpoint data, her misconduct could potentially substantially affect the results of this trial. While fabricating increased compliance may dilute the treatment effect, it would also dilute potential safety signals. A sensitivity analysis should be performed removing this site from the data set.

6- week serial spirometry trials (COPD)

6.9. Trial 1222.24/1222.25

Trials 1222.24 and 1222.25 were identically designed. These were randomized double-blind, placebo controlled 4-way cross-over trials to characterize the 24-hour FEV1 time profiles of

olodaterol (5mcg and 10mcg once daily) and Foradil (12mcg BID). Each of the four treatment periods lasted 6 weeks. Twenty four hour serial spirometry was performed after six weeks of treatment. The co-primary endpoints were FEV1 AUC(0-12) and (12-24) responses after 6 weeks of treatment. The results for trial 1222.24 are summarized in Table 9. Results for trial 1222.25 were similar and are not shown.

Table 9. Trial 1222.24. Co-primary endpoints. FEV1 AUC(0-12) and (12-24) responses after 6 weeks of treatment

| Interval | Treatment Group | FEV1 AUC (SE) | Diff from placebo (SE) | p-value |
|-------------|--------------------|----------------|------------------------|---------|
| 0-12 hours | Placebo | -0.060 (0.020) | | |
| | Olo 5 mcg qD | 0.088 (0.021) | 0.148 (0.018) | <0.0001 |
| | Olo 10 mcg qD | 0.088 (0.021) | 0.148 (0.018) | <0.0001 |
| | Foradil 12 mcg BID | 0.081 (0.021) | 0.141 (0.018) | <0.0001 |
| 12-24 hours | Placebo | -0.123 (0.021) | | |
| | Olo 5 mcg qD | -0.014 (0.022) | 0.109 (0.019) | <0.0001 |
| | Olo 10 mcg qD | 0.004 (0.022) | 0.127 (0.019) | <0.0001 |
| | Foradil 12 mcg BID | 0.049 (0.022) | 0.172 (0.019) | <0.0001 |

Source: Trial 1222.24 CSR; Tables 11.4.1.1:1, 11.4.1.2.2:1; pp 67 and 69

In both trials, both doses of olodaterol demonstrated significant difference from placebo with respect to FEV1 AUC(0-12) and FEV1 AUC(12-24). There does not appear to be significant incremental benefit of the higher dose of olodaterol.

6.10. Trial 1222.39/1222.40

Trials 1222.39 and 1222.40 were identical in design. These trials were similar in design to 1222.24 and 1222.25, however, the active comparator used in this trial was tiotropium rather than Foradil. The results for these trials were consistent with trials 1222.24/1222.25. Olodaterol and tiotropium also had similar 24-hour FEV1 curves.

Reviewer Comment on 6 week COPD trials:

The results from the 6 week trials demonstrate that olodaterol at both doses may have a sustained bronchodilatory effect for 24 hours. However, based on the 48 week COPD efficacy trials, it is not clear that the response at 6 weeks is the same as at 12 weeks. (b) (4)

Overall Reviewer Comment on clinical trials:

Based on preliminary review of the sponsor's 48 week phase 3 trials, olodaterol is effective as a bronchodilator in COPD. Based on the sponsor's dose ranging data in both asthma and COPD, doses \geq 5mcg per day are likely required for a significant bronchodilator effect. While there is an effect, below 5mcg TDD (i.e. 2mcg), it is minimal and the incremental benefit of the 5mcg dose compared to the 2mcg dose is significant. However, as doses increases to 10 and 20mcg daily, the incremental benefit becomes more modest. The dose ranging results are confirmed in the large phase 3 trials, where there was no benefit of 10mcg over 5mcg daily. Although 5mcg may be the optimum TDD, it is not clear that once daily dosing is ideal. While the COPD dose interval trial results imply that once daily dosing is acceptable, the asthma dose interval trial demonstrates that BID dosing has a greater bronchodilator effect than once daily dosing. However, while BID dosing may have increased efficacy in the 12-24 hour time period, it would not necessarily offer a safety benefit, as systemic exposure/toxicity is similar. Additionally,

based on the 48 week trials, once daily dosing demonstrates statistically and clinically significant bronchodilation compared to placebo.

With regard to safety, the common TEAEs were typical of what one would expect in a COPD trial. With regard to deaths, in the individual 48 week trials (1222.11, 1222.12, 1222.13, and 1222.14), there did not appear to be any significant imbalances. This was consistent with the analysis of the pooled 48 week safety data. With regard to SAEs, in trials 1222.11 and 1222.12 there were more SAEs in the olodaterol groups compare to placebo. However in trials 1222.13 and 1222.14, SAEs occurred with more/similar frequency in the placebo group compared to olodaterol groups. In the pooled safety analysis, overall SAEs were similar across all groups. However, based on preferred terms, atrial fibrillation, cardiac failure and pneumonia were more common in olodaterol patients compared to placebo. Note that for all other preferred terms, SAE frequency was similar between placebo and olodaterol groups. In the pooled analysis, an imbalance was noted for all MACE events when comparing placebo to Olo 10mcg. However, there was no imbalance when comparing placebo to Olo 5mcg, the proposed dose. Select combined safety results are summarized in Table 10.

Table 10. Select safety data from compiled 48-week COPD trials

| Treatment | Placebo N(%) | Olo 5mcg N(%) | Olo 10 mcg N(%) | Foradil 12 mcg N(%) |
|----------------------------------|-----------------|------------------|--------------------|------------------------|
| Number of Patients | 885 | 876 | 883 | 460 |
| Deaths* | 13 (1.5) | 13 (1.5) | 17 (1.9) | 10 (2.2) |
| Cardiac Disorders | 3 (0.3) | 2 (0.2) | 1 (0.1) | 3 (0.7) |
| Infections and Infestations | 1 (0.1) | 3 (0.3) | 4 (0.5) | 1 (0.1) |
| Respiratory Mediastinal Thoracic | 4 (0.5) | 8 (0.9) | 3 (0.3) | 2 (0.4) |
| All MACE events | 9 (1) | 4 (0.5) | 12 (1.4) | 4 (0.9) |
| Fatal MACE | 6 (0.6) | 3 (0.3) | 2 (0.2) | 6 (1.3) |
| SAEs | 145 (16.4) | 138 (15.8) | 147 (16.6) | 69 (15) |
| Atrial Fibrillation | 3 (0.3) | 5 (0.6) | 5 (0.6) | 1 (0.2) |
| Cardiac Failure** | 0 | 5 (0.5) | 3 (0.3) | 1 (0.2) |
| Pneumonia | 13 (1.5) | 14 (1.6) | 22 (2.5) | 7 (1.5) |
| AEs leading to discontinuation | 74 (8.4) | 54 (6.2) | 66 (7.5) | 37 (8) |
| TEAEs | 627 (70.8) | 622 (71) | 642 (72.7) | 318 (69.1) |

*On treatment deaths defined as deaths occurring within 12 days of the last dose of study medication

**Combines PT 'cardiac failure' and 'cardiac failure congestive'

Source: SCS; Table 2.1.1.1.1:1, 2.1.2.1.1:1, 2.1.3.2.1:1, 2.1.4.1.1:1, 2.1.7.2.2:1 ;pp47, 54, 64, 73, 89

7. Brief Review of Proposed Labeling

Proposed labeling has been included in this submission. A brief review was performed. The content and format is presented in the Physician Labeling Review (PLR) format. Issues with their label include

(b) (4)

(b) (4)

(w) (4)

8. DSI/Audit

Selection of sites for audit are based on a combination of financial disclosure, total patients randomized, percent of patients with AEs, SAEs, and MACE events. The consultation request will include the following sites for inspection:

Dr. De Salvo (site 2401 in trial 1222.13)
Centro Medico de la Dra. De Salvo
Capital Federal, Buenos Aires
Cabildo 1548, 1A
C1426ABP, Argentina

This site randomized the most patients overall and had an issue during a BI audit of the site (119 patients)

Dr. Dunn (site 1207, trial 1222.12)
Clinical Research of West Florida, Inc.
2147 North East Coachman Road
Clearwater, FL 33765

This site randomized the second most patients overall and was not previously audited by BI.

Dr. Snell (site 1119 in trial 1222.11)
Mountain View Clinical Research
405 Memorial Drive, Extension
Greer, SC 29651

Dr. Kaelin (site 1112 in trial 1222.11)
Lowcountry Lung & Critical Care
9150 Medcom Street, Suite B
Charleston, SC 29406

These two sites randomized an average number of patients, but had relatively higher reports of AEs, SAEs, and MACE events.

9. Pediatric Development

The sponsor requests a waiver for the pediatric population.

*Reviewer comment:
This is appropriate.*

10. Summary

Boehringer Ingelheim (BI) has submitted a 505(b)(1) application for olodaterol solution for oral inhalation indicated for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema (NDA 203,108). It will be administered via the Respimat inhaler. The sponsor has submitted multiple phase 2 dose ranging trials in asthma and COPD, four 48 week pivotal phase 3 trials, and six 6 week supportive phase 3 trials.

This submission is adequate to allow for filing.

11. Review Timeline

| Milestone | Target date for completion |
|------------------------------------|----------------------------|
| Filing meeting | 06/26/12 |
| Filing review | 07/09/12 |
| Dose Ranging trials | 7/14/12 |
| Trials 1222.11/1222.12 | 8/21/12 |
| Trials 1222.13/1222.14 | 9/7/12 |
| 24 hour spirometry trials | 9/28/12 |
| Analysis of key trials complete | 10/1/12 |
| Mid-cycle review | 10/14/12 |
| Integrated Summary of Efficacy | 10/21/13 |
| Integrated Summary of Safety | 10/30/13 |
| Initial Draft Primary Review to TL | 11/14/12 |
| AC Draft document | 11/17/12 |
| AC Final document | 12/28/12 |
| Draft Label Review to TL | 1/04/13 |
| Wrap up meeting | ~1/17/13 |
| Label due | ? |
| Final Primary Review | 1/17/13 |
| PDUFA Action date (10 months) | 3/14/13 |

12. Filing Checklist

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---------------------------------------|---|-----|----|----|---------|
| FORMAT/ORGANIZATION/LEGIBILITY | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | X | | | |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |

| | Content Parameter | Yes | No | NA | Comment |
|------------------|---|------------|-----------|-----------|----------------|
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (<i>e.g.</i> , are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| LABELING | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| SUMMARIES | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (<i>i.e.</i> , Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | X | | | 505(b)(1) |
| DOSE | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)? Study Number:1222.3 Study Title: Randomised, Double-Blind, Placebo Controlled, 5-Way Cross-Over Study to Assess the Efficacy and Safety of a Single Dose of Orally Inhaled BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) in COPD Patients Sample Size: 36 Arms: see title Location in submission: 5.3.5.1 Study Number:1222.5 Study Title: Randomised, Double-Blind, Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of 4 Weeks of Once Daily Treatment of Orally Inhaled BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) Delivered by the Respimat® Inhaler in Patients with COPD Sample Size: 405 Arms: see title Location in submission: 5.3.5.1 Study Number:1222.26 Study Title: Randomised, double-blind, 4-way cross-over study to determine the 24-hour FEV1-time profile of orally inhaled BI 1744 CL, delivered with the Respimat® inhaler, after 3 weeks of once daily (5 µg [2 actuations of 2.5 [g], 10 [g] [2 actuations of 5 [g]]) or twice daily (2 µg [2 actuations of 1 [g], 5 [g] [2 actuations of 2.5 [g]]) administration in patients with | X | | | |

| | Content Parameter | Yes | No | NA | Comment |
|-----------------|---|------------|-----------|-----------|--|
| | <p>Chronic Obstructive Pulmonary Disease (COPD) Sample Size: 47 Arms: see title Location in submission: 5.3.5.1</p> <p>Study Number: 1222.6 Study Title: Randomised, double-blind, placebo controlled, parallel group study to assess the efficacy (bronchodilation) and safety of 4 weeks of once daily treatment of orally inhaled BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) delivered by the Respimat® inhaler in patients with asthma Sample Size: 296 Arms: see title Location in submission: 5.3.5.1</p> <p>Study Number: 1222.27 Study Title: A Randomised, Double-Blind, Placebo and Active-Controlled, Incomplete Crossover Efficacy and Safety Comparison of 4-week Treatment Periods of Once Daily Treatment of 4 Doses of BI 1744 CL Inhalation Solution Delivered by the Respimat® in Patients with Asthma Sample Size: 198 Arms: 2, 5, 10, 20mcg, PBO Location in submission: 5.3.5.1</p> <p>Study Number: 1222.29 Study Title: Phase II, Randomised, Double-Blind, Cross-over Study to Compare the 24-hour FEV1-time Profile of Orally Inhaled Olodaterol, delivered with the Respimat® Inhaler, after 3 Weeks of Olodaterol Once Daily 5 µg [2 actuations of 2.5 [g], Twice Daily 2.5 µg [2 actuations of 1.25 [g] and Placebo or after 3 Weeks of Once Daily 10 [g [2 actuations of 5 [g], Twice Daily 5 µg [2 actuations of 2.5 [g] and Placebo Administration in Patients with Moderate to Severe Persistent Asthma Sample Size: 180 Arms: see title Location in submission: 5.3.5.1</p> | | | | |
| EFFICACY | | | | | |
| 14. | <p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: Trials 1222.11/1222.12 Indication: COPD</p> <p>Pivotal Study #2: Trials 1222.13/1222.14 Indication: COPD</p> | X | | | Olodaterol treatment arms included 5 and 10 mcg arms. Trials 1222.13 and 1222.14 included foradil as an active comparator and were conducted entirely ex-US. |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the | X | | | |

| | Content Parameter | Yes | No | NA | Comment |
|------------------------|---|------------|-----------|-----------|----------------|
| | extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | X | | | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (e.g., QT interval studies, if needed)? | X | | | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | X | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| ABUSE LIABILITY | | | | | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|------------|-----------|-----------|----------------|
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | X | | | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | X | | | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | X | | | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

13. Comments for the 74 day letter

Comments addressing the following points will be sent to the sponsor. The exact wording to be sent to the sponsor has not been finalized.

1) If you have performed any long-term olodaterol trials in asthmatics, provide trial summaries.

2) In some of your phase 3 trials, the olodaterol treatment effect at 6 weeks is numerically greater than at 12 weeks. (b) (4)

3) (b) (4)

(b) (4)

4)

5)

6)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H LIM
07/10/2012

THERESA M MICHELE
07/10/2012