Benefits of tiotropium + olodaterol over tiotropium at delaying clinically significant events in patients with COPD classified as GOLD B

Roland Buhl,[1] Lorcan McGarvey,[2] Stephanie Korn,[1] Gary T. Ferguson,[3] Lars Grönke,[4] Christoph Hallmann,[4] Florian Voß,[4] Klaus F. Rabe,[5] François Maltais[6]

[1]Pulmonary Department, Mainz University Hospital, Mainz, Germany; [2]Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK; [3]Pulmonary Research Institute of Southeast Michigan, Farmington Hills, Michigan, USA; [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [5]Lung Clinic Grosshansdorf, Grosshansdorf, Germany; [6]Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada

http://goo.gl/7Eya01

Poster P9

Background

- Two large clinical studies (TONADO® 1 + 2) demonstrated the benefits of treatment with a combination of once-daily tiotropium (T), a long-acting muscarinic antagonist, and olodaterol (O), a long-acting β_2-agonist, compared to treatment with the monocomponents in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) over 52 weeks.[1]
- Until recently, the focus of treatment had been on improving the single outcome of lung function. However, it is becoming clear that many factors come into play as COPD deteriorates, and it is of interest to investigate whether these clinically significant events can also be delayed with optimized bronchodilation, which, in turn, could lead to longer-term disease stabilization.
- A *post hoc* analysis of the UPLIFT study demonstrated that composite end points, which included clinically significant events for patients with Global initiative for chronic Obstructive Lung Disease (GOLD) 2 and GOLD stage B COPD, can be sensitive to treatment effects, with T delaying clinically significant events compared to placebo.[2]
- The two composite end points in the UPLIFT analysis evaluated the time to first clinically important deterioration in: (1) trough forced expiratory volume in 1 second (FEV_1), St. George's Respiratory Questionnaire (SGRQ) score, **severe exacerbation,** or **death**; or (2) trough FEV_1, SGRQ score, or **moderate or severe exacerbation**.[2] The first composite end point showed limitations, with the severe exacerbations and death components not of value in patients with moderate COPD.
- Using the same methodology as for the UPLIFT analysis, we investigated whether T+O is more effective than T at delaying clinically significant events in patients with GOLD stage B COPD (symptomatic COPD and a low risk of exacerbations) in a *post hoc* analysis of the TONADO® studies.

Methods

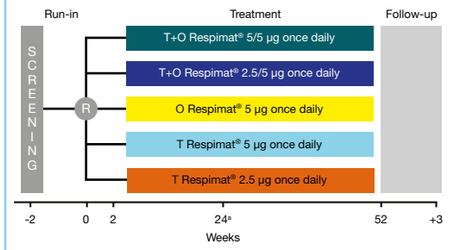
Study design

- A total of 5162 patients were randomized to T+O 2.5/5 µg or 5/5 µg, T 2.5 µg or 5 µg, or O 5 µg (delivered via Respimat® inhaler) in two 52-week, parallel-group, double-blind studies (TONADO® 1 [NCT01431274] and TONADO® 2 [NCT01431287]) (Figure 1).
- Assessment of trough FEV_1 was performed on Day 1 and at Weeks 2, 6, 12, 18, 24, 32, 40, and 52.
- SGRQ was completed on Day 1 and after 12, 24, and 52 weeks.

Analyses

- *Post hoc* analysis of time to first clinically important deterioration in patients classified as GOLD stage B using combined TONADO® study data.

Figure 1. *TONADO® 1 + 2 study designs.*



[a]Primary end-point assessment
R, randomization

- Clinically important deterioration was defined according to two composite end points.
  - Composite end point 1: time to first decrease in trough FEV_1 from baseline of ⩾100 mL, time to first increase in SGRQ total score from baseline of ⩾4 units, **time to first severe (hospitalized) exacerbation**, or **time to death**.
  - Composite end point 2: time to first decrease in trough FEV_1 from baseline of ⩾100 mL, time to first increase in SGRQ total score from baseline of ⩾4 units, or **time to first moderate or severe exacerbation**.
- The time to first occurrence of one of these events was recorded as the time to clinically important deterioration.
- Data are presented for comparisons of the licensed doses of T+O 5/5 µg and T 5 µg.

Statistical analyses

- Time to first clinically significant event (individual components of composite end points) and time to first clinical deterioration (composite end points) were calculated in days and reported for the 25th percentile (median time not reached for most events) for each treatment group.
- Hazard ratios (HRs) for treatment comparisons were obtained from fitting a Cox proportional hazard regression model with treatment as the only covariate.
- Kaplan–Meier estimates of probability of clinical deterioration based on the composite end points were generated for each treatment group.

Results

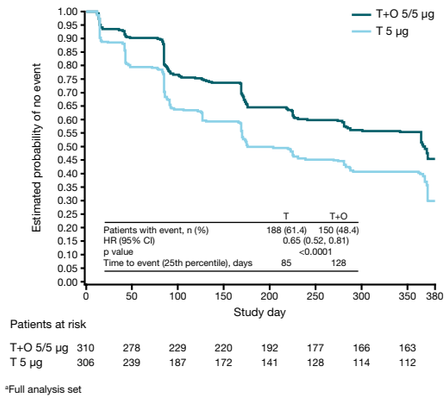
- Patient demographics and disease characteristics were comparable for GOLD stage B patients in the T+O 5/5 µg and T 5 µg treatment groups included in this analysis (Table 1).
- Using composite end point 1 (time to first trough FEV_1 decline, SGRQ total score increase, severe exacerbation, or death), time to clinically important deterioration was significantly longer with T+O 5/5 µg than T 5 µg (HR [95% confidence interval (CI)] 0.65 [0.52, 0.81]; p<0.0001) (Figure 2).

Table 1. *Baseline demographic and disease characteristics for GOLD B patients with COPD: treated set.*

	T 5 µg	T+O 5/5 µg
Patients, n	307	311
Male, n (%)	199 (64.8)	210 (67.5)
Mean ± SD age, years	63.4 ± 9.3	63.8 ± 8.4
Mean ± SD body mass index, kg/m²	26.8 ± 5.4	26.9 ± 5.4
Smoking status, n (%)		
Ex-smoker	166 (54.1)	166 (53.4)
Current smoker	141 (45.9)	145 (46.6)
Mean ± SD smoking history, pack-years	45.0 ± 26.0	47.2 ± 23.4
Mean ± SD pre-bronchodilator FEV_1,[a] L	1.53 ± 0.47	1.51 ± 0.46
Mean ± SD % of predicted FEV_1[a]	55.3 ± 10.2	55.4 ± 10.5
Medication use, n (%)	230 (74.9)	238 (76.5)
LAMA	92 (30.0)	113 (36.3)
LABA	121 (39.4)	122 (39.2)
ICS	113 (36.8)	125 (40.2)

[a]At screening.
SD, standard deviation; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-agonist; ICS, inhaled corticosteroid.

Figure 2. *Kaplan–Meier estimates of probability of decline from baseline in trough FEV_1 of ⩾100 mL, increase from baseline of ⩾4 units in SGRQ score, severe exacerbation, or death (composite end point 1) in patients with GOLD stage B COPD.[a]*



[a]Full analysis set

- For the individual clinically significant events included in composite end point 1, time to trough FEV_1 decline (HR [95% CI] 0.66 [0.51, 0.86]; p=0.0016) and time to SGRQ score increase (HR [95% CI] 0.71 [0.52, 0.96]; p=0.0271) were significantly longer with T+O 5/5 µg than T 5 µg (Table 2).
  - Event rates for time to severe exacerbation and time to death were very low (one death and 16 patients with severe exacerbations across both treatment groups) and 25th percentiles were non-estimable.

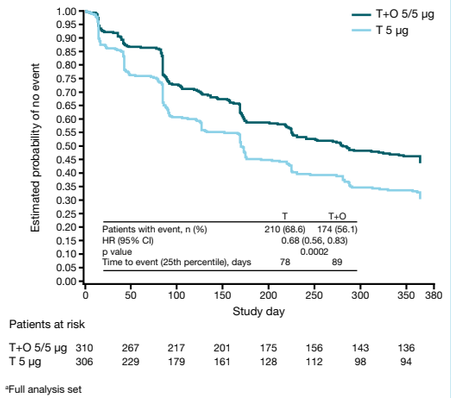
Table 2. *Individual components of composite end points: event rates and time to first event (25th percentile).*

	Event, n (%)		Time to first event (25th percentile), days		Time to first event treatment comparison (T+O – T)	
	T 5 µg (n=306)	T+O 5/5 µg (n=310)	T 5 µg (n=306)	T+O 5/5 µg (n=310)	HR (95% CI)	p value
Trough FEV_1 decline from baseline ⩾100 mL[a]	135 (44.1)	103 (33.3)[b]	91	226[b]	0.66 (0.51, 0.86)	0.0016
SGRQ score increase from baseline ⩾4 units[a]	95 (32.5)[c]	73 (24.4)[d]	175[c]	369[d]	0.71 (0.52, 0.96)	0.0271
Moderate or severe exacerbation	69 (22.5)	67 (21.6)	NE	NE	0.94 (0.67, 1.32)	NS
Severe exacerbation	6 (2.0)	10 (3.2)	NE	NE	1.64 (0.60, 4.51)	NS
Death	0 (0.0)	1 (0.3)	NE	NE	–	–

[a]Only patients with baseline and post-baseline trough FEV_1 and SGRQ score values are included; [b]n=309; [c]n=292; [d]n=299.
NE, non-estimable, NS, not significant.

- For time to moderate or severe exacerbation, the HR (95% CI) was 0.94 (0.67, 1.32) and 25th percentiles were non-estimable (Table 2). However, event rates were greater than for severe exacerbations: T+O 5/5 µg, 67 patients (21.6%); T 5 µg, 69 patients (22.5%).
- Using composite end point 2 (including time to first trough FEV_1 decline, SGRQ total score increase, or moderate or severe exacerbation, and excluding severe exacerbation or death), time to clinically important deterioration was significantly longer with T+O 5/5 µg than T 5 µg (HR [95% CI] 0.68 [0.56, 0.83]; p=0.0002) (Figure 3)

Figure 3. *Kaplan–Meier estimates of probability of decline from baseline in trough FEV_1 of ⩾100 mL, increase from baseline of ⩾4 units in SGRQ score, or moderate or severe exacerbation (composite end point 2) in patients with GOLD stage B COPD.[a]*



[a]Full analysis set

Limitations

- In contrast to the UPLIFT study analysis,[2] a clinically significant event did not have to be confirmed at a second clinic visit in order to be included in the analysis. This was a consequence of the length of the TONADO® studies (52 weeks) and the number of assessments occurring during this period (only three SGRQ assessments).
- The temporal relationship between clinically significant events is not known, as only the time to first individual event is included in the analysis.

Conclusions

- **In the TONADO® studies, T+O increased time to clinically important deterioration compared to T alone in patients with GOLD stage B COPD, suggesting that T+O is more effective than T in preventing these significant events in this patient population.**
- **Based on these results, T+O not only significantly improves lung function but may also lead to a slower clinical deterioration of the disease through its effects beyond lung function.**
- **For this patient population with less severe disease, and in which severe exacerbations and deaths occur infrequently, it appears that comparing the effectiveness of different treatments in delaying clinically important deterioration can be achieved using a composite end point that includes time to first trough FEV_1 decline or SGRQ score increase, or moderate or severe exacerbation.**
- **Further studies are warranted to prospectively study this effect.**

References

1. Buhl R et al. Eur Respir J 2015; 45: 969–979.
2. Rabe K et al. Abstract presented at the American Thoracic Society Annual Meeting, San Francisco, California, USA, May 13–18, 2016.

Acknowledgments

This study was supported by Boehringer Ingelheim. Under the authors' conceptual direction, medical writing assistance for this poster was provided by Gail Rickard at Complete HealthVizion; medical writing assistance was supported by Boehringer Ingelheim.

Disclosures

RB reports financial support to his institution from Boehringer Ingelheim during the conduct of the study, and outside of the submitted work, financial support from Boehringer Ingelheim, AstraZeneca, Chiesi, Novartis, TEVA, Roche, and GlaxoSmithKline for attendance at advisory boards and speaking activities, and research support to his institution from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche. FM reports financial support from Boehringer Ingelheim during the conduct of the study, and, outside of the submitted work, financial support from Boehringer Ingelheim and GlaxoSmithKline for attendance at advisory boards, financial support from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and Novartis for speaking activities, and research support from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Nycomed, and Novartis.

Poster presented at the American Thoracic Society International Conference, San Francisco, California, USA, May 13–18, 2016