Reduction in fatal events with extrafine inhaled corticosteroid (ICS)-containing medications: results of pooled safety analysis of the TRILOGY, TRINITY and TRIBUTE studies.

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This analysis was sponsored by Chiesi Farmaceutici, S.p.A.

Background

- BDP/FF/G 87/5/9 µg is a fixed-dose combination of an extrafine inhalation solution formulation of beclomethasone dipropionate, formoterol fumarate and glycopyrronium, EMA-approved since July 2017 for maintenance treatment in patients with moderate to severe COPD not adequately treated by ICS/LABA [1]
- BDP/FF/G has been shown to reduce moderate-to-severe COPD exacerbations compared to a LAMA (tiotropium), an ICS/LABA (BDP/FF) and a LABA/LAMA (IND/GLY) in patients with severe-very severe airflow limitation at risk for exacerbations (≥ 1 exacerbation in previous year) [2, 3, 4]
- The effect of BDP/FF/GB on mortality in patients with COPD remains unexplored

1. TRIMBOW® SmPC 2017.
2. Vestbo J et al. Lancet 2017; 389: 1919–1929.
3. Sing D et al. Lancet 2016; 388: 963–973.
4. Papi A et al. Lancet 2018; 391: 1076–1084.

METHODS (2/2)

Time to death was analysed using a Cox proportional hazards model including only the effect of treatment. Hazard ratios (HRs) of the following comparisons were calculated:

- all extrafine ICS-containing combinations (BDP/FF/G, BDP/FF, BDP/FF+TIO) versus ICS-free treatments (TIO, IND/GLY)
- extrafine BDP/FF/G versus ICS-free treatments (TIO, IND/GLY)

As an additional evaluation, events were stratified based on the System Organ Class (SOC): 'Respiratory, thoracic and mediastinal disorders' vs all other SOCs

RESULTS

Fatal Adverse Events integrated distribution and analysis, by event type

Patients (%) with Fatal AEs and Hazard Ratios for the Treatment Group Comparisons in Pooled TRILOGY, TRINITY and TRIBUTE Studies (Safety Population)

Fatal AEs	N of patients with events (%) TIO, IND/GLY (N=1844)	N of patients with events (%) BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	Hazard Ratio (95% CI) p-value	N of patients with events (%) BDP/FF/G (N=2528)	Hazard Ratio (95% CI) p-value
RESPIRATORY	9 (0.5%)	19 (0.5%)	1.01 (0.45; 2.22) p=0.989	13 (0.5%)	1.02 (0.43, 2.38) p=0.972
NON-RESPIRATORY	41 (2.2%)	56 (1.5%)	0.65 (0.43; 0.97) **p=0.037**	38 (1.5%)	0.65 (0.42, 1.01) p=0.058

BDP = beclometasone dipropionate; FF = formoterol fumarate; G or GLY = glycopyrronium; IND = indacaterol; HR = hazard ratio; CI = confidence interval.

[1] Vestbo J et al. Lancet 2017; 389: 1919–1929; [2] Sing D et al. Lancet 2016; 388: 963–973 ; [3] Papi A et al. Lancet 2018; 391: 1076–1084

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Singh D et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016 Sep 3;388(10048):963-73

Vestbo J et al, Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet. 2017 May 13;389(10082):1919-1929

Papi AA et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet. 2018 Mar 17;391(10125):1076-1084

The 3 studies were sponsored by Chiesi Farmaceutici, S.p.A.

BACKGROUND

- By 2020, COPD is projected to become the 3rd leading cause of death worldwide [1]
- Patients with COPD have a significantly shorter survival than comorbidity-matched controls [2]
- Most common causes of death in patients with COPD are non-respiratory, and particularly cardiovascular diseases (myocardial infarction and stroke), and cancer [2, 3]
- Previous exacerbations and hospitalizations, comorbidities, reduced lung function, and poor health status are the strongest predictors of death in patients with COPD. [4, 5, 6]
- To date, no pharmacologic treatment has convincingly demonstrated to have a significant survival benefit in patients with COPD. [7]

1. Lozano R, et al. Lancet. 2012;380(9859):2095–2128.
2. Miniati M, et al. Medicine 2014;93(12):e76
3. Wise R, et al. (TIOSPIR). NEJM 2013;369:1491-501.
4. Cardoso J, et al. Int'l J COPD 2018:13 1105–1113.
5. Mannino DM, et al. Eur Respir J 2008;32:962-969
6. Müllerova H, et al. COPD 2017;4(2):141-149.
7. GOLD Report 2018

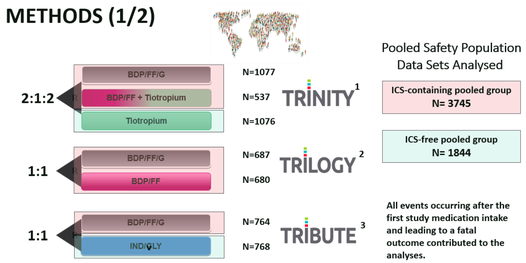
AIM OF THE STUDY

In the present study we conducted a pooled analysis of fatal adverse events (AEs) on the safety populations and compared extrafine ICS-containing regimen to ICS-free treatments from the 3 phase III RCTs

TRINITY, TRILOGY, and TRIBUTE [1, 2, 3]

[1] Vestbo J et al. Lancet 2017; 389: 1919–1929; [2] Sing D et al. Lancet 2016; 388: 963–973 ; [3] Papi A et al. Lancet 2018; 391: 1076–1084

METHODS (1/2)



Pooled Safety Population Data Sets Analysed

ICS-containing pooled group N= 3745

ICS-free pooled group N= 1844

All events occurring after the first study medication intake and leading to a fatal outcome contributed to the analyses.

[1] Vestbo J et al. Lancet 2017; 389: 1919–1929; [2] Sing D et al. Lancet 2016; 388: 963–973 ; [3] Papi A et al. Lancet 2018; 391: 1076–1084

RESULTS

Fatal Adverse Events distribution by study

Patients (%) with Fatal AEs for the Treatment Group Comparisons in TRILOGY, TRINITY and TRIBUTE Studies (Safety population)

Individual Studies	Test Drug	Comparator	Number of patients with event (%) Test Drug	Number of patients with event (%) Comparator
TRILOGY[1]	BDP/FF/G (N=687)	BDP/FF (N=680)	15 (2.2%)	16 (2.4%)
TRINITY[2]	BDP/FF/G (N=1077)	TIO (N=1076)	20 (1.9%)	29 (2.7%)
		BDP/FF+TIO (537)		8 (1.5%)
TRIBUTE[3]	BDP/FF/G (N=764)	IND/GLY (N=768)	16 (2.1%)	21 (2.7%)

BDP = beclometasone dipropionate; FF = formoterol fumarate; G or GLY = glycopyrronium; IND = indacaterol.

[1] Sing D et al. Lancet 2016; 388: 963–973; [2] Vestbo J et al. Lancet 2017; 389: 1919–1929; [3] Papi A et al. Lancet 2018; 391: 1076–1084

RESULTS

Fatal Adverse Events integrated distribution and analysis

Patients (%) with Fatal AEs and Hazard Ratios for the Treatment Group Comparisons in Pooled TRILOGY, TRINITY and TRIBUTE Studies (Safety Population)

	Test Drug	Comparator	Number of patients with event (%) Test Drug	Number of patients with event (%) Comparator	Hazard Ratio (95% CI) p-value
ICS-containing regimens	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GLY (N=1844)	75 (2.0%)	50 (2.7%)	0.71 (0.50; 1.02), p=0.066
TRIPLE regimen	BDP/FF/G (N=2528)	TIO, IND/GLY (N=1844)	51 (2.0%)	50 (2.7%)	0.72 (0.49; 1.06), p=0.096

BDP = beclometasone dipropionate; FF = formoterol fumarate; G or GLY = glycopyrronium; IND = indacaterol; HR = hazard ratio; CI = confidence interval.

[1] Vestbo J et al. Lancet 2017; 389: 1919–1929; [2] Sing D et al. Lancet 2016; 388: 963–973 ; [3] Papi A et al. Lancet 2018; 391: 1076–1084

CONCLUSIONS-1

- Pooled results from 3 phase III RCTs suggest that treatment with extrafine ICS-containing medications compared to ICS-free treatments may be associated with a lower rate of mortality driven by non-respiratory events in symptomatic patients with COPD and severe-very severe airflow limitation who are at risk for exacerbations
- The difference was statistically significant only in non-respiratory deaths
- A lower rate of mortality was also observed in ICS-containing treatment arms compared to non-ICS containing treatment in the IMPACT study [1] and in a pooled analysis from 7 RCTs involving more than 5,000 patients with stable COPD [2]

1.Lipson DA, et al for the IMPACT Investigators. NEJM 2018;378(18):1671-1680; 2. Sin DD et al. Thorax 2005;60:992–997.

CONCLUSIONS-2

- *"Nevertheless, given the unidirectional effects seen in this analysis and the 4 previously cited studies [1-4], there may be cause for more optimism regarding the effect of more intense ICS-containing treatments on survival in symptomatic patients with severe and very severe COPD. Particularly considering that combination therapy, and especially triple therapy, is almost invariably required in these patients either to improve symptoms, quality of life, and/or to reduce exacerbations and hospiatlisations.*
- *Of course, a properly designed and powered new study with mortality as primary outcome in these patients is required for this optimism to be confirmed."*

[1] Calverly PM et al. TORCH study. NEJM 2007; 356: 775-89;
[2] Vestbo J et al. SUMMIT study. Lancet 2016; 387: 1817-26;
[3] Wedzicha JA et al. INSPIRE study. AJRCCM Med 2008; 177: 19-26;
[4] Lipson D et al. IMPACT study. NEJM 2018;378(18):1671-1680.

Vestbo et al. Combinations containing inhaled corticosteroids may reduce mortality in COPD. European Respiratory Journal, Research Letter in press in 2018