ACTIVATE: the effect of aclidinium/formoterol on hyperinflation, exercise capacity, and physical activity in patients with COPD.

Watz et al., Int J of COPD 2017.
Context

Methods

Results

Conclusion

Discussion

Duaklir Genuair
COPD patients often suffer from breathlessness that affects their ability to exercise and go about their daily activities. Being less physical active can lead to an increase in COPD symptoms and a worsening of the patient’s COPD, which in turn can result in further reductions of physical activity\(^1\).

Therefore, a key part of COPD management is helping patients to increase their activity levels and to stay active\(^1\).

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1. Watz et al., Int J of COPD. 2017; 12: 2545-58
SYMPTOMS LIMIT COPD patients physical activity, even early in the disease, leading to a worse prognosis\textsuperscript{1-5}

Patients suffer breathlessness with activities

Patients limit their activity levels to avoid symptoms

Deconditioning aggravates symptoms

Increase of hospital admission and mortality

2. García-Aymerich et al. Thorax. 2006; 61(9): 772-8
Regular physical activity reduces the risk of mortality and hospital admissions\(^1\)

Level of physical activity equivalent to walking or cycling 2 hours/week or more reduces by 30-40% the risk of mortality and hospital admission\(^1\)

\(p<0.0001\)

very low: physical activity; corresponding to those who reported mainly sitting during work, no activity during leisure time, and no jogging or cycling

low: engaging in light physical activity such as walking or biking for less than 2 hours/week;

moderate: engaging in light physical activity for 2–4 hours/week;

high: engaging in light physical activity for more than 4 hours/week or in more vigorous activity for any frequency.

1. Garcia-Aymerich et al., Thorax. 2006; 61: 772-778
GOLD 2017 recognizes the importance of physical activity

Patients should receive general advice that physical exercise is safe and encouraged

- Expands on the concept of improving physical activity compared with previous guidelines
- Guidelines acknowledge the “downward spiral of inactivity” (i.e. reduced quality of life, hospitalisation and mortality)
- Highlights the importance of encouraging behavioural interventions to improve physical activity
- Maintaining or increasing physical activity is suggested across all GOLD Groups

Study Objective

Study objectives were the effect of AB/FF versus placebo on lung hyperinflation, exercise endurance time and physical activity with/without BI.

1. Lung hyperinflation compared with placebo in moderate to severe COPD patients

2. Exercise capacity and physical activity before and after behavioural intervention compared with placebo in moderate to severe COPD patients

Primary endpoint:

- Change from baseline in trough Functional Residual Capacity after 4 weeks of treatment

Secondary endpoints:

- Change from baseline in Endurance Time after 8 weeks of treatment
- Percentage of inactive patients (<6000 steps per day) after 8 weeks of treatment

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Context

**Methods**

Results

Conclusion

Discussion

Duaklir Genuair

AstraZeneca

Respi4Doctors
Study design

ACTIVATE is a phase IV, multi-center, 8-week, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group study. Patients were aged ≥ 40 years, current or former cigarette smokers with a clinical diagnosis of moderate/severe COPD.

Patients were randomized to receive AB/FF or placebo. During the first 4 weeks of the study, patients received pharmacotherapy alone and, during the second 4 weeks, behavioural intervention (BI) was added to both treatment arms.

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Study design

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=133)</th>
<th>AB/FF 400/12 µg (n=124)</th>
<th>Total (n=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>62.1 (7.7)</td>
<td>62.6 (7.9)</td>
<td>62.3 (7.8)</td>
</tr>
<tr>
<td>Male, %</td>
<td>59.4</td>
<td>60.5</td>
<td>59.9</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>62.4</td>
<td>63.4</td>
<td>62.9</td>
</tr>
<tr>
<td>Smoking history, mean pack-years (SD)</td>
<td>46.4 (21.6)</td>
<td>48.4 (24.0)</td>
<td>47.4 (22.8)</td>
</tr>
<tr>
<td>COPD severity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>82.0</td>
<td>76.7</td>
<td>79.3</td>
</tr>
<tr>
<td>Severe</td>
<td>18.0</td>
<td>33.3</td>
<td>20.7</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 predicted, mean (SD)</td>
<td>61.0 (10.7)</td>
<td>60.3 (10.7)</td>
<td>60.7 (10.7)</td>
</tr>
<tr>
<td>FRC (% predicted, mean (SD))</td>
<td>148.0 (26.2)</td>
<td>151.4 (27.7)</td>
<td>149.7 (27.0)</td>
</tr>
<tr>
<td>mMRC score, %</td>
<td>8.3</td>
<td>9.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Grade 2</td>
<td>91.7</td>
<td>91.0</td>
<td>91.4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8.3</td>
<td>9.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Prior medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA, n (%)</td>
<td>23 (17.3)</td>
<td>34 (17.9)</td>
<td>47 (17.6)</td>
</tr>
<tr>
<td>LABA, n (%)</td>
<td>11 (8.3)</td>
<td>16 (11.9)</td>
<td>27 (10.1)</td>
</tr>
<tr>
<td>ICS, n (%)</td>
<td>8 (6.0)</td>
<td>12 (9.6)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>LABA/LABA, n (%)</td>
<td>40 (30.1)</td>
<td>34 (25.4)</td>
<td>42 (27.7)</td>
</tr>
<tr>
<td>LABA/ICS, n (%)</td>
<td>14 (10.5)</td>
<td>17 (12.7)</td>
<td>31 (16.4)</td>
</tr>
<tr>
<td>LAMA/LABA/ICS, n (%)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Number of exacerbations in previous year, mean (SD)</td>
<td>0.4 (0.9)</td>
<td>0.3 (0.5)</td>
<td>0.3 (0.8)</td>
</tr>
<tr>
<td>Mean endurance time, s (SD)</td>
<td>456.9</td>
<td>455.8</td>
<td>456.3</td>
</tr>
<tr>
<td>Inactive patients, %</td>
<td>40.1</td>
<td>54.6</td>
<td>51.4</td>
</tr>
<tr>
<td>Mean number of steps per day (SD)</td>
<td>6166.9</td>
<td>6360.4</td>
<td>6278.0</td>
</tr>
<tr>
<td>D-PPAC Total score, mean (SD)</td>
<td>62.5 (9.7)</td>
<td>62.5 (10.1)</td>
<td>62.5 (9.9)</td>
</tr>
<tr>
<td>Difficulty domain, mean (SD)</td>
<td>70.8 (13.9)</td>
<td>69.6 (13.6)</td>
<td>70.1 (13.7)</td>
</tr>
<tr>
<td>Amount domain, mean (SD)</td>
<td>53.7 (14.2)</td>
<td>54.5 (13.0)</td>
<td>54.1 (13.5)</td>
</tr>
</tbody>
</table>

Note: inactive patients classified as logging <6000 steps per day.

Abbreviations: AB, aclidinium bromide; D-PPAC, Daily PROactive Physical Activity in COPD; FEV1, forced expiratory volume in 1 s; FF, formoterol fumarate; FRC, functional residual capacity; ICS, inhaled corticosteroids; ITT, intent-to-treat; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; SD, standard deviation.

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Results
AB/FF patients demonstrated a greater reduction in trough FRC vs placebo at week 4 (non-significant)\(^1\).

\[ \Delta = -0.125 \text{ L} \]
\[ (-0.259, 0.010) \]
\[ p = 0.0690 \]

- Post hoc sensitivity analysis on influential outliers was statistically significant ($\Delta -0.196 \text{ L}, p=0.0010$)
- A post hoc analysis based on a non-parametric Wilcoxon-Mann-Whitney test showed a shift between AB/FF 400/12 $\mu$g and Placebo ($\Delta -0.170 \text{ L}, p = 0.0034$).

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Significant improvement in pre-dose (trough) FEV$_1$ with AB/FF vs placebo at week 4$^1$. 

\[ \Delta = 0.209 \text{L} \] 
\[ (0.161, 0.258) \] 
\[ p < 0.0001 \] 

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Post-dose lung hyperinflation measurements showed significant improvements\(^1\).

\[ \Delta = -0.366 \text{ L} \quad (0.515, -0.216) \quad p < 0.0001 \]

\[ \Delta = -0.465 \text{ L} \quad (0.648, -0.281) \quad p < 0.0001 \]

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Patients treated with AB/FF had greater improvements in exercise capacity compared to patients treated with placebo\(^1\).

**RESULTS**

<table>
<thead>
<tr>
<th>Change from baseline in Endurance time (sec)</th>
<th>LS Mean</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy only</td>
<td>-13.43</td>
<td>-4.55</td>
<td>50.67</td>
</tr>
<tr>
<td>Pharmacotherapy + Behavioural intervention</td>
<td>45.51</td>
<td>55.2 s (5.6, 104.8)</td>
<td>p=0.0292</td>
</tr>
</tbody>
</table>

\(\Delta = 58.9 \text{ s (14.9, 102.9)} \quad \text{p=0.0089}\)

\(\Delta = 55.2 \text{ s (5.6, 104.8)} \quad \text{p=0.0292}\)

**Baseline ET**

7.6 min

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
After 4 weeks, the percentage of inactive patients on AB/FF was significantly lower compared with placebo\textsuperscript{1}.

\textbf{RESULTS}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart}
\caption{Physical Activity}
\end{figure}

\textsuperscript{1} Watz et al., Int J of COPD. 2017; 12: 2545-58
Patients receiving AB/FF showed significant improvements in the number of steps per day compared with a decrease in placebo\(^1\).

Number of steps per day increased with 621 in the treatment group and decreased with 110 in the control group during the pharmacotherapy period reaching a significant difference of 731 steps per day at week 4.

Treatment group steps remained stable to the behavioural intervention while control group achieved a 253 steps improvement through behavioural intervention at week 8.

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1. Watz et al., Int J of COPD. 2017; 12: 2545-58
The D-PPAC questionnaire total score, amount and difficulty domains improved significantly in the AB/FF group vs placebo at week 4\(^1\).

Patients practiced more physical activity and it was less difficult for them.

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Conclusion

Discussion

Duaklir Genuair
Patients treated with AB/FF reported less difficulty with physical activity, an effect not observed with BI only.

Taken together with the improved levels of physical activity observed with AB/FF, the results suggest that an increase in physical activity due to bronchodilation does not result in an unpleasant, burdensome experience for patients when increasing their activity levels.

This is potentially highly relevant for health care providers trying to motivate patients to adopt and maintain a more active lifestyle.

1. Watz et al., Int J of COPD. 2017; 12: 2545-58
Discussion

Duaklir Genuair
Symptoms limit COPD patient’s physical activities, even early in the disease, leading to a worse prognosis\textsuperscript{1-5}

5. Shrikrishna et al., Eur Respir J. 2012; 40: 1115-1122
COPD patients with >600 steps improvement reduce their risk for hospital admission\(^1\)

**DISCUSSION**

Time to first hospitalization:

Difference between:
- 🧲 patients exceeding the MID (dotted line)
- 🧲 patients not exceeding the MID (solid line)

Based on
- a) SEM\(^*\) cutoff
- b) empirical rule effect size and
- c) cohen effect size and 0.5 SD\(^**\).

---

*SEM: standard error of measurement
**SD: standard deviation

**DISCUSSION**

Only AB/FF was able to demonstrate an improvement in physical activity above the MCID*\(^1,2,3\)

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>Duration weeks</th>
<th>Baseline characteristics</th>
<th>Δ in step count Vs Placebo</th>
<th>Activity monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTIBRO(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOVE</td>
<td>3</td>
<td>FEV1 61% Steps/day: 5725 Min mod act: 128 CAT= 16</td>
<td>358 (6%) p&lt;0.029</td>
<td>SenseWear multisensory armband</td>
</tr>
<tr>
<td>Watz (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>194</td>
<td></td>
<td></td>
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<tr>
<td>Types of Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacol Tx</td>
<td></td>
<td>Indac+GLY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration weeks</td>
<td>3</td>
<td>3 Crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline charactistics</td>
<td></td>
<td>FEV1 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ in step count Vs Placebo</td>
<td></td>
<td>296 (T+O) p&gt;0.05 (NS)</td>
<td></td>
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<tr>
<td>Activity monitor</td>
<td></td>
<td>Dynaport MoveMonitor &amp; Omron HJ-321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIOLTO(^3)</td>
<td></td>
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<tr>
<td>PHYSACTO</td>
<td>12</td>
<td>FEV1 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troosters (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>274</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of Intervention</td>
<td></td>
<td>Tio+Olodaterol Tiotropium (Respimat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacol Tx</td>
<td></td>
<td>Pharm + BI +/- exercise training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration weeks</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline charactistics</td>
<td></td>
<td>FEV1: 60.7% Steps/day: 6278</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ in step count Vs Placebo</td>
<td></td>
<td>731 p=0.0016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity monitor</td>
<td></td>
<td>Dynaport Movemonitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUAKLIR(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTIVATE</td>
<td>8</td>
<td>FEV1: 60.7% Steps/day: 6278</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watz (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>267</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of Intervention</td>
<td></td>
<td>Pharm + BI (week 4 - 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacol Tx</td>
<td></td>
<td>AB/FF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration weeks</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*No direct comparison between different treatments available.
Duaklir Genuair reduces breathlessness & overall symptoms during night time, early-morning and daytime\(^1,2\)

Duaklir Genuair reduces limitation of early-morning activities\(^1\)

Duaklir Genuair delays the time to the first moderate or severe exacerbation and reduces the rate of moderate or severe exacerbations\(^1,2\)

1. Bateman et al., Respir Res. 2015; 16(1): 92
2. SmPC Duaklir Genuair (340/12), latest edition

Duaklir is not indicated for sleep impairment
Duaklir® Genuair® significantly improves breathlessness versus mono-components, demonstrating this improvement night time, early-morning and daytime\textsuperscript{1}

TDI focal score at week 24

\begin{figure}
\centering
\includegraphics[width=\textwidth]{TDI_focal_score.png}
\caption{TDI focal score at week 24}
\end{figure}

\textsuperscript{1} Bateman et al., Respir Res. 2015; 16(1): 92

* Figure shows data on improvement of dyspnea during daytime
Duaklir® Genuair® significantly improves overall symptoms versus mono-components, demonstrating this improvement night time, early-morning and daytime.¹

![Graph showing percentage change in early-morning, daytime and night time symptom severity vs baseline at week 24.](image-url)

**Night time**:
-21.6% *p<0.001 vs aclidinium, p<0.01 vs formoterol; p<0.001 vs aclidinium and formoterol.

**Early-morning**:
-17.0% *p=0.04 vs aclidinium and formoterol; p=0.001 vs aclidinium, p=0.05 vs formoterol.

**Daytime**:
-18.6% *p<0.001 vs aclidinium and formoterol.

**Symptoms:**
Breathlessness, cough, difficulties bringing up phlegm, wheezing

¹ Bateman et al., Respir Res. 2015; 16(1): 92
Duaklr® Genuair® significantly improves physical activity versus placebo

COPD patients limit their activities to avoid symptoms

Duaklr Genuair increases physical activity

Study Activate DUAKLR® GENUAIR®

Study MOVE indacaterol/glycopyrronium

731 Steps/Day

358 Steps/Day

+600 steps/day

Reduced risk for hospital admission

No direct comparison between different treatments available.

1. Watz et al., Int J of COPD. 2017; 12: 2545-58

*vs placebo
Duaklir® Genuair® delays the time to the first moderate or severe exacerbation and reduces the rate of moderate or severe exacerbations¹

1. Bateman et al., Respir Res. 2015; 16(1): 92
Figure shows data on rate reduction
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