TONADO™ 1+2

PIVOTAL PHASE III STUDIES FOR TIOTROPIUM + OLODATEROL RESPIMAT® FIXED-DOSE COMBINATION (FDC)*

What is TONADO™?

TONADO™ 1&2 are the pivotal phase III studies which investigated the efficacy and safety of tiotropium + olodaterol Respimat®, the only fixed-dose combination (FDC) containing tiotropium, the active ingredient of Spiriva®. Spiriva® (tiotropium) is the most prescribed COPD maintenance treatment worldwide with unsurpassed real-life experience[1-7] and olodaterol (Striverdi®) has been specifically designed with equivalent pharmacodynamic properties to be its preferred combination partner.[8]

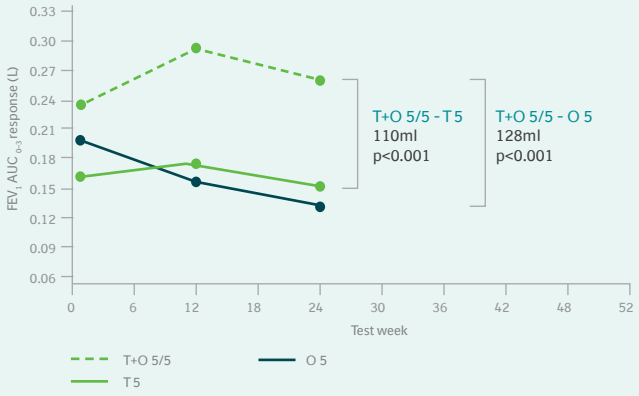
What were the key findings from the TONADO™ studies?

All primary endpoints of the TONADO™ studies were met†. The pooled analysis of TONADO™ 1&2 showed:[9]

- Significant increase in lung function with tiotropium + olodaterol Respimat® FDC compared to the mono-components‡
- Significant improvement in quality of life (as measured by SGRQ score) with tiotropium + olodaterol Respimat® FDC compared to the mono-components

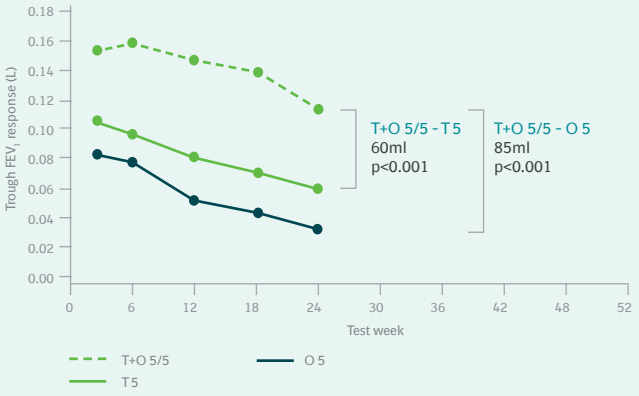
Data also showed that tiotropium + olodaterol Respimat® FDC was well tolerated with a favourable safety profile that was similar to tiotropium or olodaterol alone.[10]

FEV_1 AUC_{0-3} response
Primary end point at 24 weeks



- FEV_1 AUC_{0-3} response for tiotropium + olodaterol Respimat® FDC was 110ml greater than tiotropium alone and 128ml greater than olodaterol alone (p<0.001 for both comparisons)

Trough FEV_1 response
Primary end point at 24 weeks



- Trough FEV_1 response for tiotropium + olodaterol Respimat® FDC was 60ml greater than tiotropium alone and 85ml greater than olodaterol alone (p<0.001 for both comparisons)

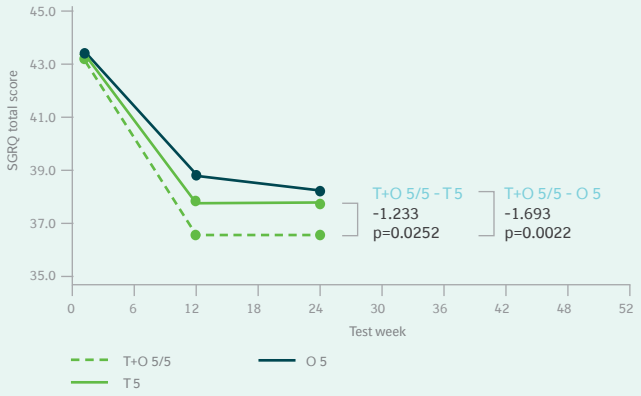
* The fixed-dose combination of tiotropium + olodaterol is an investigational treatment. Its safety and efficacy have not yet been fully established.

† TONADO™ consists of two replicate studies: TONADO™ 1&2. In the studies two doses of tiotropium + olodaterol Respimat® FDC were investigated: 2.5µg/5µg and 5µg/5µg. The data included in this fact sheet refer to the tiotropium 5µg/ olodaterol 5µg dose (administered as 2 puffs of tiotropium + olodaterol 2.5/2.5 µg once daily), which is the FDC dose submitted to the regulatory authorities for marketing authorisation. All primary endpoints in TONADO™ were measured at 24 weeks.

‡ The lung function primary end points were defined on an individual trial basis. The results of the individual trials are consistent with the pooled analysis.

Boehringer Ingelheim

SGRQ total scores
Primary end point at 24 weeks



- SGRQ total scores improved from baseline by 6.8 points for tiotropium + olodaterol Respimat® FDC compared to 5.6 for tiotropium alone and 5.1 for olodaterol alone
- The improvement of SGRQ score with tiotropium + olodaterol Respimat® FDC is 1.2 points compared to tiotropium ($p<0.05$) and 1.7 compared to olodaterol ($p<0.01$)

What are the implications of these findings?

- The TONADO™ results indicated that tiotropium + olodaterol Respimat® FDC brought even further lung function and quality of life benefits to patients than either compound alone.[9] By adding to the significant benefits patients already get from tiotropium, the active ingredient of Spiriva®, the results indicated that an even greater number of patients treated with tiotropium + olodaterol Respimat® FDC may be able to return to a more independent life[9,11]
- The results of TONADO™, together with the VIVACITO™ data presented earlier this year,[8] underpin the potential of tiotropium + olodaterol Respimat® FDC as a fast-acting, long-lasting once-daily maintenance treatment option for patients with COPD
- These data formed a major part of the recent regulatory submissions in Europe and US for tiotropium + olodaterol Respimat® FDC in COPD

TONADO™ study methodology and endpoints

TONADO™ consisted of two replicate 52-week, double-blind, parallel-group studies (TONADO™ 1&2) in a total of more than 5,000 patients with moderate to very severe COPD.

In these studies, the effect of two doses of tiotropium + olodaterol Respimat® FDC (2.5/5 µg, 5/5 µg) was compared to respective doses of the mono-components, tiotropium or olodaterol

The primary endpoints of the studies (measured at 24 weeks) were:

- as measures of lung function:
  - trough forced expiratory volume (FEV_1) response (change from baseline) and
  - FEV_1 area under the curve from 0–3 hours (AUC_{0-3})
- as a measure of health–related quality of life:
  - St George's Respiratory Questionnaire (SGRQ) total score analysed in a pre-specified combined analysis of data from both studies

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8 Derom E, Westerman J, Groenke L, et al. The 24-hour lung function profile of once-daily tiotropium and olodaterol fixed-dose combination compared with placebo and monotherapies in chronic obstructive pulmonary disease. ATS 2014 Abstract #A148; Thematic Poster Session: D44
9 Buhl R, Derom E, Ferguson G et al. Once-daily tiotropium and olodaterol fixed-dose combination via the Respimat® improves outcomes vs mono-components in COPD in two 1-year studies. ERS 2014 abstract No. 1895
10 Buhl R, Abrahams R, Bjermer L, et al. Safety of once-daily tiotropium and olodaterol fixed-dose combination via the Respimat in chronic obstructive pulmonary disease in two 1-year studies. ERS 2014 abstract No. P922
11 Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19: 398–404