NEWER BRONCHODILATORS

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Topics to be covered

- Ultra LABA (+/-ICS)
- Newer LAMA
- LAMA + LABA
- Novel Bronchodilators

Why the need for newer BD?

- OD dosing convenient and hence improves compliance and adherence
- BDs that provide rapid relief provide patients with reassurance after first dose and thus also improve compliance
- BDs with rapid onset of action also suitable for asthma
- Once-daily agents may also affect stability of airway tone, with reduced fluctuations in airway patency leading to increased morning FEV1

Murphy et al. Turning a Molecule into a Medicine: the Development of Indacaterol as a Novel Once-Daily Bronchodilator Treatment for Patients with COPD. Drugs (2014) 74:1635–1657

Ultra long acting Beta 2 Agonists

- **Indacaterol**
- **Vilanterol**
- **Olodaterol**
- Carmoterol
- Milveterol
- Abediterol
- GSK-642444
- PF-610355

Indacaterol

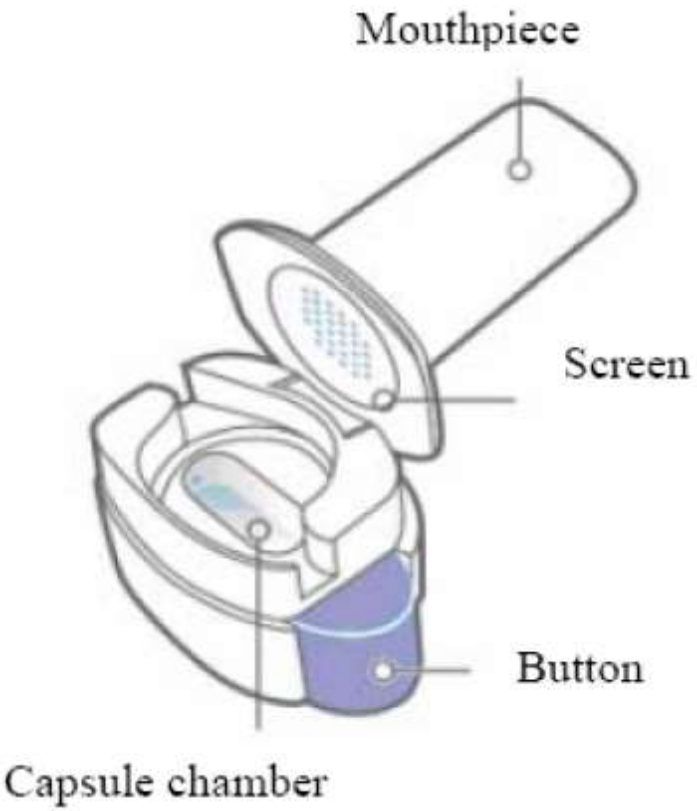
- QAB-149
- First once daily ultra-LABA to be developed
- Approved for COPD in Europe in 2009, US and Japan in 2011, and China in 2012

Pharmacology

- Fast onset of action*
- Sustained bronchodilation (~24 hrs)**
  - Lipophilic – remains membrane bound
  - High intrinsic affinity to Beta2 receptors
- Delivered via Breezhaler® single dose DPI device
- 150, 300 mcg capsules

*Balint B et al. INSURE Trial. Int J Chron Obstruct Pulmon Dis. 2010;5:311–8.
**Laforce C et al. INTEGRAL study. Pulm Pharmacol Ther. 011;24(1):162–8.


onbrez
breezhaler


Mouthpiece
Screen
Button
Capsule chamber

Other potential mechanisms

- Anti-inflammatory effect
- Anti-tumour effect
- May inhibit NF-kB activity and MMP-9 pathway preventing lung damag
- Improves airway responsiveness to SABAs

The INERGIZE programme

- INERGIZE = INdacaterol: Empowerment, bReathlessness relief and lunG function optimIZed for patiEnts with COPD
- 4 ‘pivotal’ phase III double-blind RCTs
  - INVOLVE
  - INHANCE (stage 1 and 2)
  - INLIGHT 1
  - INLIGHT 2
- 9 other RCTs also done
- INHANCE stage 1 dose finding study for other trials – 150, 300 mcg selected

Inclusion criteria

- Age > 40 yrs
- Post BDR FEV1/FVC < 0.7
- > 10 pack-years h/o smoking
- Moderate-Severe COPD (GOLD)
- 80% > FEV1 > 30% predicted
- Concomitant ICS use allowed wherever indicated
- Asthma/other lung diseases excluded

Study	N	Comparator	Dose	Duration	1º and 2º Endpoints	Result
INHANCE Stage2 Donohue et al. 2010 Double blind, double dummy parallel grp RCT	1683	Placebo, Tiotropium 18 mcg dpi od	150, 300	26 wks	24 hr post dose trough FEV1 at 12 wks, TDI score, SGRQ score	Both doses better than placebo & superior to tiotropium at 12 wks FEV1 and SABA use ($p<0.01$), 300 mcg dose better TDI score than tio, SGRQ same as Tio
INLIGHT-1 Feldman et al. 2010 Double blind, parallel grp RCT	416	Placebo	150	12 wks	24 hr post dose trough FEV1 after 1st dose, and after 12 wks, days of poor COPD control	Safety and efficacy confirmed when compared to placebo
INLIGHT-2 Kornmann et al. 2011 Double blind, parallel grp RCT	1002	Placebo, Salmeterol 50 mcg dpi bd	150	26 wks	24 hr post dose trough FEV1, days of poor COPD control, SGRQ, TDI	Superior to Salmeterol w.r.t FEV1 at all times, days free from SABA use and TDI, SGRQ at wk 12
INVOLVE Dahl et al. 2010 Double blind, Double dummy RCT	1732	Placebo, Formoterol 12 mcg dpi bd	300, 600	52 wks	24 hr post dose trough FEV1, mMRC, BODE, SGRQ, 6MWT, exacerbations	Superior to Formoterol in FEV1 at all times, SABA use, TDI at wk 12. Form and Ind (600 mcg) had lesser exacerbation rates than placebo but no diff b/w them

Study	N	Comparator	Dose	Duration	1º and 2º Endpoints	Result
INDORSE Chapman et al. 2011 (contd from INHANCE)	415	Placebo	150, 300	26 wks (Total 52 wks)	24 hr post dose trough FEV1 at 26 wks, TDI score, SGRQ score, exacerbations	Safety confirmed, Significant improvement in FEV1, SGRQ. Trend toward lesser exacerbations in both doses but not sig.
INPUT Magnussen et al. 2010 (Crossover)	96	Placebo, Salmeterol 50 mcg dpi bd	300 mcg AM vs PM	3 x 14 d	24 hr post dose trough FEV1 on day 14	No difference in morning vs evening dosing (8-11 am/pm)
INSIST Korn et al. 2011	1123	Salmeterol 50 mcg dpi bd	150	12 wks	24 hr post dose trough FEV1, SABA use, TDI	Superior across all subgroups, no diff in ADR
INSURE Balint et al. 2010 (Crossover)	89	Salbutamol 200 mcg, salmeterol/ fluticasone 50/500 mcg, Placebo	150, 300	Single doses	5 min post dose FEV1	Onset of action as rapid as salbutamol and faster than salmeterol
INTEGRAL LaForce et al. 2011 (Crossover, open label)	68	Placebo, Salmeterol 50 mcg dpi bd	300	3 x 14 d	24-h post-dose trough FEV1 on Day 14	Superiority vs placebo for FEV1 at each scheduled time-point post-dose, and vs Salm in 24 hr trough FEV1

Study	N	Comparator	Dose	Duration	1º and 2º Endpoints	Result
INTENSITY Buhl et al. 2011	1593	Tiotropium 18 mcg dpi od	150	12 wks	24 hr post dose trough FEV1 at 12 wks, TDI score, SGRQ score	Non-inferior to tiotropium in FEV1, better than tio in SGRQ, TDI, SABA use
INTIME Vogelmeier et al. 2010 (crossover)	169	Placebo, Tiotropium 18 mcg dpi od	150, 300	14 d	24 hr post dose trough FEV1 at day 14	Both doses Non-inferior to tiotropium, 150 mcg dose better than tiotropium
INTRUST-1/2 Mahler et al. 2012	1134 1142	Placebo + Tio 18 mcg dpi od	Ind 150 mcg + Tio 18 mcg od	12 wks	24 hr post dose trough FEV1, SABA use, SGRQ, TDI	Combination superior to Tio alone in FEV1(60-90 ml) and symptom scores, SABA use
INVIGORATE Decramer et al. 2013	3444	Tiotropium 18 mcg dpi od	150	52 wks	24 hr post dose trough FEV1, TDI, SGRQ, exacerbations	Non-inferior to tiotropium in FEV1, SGRQ but **Significantly more exacerbations with Indacaterol**

Summary

- Indacaterol is an effective ultra long acting BD
- Rapid onset and sustained bronchodilation
- Benefits shown in Symptom scores, Quality of Life*, lung function* and exercise tolerance**
- But not effective as LAMA in preventing exacerbations

*Efficacy of indacaterol on quality of life and pulmonary function in patients with COPD and inhaler device preferences. International Journal of COPD 2014:9 107–114

** Indacaterol improves daily physical activity in patients with chronic obstructive pulmonary disease. International Journal of COPD 2013:8 1–5

Olodaterol

- BI 1744 CL
- Rapid onset of action
- Long duration of action ~ 24 hrs
- Dose 5-10 mcg via Respimat® breath actuated inhaler
- May also have anti-inflammatory and anti-fibrotic effects

Study	N	Comparator	Dose	Duration	1º and 2º Endpoints	Result
Ferguson et al. 2014	1266 (2 studies combined)	Placebo	5, 10	48 wks	24 hr post dose trough FEV1 at 12/24/48 wks, PGR, SABA use	Both doses equally superior to placebo
Feldman et al. 2014	199 (2 studies combined)	Placebo, Formoterol 12 mcg bd	5, 10	6 wks	24 hr post dose trough FEV1 at 6 wks	Both doses Non-inferior to formoterol
Koch et al. 2014	906 937	Placebo, Formoterol 12 mcg bd	5, 10	48 wks	$FEV1_{0-3}$ AUC, 24 hr post dose trough FEV1, SABA use, SGRQ, TDI, exacerbations	Both doses Non-inferior to formoterol, Better than formoterol in SGRQ, TDI no diff in exacerbations
Lange et al. 2014	230	Placebo, Tiotropium 18 mcg	150	6 wks	24 hr post dose trough FEV1	Non-inferior to tiotropium in FEV1

- GOLD 2-4 included in studies

Summary

- Olodaterol non-inferior to formoterol in long term
- But more long term data in comparison with Tiotropium required

Vilanterol

- Approved in combination with Fluticasone furoate
- Dose = 100 mcg Fluticasone + 25 mcg Vilanterol
- ELLIPTA® DPI device
- Rapid onset, ultra long acting
- May be used both in Asthma or COPD as once daily medication

Study (COPD)	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
Dransfield et al. 2013	1622	FF+Vil 50/25, 100/25, 200/25	Vilanterol 25 mcg	52 wks	Rate of exacerbations	All combination arms better than Vil arm, but most benefit in 100/25, 200/25 arms
Martinez et al. 2013	1224	FF+Vil 200/25, 100/25	Vil 25mcg, FF 50, FF 100, Placebo	24 wks	Trough FEV1 at 24 wks, SABA use, SGRQ, TDI	Both doses of FF+Vil and Vil alone superior to placebo but only higher dose combn superior to FF 100
Kerwin et al. 2013	1030	FF+Vil 50/25, 100/25	Vil 25mcg, FF 100mcg, Placebo	24 wks	Trough FEV1 at 24 wks, SABA use, SGRQ, TDI	FF+Vil (100/25) superior to individual components, Both doses of combn and Vil alone superior to placebo
Agusti et al. 2014	528		Salmeterol/ Fluticasone (50/250) bd	12 wks	24 hr post dose trough FEV1, Change in FEV1 from baseline, SGRQ, SABA use	Trend to favour FF/Vil but not statistically significant
Dransfield et al. 2014	1860		Salmeterol/ Fluticasone (50/250) bd	12 wks	24 hr post dose trough FEV1, Change in FEV1 from baseline, SABA use	Significant improvement in FEV1, no difference in rescuer use

FF + Vilanterol in asthma

Study	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
Bateman et al. 2014	2019	FF+Vil 100/25	FF 100 mcg	24-78 wks (330 events)	Rate of exacerbations, Trough FEV1	Combination better than FF alone
Woodcock et al. 2013	806	FF+Vil 100/25	Salmeterol/ Fluticasone (50/250) bd	24 wks	Trough FEV1 at 24 wks, SABA use, AQLQ, exacerbations	No difference between the 2 arms
O'Byrne et al. 2014	586	FF+Vil 200/25	FF 200mcg od, FP 500mcgbd	24 wks	Trough FEV1 at 24 wks, SABA use, AQLQ, exacerbations	FF+Vil better than FF or FP in FEV1 and rescuer use, no difference in AQLQ
Bleecker et al. 2014	609	FF+Vil 100/25	Placebo, FF 100mcg od	12 wks	24 hr post dose trough FEV1, Change in FEV1 from baseline, SABA use	Both treatments superior to placebo, B/w them trend to favour FF/Vil but not statistically significant

Summary

- Flu + Vil comparable in efficacy to Salmeterol + FP in both asthma and COPD
- Convenient once daily dosing and rapid onset of action make it an attractive option in both diseases
- Studies comparing them with LAMA are required

Carmoterol

- CHF-4226, TA-2005
- Rapid onset, ulta-long acting BA
- Dose 2 mcg od
- Was found to be non=inferior to formoterol in asthma
- Further trials withheld by the manufacturer after phase 2 and early phase 3 trials as it was not found to be “competitive”

Milveterol

- GSK-159797, TD-3327
- Currently undergoing phase 3 trials in asthma and COPD

Newer LAMA

- Aclidinium bromide
- Glycopyrronium bromide
- Umeclidinium bromide
- CHF-5407
- TD-4208
- AZD8683
- V-0162

Aclidinium bromide

- Aclidinium is a quaternary ammonium derivative of a (3R)-quinuclidinol ester → Hence low systemic exposure
- Maybe used od or bd
- Dose 400 mcg bd approved by FDA
- Delivered via Genuair® DPI
- Rapid onset of action compared to tiotropium

Study acronym and reference	Study treatments	*N*	Duration (weeks)	Key efficacy outcomes
Twice-daily dosing studies				
ACCORD COPD I [17]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	185 190 186	12	Trough FEV_1 change from baseline vs. placebo • 200 μg: 86 mL (95% CI 45–127; $P \leq 0.0001$) • 400 μg: 124 mL (95% CI 83–164; $P \leq 0.0001$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 146 mL (95% CI 101–190; $P \leq 0.0001$) • 400 μg: 192 mL (95% CI 148–236; $P \leq 0.0001$)
ATTAIN [18]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	277 269 272	24	Trough FEV_1 change from baseline vs. placebo • 200 μg: 99 mL ($P < 0.0001$) • 400 μg: 128 mL ($P < 0.0001$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 185 mL ($P < 0.0001$) • 400 μg: 209 mL ($P < 0.0001$)
ACCORD COPD II [19]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	182 177 182	12	Trough FEV_1 change from baseline vs. placebo • 200 μg: 51 mL ($P < 0.01$) • 400 μg: 72 mL ($P < 0.05$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 115 mL ($P < 0.0001$) • 400 μg: 125 mL ($P < 0.0001$)
ACCORD COPD I extension [21]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d.	291	52	Improvements in peak and trough FEV_1 achieved during the lead-in phase were maintained to the end of the extension phase (week 64)
LAS-MD-35 [20]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d.	312 293	52	Trough FEV_1 change from baseline at week 52 (maximal values during the study) • 200 μg: 34 mL (62 mL) • 400 μg: 72 mL (101 mL) Peak FEV_1 change from baseline at week 52 (maximal values during the study) • 200 μg: 185 mL (226 mL) • 400 μg: 214 mL (235 mL)

Once-daily dosing studies

ACCLAIM COPD I [6]	Aclidinium 200 µg q.d. Placebo	627 216	52	**Week 12:** Trough FEV_1 change from baseline vs. placebo: 61 mL ($P < 0.001$) **Week 28:** Trough FEV_1 change from baseline vs. placebo: 67 mL ($P < 0.001$) More patients achieved a clinically meaningful improvement in SGRQ (≥4 points) at week 52 (48.1% vs. 39.5%; $P = 0.025$)
ACCLAIM COPD II [6]	Aclidinium 200 µg q.d. Placebo	600 204	52	**Week 12:** Trough FEV_1 change from baseline vs. placebo: 63 mL ($P < 0.001$) **Week 28:** Trough FEV_1 change from baseline vs. placebo: 69 mL ($P < 0.001$) Time to first moderate-severe COPD exacerbation significantly delayed vs. placebo (HR 0.7; 95% CI 0.55-0.92; $P = 0.01$)

Glycopyrronium

- NVA 237
- Used 50 mcg od
- Delivered via Breezhaler® DPI device
- 3 major trials – GLOW 1, 2, 3

Study	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
D'Urzo et al GLOW1. 2011	817	Glyco 50 mcg od	Placebo	26 wks	FEV1, VC, TDI, SGRQ	Better than placebo
Kerwin et al GLOW2. 2012	792	Glyco 50 mcg od	Placebo, Tiotropium 18 mcg od	52 wks	FEV1, VC, TDI, SGRQ	Better than tiotropium at 26 wks but not at 52 wks, No diff in TDI or SGRQ
Beeh et al. 2013	108	Glyco 50 mcg od	Placebo	26 wks	FEV1, VC, TDI, SGRQ	Better than placebo

Umeclidinium

- Novel LAMA with strong affinity to M3 receptors
- Faster and longer acting compared to Tiotropium
- Approved in combination with Vilanterol as DPI (125/25 mcg or 62.5/25 mcg)

Study	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
Donohue et al. 2013	1532	62.5/25	Umec 62.5 Vil 25 Placebo	24 wks	Trough FEV1, symptom scores, Rescue SABA use	Improvement in FEV1 when compared with monotherapies for both doses. No difference in exacerbation rates or dyspnea scores/SGRQ.
Celli et al. 2014	1493	125/25	Umec 125 Vil 25 Placebo	24 wks	Trough FEV1, symptom scores, Rescue SABA use	
Anzueto et al. 2014	843	125/25 62.5/25	Vil 25 mcg, Tiotropium 18 mcg od	24 wks	Trough FEV1, symptom scores, Rescue SABA use	
Decramer et al. 2014	1141 1191	125/25 62.5/25	Vil 25 mcg, Tiotropium 18 mcg od, Umec 125 mcg	24 wks	Trough FEV1, symptom scores, Rescue SABA use	

MABA therapy

- Combination of LABA and LAMA in a single fixed dose system
- Synergistic effect as they act via diff pathways

QVA 149

- Fixed dose combination of 110 µg indacaterol + 50 µg glycopyrronium
- DPI administered od via Breezhaler®
- Series of 8 Phase III trials done as part of IGNITE program
- Approved in Europe, FDA approval pending

Study	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
Dahl et al. BEACON 2013	193	110/50 mcg od	Ind 150 mcg + Glyco 50 mcg od	4 wks	Trough FEV1, symptom scores, Rescue SABA use	Non-inferior in all aspects
Dahl et al. ENLIGHTEN 2013	339	110/50 mcg od	Placebo	52 wks	Safety, Trough FEV1, symptom scores, Rescue SABA use	Better than placebo in all, safe
Mahler et al BLAZE 2014 (crossover)	247	110/50 mcg od	Placebo, Tiotropium 18 mcg od	6 wks x 3	BDI/TDI score, FEV1, FVC	Better than both tiotropium and placebo
Beeh et al. BRIGHT 2014 (crossover)	85	110/50 mcg od	Placebo, Tiotropium 18 mcg od	3 wks x 3	Exercise tolerance, FEV1, VC, Lung volumes, SABA use	Better than placebo in all, Better than tio in FEV1, VC, SABA use
Asai et al. ARISE 2013 (open label)	160	110/50 mcg od	Tiotropium 18 mcg od	52 wks	FEV1, FVC, symptom scores, rescue SABA use	Better than tiotropium in all

Study	N	Dose	Comparator	Duration	1º and 2º Endpoints	Result
Vogelmeier et al. ILLUMINATE 2013	259	110/50 mcg od	Salmeterol/ Fluticasone 50/500 mcg bd	26 wks	FEV1, FVC, SGRQ, TDI rescue SABA use, exacerbations	QVA149 significantly better in all except SGRQ, no diff in exacerbations, ADR
Bateman et al. SHINE 2013	2144	110/50 mcg od	Placebo, Ind 150 mcg, Glyco 50mcg, Tiotropium 18 mcg od	26 wks	Safety, Trough FEV1, symptom scores, Rescue SABA use	Better than placebo in all, safe
Wedzicha et al SPARK 2013*	2224	110/50 mcg od	Glyco 50mcg od, Tiotropium 18 mcg od	64 wks	Rate of exacerbations, FEV1, symptom scores, Rescue SABA use	QVA vs Glyco **Mild: 0.85 (p=0.0072)** **Mod-severe: 0.88 (p=0.038)** **All: 0.85 (p=0.0012)** **SGRQ and FEV1 better** QVA vs Tio **Mild: 0.84 (p=0.0052)** **All: 0.86 (p=0.0017)** **SGRQ and FEV1 better** Glyco vs Tio **Severe: 1.43 (p=0.025)**

*Included patients with Severe/V.severe COPD (GOLD 3/4), FEV1 < 50 %, at least 1 exacerbation in past 1 yr

Summary of Results

- No significant increase in cardiac AEs
- LAMA+LABA produces significantly more bronchodilatation than individual drugs (60-90 ml improvement in FEV1)
- Significant improvement in dyspnea also seen
- QVA149 better in reducing exacerbations than Glycopyrronium/Tiotropium alone, but similar to LABA+ICS

Novel Bronchodilator targets

Table 1. Summary of potential novel targets limited to in-vitro and in-vivo studies in humans

Drug	Protein target	Endogenous stimuli	Comment	Authors
PL-3994	NPR-A, NPR-B, NPR-C	ANP, BNP and CNP, respectively	PL-3994 (NPR-A, NPR-C selective agonist) stimulates cyclic GMP. Relaxation of human precision-cut lung slice	[3▪]
Ro 25-1553	VPAC2-R	VIP	Ro 25-1553 caused rapid bronchodilation in asthma patients; 4–6 h duration (600 μg)	[4]
L-9026885	EP4-R	Prostaglandin E2	Relaxation of precontracted human bronchial preparations. More potent than salbutamol and salmeterol, anti-inflammatory	[5▪]
Y-27632	ROCK	rhoA	Relaxation of human airways, anti-inflammatory	[6]
NS1619	$K_{Ca}1.1$	Ca^{2+}, PKA, β2-receptor coupling	No in-vitro relaxant effect	[7–9]
Bimakalim, BRL38227	Kir6	ATP	No bronchodilator effect following inhaled bimakalim; oral BRL 38227 caused bronchodilation at the expense of headache	[10,11]
RPL554	PDE	Cyclic AMP	RPL554 caused relaxation of human bronchial smooth muscle; bronchodilator in asthma patients and in COPD, anti-inflammatory	[12▪,13,14]
TASR2 agonists	TASR2	Bitter tastants	Chloroquine, quinine cause relaxation of human airway smooth muscle	[15▪]
8-pCPT-2-O-Me-cAMP, Sp-8-pCPT-2′-O-Me-cAMPS	Epac1/2	Cyclic AMP	Epac activators cause relaxation of airway smooth muscle, antiproliferative	[16,17▪▪]
R837 (imiquimod)	TLR7	Single-strand viral RNA	Relaxation of human airway smooth muscle via release of nitric oxide from airway sensory neurones	[18▪]