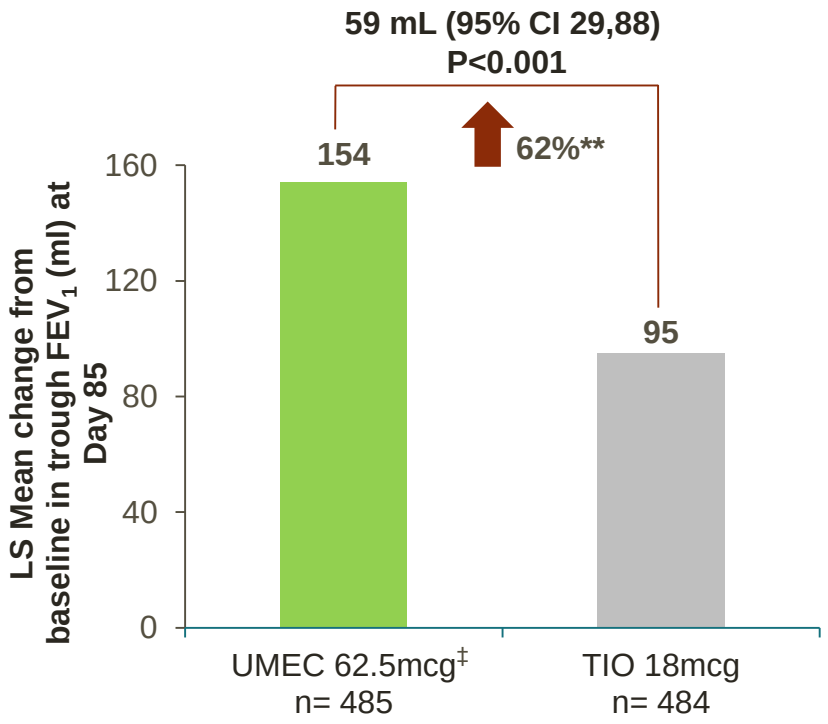
Umeclidinium/vilanterol (UMEC/VI) vs tiotropium/olodaterol (TIO/OLO) study (204990) Key study and sub analysis results

Pm-il-ucv-ppt-200002 June 2020

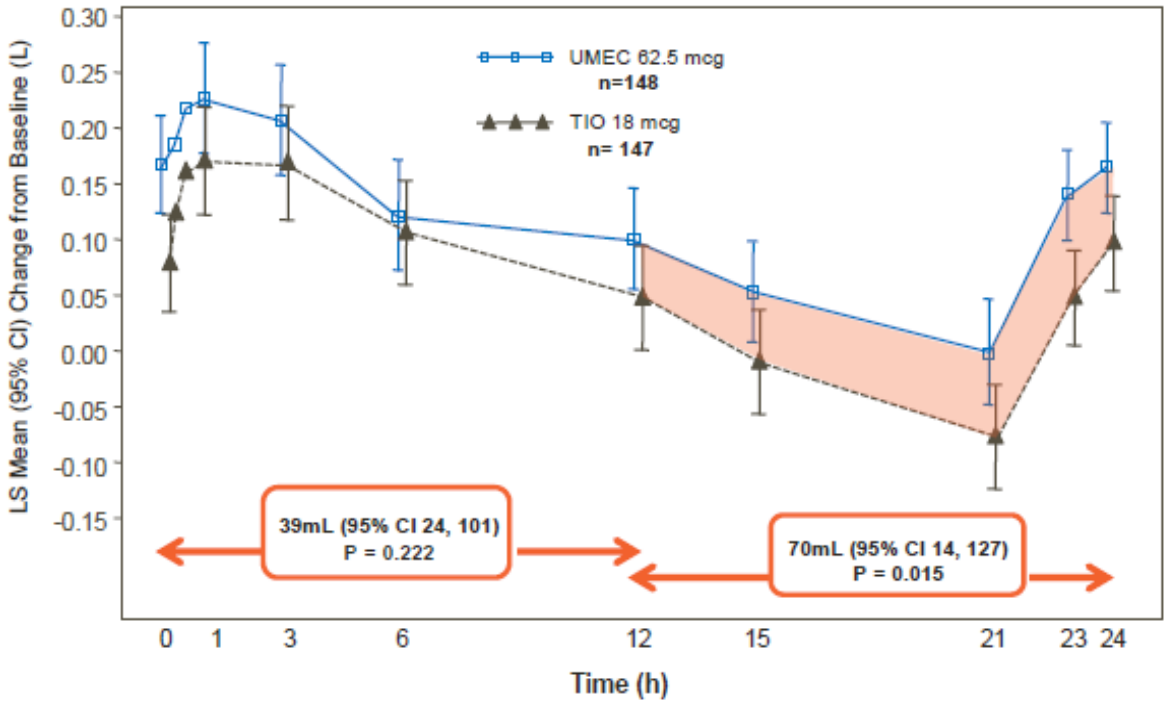
Greater improvement in FEV_1 with umeclidinium compared with tiotropium

12-week blinded H2H trial in symptomatic patients with moderate to severe COPD

Trough FEV_1 at Day 85 (Primary Endpoint, Per Protocol)*



Mean change from baseline in weighted mean 0-12h and 12-24h serial FEV_1 at Day 85 (ITT population)

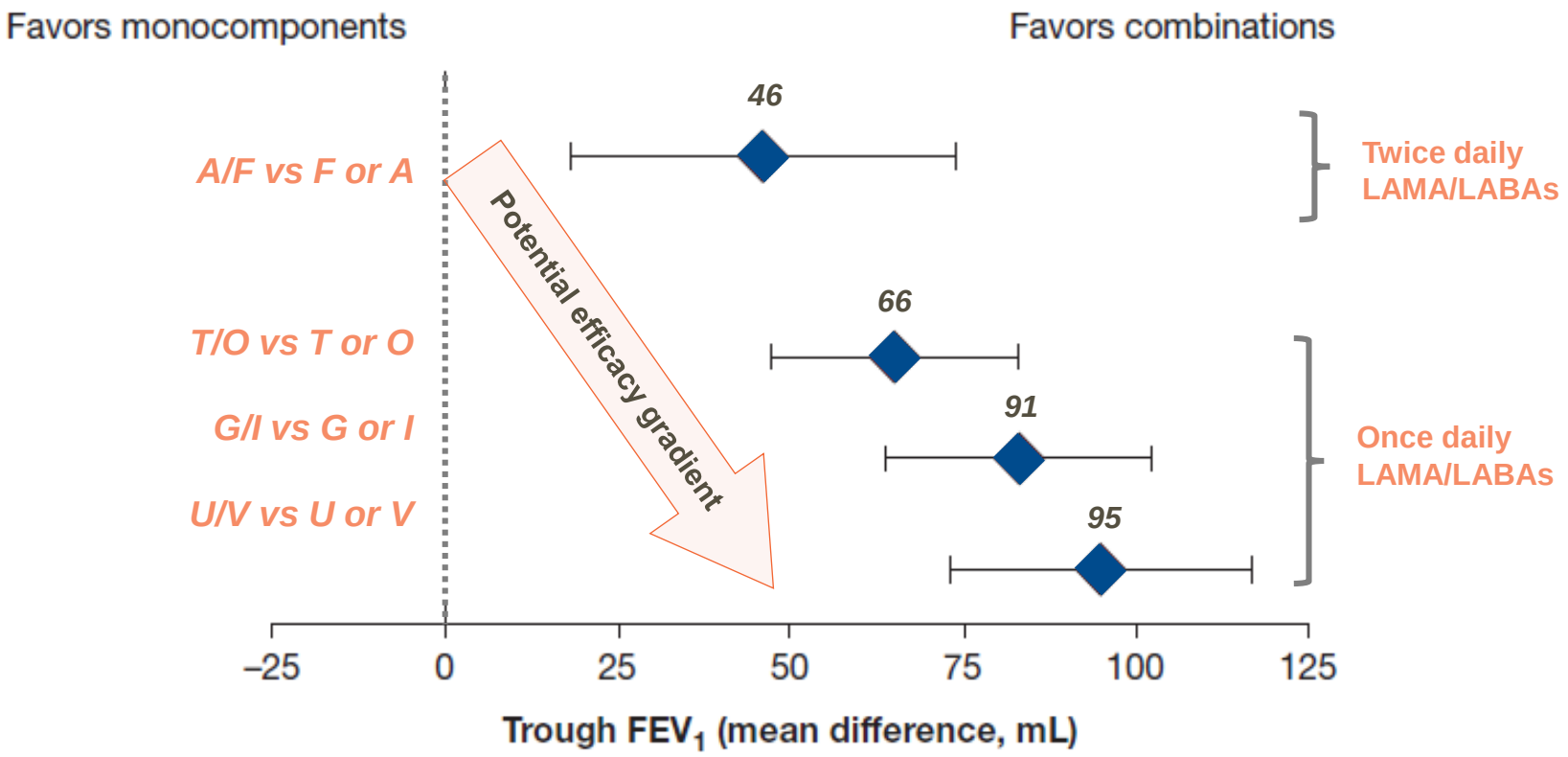


* A non-inferiority margin of -50 mL was set for the primary per-protocol analysis, ** greater improvement in trough FEV_1 compared to TIO (estimated calculation only)
‡ Delivered doses for UMEC 55mcg; LS mean, least squares mean

Adapted from: Feldman G, *et al Int. Journal of COPD* 2016: 11. 719–730.

LAMA/LABA vs their individual LAMA or LABA

Meta-analysis of 15 RCTs ≥12 weeks in length, n=23,168 patients; Primary Endpoint – trough FEV_1



All fixed-dose LAMA/LABAs were superior to their individual component LAMAs and LABAs with a range of improvement with two vs one drug ranging from 46 mL with A/F to 95 mL with U/V

A/F, aclidinium/formoterol 400/12 µg; T/O, tiotropium/olodaterol 5/5 µg; G/I, glycopyrronium/indacaterol 50/110 µg; U/V, umeclidinium/vilanterol 62.5/25 µg

Adapted from Calzetta L, et al. *Chest* 2016;149:1181–1196.

Is there a gradient in effectiveness between the LAMA/LABAs?

How do they compare indirectly on trough FEV_1 in moderate COPD?

Results of the network meta-analysis for trough FEV_1, at 24 weeks with estimated differences (mL) in change from baseline [95% Credibility Interval]) for patients with moderate COPD

Intervention A	Comparator B				
	Placebo	TIO 18 or 5 mcg	TIO 18 + FOR 12	TIO/OLO 5/5	IND/GLY 110/50
TIO 18 or 5	157.3 (128.4, 186.3)				
TIO 18 + FOR 12	146.8 (88.5, 205.2)	-10.6 (-65.8, 45.2)			
TIO/OLO 5/5	217.3 (177.6, 257.4)	60.0 (32.6, 87.5)	70.5 (8.6, 132.0)		
IND/GLY 110/50	230.3 (193.0, 267.7)	73.1 (40.6, 105.5)	83.5 (38.3, 128.4)	13.1 (-29.8, 55.5)	
UMEC/VI 62.5/25	276.1 (228.5, 324.1)	118.8 (80.6, 157.1)	129.3 (61.6, 196.7)	58.8 (11.5, 105.8)	45.6 (-4.4, 95.9)

The probability of improved outcome using treatment A vs B was >99% for all comparisons shown in black text

This network meta-analysis predicts a statistically significant difference in trough FEV_1 exists between UMEC/VI and TIO/OLO in subjects with moderate COPD = 59 mL

TIO, tiotropium; FOR, formoterol; TIO/OLO, tiotropium/olodaterol; IND/GLY, indacaterol/glycopyrronium; UMEC/VI, umeclidinium/vilanterol.

Adapted from Sion KYJ et al. *Pulm Ther.* 2017;3:297–316 (supplementary table:S15).

Summary

- Bronchodilation, with a LAMA and/or a LABA, forms the cornerstone of pharmacological treatment for COPD[1]
- Systematic review of RCTs have demonstrated greater improvements in lung function with LAMA/LABA combinations vs LAMA or LABA monotherapies in patients with stable COPD[2]
- In the LAMA class, UMEC was found to have superior efficacy to TIO, providing significantly greater increases in trough FEV_1 after 12 weeks[3]
- Indirect evidence of LAMA/LABA comparisons suggests that a potential effectiveness gradient exists between LAMA/LABA combination therapies however, direct head-to-head data are required to confirm these findings[4]

RCT, Randomised Controlled Trial

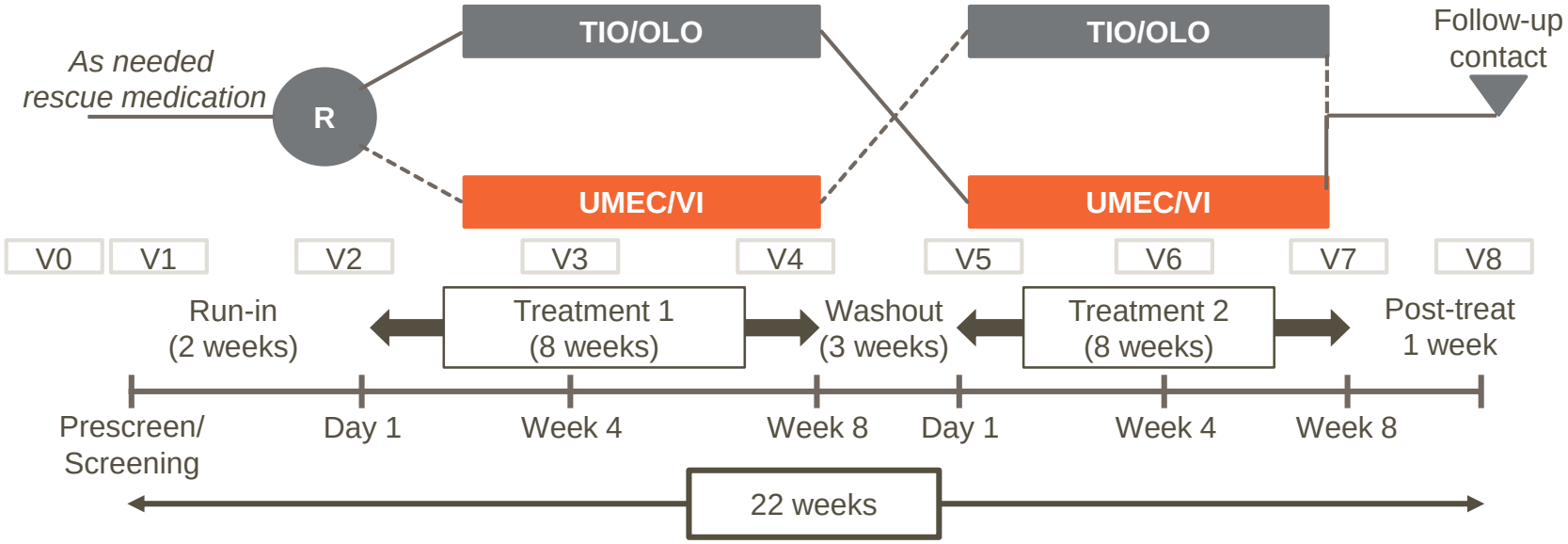
1. Global Initiative for Chronic Obstructive Lung Disease;GOLD;2020; 2. Calzetta L, et al. *Chest*. 2016;149:1181–1196;
3. Feldman GJ, et al. *Int J Chron Obstruct Pulmon Dis.* 2016;11:719–730; 4. Sion KYJ, et al. *Pulm Ther.* 2017;3:297–316;

A randomised, open label, 8-week crossover study to compare UMEC/VI (62.5/25µg)* once daily with TIO/OLO (5/5µg) once daily in patients with COPD (204990)

* Delivered doses for UMEC/VI (55/22 µg)

Study design (I)

Non-inferiority, randomised, two-period 8 week crossover study



- Open label treatment*
  - UMEC/VI 62.5/25 µg† 1 inhalation once daily via the ELLIPTA inhaler
  - TIO/OLO 5/5 µg (2.5/2.5 µg x 2 inhalations) once daily via the Respimat‡ inhaler
- Study conducted in Germany, Spain, UK and US
- Primary endpoint: Change from baseline in trough FEV_1 at Week 8
- All patients had appropriate training on how to use both the ELLIPTA and Respimat inhalers

* All technicians performing spirometry were blinded to treatment allocation throughout the study; † Delivered doses for UMEC/VI (55/22 µg) ‡ Respimat is a trademark from Boehringer Ingelheim.

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Study design (II)

Key eligibility criteria and study endpoints

Key eligibility criteria

- **Age ≥40 years**
- **COPD diagnosis (ATS & ERS definition)**
- **Smoking history ≥10 pack-years**
- **Post-bronchodilator FEV_1/FVC ratio <0.70**
- **Post-bronchodilator FEV_1 ≤70–≥50%**
- **mMRC dyspnoea score ≥2**
- **Not receiving ICS-containing therapy at inclusion**

Primary endpoint

- **Change from baseline in trough FEV_1 at Week 8**

Other endpoints

- Change form baseline in trough FEV_1 at week 4
- % FEV_1 responders (≥100 mL change from baseline) at Week 4 and 8
- Change form baseline in trough FVC and IC at Weeks 4 and 8
- Change from baseline in CAT score and % responders* at Weeks 4 and 8
- Rescue use and % rescue-free days (weeks 1-8)
- Weekly change from baseline in E-RS $_{COPD}$ symptom score and weekly % responders**
- Inhaler ease-of-use

Safety endpoints

- Incidence of adverse events and serious adverse events
- Incidence of COPD exacerbations

* Responders defined as patients with a reduction of ≥2 units from baseline CAT score; ** Responders defined as patients achieving a reduction from baseline E-RS score of ≥2 units,
CAT, COPD assessment tool; E-RS, EXACT-Respiratory Symptoms; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; ICS, inhaled corticosteroids; MDI, metered dose inhaler; mMRC, modified Medical Research Council.

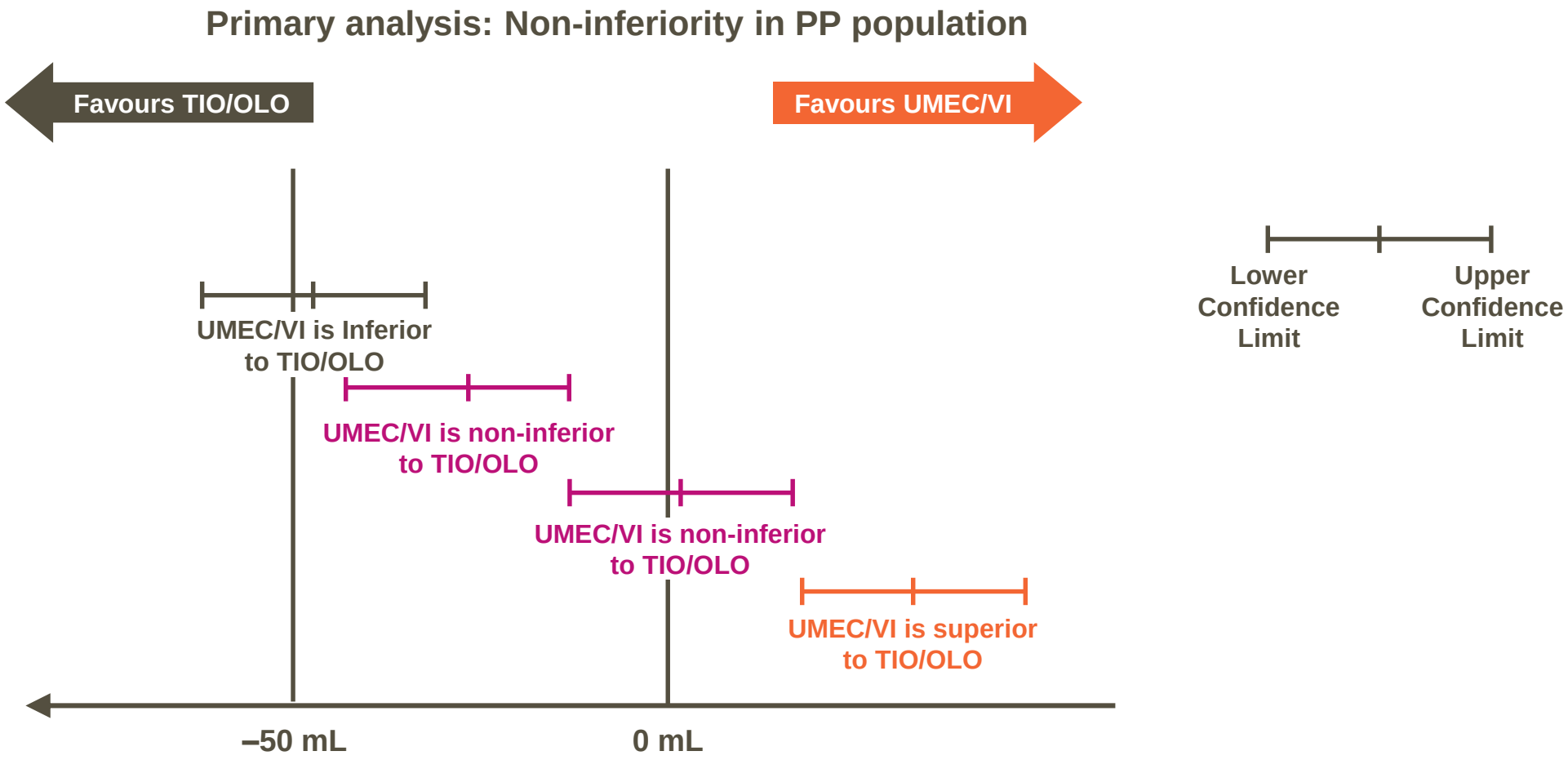
Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Statistical considerations

- A population of 220 patients was calculated to have 90% power to detect the non-inferiority of UMEC/VI compared with TIO/OLO on trough FEV_1[1]
- A non-inferiority margin of –50 mL was set for the primary per-protocol analysis. The margin of non-inferiority was at -50mL as this represents 50% of the minimum clinically important difference in trough FEV_1, and has consistently been used as a non-inferiority margin in similar studies in COPD[2,3]
- If the non-inferiority of UMEC/VI to TIO/OLO was demonstrated (i.e. if the lower boundary of the two-sided 95% confidence interval [CI] for the estimated treatment difference was greater than –50 mL), statistical superiority was then investigated on the primary endpoint in the ITT population
- UMEC/VI was considered superior to TIO/OLO on the primary endpoint in the ITT population if the lower estimate of the treatment difference (95% CI) was >0 mL

1. Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533; 2. Feldman G, et al. *Int J Chron Obstruct Pulmon Dis*. 2016;11:719–730; 3. Chapman KR, et al. *BMC Pulm Med*. 2014;14:4.

Interpreting non-inferiority



Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Study population

Intention-to-treat (ITT) population

All randomised patients who received one dose of study medication

N=236

Per-protocol (PP) population

ITT population without protocol violations considered to have the potential to impact efficacy

N =227 (96%)

Inhaler-naive population

Population with no prior experience handling either the ELLIPTA inhaler or Respimat inhaler

N=75 (32%)

In total, 443 patients were enrolled in the study, 421 attended screening of these 236 (56%) were randomised

Completed

N=225 (95%)

The reasons for study withdrawal were:

- patient decision (3%)
- loss to follow-up (<1%)
- adverse event (<1%)
- protocol deviation (<1%)

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Baseline demography and clinical characteristics

ITT population

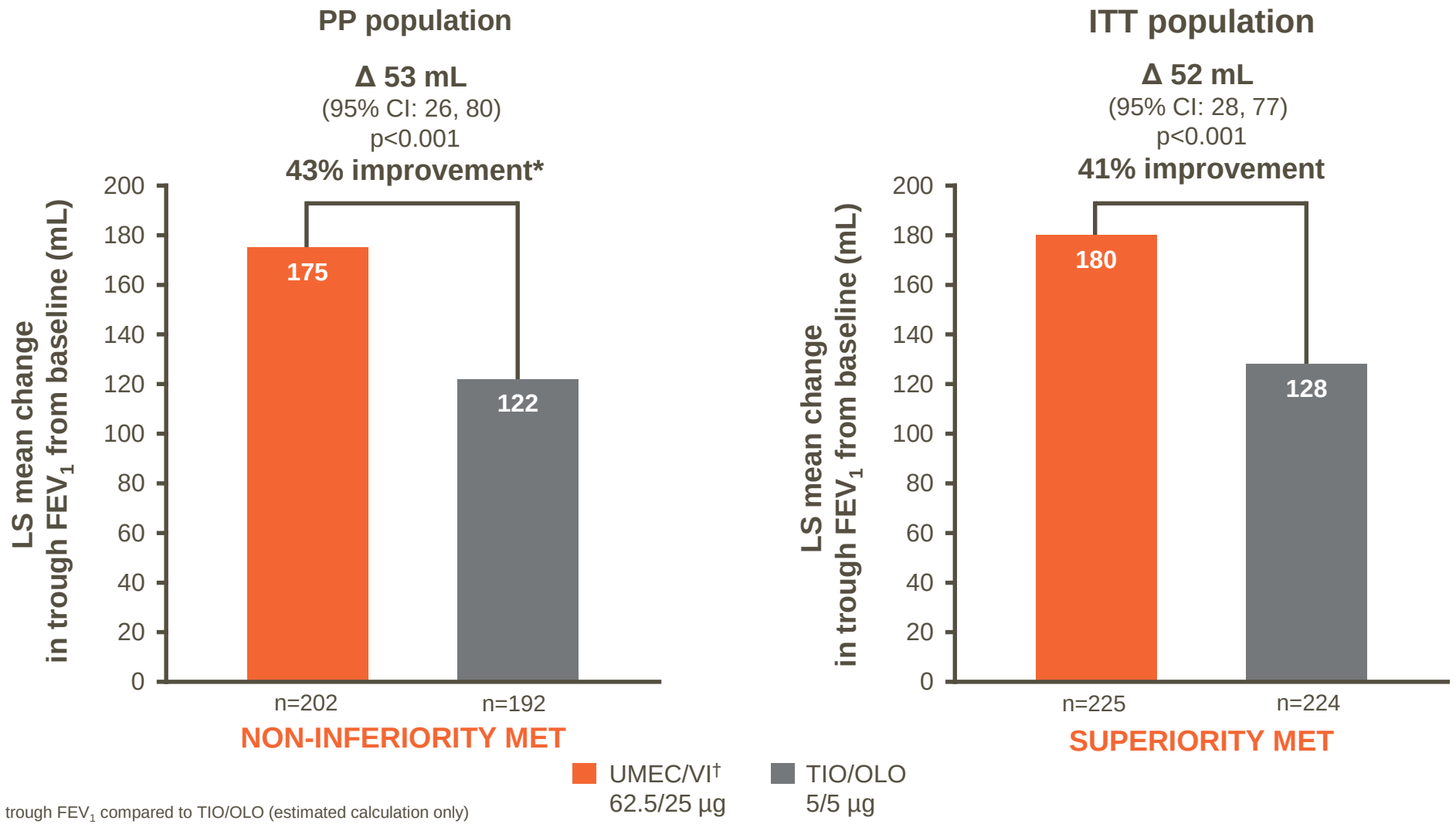
		Total (N = 236)
Mean age, y (SD)		64.4 (8.5)
Male, n (%)		142 (60)
Current smoker at screening, n (%)		125 (53)
Smoking pack-years		50.2 (25.5)
COPD exacerbation history (12 months prior to screening), n (%):	≥1 requiring OCS/antibiotics 2 requiring OCS/antibiotics Requiring hospitalisation	33 (14) 4 (2) 6 (3)
Mean post-bronchodilator FEV_1, % predicted (SD)		59.6 (5.6)
GOLD 2017 mMRC / Exacerbation category, n (%):	GOLD B GOLD D	224 (95) 12 (5)
mMRC score, n (%):	2 (moderate) 3 (severe) 4 (very severe)	156 (66) 71 (30) 9 (4)
Respiratory maintenance meds used prior to run-in, n (%):*	LAMA LABA LAMA/LABA ICS	38 (16) 29 (12) 30 (13) 10 (4)

* Removed prior to run-in.
All data are presented as mean (SD) unless stated otherwise.
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITT, intent-to-treat; OCS, oral corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnoea scale; SD, standard deviation

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Efficacy results

Trough FEV_1 at Week 8 – Primary Endpoint

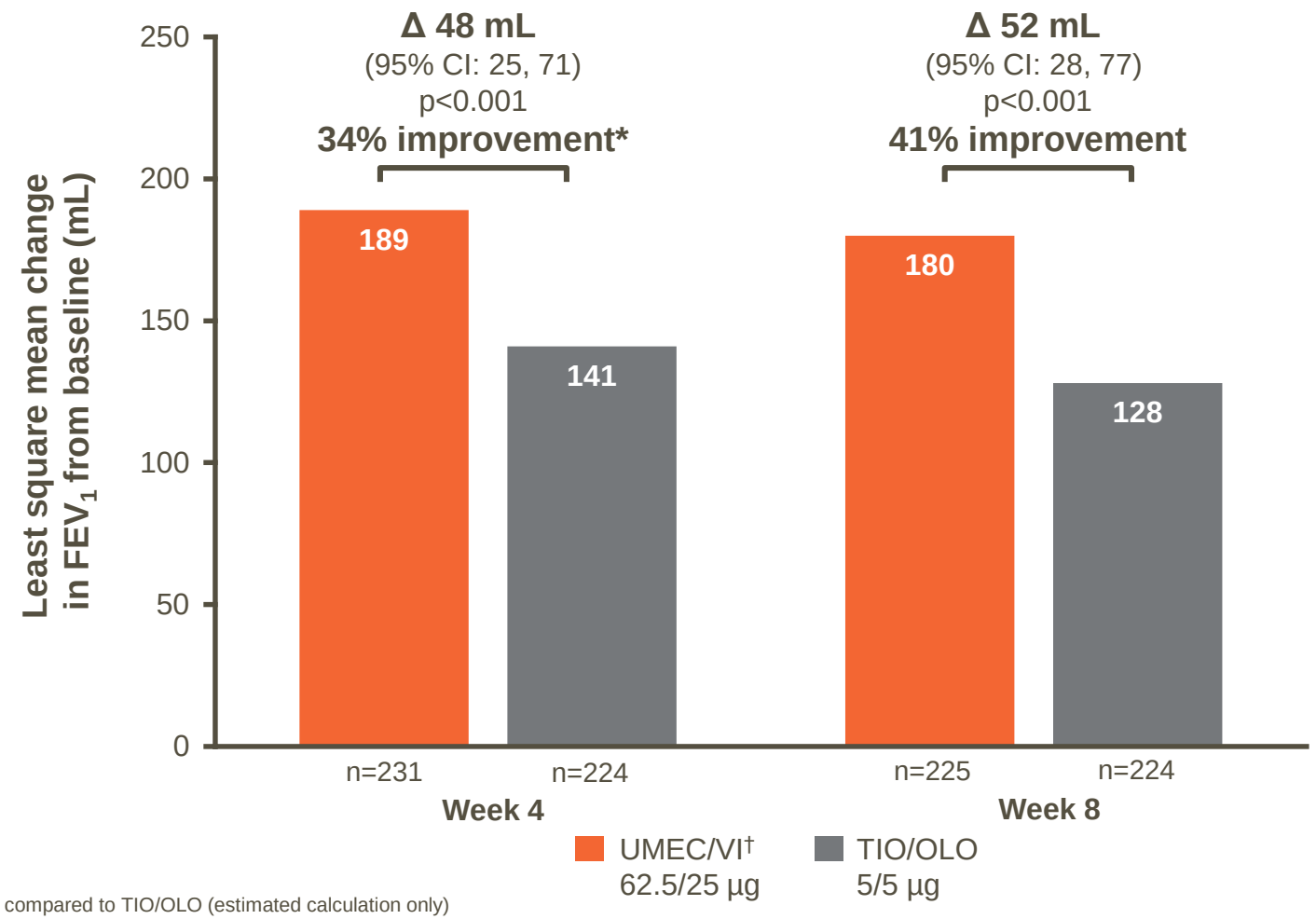


* Greater improvement in trough FEV_1 compared to TIO/OLO (estimated calculation only)
† Delivered doses for UMEC/VI (55/22 µg).

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Trough FEV_1 at Weeks 4 and 8

ITT population



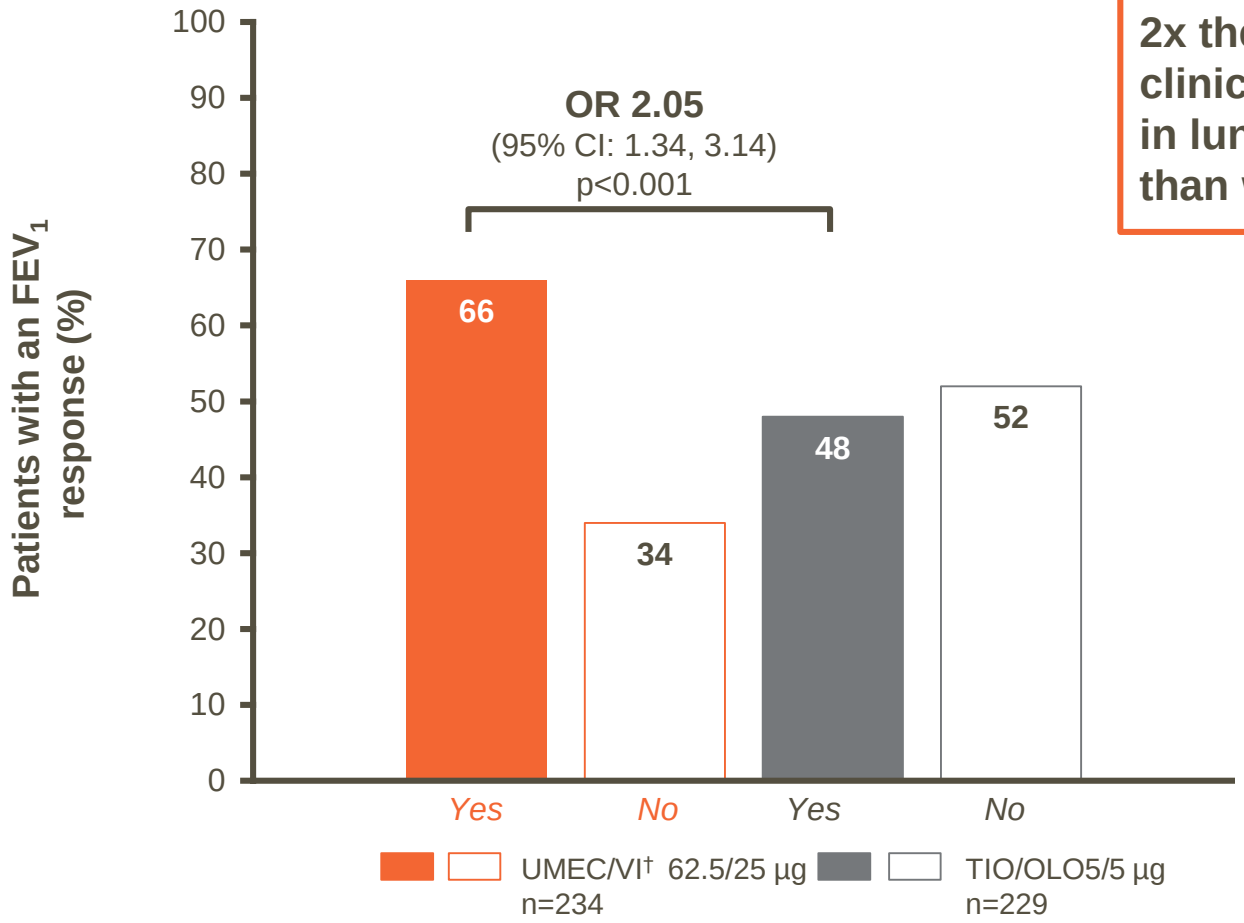
Change from baseline in Trough FEV_1 plateaued at Week 4 during each treatment period

* Greater improvement in trough FEV_1 compared to TIO/OLO (estimated calculation only)
† Delivered doses for UMEC/VI (55/22 µg)

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Trough FEV_1 at Week 8: Responder analysis*

ITT population[1,2]



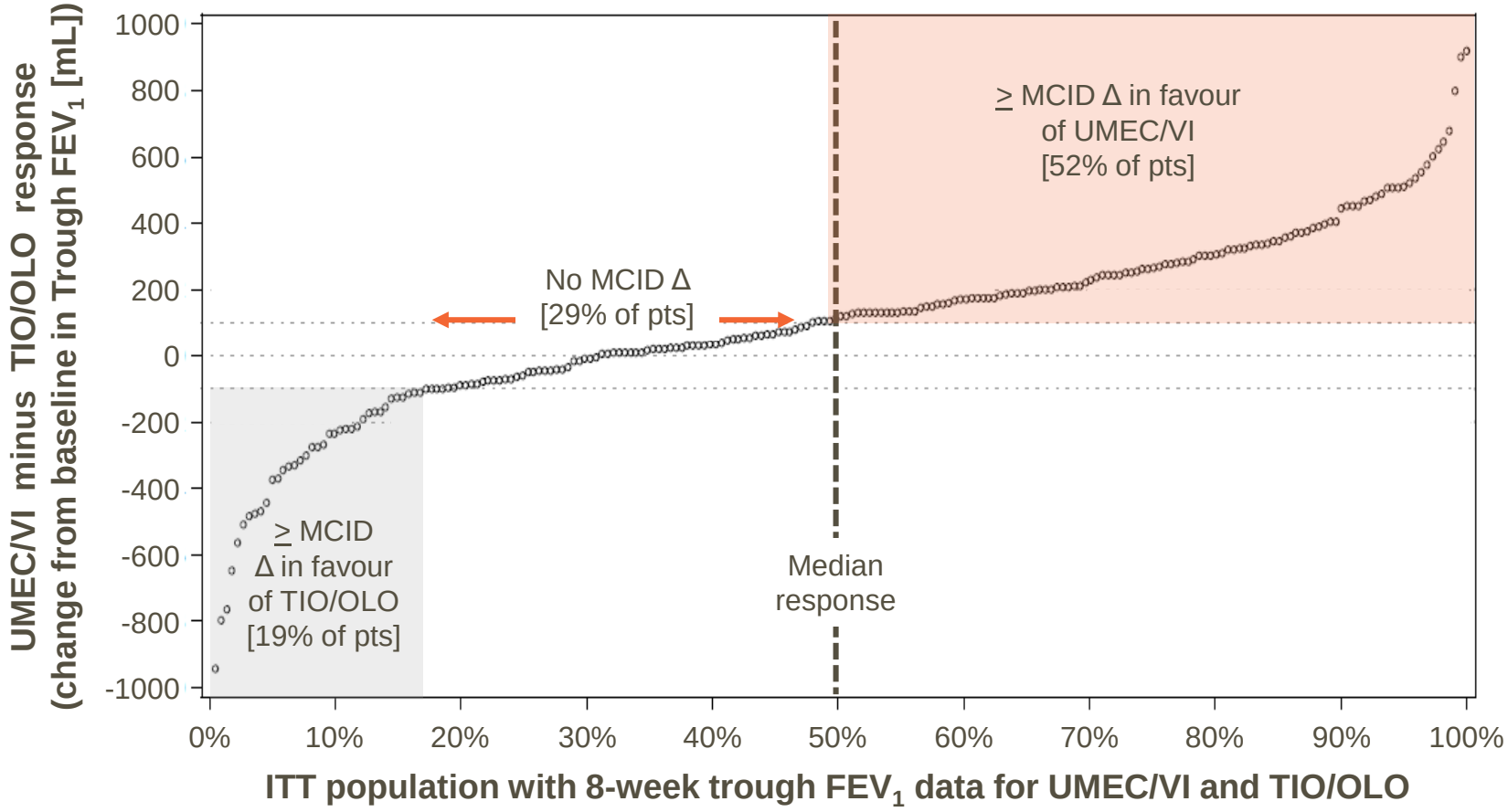
2x the odds of achieving a clinically meaningful improvement in lung function with UMEC/VI than with TIO/OLO

*Response defined as ≥100 mL change from baseline in trough FEV_1;
† Delivered doses for UMEC/VI (55/22 µg)

1. Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533; 2. GlaxoSmithKline. Data on File RF/UCV/0073/17.

How many individual patients show important efficacy differences* between the LAMA/LABAs after 8 weeks on each treatment?

ITT population



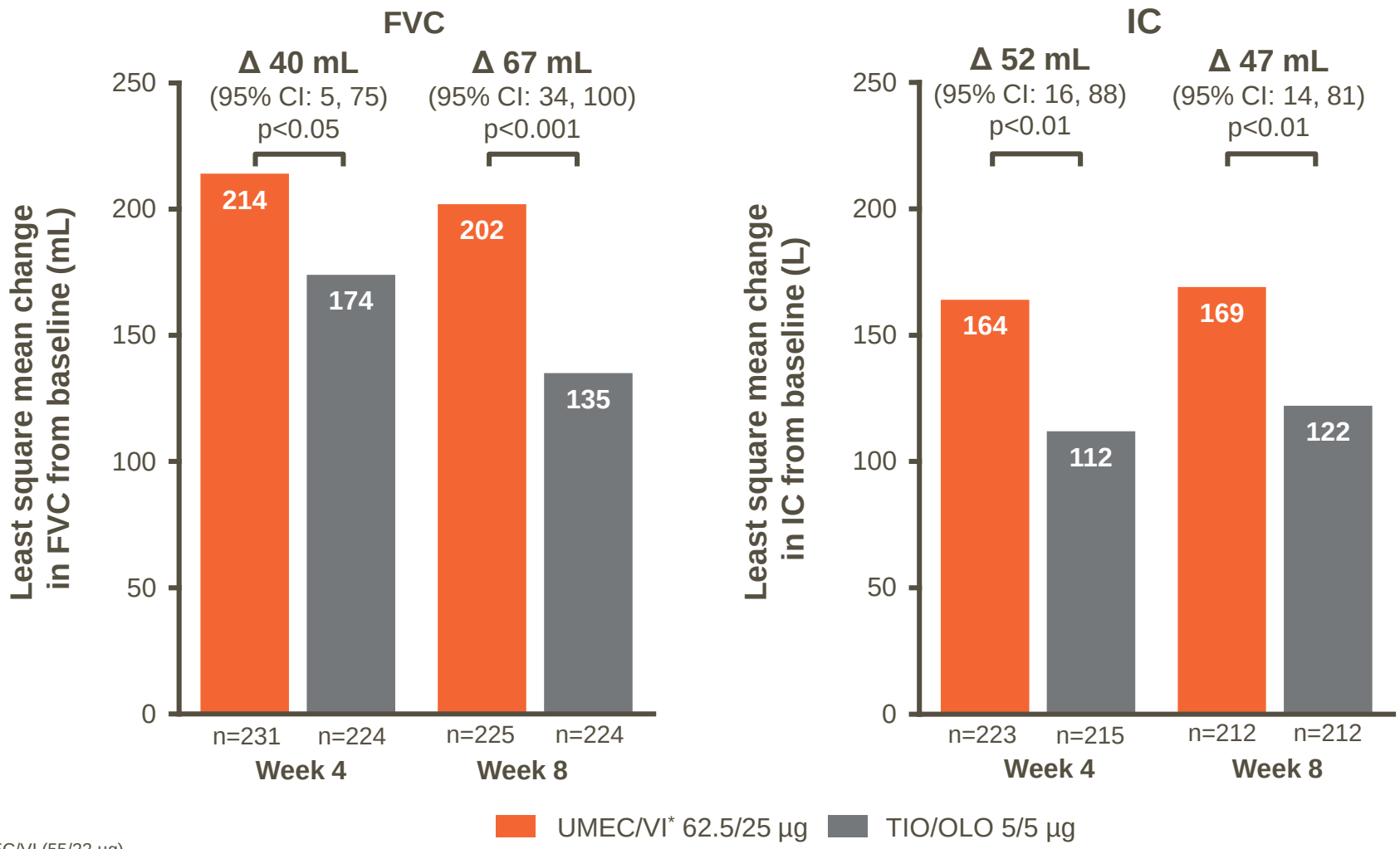
Using descriptive analyses across the entire ITT population it was observed that 52% had clinically important within patient efficacy difference in trough FEV_1 in favour of UMEC/VI (median D = 120 mL)

* MCID, minimum clinically important difference (≥100 mL) observed in trough FEV_1 in an individual patient

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Other lung volume parameters: Forced Vital Capacity (FVC) and Inspiratory Capacity (IC) at Weeks 4 and 8

ITT population

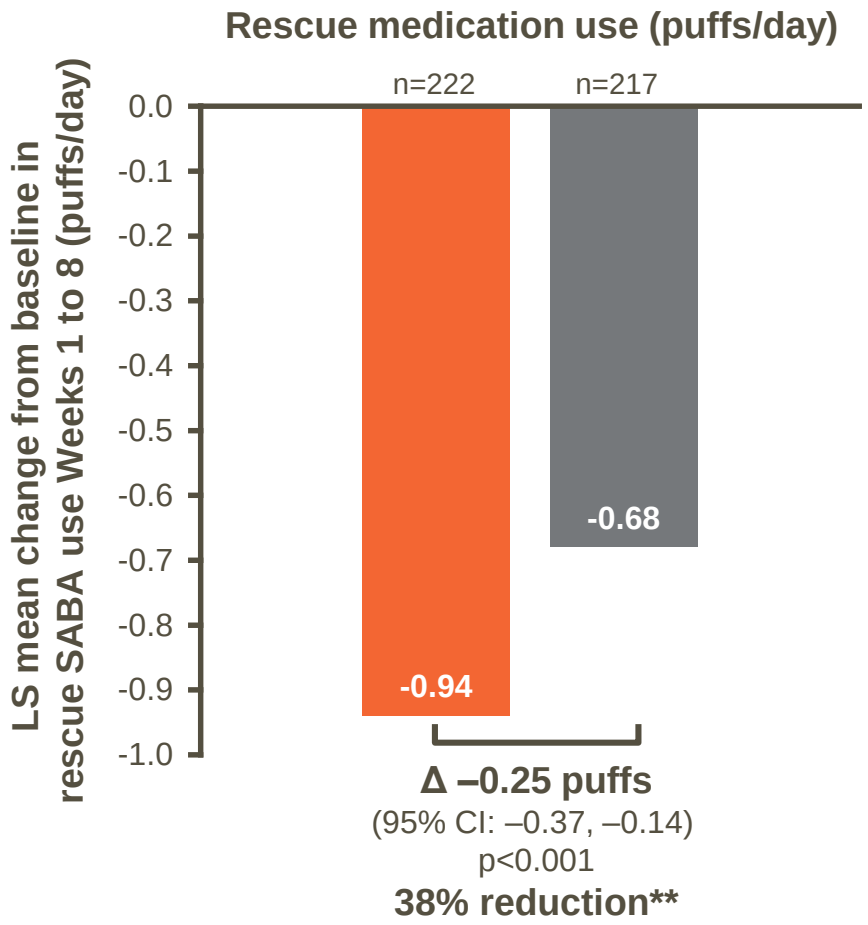


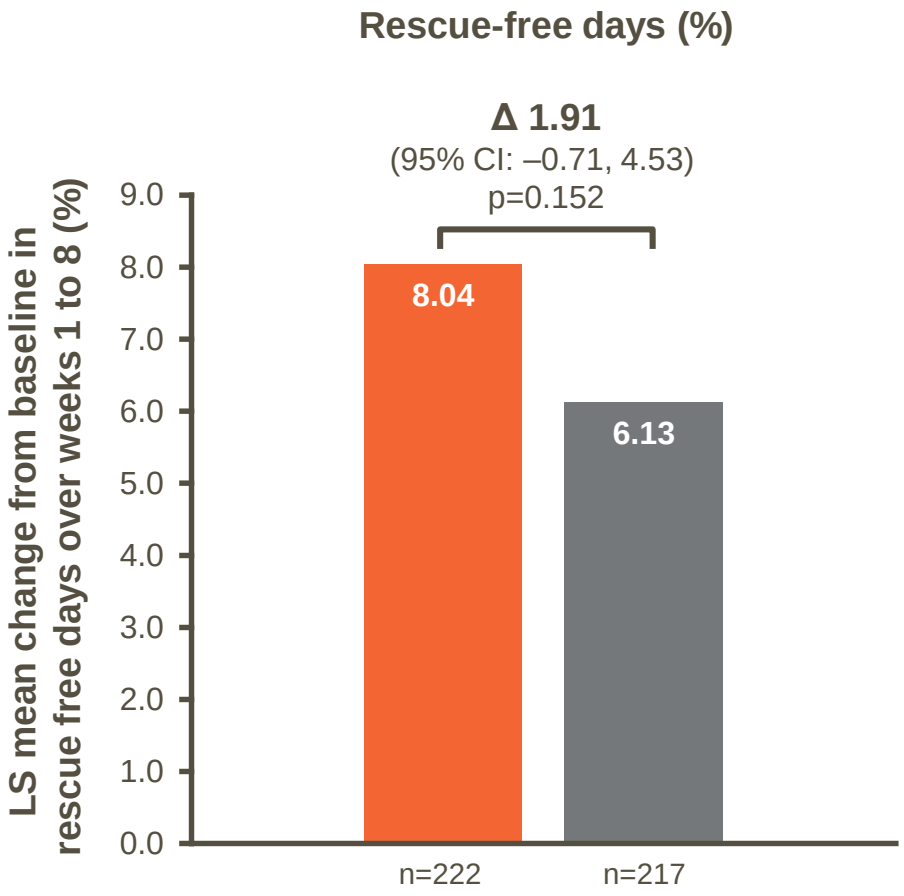
* Delivered doses for UMEC/VI (55/22 µg)

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Rescue medication use (puffs/day) and % rescue-free days over Weeks 1–8

ITT population





UMEC/VI* 62.5/25 µg

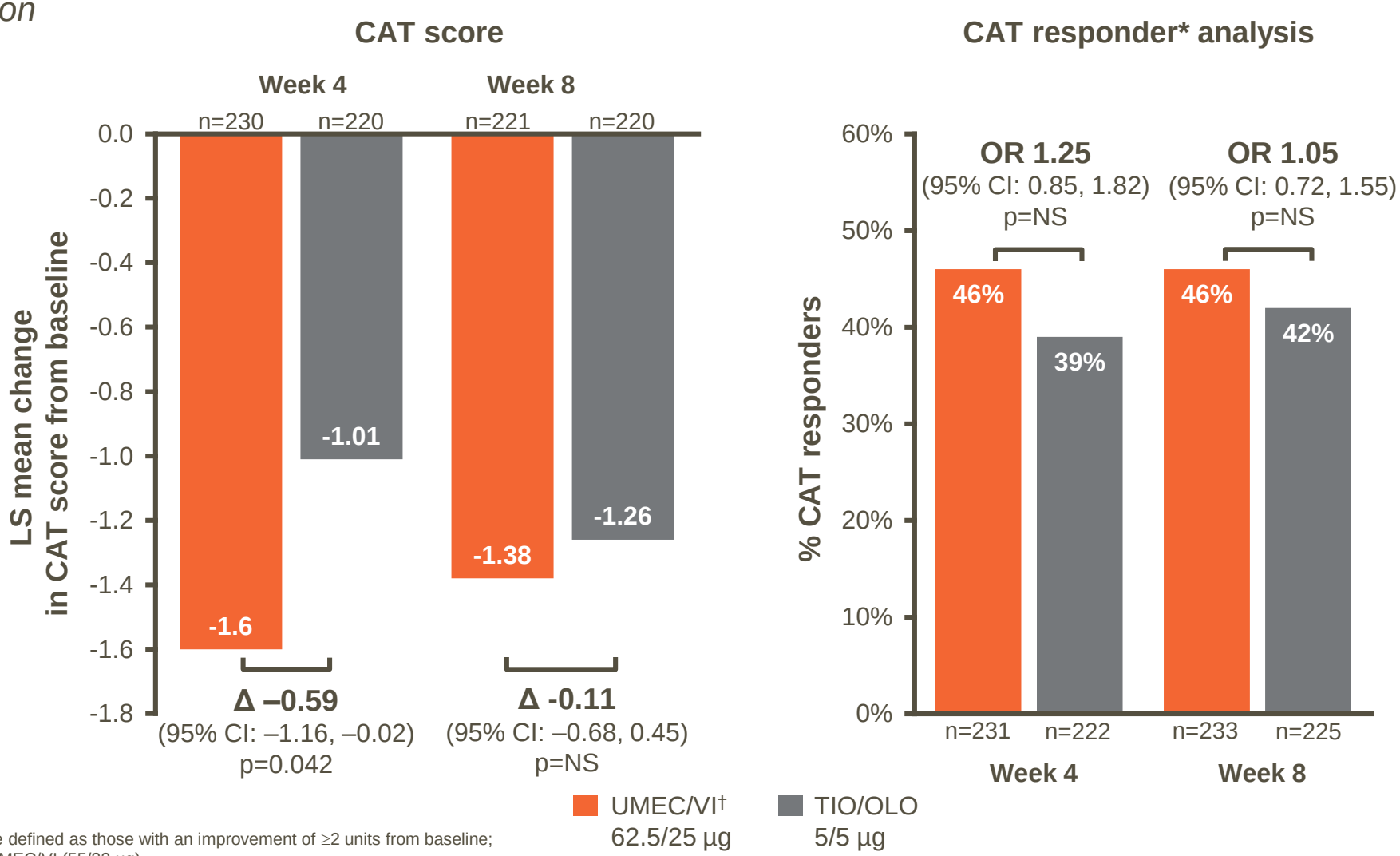
TIO/OLO 5/5 µg

* Delivered doses for UMEC/VI (55/22 µg)
** Greater reduction in rescue use compared to TIO/OLO (estimated calculation only)
SE = standard error

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

CAT score and CAT responder analysis: Weeks 4 and 8

ITT population

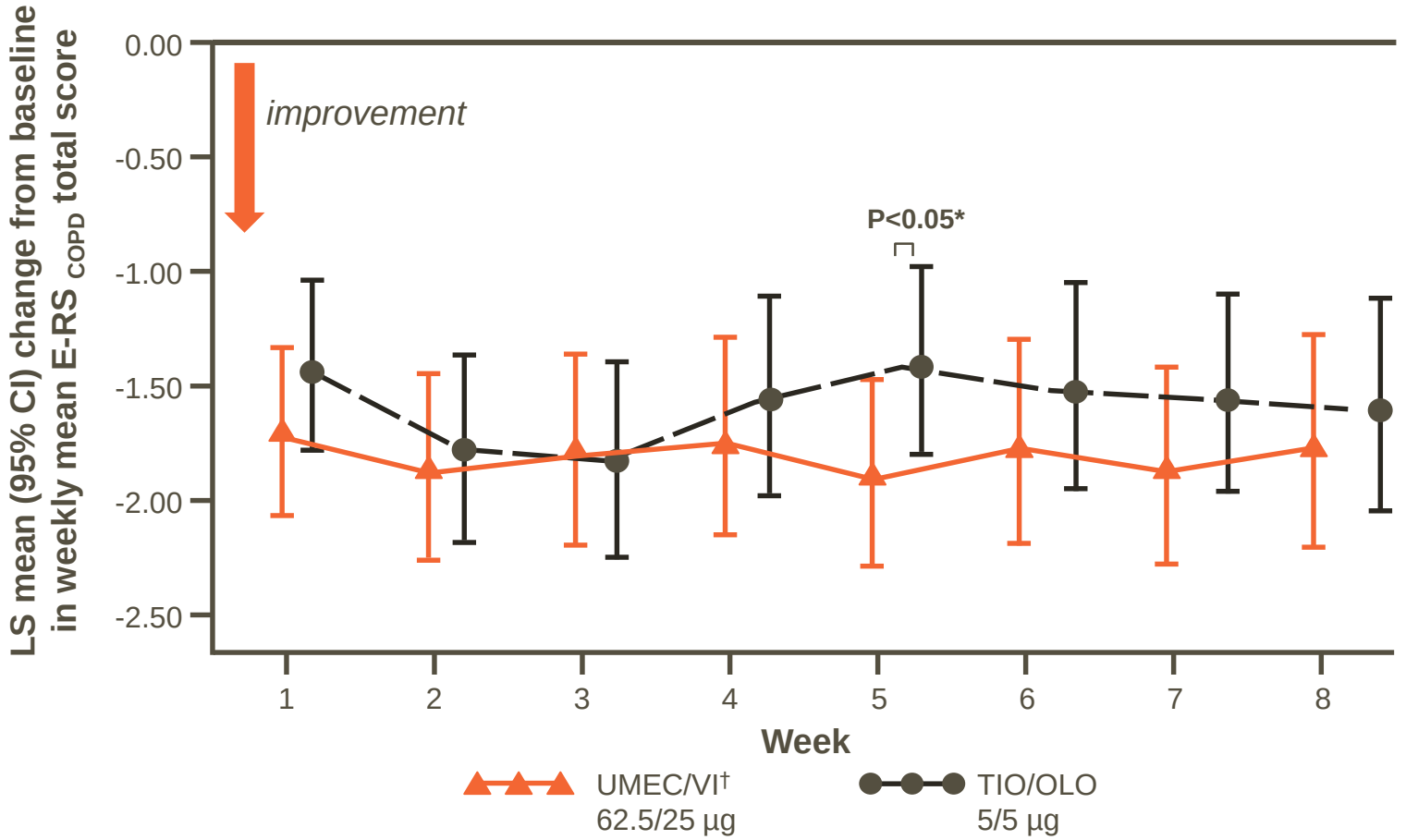


* CAT responders were defined as those with an improvement of ≥2 units from baseline;
† delivered doses for UMEC/VI (55/22 µg).

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Changes in E-RS$_{COPD}$ score over Weeks 1–8

ITT population



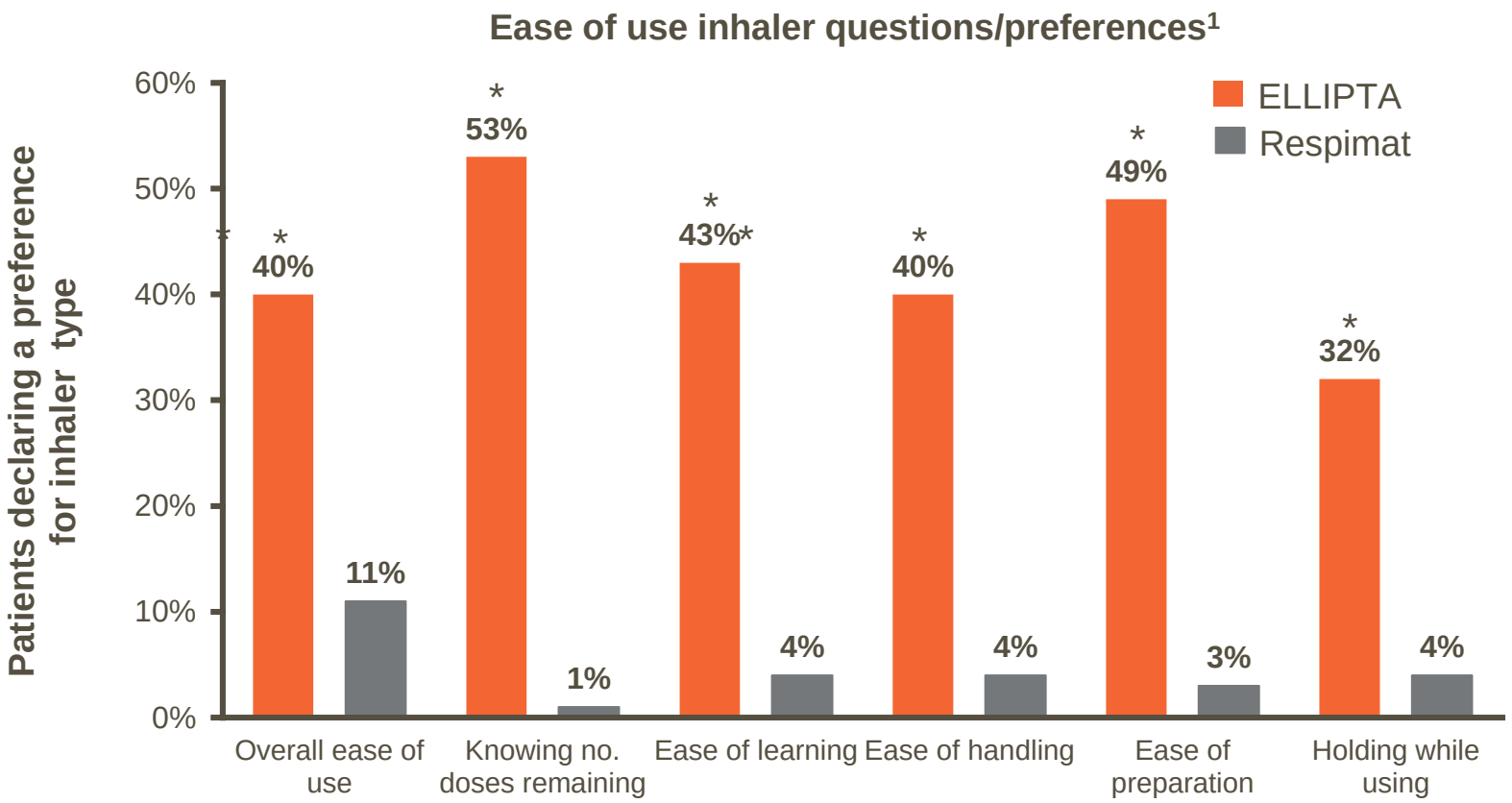
NOTE: Responder rates were similar between the two regimen during all study weeks

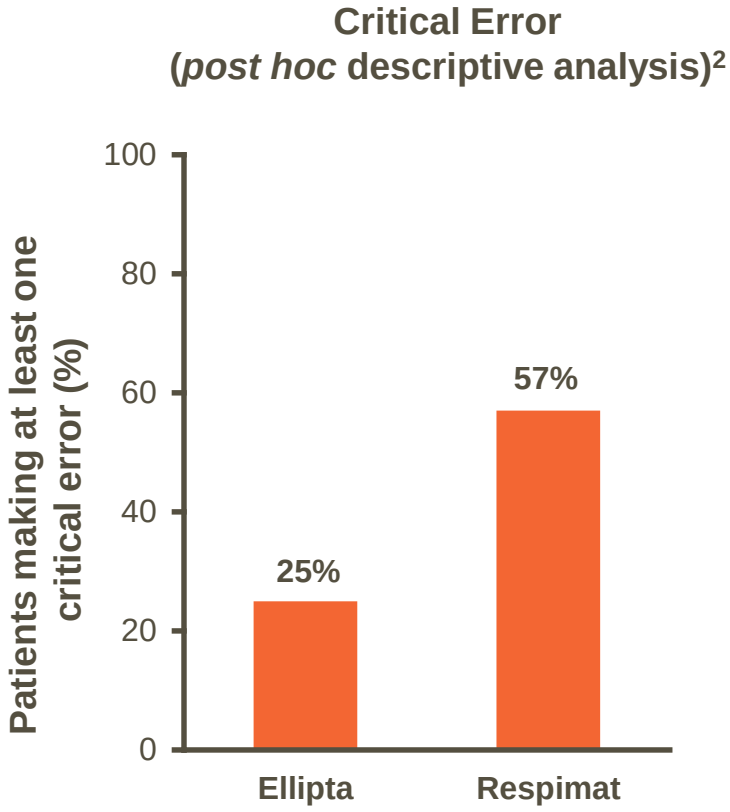
* Statistically significance was achieved at Week 5 only; † Delivered doses for UMEC/VI (55/22 µg).

Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533.

Inhaler ease-of-use assessments

Inhaler Naive population (n=75)





* All declared preferences in terms of ease of use were higher for the ELLIPTA (p<0.001 vs Respimat);
All patients had appropriate training on how to use both the Ellipta and Respimat inhalers;
Respimat is a trademark form Boehringer Ingelheim.

1. Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533 (supplementary appendix);
2. Compton C, et al. Poster P275 British Thoracic Society Winter Meeting, London, UK, 6–8 December 2017

Safety results

Overview of on-treatment AEs

Adverse events, n (%)[1]	UMEC/VI* 62.5/25 µg (n = 235)	TIO/OLO 5/5 µg (n = 230)
Any AE	59 (25)	71 (31)
Any AE leading to permanent study treatment discontinuation or withdrawal from study	1 (<1)	0
Any SAE	3 (1)	2 (<1)
Any fatal SAE	0	0
COPD exacerbations		
0	217 (92)	211 (92)
1	15 (6)	18 (8)
2	3 (1)	1 (<1)

Frequent AEs (in ≥3% of patients):

- **Viral upper respiratory tract infections: 5% (UMEC/VI) vs 6% (TIO/OLO)**
- **Upper respiratory tract infections: 3% (UMEC/VI) vs 3% (TIO/OLO)**

- Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including UMEC/VI. Therefore, UMEC/VI should be used with caution in patients with severe cardiovascular disease[2]
- Due to antimuscarinic activity (i.e. LAMA class activity), UMEC/VI should be used with caution in patients with urinary retention or with narrow-angle glaucoma[2]

* Delivered doses for UMEC/VI (55/22 µg)

1. Adapted from Feldman GJ, et al. *Adv Ther.* 2017;34:2518–2533; 2. Anoro Ellipta 55/22 mcg P.I. approved by Israeli MoH

ANORO ELLIPTA 55/22 mcg V 3/2017

For full information see MOH approved prescribing information

- **Indication** - ANORO ELLIPTA is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.
- **Special warnings and precautions for use** - **Asthma -** Umeclidinium/vilanterol should not be used in patients with asthma since it has not been studied in this patient population. **Paradoxical bronchospasm** - As with other inhalation therapies, administration of umeclidinium/vilanterol may produce paradoxical bronchospasm that may be life-threatening. **Cardiovascular effects** - Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including umeclidinium/vilanterol.
- **Contraindications:** Hypersensitivity to the active substances or to any of the excipients
- **Common adverse drug reactions (ADRs) (≥1/100 to <1/10**) - Urinary tract infection, Sinusitis, Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Headache, Cough, Oropharyngeal pain, Constipation and dry mouth
-

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- **Medical information service**: il.medinfo@gsk.com
- **Adverse events reporting service**: il.safety@gsk.com,
  Tel: 03-9297100

Full PI can be found with GSK representative