Indacaterol (Arcapta™ Neohaler™)
National Drug Monograph
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Indacaterol is approved for maintenance treatment of COPD. It is NOT used to treat acute exacerbations of COPD or to treat asthma.
- The dose is 75mcg (contents of 1 capsule) inhaled once daily. Administer using the Neohaler device only.
- Doses ≥ 150mcg daily comprise the majority of the available clinical data. Only 449 patients were exposed to the approved dose of 75mcg daily for up to 3 months. There are 4 studies evaluating the 75mcg dose (two 2-week dose-ranging studies and two 12-week trials).
- The primary endpoint for these trials was trough FEV1. The difference from placebo (treatment – placebo) of trough FEV1 of 0.12L was considered to be a minimally clinically important difference. This goal was met in the 12-week trials and one of the 2-week trials. In the 2-week trials, trough FEV1 for indacaterol 75mcg was comparable to the comparators (formoterol, salmeterol, tiotropium).
- The transitional dyspnea index (TDI) was used to assess relief of dyspnea. A difference from placebo in score by ≥ +1unit is considered to be clinically meaningful. The difference from placebo was 1.23 and 0.45 for the 12-week trials B2354 and B2355 respectively.
- Indacaterol significantly reduced the number of puffs/day of rescue inhaler (diff. from placebo -1.16 and -0.66 puff/day in studies B2354 and B2355 respectively) and increased the percentage of days with no rescue use (diff. from placebo 13.7 and 8.4% in studies B2354 and B2355 respectively).
- Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). An improvement in score of ≥4 units is considered to be clinically meaningful. The difference from placebo, while statistically significant, did not achieve clinical significance. However, there were significantly more patients achieving improvement in score of ≥4 units in the indacaterol groups compared to placebo.
- The most common adverse reactions reported in more than 2% of patients and with higher incidence than placebo in 449 patients taking indacaterol 75 mcg for at least 3 months were cough, nasopharyngitis, headache, nausea, and oropharyngeal pain.
- The rate of overall cardiovascular (CV) events in the 75mcg group was 2.5%. No specific CV event occurred at a rate ≥ 1% and greater than placebo. Events included ventricular extrasystoles, ventricular tachycardia, 1st degree AV block, atrial flutter, cerebrovascular accident (CVA), transient ischemic attack (TIA), and supraventricular asystole.

Introduction

Indacaterol was approved in July 2011 and is the first long-acting beta-agonist (LABA) that is dosed once daily. A New Drug Application (NDA) for indacaterol 150mcg and 300mcg was submitted in 2009; however, the drug was not approved at that time because a meaningful difference in efficacy between the proposed doses (150 and 300mcg) and a lower dose of 75mcg could not be discerned and because of concerns regarding safety with the higher doses. To better delineate dose-response at lower doses, the FDA requested a study in patients with asthma, a condition that is more responsive to bronchodilators than COPD. In addition to dose-ranging studies in asthma, the sponsor provided a second dose-ranging trial in patients with COPD and separate 12-week confirmatory trials using the 75mcg and 150mcg doses.

In both the asthma and COPD dose-ranging studies, there was no clear separation between the 75mcg and 150mcg doses in the FEV1 time profile. As for the non-comparative confirmatory trials, both the 75mcg and 150mcg doses had significantly higher trough FEV1 values than placebo. Because these studies did not directly compare the 2 doses, it is difficult to conclude if the 150mcg is more effective than the 75mcg dose. As a result, the FDA supported approval of the 75mcg dose based on the overall risk-benefit assessment.[1, 3] The European Medicines Agency approved the 150mcg and 300mcg doses in November 2009.

The indacaterol COPD safety set includes 4764 patients exposed to indacaterol at doses of 75, 150, 300, and 600mcg daily. Only 449 patients were exposed to the approved dose of 75mcg daily for up to 3 months. [1]

Pharmacokinetics

The pharmacokinetic parameters for indacaterol are shown in table 1.

Table 1: Pharmacokinetics of Indacaterol

Absolute Bioavailability	43-45% (after inhaled dose)
Time to maximum concentration	~15 minutes (after single or repeated inhaled doses)
Ratio of AUC_{0-24h} (Day 14-15: Day 1)	2.9-3.8 (after inhaled doses ranging from 75-600mcg once daily)
Effective half-life	40-56 hours
Protein binding	94-96% (after IV infusion)
Volume of Distribution	2,361 to 2,557L (after IV infusion)
Metabolism	Approx. 1/3 of dose is unchanged in serum Hydroxylation via CYP3A4 (major route), glucuronidation via UGT1A1, and oxidative metabolites via CYP 1A1, CYP2D6, CYP3A4
Elimination	≥ 90% of dose (fecal); 2-6% (renal) (after oral administration)

Data obtained from product package insert

FDA Approved Indications

Indacaterol is approved for maintenance treatment of COPD.
It is NOT used to treat acute exacerbations of COPD or to treat asthma.

Potential Off-Label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

- Treatment of asthma

Current VA Formulary Alternatives

LABA class - formoterol

Dosing/Administration

75mcg (contents of 1 capsule) inhaled once daily. Administer using the Neohaler device only. Capsules must not be swallowed. Remove capsule from blister packet immediately before use.

No dosage adjustment is needed for geriatric patients, patients with renal impairment, or patients with mild and moderate hepatic impairment. Data are not available for patients with severe renal impairment.

Dosage Form/Strengths

Inhalation powder – 75mcg capsule packaged in aluminum blister cards (box of 30 capsules: 5 blister cards with 6 capsules each). Store in a dry place at 77°F; excursions permitted between 59-86°F.

Efficacy

Doses ≥ 150mcg daily comprise the majority of the available clinical data. Only 449 patients were exposed to the approved dose of 75mcg daily for up to 3 months.

Efficacy data for those studies evaluating doses other than 75mcg once daily will not be presented in this review. A list of those trials is presented in Appendix 1 for interested parties. In addition, asthma trials, including the dose-ranging studies, will not be presented.

The studies shown in table 2 included the 75mcg dose (detailed information on these trials can be found in Appendices 2 and 3). The first 2 studies (B2335S and B2356) were dose-finding studies. In study B2335S, the 2-week dose-finding phase was used to select those doses of indacaterol, that met pre-defined efficacy criteria, for entry into the 26-week confirmatory phase.[2] The pre-defined efficacy criteria were for trough FEV1 of indacaterol to be at least 0.12L higher than placebo and higher than values obtained for formoterol and tiotropium *and* for post-dose FEV1 $AUC_{1\text{-}4h}$ to be greater than formoterol and tiotropium. The lowest dose fulfilling these criteria and the next highest dose would be selected for the confirmatory phase. The 150mcg and 300mcg doses of indacaterol, tiotropium, and placebo groups went on to complete 26 weeks.

In this same study, the FDA requested data beyond 14 days for all treatment arms. Patients completing the 2 week dose-finding phase continued on their treatments until the Drug Monitoring Committee review of the interim analysis were complete. Approximately 50% of patients in the discontinued arms (indacaterol 75mcg, 600mcg and formoterol) were exposed to study drug beyond 2 weeks (12-week data are available).[1, 2]

Pulmonary function

The primary endpoint for these trials was trough FEV1. The difference from placebo (treatment – placebo) in trough FEV1 of 0.12L was considered to be a minimally clinically important difference. This goal was met in the 12-week trials and in study B2335S. In the 2-week trials, trough FEV1 for indacaterol 75mcg was comparable to the comparators formoterol, salmeterol, and tiotropium (Table 2).

In the 12-week trials, the change in trough FEV1 from baseline in study 2354 was 130mL for indacaterol 75mcg compared to 10mL for placebo. For study 2355 the changes were 160mL and 10mL for indacaterol and placebo respectively. (Personal Communication with Novartis)

There was no evidence of tolerance or tachyphylaxis over 12 weeks with the 75mcg dose. In study B2354, the mean improvement in peak FEV1 relative to baseline after the first dose and at week 12 was 0.11L and 0.16L respectively. Likewise for study 2355, the improvement was 0.11L (first dose) and 0.17L (week 12).[5] The 150 and 300mcg doses also showed no evidence of tolerance or tachyphylaxis over 52-weeks.[1]

Table 2: Trough FEV1[1, 2]

	Duration	n	Treatment	Trough FEV1 (L)	Trough FEV1 (L) Difference from PBO LS mean [95%CI]
Study B2335S Dose-finding study	2-weeks	801	Indacaterol 75mcg (n=115)	1.46	0.15 [0.09, 0.20]
			Indacaterol 150mcg (n=111)	1.49	0.18 [0.12, 0.24]
			Indacaterol 300 mcg (n=114)	1.52	0.21 [0.15, 0.27]
			Indacaterol 600 mcg (n=111)	1.51	0.20 [0.14. 0.25]
			Formoterol 12mcg (n=112)	1.42	0.11 [0.06, 0.17]
			Tiotropium 18mcg (n=119)	1.45	0.14 [0.08, 0.19]
			Placebo (n=119)	1.31	-
Study B2356 Dose-finding study	2-weeks	552	Indacaterol 18.75 mcg (n=89)	1.35	0.07 [0.02, 0.12]
			Indacaterol 37.5 mcg (n=90)	1.38	0.10 [0.05, 0.16]
			Indacaterol 75 mcg (n=94)	1.38	0.10 [0.04, 0.15]
			Indacaterol 150mcg (n=92)	1.40	0.12 [0.07, 0.17]
			Salmeterol 50mcg (n=92)	1.39	0.10 [0.05, 0.16]
			Placebo (n=91)	1.28	-
Study B2354	12-weeks	323	Indacaterol 75mcg (n=163)	1.49	0.14 [0.10, 0.18]
			Placebo (n=160)	1.35	
Study B2355	12-weeks	318	Indacaterol 75mcg (n=159)	1.38	0.12 [0.08, 0.15]
			Placebo (n=159)	1.26	

Indacaterol and tiotropium were administered once daily; salmeterol and formoterol were administered twice daily

As discussed earlier, the FDA requested data beyond 14 days for all treatment arms for study B2335S. Data at 12-weeks are available for a subgroup of patients from the discontinued treatment arms: indacaterol 75mcg, 600mcg, and formoterol (Table 3).[2]

Table 3: 12-week data from Study B2335S ‡

Treatments	IND 75mcg	IND 150mcg	IND 300mcg	IND 600mcg	FOR	TIO
Trough FEV1 (mL) {Difference vs. PBO}	170	180	180	190	120	130

Values estimated from graph from Briefing Document
‡Data at 12-weeks available for approximately 50% of patients in the indacaterol 75, 600mcg and formoterol groups
Abbreviations: FOR=formoterol; IND=indacaterol; PBO= placebo; TIO=tiotropium

Dyspnea

The transitional dyspnea index (TDI) was used to assess relief of dyspnea. A difference from placebo in score of ≥ +1 unit is considered to be clinically meaningful. The difference from placebo in study B2354 was significant; however, significance was not reached for study B2355. In study B2355, the proportion of patients with TDI improvement ≥ 1.0 units was 46.6% and 35.6% respectively for indacaterol and placebo (OR=1.58; p=0.065).[1, 2]

Table 4: Transitional Dyspnea Index for 75mcg Dose

	Indacaterol	Placebo	Difference from Placebo
Study B2354	1.34 ± 0.284	0.11 ± 0.287	1.23 [0.57, 1.89]*
Study B2355	1.22 ± 0.234	0.76 ± 0.235	0.45 [-0.18, 1.09]

*Significant vs. placebo

Rescue inhaler use

Compared to placebo, indacaterol significantly reduced the number of puffs/day of rescue inhaler and increased the percentage of days with no rescue use.[1, 2]

Table 5: Rescue Albuterol Use

	Study B2354			Study B2355		
	Indacaterol	Placebo	Difference from Placebo	Indacaterol	Placebo	Difference from Placebo
Rescue albuterol (puffs/day)	-1.58±0.19	-0.42±0.19	-1.16±0.26*	-1.15±0.19	-0.49±0.184	-0.66±0.25*
Days with no rescue use (%)	42.4 ± 2.3	28.8 ± 2.4	13.7±3.3*	39.3±2.4	30.9±2.4	8.4± 2.9*

*Significant vs. placebo

Health-related quality of life

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). The SGRQ is widely used in clinical trials to measure symptoms, activities, and impact of COPD on daily life as reported by patients. An improvement in score of ≥4 units is considered to be clinically meaningful. In the 12-week trials, the difference from placebo, while statistically significant, did not achieve clinical significance. However, there were significantly more patients achieving improvement in score of ≥4 units in the indacaterol groups compared to placebo.[1, 2]

Table 6: Health-related Quality of Life

	Study B2354			Study B2355		
	Indacaterol	PBO	Diff from PBO or Odds Ratio	Indacaterol	PBO	Diff from PBO or Odds Ratio
SGRQ (change from baseline)	-5.8	-2.0	?	-4.9	-0.9	?
SGRQ (value at endpoint)	43.4± 0.86	47.2± 0.87	-3.8 ± 121*	45.9± 1.0	49.5± 1.02	-3.6 ± 1.4*
SGRQ improvement ≥ 4 units (% pts)	47.6	34.5	OR=1.8*	50.7	37.2	OR= 1.71*

*Significant vs. placebo

Abbreviations: OR=odds ratio; PBO=placebo; SGRQ= St George's Respiratory Questionnaire

Exercise Endurance

There are no clinical trials evaluating exercise endurance using the approved dose of 75mcg. There is a cross-over trial (3 weeks per arm) comparing the 300mcg dose to placebo. Using constant-load cycle ergometry (performed at 75% of peak work rate of screening test), indacaterol 300mcg improved exercise endurance time by 111 seconds compared to placebo after 3 weeks. Additionally, end-exercise inspiratory capacity increased by 0.28L compared to placebo.[15]

Adverse Events (Safety Data)

The most common adverse reactions reported in more than 2% of patients and with higher incidence than placebo in 449 patients taking indacaterol 75 mcg for at least 3 months were cough, nasopharyngitis, headache, nausea, and oropharyngeal pain. Cough generally occurred within 15 seconds of inhalation and lasted for ≤ 15 seconds.

The rate of overall cardiovascular (CV) events in the 75mcg group was 2.5%. No specific CV event occurred at a rate ≥ 1% and greater than placebo.[5] Events included ventricular extrasystoles, ventricular tachycardia, 1st degree AV block, atrial flutter, cerebrovascular accident (CVA), transient ischemic attack (TIA), and supraventricular asystole. Two events (CVA and TIA) were considered to be serious.[1]

Table 7: Adverse Drug Reactions ≥ 2% and Higher than Placebo

	Indacaterol 75mcg n (%)	Placebo n (%)
n	449	445
Cough	29 (6.5)	20 (4.5)
Oropharyngeal pain	10 (2.2)	3 (0.7)
Nasopharyngitis	24 (5.3)	12 (2.7)
Headache	23 (5.1)	11 (2.5)
Nausea	11 (2.4)	4 (0.9)
Cardiovascular †	2.5	1.6

Data obtained from product package insert

†Overall values shown

Because of the very limited safety data on use of the 75mcg dose beyond 3 months, data for serious adverse events (SAEs) for the higher unapproved doses are provided (see Appendix 4). In the 75mcg group, SAEs using the following preferred terms were reported: COPD (n=4), pneumonia (n=2), CVA (n=1), upper respiratory tract infection-bacterial (n=1), non-cardiac chest pain (n=2).[1]

In an analysis of the overall safety database for COPD (23 trials), there were no safety signals identified with the 75mcg and 150mcg doses of indacaterol. [4]

Deaths
There were no deaths reported in the indacaterol 75mcg group. In the COPD safety population, 11 deaths were reported with indacaterol (n=4 150mcg; n=2 300mcg; n=1; 600mcg n=4 IND150mcg + TIO). There were 14 deaths in the placebo groups, and 9 in the active comparator groups (n=4 formoterol; n=4 tiotropium; n=1 salmeterol).[1]

Serum Potassium and Glucose
Changes in serum potassium were minimal and ranged from -0.04 to +0.04mEq/L at various time points (day 1, week 2, month 3) for the 75mcg group. The largest change was -0.11mEq/L on day 1 which occurred in the 600mcg group. Subsequent changes in serum potassium in the 600mcg group ranged between -0.02 to -0.04mEq/L (week 2 and months 3, 6, 12).[1]

In the 3-month COPD safety population, the incidence of serum glucose > 180mg/dL ranged from 4.0-6.4% with the highest incidence occurring in the 600mcg group. The greatest mean change (25min pre-dose to 1 hour post-dose) was 6.3mg/dL which occurred in the 600mcg group on day 1.[1]The mean change in the 75mcg arm was 1.3mg/dL.[5]

QT-interval
QTcF (QT interval corrected for heart rate using Fridericia's formula) was evaluated in healthy subjects in a 14-day study. Subjects were randomized to indacaterol 150mcg (n=108), 300mcg (n=108), 600mcg (n=54), placebo (n=107), or placebo + moxifloxacin 400mg single dose on day 14 (n=27). ECG recordings were collected at each of the following times on Days 1 and 14: at predose, and at 10, 20, and 40 min, and 1, 2, 3, 4, 6, 12, and 24 h post-dose. The mean change from baseline versus placebo were below 5msec (the threshold of regulatory concern) for all doses of indacaterol. The greatest change from baseline vs. placebo occurred 2-hours post-dose with indacaterol 150mcg (2.66msec) and 300mcg (2.98msec), and 6-hours post-dose with 600mcg (3.34msec). Study sensitivity was confirmed with moxifloxacin which showed a significant maximal time-matched QTcF prolongation of 13.90 msec compared to placebo. [7]

QTc-interval was also assessed in the COPD safety population and the information is shown in table 8.[1]

Table 8: QTcF from COPD Safety Population

	3-month COPD Safety Population	6-month COPD Safety Population	12-month COPD Safety Population
QTcF > 500msec	2 cases (150mcg), 2 cases (TIO)	2 cases (150mcg), 1 case (300mcg), 1 case (TIO)	No cases
QTcF increase > 60msec	150mcg (3 pts, 0.12%) 300mcg (1 pt, 0.09%) 600mcg (1pt, 0.19%) PBO (6 pts, 0.3%)	150mcg (3 pts, 0.3%) 300mcg (3 pts, 0.3%) 600mcg (1pt, 0.20%) PBO (7 pts, 0.5%)	1 case (150mcg), 3 cases (300mcg), 1 case (600mcg), 1 case (FOR), 1 case (PBO)
QTcF increase 30-60msec	150mcg (155 pts, 5.96%) PBO (105 pts, 5.27%)	Highest in TIO and PBO groups with 0.5% for both	Highest in the 150mcg group (0.7%). PBO (0.2%)

Contraindications
Safety and efficacy have not been established in patients with asthma. Indacaterol is NOT indicated for the treatment of asthma.

Warning and Precautions
- Do not initiate indacaterol in patients with acutely deteriorating COPD
- Do not use in for relief of acute symptoms (e.g., rescue therapy). A short acting beta$_2$-agonist should be prescribed for acute use.
- As with other beta$_2$-agonists, indacaterol may cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, discontinue indacaterol and institute alternative therapy.
- As with other beta$_2$-agonists, indacaterol may cause clinically significant cardiovascular effects (i.e., increases in pulse rate or blood pressure). Indacaterol may need to be discontinued should these effects occur.

- Because beta-agonists can produce ECG changes (e.g., flattening of T wave, QTc interval prolongation, ST segment depression), use indacaterol with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Sympathomimetic amines such as beta-agonists should be used with caution in patients with convulsive disorders, thyrotoxicosis, and those unusually responsive to sympathomimetic amines.

Sentinel Events

None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion.

Table 9: LASA Error Risk Potential

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Indacaterol Inhaler	None	None	None	None	Inderal
Arcapta	None	None	None	None	Arcalyst

Drug Interactions

Indacaterol is unlikely to significantly inhibit or induce the CYP450 enzymes or the transporter proteins P-gp or MRP2. It has also been shown to be unlikely to inhibit the transporter protein BCRP, the cationic substrate transporters hOCT1, hOTC2, and the human multidrug and toxin extrusion transporters hMATE1 and hMATE2K.

Table 10: Drug Interactions

Drugs	Potential Effect
Additional adrenergic agents	May potentiate the sympathetic effects of indacaterol
Xanthine derivatives, diuretics (loop or thiazide), or steroids	May potentiate the hypokalemic effect of indacaterol
QTc prolonging drugs (e.g., monoamine oxidase inhibitors, tricyclic antidepressants, etc.)	Action of indacaterol on the cardiovascular system may be potentiated by these agents. Drugs that prolong QTc interval may have an increased risk of ventricular arrhythmias.
Beta-blockers	Concomitant use may interfere with the effect of each other
Inhibitors of CYP3A4 and P-gp efflux transporter	**Concomitant use of a strong dual inhibitors** • Ketoconazole (200mcg bid x 7 days) and indacaterol (300mcg single dose): 1.9-fold increase in indacaterol AUC0-24h and 1.3-fold increase in indacaterol Cmax • Verapamil (80mcg tid x 4 days) with indacaterol (300mcg single dose): • 2-fold increase in indacaterol AUC0-24 and 1.5-fold increase in indacaterol Cmax • Erythromycin (400mg qid x 7 days) with indacaterol (300mcg single dose): 1.4-fold increase in indacaterol AUC0-24 and 1.2-fold increase in indacaterol Cmax • Ritonovir (300mcg bid x 7.5 days) with indacaterol (300mcg single dose): 1.7-fold increase in indacaterol AUC0-24

Information obtained from product package insert

Comparative Cost

Please refer to the last page for VA acquisition costs for the long-acting beta-agonists. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Conclusions

Indacaterol is the first once daily long-acting beta-agonist and is approved for use in COPD. At this time, efficacy and safety data and comparative effectiveness relative to other LABAs with the approved dose of 75mcg is limited. The lack of a combination product with an inhaled corticosteroid further limits the usefulness of indacaterol. Indacaterol or salmeterol are non-formulary options for those who are unable to use formoterol, the VA formulary agent. For those patients who require a long-acting beta-agonist and are unable to use formoterol, non-formulary salmeterol should be preferred until more safety and efficacy data is available for indacaterol.

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Appendix 1: Trials ≥ 12 weeks Using Unapproved Doses

Author	Study	Severity of COPD	Duration	Treatment Arms
Feldman et al. BMC Pulm Med 2010	B2346 INLIGHT-1	Moderate- severe COPD	12-weeks	IND 150 mcg (n = 211) Placebo (n = 205)
Kornmann et al. Eur Respir J 2011	B2336 INLIGHT-2	Moderate- severe COPD	6-months	IND 150 mcg SAL 50 mcg BID Placebo
Dahl et al. Thorax 2010	B2334 INVOLVE	Moderate- severe COPD	52-weeks	IND 300 mcg (n=437) or 600 mcg (n=428) FOR 12 mcg BID (n=435) Placebo (n=432)
Donahue et al. Am J Respir Crit Care Med 2010	B2335S INHANCE	Moderate- severe COPD	26-weeks	IND 150mcg (n=416) or 300 mcg (n=416) Placebo (n=418) Open-label TIO 18 mcg (n=415)
Dunn LJ, et al. Presented at: The American College of Chest Physicians Annual Meeting 2010.	B2350 INTENSITY	Moderate- severe COPD	12-weeks	IND 150mcg (n=794) TIO 18mcg (n=799)
Korn et al. Respir Med 2011	B2349 INSIST	Moderate- severe COPD	12-weeks	IND 150 mcg (n=559) SAL 50 mcg BID (n=562)
FDA	B1302	Moderate- severe COPD	12-weeks	IND 150mcg (n=) or 300mcg (n=) Placebo (n=
FDA	B2333	Moderate- severe COPD	26-weeks	IND 150mcg (n=) or 300mcg (n=) Placebo (n=
Mahler et al Presented at: ATS International Conference, 2011	B2351	Moderate- severe COPD	12-weeks	IND 150 mcg + TIO 18 mcg (n=543) TIO 18 mcg (n=533)
Mahler et al. Presented at: ATS International Conference, 2011	B2341	Moderate- severe COPD	12-weeks	IND 150 mcg + TIO 18 mcg (n=570) TIO 18 mcg (n=564)
Chapman et al. Chest 2011	Study 2335SE (Extension of study B2335S)	Moderate- severe COPD	Additional 26-weeks (total 52-weeks)	IND 150mcg or 300mcg Placebo

BID=twice daily; FOR=formoterol; IND=indacaterol; SAL=salmeterol; TIO=tiotropium

Appendix 2: Randomized-Controlled Trials

Study	Inclusion/Exclusion Criteria	Dosing	Demographics/Baseline Data	Results
Study B2354 R, DB, PC 12-weeks N=323 Full-analysis set	**Inclusions** Moderate-severe COPD ≥40 years old Smoking history ≥ 10 pack-years Post-bronchodilator FEV1 <80 and ≥30% predicted Post-bronchodilator FEV1/FVC ratio <70% **Exclusions** Hospitalized for COPD within 6 weeks of study History of asthma or concomitant pulmonary disease Pregnant or nursing Family history of long QT syndrome Required oxygen Had respiratory tract infection Type 1 diabetes or uncontrolled type 2 diabetes History of lung cancer	Indacaterol 75mcg once daily (n=163) Placebo (n=160) Albuterol allowed for rescue ICS if receiving prior to study entry	**Values for indacaterol and placebo respectively** **Males (%):** 55; 54 **Mean age (yrs):** 64±8.3; 64.1±9.4 **Duration of COPD (yrs):** 7.2±6.3; 7.3±6.4 **Severe/very severe COPD (%):** 41; 44 **Mean smoking history (pack-yrs):** 52.9±26.8; 51.2±24.8 **Current smokers (%):** 44; 44 **ICS use (%):** 43; 48 **FEV1 % pred:** 54±13; 53±13 **FEV1/FVC:** 53.1±9.5; 51.6±10.6 **Reversibility post SABA (%):** 15±13; 17±14 No info on other baseline meds such as anticholinergics, LABAs	

	IND	PBO	Diff vs. PBO
Completed study (%)	84.8		
Trough FEV1 (L)	1.38 ± 0.013	1.26 ± 0.013	0.12±0.019*
Peak FEV1 (L)	1.52± 0.014	1.36± 0.014	0.16±0.02*
TDI focal score	1.34 ± 0.284	0.11 ± 0.287	1.23 [0.57, 1.89]*
SGRQ	43.4± 0.86	47.2± 0.87	-3.8 ± 121*
SGRQ imp. ≥ 4 units (% pts)	47.6*	34.5	OR=1.8*
Nights with no awakenings (%)	69.4±1.9	66.8±1.9	2.7±2.5
Days with no daytime sxs (%)	9.5±1.1	5.0±1.1	4.6±1.6*
Days able to perform usual activities (%)	38.7±2.1	33.6±21	5.1±2.9
Rescue albuterol (puffs/day)	-1.58 ±0.19	-0.42 ±0.19	-1.16±0.26*
Days with no rescue use (%)	42.4 ± 2.3	28.8 ± 2.4	13.7±3.3*
Exacerbations (rate/yr)	0.37	0.53	
Mean no. exacerbations	0.08	0.11	

Mean ± SE
*Significant vs. PBO

Study	Inclusion/Exclusion Criteria	Dosing	Demographics/Baseline Data	Results
Study B2355 R, DB, PC 12-weeks N=318 Full analysis set	Same inclusions/exclusions as study B2354	Indacaterol 75mcg once daily (n=159) Placebo (n=159) Albuterol allowed for rescue ICS if receiving prior to study entry	**Values for indacaterol and placebo respectively** **Males (%):** 52; 56 **Mean age (yrs):** 61.3±9.8; 61.5±9.9 **Duration of COPD (yrs):** 6.7±6.1; 6.8±6.1 **Severe/very severe COPD (%):** 32; 45 **Mean smoking history (pack-yrs):** 52.4±28.1; 52.4±28.4 **Current smokers (%):** 58; 60 **ICS use (%):** 40; 35 **FEV1 % pred:** 56±13; 54±13 **FEV1/FVC:** 52.4±10.3; 52.6±9.9 **Reversibility post SABA (%):** 18±17; 16±14 No info on other baseline meds such as anticholinergics, LABAs	

	IND	PBO	Diff vs. PBO
Completed study (%)	91.2		
Trough FEV1 (L)	1.49 ± 0.016	1.35 ± 0.015	0.14 ±0.021*
Peak FEV1 (L)	1.48±0.01	1.44±0.01	0.11±0.013*
TDI focal score	1.22 ± 0.234	0.76 ± 0.235	0.45±0.325
TDI imp. ≥ 1.0 units (% pts)	46.6	35.6	OR=1.58
SGRQ	45.9± 1.0	49.5± 1.02	-3.6 ± 1.4*
SGRQ imp. ≥ 4 units (%pts)	50.7	37.2	OR= 1.71*
Nights with no awakenings (%)	63.4±1.8	61.5±1.8	1.9±2.44
Days with no daytime sxs (%)	8.0 ±1.2	5.2±1.2	2.8±1.66
Days able to perform usual activities (%)	39±2.0	30.3±1.9	8.7±2.5*
Rescue albuterol (puffs/day)	-1.15± 0.19	-0.49± 0.184	-0.66±0.25*
Days with no rescue use (%)	39.3±2.4	30.9±2.4	8.4± 2.9*
Exacerbations (rate/yr)	0.39	0.40	
Mean no. exacerbations	0.9	0.9	

Mean ± SE
*Significant vs. PBO

Appendix 3: Dose-ranging Studies

Study	Inclusion/Exclusion Criteria	Dosing	Demographics/Baseline Data	Results
Barnes 2010 B2335S R, DB, DD, PC N=801 <u>Stage 1</u> 2-weeks (included all doses) <u>Stage 2</u> 24-weeks (included indacaterol 150, 300mcg, tiotropium, placebo)	**<u>Inclusions</u>** Moderate-severe COPD ≥40 years old Smoking history ≥ 20 pack-years Post-bronchodilator FEV1 <80 and ≥30% predicted Post-bronchodilator FEV1/FVC ratio <70% **<u>Exclusions</u>** Hospitalized for COPD within 6 weeks prior to screening Received oral steroids in month prior to screening History of asthma Prolonged QTc interval Clinically relevant lab abnormality or condition which might compromise patient safety or compliance	14-day run-in Indacaterol 75mcg q AM (n=115) Indacaterol 150mcg q AM (n=111) Indacaterol 300mcg q AM (n=114) Indacaterol 600mcg q AM (n=111) Formoterol 12mcg bid (n=112) Tiotropium 18mcg q AM [open-label] (n=119) Placebo (n=119) Prestudy ICS continued. ICS/LABA combination replaced with equivalent monotherapy ICS Albuterol allowed for rescue Randomization stratified by smoking status	**Males (%):** 61.6; 56.4; 62.3; 60.4; 55.9; 56.8; 53.4 **Age (yrs):** 65.7; 64.5; 62.8; 64.4; 64.7; 65.4; 65.1 **Duration of COPD (yrs):** 7.1; 7.2; 7.1; 6.5; 7.3; 5.9; 7.1 **FEV1 (L):** 1.50; 1.56; 1.57; 1.52; 1.42; 1.43; 1.50 **FEV1 % pred:** 52.1; 55.1; 53.9; 53.7; 51.1; 50.5; 54.3 **Ex-smoker (%):** 60.7; 59.1; 57.9; 60.4; 59.3; 58.6; 57.8 **Current smoker (%):** 39.3; 40.9; 42.1; 39.6; 40.7; 41.4; 42.2 **Concomitant ICS (%):** 42.9; 40; 34.2; 35.1; 32.2; 49.5; 34.5	**Results for Stage 1 (day 15)** **75 / 150 / 300 / 600 / FOR / TIO / PBO** Trough FEV1 (L): 1.46± 0.024 / 1.49± 0.024 / 1.52± 0.024 / 1.51± 0.024 / 1.42± 0.024 / 1.45± 0.023 / 1.31± 0.024 AUC_{1-4h} FEV1 (L): 1.50± 0.034 / 1.53± 0.034 / 1.58± 0.034 / 1.53± 0.034 / 1.52± 0.035 / 1.49± 0.034 / 1.30± 0.033 Per FDA, data beyond 14 days was requested for treatment arms. Patients completing Stage 1 (2 weeks) continued on their treatments until the DMC review of the interim analysis was complete. Approx. 50% of patients in the discontinued arms (75mcg, 600mcg and formoterol) were exposed to study drug beyond 2 weeks. Therefore, 12-week data are available. **Difference in trough FEV1 vs. placebo (mL) at week 12** **75mcg / 150mcg / 300mcg / 600mcg / FOR / TIO** 170 / 180 / 180 / 190 / 120 / 130 Values estimated from graph
Study B2356 R, DB, DD, PC N=552 2weeks	**<u>Inclusions</u>** Moderate-severe COPD ≥40 years old Smoking history ≥ 10 pack-years Post-bronchodilator FEV1 <80 and ≥30% predicted Post-bronchodilator FEV1/FVC ratio <70% **<u>Exclusions</u>** Hospitalized for COPD within 6 weeks prior to screening History of asthma Prolonged QTc interval History of respiratory infection Clinically relevant lab abnormality or condition which might compromise patient safety or compliance	Indacaterol 18.75mcg q AM (n=82) Indacaterol 37.5mcg q AM (n=84) Indacaterol 75mcg q AM (n=87) Indacaterol 150mcg q AM (n=90) Salmeterol 50mcg bid (n=88) Placebo (n=86) Prestudy ICS continued. ICS/LABA combination replaced with equivalent monotherapy ICS Albuterol allowed for rescue Randomization stratified by smoking status and ICS use	**Males (%): 54** **Age (yrs):** 62.6 (range 40-87) **Current smoker (%):** 55 **Concomitant ICS (%):** 37	**18.75 / 37.5 / 75 / 150 / SAL / PBO** Trough FEV1 (L): 1.35± 0.020 / 1.38± 0.019 / 1.38± 0.019 / 1.40± 0.019 / 1.39± 0.019 / 1.28± 0.019 Peak FEV1 (L): 1.48± 0.018 / 1.52± 0.017 / 1.52± 0.017 / 1.52± 0.017 / 1.51± 0.017 / 1.39± 0.018 All active treatments were significant better than PBO

Appendix 4: Serious Adverse Events Affecting ≥ 2 Patients in any Treatment Group (%)

	3-month safety population								6-month safety population								12-month safety population				
	75	**150**	**300**	**600**	**FOR**	**TIO**	**SAL**	**PBO**	**75**	**150**	**300**	**600**	**FOR**	**TIO**	**SAL**	**PBO**	**150**	**300**	**600**	**FOR**	**PBO**
N	449	2611	1157	547	556	1214	895	2012	127	933	1041	547	556	415	333	1371	144	583	425	434	556
Pts. with SAEs	3.3	3.8	3.3	3.1	3.8	4.2	3.0	4.4	7.1	8.2	7.2	6.2	8.1	8.2	5.7	8.0	10.4	13.9	12.0	15.9	11.0
COPD	0.89	1.15	0.69	0.73	1.62	0.99	1.23	1.59	2.4	2.7	2.3	1.3	3.1	1.7	1.2	2.8	2.8	4.0	2.8	7.4	4.1
Dyspnea	0	0.04	0.17	0	0	0.25	0	0.15	0.8	0	0.3	0	0	0	0	0.4					
Respiratory failure	0	0	0.09	0	0.18	0.08	0.22	0.05	0	0	0.2	0	0.2	0.2	0	0.1					
Pneumonia	0.45	0.27	0.35	0	0.36	0.25	0	0.20	0.8	0.3	0.4	0.2	0.5	1.0	0.9	0.3					
Lower RTI	0	0.11	0.09	0	0.18	0	0.22	0.20	0	0.4	0.1	0	0.2	0	0.6	0.4					
Upper RTI bacterial	0.22	0.08	0	0	0.18	0	0.22	0.20	0.8	0.2	0.4	0	0.2	0	0.6	0.4					
Upper RTI									0	0.1	0	0	0.5	0	0	0.1	0.7	0	0	0.7	0
Bronchitis									0.8	0	0.2	0	0	0.2	0	0.3					
Lung Cancer	0	0.08	0	0	0	0.08	0	0	0	0	0.1	0.4	0.2	0	0	0					
Angina Pectoris	0	0.15	0.09	0	0	0	0	0.10	0.8	0.3	0.1	0.2	0	0	0.3	0.2	0	0.3	0.2	0	0.2
Unstable angina									0.8	0	0.2	0.2	0	0	0	0.1					
AMI	0	0.11	0.09	0	0	0	0.11	0	0	0.2	0.1	0	0	0	0.3	0					
CAD	0	0.11	0.09	0.18	0	0.08	0.11	0	0	0.1	0.2	0.4	0	0	0.6	0.1					
MI	0	0.11	0.09	0.18	0	0	0.11	0.20	0	0.1	0.1	0.2	0.2	0	0.3	0.2					
Atrial Fibrillation	0	0.08	0	0	0	0.25	0.11	0.05	0.8	0.3	0	0	0	0.7	0.3	0.2	0.7	0.5	0	0.2	0.2
Heart failure																	0	0.3	0	0	0.2
Aortic aneurysm																	0	0.3	0	0	0.2
Sudden death									0	0.1	0.1	0	0	0	0	0.2					
Cerebral infarct	0	0.08	0	0	0	0	0	0													
CAO	0	0	0	0	0	0.16	0	0	0	0	0	0	0	0.5	0	0					
Presyncope	0	0	0.17	0	0	0	0	0	0	0	0.2	0	0	0	0	0					
CVA	0.22	0.08	0	0	0	0.16	0	0													
Hemiparesis	0	0.08	0	0	0	0	0.11	0													
Syncope	0	0.08	0.26	0	0	0.16	0.11	0	0	0.1	0.3	0	0	0.5	0	0	0.7	0.3	0	0	0
TIA									0.8	0	0	0	0	0	0	0.2					
Fall	0	0.11	0	0	0	0.08	0	0.05													
Foot fracture	0	0.04	0.09	0.37	0	0	0	0	0	0	0.1	0.4	0	0	0	0					
Non-cardiac chest pain	0.45	0.04	0	0.18	0	0.08	0	0.05													
Rib fracture	0	0	0.17	0	0.18	0.16	0	0	0	0	0.3	0	0.2	0.2	0	0					
Traffic accident	0	0	0.09	0	0	0.16	0	0	0	0	0.2	0	0	0.5	0	0					
Cataract									0.8	0	0.2	0	0.2	0	0	0.1					
BPH	0	0.04	0	0.18	0	0	0	0.10	0	0.1	0	0.2	0	0	0	0.2	0	0	0.2	0	0.4
Cholelithiasis	0	0.11	0	0	0.18	0	0	0.05	0	0.2	0.1	0	0.2	0	0	0.1					

Abbreviations: AMI-acute myocardial infarction; BPH=benign prostatic hyperplasia; CAD=coronary artery disease; CAO=coronary artery occlusion; CVA=cerebrovascular accident; RTI=respiratory tract infection; TIA=transient ischemic attack