Original Research

Long-Term Maintenance Bronchodilation With Indacaterol/Glycopyrrolate Versus Indacaterol in Moderate-to-Severe COPD Patients: The FLIGHT 3 Study

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eTable 1. Exclusion Criteria

Pregnant or nursing (lactating) women.
Women of child-bearing potential, unless using effective methods of contraception during the study treatment period.
Patients with Type 1 or uncontrollable Type 2 diabetes.
Patients with a history of long QT syndrome or whose QTc measured at run-in was prolonged (>450 ms by Fridericia method) and confirmed by a central assessor.
Patients who had a clinically significant ECG abnormality at run-in
Patients who had a clinically significant laboratory abnormality at run-in
Patients with a body mass index (BMI) of more than 40 kg/m^2.
Patients with clinically significant renal, CV disease (such as but not limited to unstable ischemic heart disease, New York Heart Association Class 3/4 left ventricular failure, myocardial infarction [MI]), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the efficacy and safety assessments.
Patients with paroxysmal atrial fibrillation. Patients with persistent atrial fibrillation controlled with a rate control strategy (resting ventricular rate < 100/min at Visit 101 and Visit 102) could be considered for inclusion.
Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to muscarinic antagonist agents, long- and short-acting β2 agonists, sympathomimetic amines, lactose or other excipients, and similar class or component.
Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years with exception of localized basal cell carcinoma of the skin.
Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention.
Patients who had not achieved an acceptable spirometry result at run-in in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability.
Patients who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit.
Patients developing COPD exacerbation between screening (Visit 1) and treatment (Visit 201) were not eligible but were permitted to be re-enrolled 6 weeks after the resolution.
Patients who had a respiratory tract infection within 4 weeks prior to screening.
Patients who developed a respiratory tract infection between screening and prior to treatment were not eligible, but were permitted to be re-enrolled 4 weeks after the resolution.
Patients requiring long term oxygen therapy prescribed for >12 hours per day.
Patients with any history of asthma.
Patients with an onset of respiratory symptoms, including a COPD diagnosis, prior to age 40 years.
Patients with a blood eosinophil count > $600/mm^3$ at run-in.
Patients with allergic rhinitis on H1 antagonist or intra-nasal corticosteroids intermittently.
Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension).
Patients with clinically significant bronchiectasis.
Patients with a diagnosis of α-1 anti-trypsin deficiency.
Patients with active pulmonary tuberculosis.
Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
Patients who participated in or planned to participate in the active phase of a supervised pulmonary rehabilitation program during the study.
Patients receiving any prohibited medications such as (non-potassium sparing diuretics, non-selective beta blocking agents, cardiac anti-arrhythmics Class Ia and III, drugs with QT prolongation potential, tricyclic antidepressants, antipsychotic agents, etc.)
Patients receiving any prohibited COPD related medications (LAMA, LABA/ICS, short-acting muscarinic antagonist (SAMA), SABA, SABA/SAMA, etc) were to undergo washout prior to Visit 101.
Patients receiving selective serotonin reuptake inhibitors, ICS, intra-nasal steroids H1-antagonists, inactivated influenza, pneumococcal or any other inactivated vaccine were to be excluded unless on stable dose.
Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of randomization.
Patients unable to use an electronic patient diary (eDiary).
Patients unable to use a dry powder inhaler device or a pressurized metered-dose inhaler (rescue medication) or comply with the study regimen.
Investigational site staff, their immediate family, or sponsor staff concerned with this study, were excluded from participation.

eTable 2. ECG Parameters (as measured by QTcF)

Number of Patients With Newly Occurring or Worsening Clinically Notable Fridericia's Qtc Values and Increases From Baseline at Any Time Post-Baseline (Safety Set)

Variable Criterion	IND/GLY 27.5/15.6 bid N=204 n/m (%)	IND/GLY 27.5/31.2 bid N=204 n/m (%)	IND 75 µg N=206 n/m (%)
QTc (Fridericia)			
N*	204	204	206
> 450 ms	14 (6.9)	18 (8.8)	19 (9.2)
> 480 ms	3 (1.5)	1 (0.5)	0
> 500 ms	0	0	0
Change from baseline in QTc (Fridericia)			
N*	204	204	206
Increase 30 – 60 ms	26 (12.7)	24 (11.8)	27 (13.1)
Increase > 60 ms	1 (0.5)	2 (1.0)	1 (0.5)

n = number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value or had a worsening of a value during treatment which was already notable at baseline. For patients with a missing value at baseline, any post-baseline notable value was considered as newly occurring.

N* = number of patients with a post-baseline QTcF value, considering data from scheduled, unscheduled or premature discontinuation visits up to 7 days after last dose. For the increase from baseline both a post-baseline and baseline QTcF value must be available.

Notable QTc categories are not mutually exclusive. ECG: electrocardiogram, QTc: Corrected QT interval

Etable 3. Vital Signs (Number of Patients with Newly Occurring or Worsening Clinically Notable Vital Signs at Any Time Post-Baseline (Safety Set)

Number of Patients with Newly Occurring or Worsening Clinically Notable Vital Signs at Any Time Post-Baseline (Safety Set)

Parameter	Notable criterion	IND/GLY 27.5/15.6 bid N=204 n/m (%)	IND/GLY 27.5/31.2 bid N=204 n/m (%)	IND 75 µg N=206 n/m (%)
Pulse rate	Low	4/204 (2.0)	3/204 (1.5)	3/206 (1.5)
	High	1/204 (0.5)	0/204	1/206 (0.5)
Systolic blood pressure	Low	2/204 (1.0)	1/204 (0.5)	2/206 (1.0)
	High	3/204 (1.5)	5/204 (2.5)	3/206 (1.5)
Diastolic blood pressure	Low	1/204 (0.5)	0/204	2/206 (1.0)
	High	3/204 (1.5)	3/204 (1.5)	2/206 (1.0)
Body weight	Low	19/189 (10.1)	8/191 (4.2)	17/192 (8.9)
	High	14/189 (7.4)	20/191 (10.5)	18/192 (9.4)

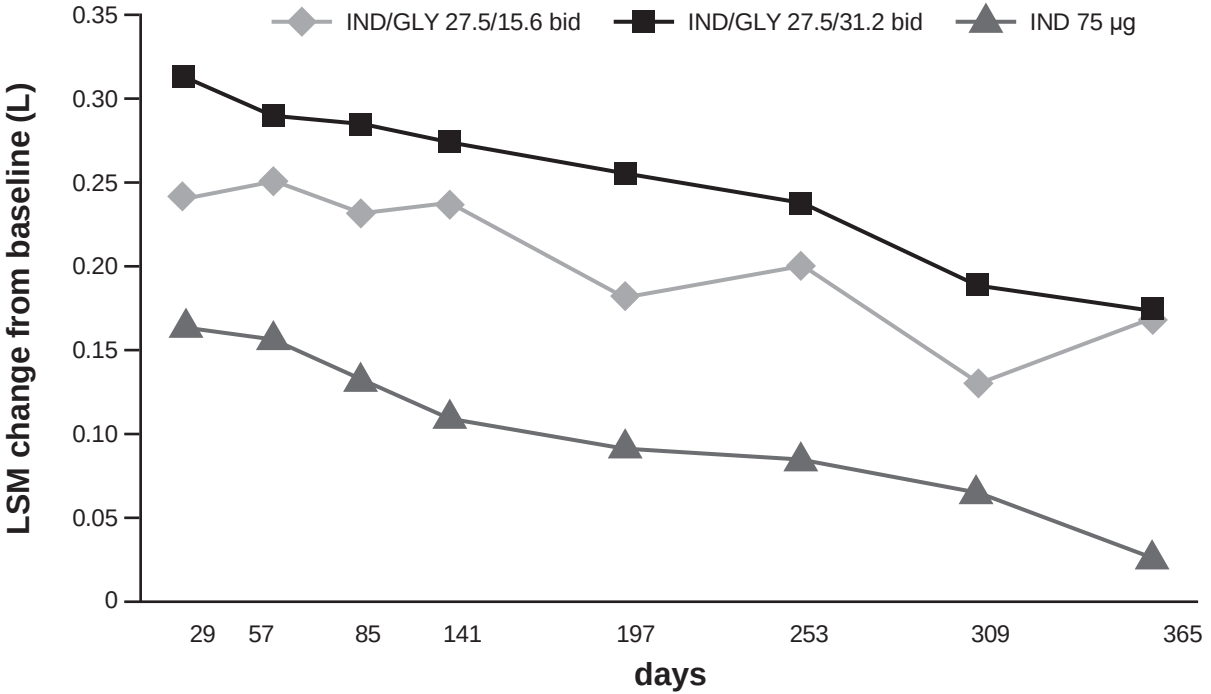
Notably abnormal vital signs and body weight:

Low pulse rate: < 40 bpm, or ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

High pulse rate: > 130 bpm, or ≥ 120 bpm with increase from baseline of ≥ 15 bpm

Low systolic blood pressure: < 75 mmHg, or ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg; High systolic blood pressure: > 200 mmHg, or ≥ 180 mmHg with increase from baseline of ≥ 20 mmHg; Low diastolic blood pressure: < 40 mmHg, or ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg; High diastolic blood pressure: > 115 mmHg, or ≥ 105 mmHg with increase from baseline of ≥ 15 mmHg; Low body weight: > 7% decrease from baseline High body weight: > 7% increase from baseline

eFigure 1. LS mean change from baseline in pre-dose trough FVC (L)



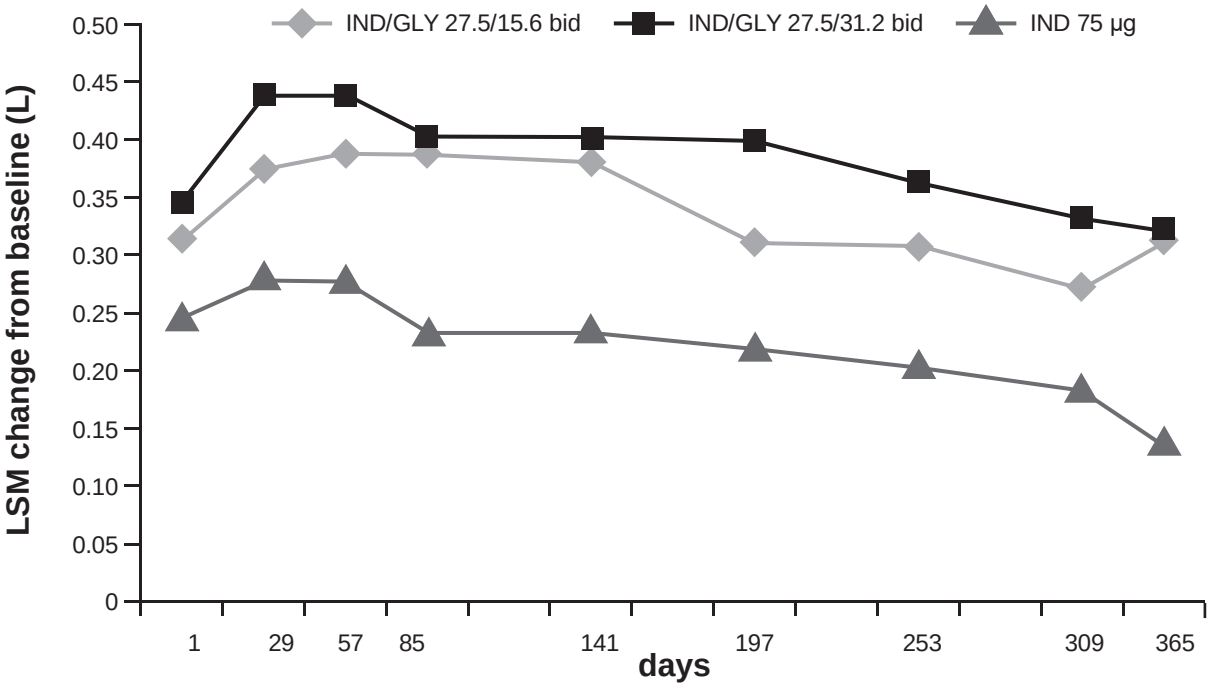
MMRM: Change from baseline in pre-dose trough FVC = treatment + baseline FVC + smoking status at baseline + baseline ICS use + airflow limitation severity + region + visit + treatment*visit interaction + baseline FVC*visit interaction.

Pre-dose trough FVC is defined as the mean of FVC at -45 min and -15 min before morning dose.

Baseline FVC is defined as the average of the -45 min and -15 min FVC values taken on Day 1 prior to first dose.

b.i.d., twice daily; GLY glycopyrronium; IND indacaterol; ICS, inhaled corticosteroid; LSM, least square mean; MMRM, mixed-model repeated-measures; FVC, forced vital capacity; o.d., once daily

eFigure 2. LS mean change from baseline in 1 hour post-dose FVC (L)



MMRM: Change from baseline in pre-dose trough FVC = treatment + baseline FVC + smoking status at baseline + baseline ICS use + airflow limitation severity + region + visit + treatment*visit interaction + baseline FVC*visit interaction.

Pre-dose trough FVC is defined as the mean of FVC at -45 min and -15 min before morning dose.

Baseline FVC is defined as the average of the -45 min and -15 min FVC values taken on Day 1 prior to first dose.

b.i.d., twice daily; GLY glycopyrronium; IND indacaterol; ICS, inhaled corticosteroid; LSM, least square mean; MMRM, mixed-model repeated-measures; FVC, forced vital capacity; o.d., once daily

eTable 4. Symptom Endpoints Over the 52 Weeks of Treatment Based on Data of he Patient Diary (FAS)

					Treatment difference		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
CFB in mean daily total symptom score							
All	595	6.44					
IND/GLY 27.5/15.6 bid	198	6.35	-1.57 (0.133)	IND 75 µg	-0.26 (0.177)	(-0.61, 0.09)	0.143
IND/GLY 27.5/31.2 bid	199	6.50	-1.56 (0.133)	IND 75 µg	-0.25 (0.178)	(-0.60, 0.10)	0.166
IND 75 µg	198	6.48	-1.31 (0.135)				
CFB in mean daytime total symptom score							
All	587	5.88					
IND/GLY 27.5/15.6 bid	194	5.71	-1.37 (0.130)	IND 75 µg	-0.21 (0.172)	(-0.55, 0.12)	0.215
IND/GLY 27.5/31.2 bid	196	5.93	-1.35 (0.129)	IND 75 µg	-0.20 (0.172)	(-0.54, 0.14)	0.251
IND 75 µg	197	5.99	-1.15 (0.130)				
CFB in mean nighttime total symptom score							
All	590	5.28					
IND/GLY 27.5/15.6 bid	196	5.26	-1.29 (0.133)	IND 75 µg	-0.27 (0.176)	(-0.61, 0.08)	0.130
IND/GLY 27.5/31.2 bid	199	5.30	-1.28 (0.133)	IND 75 µg	-0.25 (0.176)	(-0.60, 0.09)	0.149
IND 75 µg	195	5.27	-1.02 (0.135)				
CFB in the percentage of nights with no nighttime awakenings							
All	590	48.2					
IND/GLY 27.5/15.6 bid	196	50.3	18.0 (2.30)	IND 75 µg	5.1 (2.87)	(-0.6, 10.7)	0.078
IND/GLY 27.5/31.2 bid	199	46.1	18.6 (2.29)	IND 75 µg	5.7 (2.88)	(0.0, 11.3)	0.049
IND 75 µg	195	48.2	12.9 (2.32)				
CFB in the percentage of days with no daytime symptoms							
All	587	4.3					
IND/GLY 27.5/15.6 bid	194	4.7	10.2 (1.71)	IND 75 µg	5.5 (2.27)	(1.1, 10.0)	0.015
IND/GLY 27.5/31.2 bid	196	4.8	6.5 (1.71)	IND 75 µg	1.8 (2.27)	(-2.7, 6.2)	0.440
IND 75 µg	197	3.6	4.7 (1.72)				
CFB in the percentage of days able to perform usual daily activities							
All	587	30.2					
IND/GLY 27.5/15.6 bid	194	33.0	14.7 (2.25)	IND 75 µg	7.4 (2.86)	(1.8, 13.1)	0.010
IND/GLY 27.5/31.2 bid	196	29.2	11.1 (2.24)	IND 75 µg	3.8 (2.86)	(-1.8, 9.4)	0.187
IND 75 µg	197	28.3	7.3 (2.26)				

All LS Means, SEs, CIs, and p-values are from a LMM: Change from baseline (CFB) in mean score or percentage of nights/days = treatment + baseline value + smoking status at baseline + baseline ICS use + airflow limitation severity + region + random effect of center nested within country.

Baseline raw means are not from the model.

Only the scores for the 6 COPD symptoms (respiratory symptoms, cough, wheeze, production of sputum, sputum color, breathlessness) were used to derive the total symptom score.

eTable 5. Rescue Medication Intake Over the 52 Weeks of Treatment Based on Data of the Patient Diary (FAS)

Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	Treatment difference LS Mean (SE)	(95% CI)	p-value
CFB in mean daily number of puffs of rescue medication							
All	595	4.03					
IND/GLY 27.5/15.6 bid	198	4.13	-1.89 (0.164)	IND 75 µg	-0.16 (0.210)	(-0.58, 0.25)	0.440
IND/GLY 27.5/31.2 bid	199	4.07	-1.62 (0.164)	IND 75 µg	0.11 (0.211)	(-0.30, 0.53)	0.592
IND 75 µg	198	3.88	-1.73 (0.166)				
CFB in mean daytime number of puffs of rescue medication							
All	587	2.33					
IND/GLY 27.5/15.6 bid	194	2.41	-1.11 (0.093)	IND 75 µg	-0.08 (0.122)	(-0.32, 0.16)	0.508
IND/GLY 27.5/31.2 bid	196	2.36	-0.95 (0.093)	IND 75 µg	0.08 (0.122)	(-0.16, 0.32)	0.517
IND 75 µg	197	2.21	-1.03 (0.093)				
CFB in mean nighttime number of puffs of rescue medication							
All	590	1.67					
IND/GLY 27.5/15.6 bid	196	1.68	-0.77 (0.076)	IND 75 µg	-0.10 (0.098)	(-0.29, 0.09)	0.306
IND/GLY 27.5/31.2 bid	199	1.69	-0.66 (0.075)	IND 75 µg	0.01 (0.098)	(-0.18, 0.20)	0.910
IND 75 µg	195	1.63	-0.67 (0.077)				
CFB in the percentage of days with no rescue medication use							
All	593	20.9					
IND/GLY 27.5/15.6 bid	197	21.8	27.1 (2.76)	IND 75 µg	6.6 (3.51)	(-0.3, 13.5)	0.061
IND/GLY 27.5/31.2 bid	199	20.4	18.1 (2.76)	IND 75 µg	-2.4 (3.51)	(-9.3, 4.5)	0.503
IND 75 µg	197	20.5	20.5 (2.79)				

All LS means, SEs, CIs, and p-values are from a LMM: Change from baseline (CFB) in mean number of puffs or percentage of days = treatment + baseline value + smoking status at baseline + baseline ICS use + airflow limitation severity + region + random effect of center nested within region.

Baseline raw means are not from the model.

eTable 6. CAT Total Score, Change From Baseline, at Post-Baseline Visits (EAS)

Visit	Treatment	Baseline Raw Mean	LS Mean (SE)	Comparator	Treatment Difference		
					LS Mean SE	95% CI	p-value
Baseline	All						
Day 85 CFB	IND/GLY 27.5/15.6 bid	16.7	-2.8 (0.39)	IND 75 µg	-0.7 (0.54)	(-1.8, 0.3)	0.164
	IND/GLY 27.5/31.2 bid	17.7	-2.7 (0.38)	IND 75 µg	-0.7 (0.53)	(-1.7, 0.4)	0.199
	IND 75 µg	17.1	-2.0 (0.38)				
Day 197 CFB	IND/GLY 27.5/15.6 bid	16.7	-2.5 (0.41)	IND 75 µg	-0.2 (0.57)	(-1.3,0.9)	0.691
	IND/GLY 27.5/31.2 bid	17.4	-1.8 (0.40)	IND 75 µg	-0.5 (0.56)	(-0.6,1.6)	0.401
	IND 75 µg	16.9	-2.2 (0.41)				
Day 309 CFB	IND/GLY 27.5/15.6 bid	16.7	-2.0 (0.43)	IND 75 µg	-0.6 (0.6)	(-1.8,0.6)	0.307
	IND/GLY 27.5/31.2 bid	17.4	-1.4 (0.42)	IND 75 µg	0.0 (0.59)	(-1.2,1.1)	0.973
	IND 75 µg	17.0	-1.3 (0.43)				
Day 365 CFB	IND/GLY 27.5/15.6 bid	16.6	-2.3 (0.42)	IND 75 µg	-0.9 (0.58)	(-2.0,0.3)	0.127
	IND/GLY 27.5/31.2 bid	17.4	-1.1 (0.41)	IND 75 µg	0.4 (0.58)	(-0.7,1.5)	0.5
	IND 75 µg	17.0	-1.4 (0.42)				

All LS Means, SEs, CIs, and p-values are from a MMRM: Change from baseline (CFB) in CAT score = treatment + baseline CAT score + smoking status at baseline + baseline ICS use + airflow limitation severity + region + visit + treatment* visit interaction + baseline CAT score *visit interaction

Baseline raw means are not from the model

CAT total score

(Number of patients included in the analysis – IND/GLY 27.5/15.6 bid: n=186, IND/GLY 27.5/31.2 bid: n=193, IND 75 od: n=192)