Novartis’ Ultibro® Breezhaler® improved lung function and COPD symptoms after direct switch from previous treatment

- **Ultibro® Breezhaler®** improved lung function and breathlessness after direct switch from long-acting bronchodilators or steroid-containing combination therapies

- Results further support the 2017 GOLD recommendations that dual bronchodilation should be the foundation treatment for the majority of symptomatic COPD patients

- Data from the pragmatic CRYSTAL study showcased for the first time at the 2016 British Thoracic Society Winter Meeting in London, UK

**Basel, December 8, 2016** – Novartis today announced positive results from the first large-scale study exploring the effects of directly switching symptomatic, non-frequently exacerbating patients with moderate COPD from their current treatments, including steroid-containing combinations and long-acting bronchodilators, to the dual bronchodilator Ultibro® Breezhaler® (indacaterol/glycopyrronium) 110/50 mcg.

In the CRYSTAL study, patients with moderate COPD who were switched to Ultibro Breezhaler from their previous therapy (LABA+ICS or LABA or LAMA) experienced superior improvements in lung function (trough FEV\(_1\)) and breathlessness\(^*\) at week 12 (p<0.0001). Significantly, CRYSTAL is the first LABA/LAMA pragmatic trial, designed to mimic clinical practice, so treatment switching occurred without a washout period\(^1\).

“Today’s results are significant as they show for the first time the positive effect of directly switching to Ultibro Breezhaler from other COPD treatments, such as inhaled steroid-containing combination therapies,” said Vasant Narasimhan, Global Head Drug Development and Chief Medical Officer for Novartis. “By showing that improved symptom control can be achieved through using Ultibro Breezhaler, the CRYSTAL study provides further support to limit the use of inhaled steroid-containing therapies to specific patient types that really need it.”

Ultibro Breezhaler was also well tolerated in the CRYSTAL study\(^1\).

**About CRYSTAL**

CRYSTAL was a prospective, multicenter, 12-week, randomized, pragmatic, open-label trial. Patients were recruited into four groups according to previous medication and symptoms, and randomized to a direct switch to Seebri® Breezhaler® (glycopyrronium) 50 mcg or Ultibro® Breezhaler® (indacaterol/glycopyrronium)110/50 mcg once daily vs. continuation of previous treatment. The study enrolled a total of 4,389 symptomatic, non-frequently exacerbating (up to one exacerbation in the previous year) patients with moderate COPD and 2,159 patients received Ultibro Breezhaler or continued their baseline therapy. The Seebri Breezhaler treatment arms of the study were underpowered due to sample size.
Co-primary objectives of the study were:

- Superiority of Ultibro Breezhaler vs. LABA, LAMA and LABA+ICS in terms of improvement of lung function (trough FEV\textsubscript{1}) and breathlessness (transition dyspnoea index) at week 12.
- Superiority of Seebri Breezhaler vs. previous SABA and/or SAMA\textsuperscript{5} treatment in terms of improvement of lung function (trough FEV\textsubscript{1}) and breathlessness (transition dyspnoea index) at week 12.
- Non-inferiority of Seebri Breezhaler vs. previous LABA or LAMA treatment in terms of improvement of lung function (trough FEV\textsubscript{1}) and breathlessness (transition dyspnoea index) at week 12.

**About Ultibro Breezhaler**
Ultibro Breezhaler (indacaterol/glycopyrronium) 110/50 mcg is a once-daily LABA/LAMA dual bronchodilator approved in the European Union (EU) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD\textsuperscript{2}. Clinical trials have shown that it offers statistically significant improvements in bronchodilation compared to treatments widely used as current standards of care, including SFC 50/500 mcg\textsuperscript{3,5} and open-label tiotropium (18 mcg). Ultibro Breezhaler is also currently the only steroid-free treatment to offer prescribers clinically proven superiority over the most prescribed ICS/LABA combination\textsuperscript{18} in preventing COPD exacerbations\textsuperscript{8}. Ultibro Breezhaler is currently approved for use in over 90 countries worldwide, including countries within the EU and Latin America, Japan, Canada, Switzerland and Australia.

Glycopyrronium and certain use and formulation intellectual property were exclusively licensed to Novartis in April 2005 by Sosei and Vectura.

**About Seebri Breezhaler**
Seebri Breezhaler (glycopyrronium) 50 mcg is a once-daily LAMA bronchodilator approved in the European Union (EU) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD\textsuperscript{7}. Seebri Breezhaler is approved for use in over 90 countries, including countries within the EU and Latin America, Japan, Canada, Switzerland and Australia.

Glycopyrronium and certain use and formulation intellectual property were exclusively licensed to Novartis in April 2005 by Sosei and Vectura.

**About the Novartis COPD portfolio**
Novartis is committed to addressing the unmet medical needs of COPD patients and improving their quality of life by providing innovative medicines and devices. The Novartis COPD portfolio includes Ultibro Breezhaler (indacaterol/glycopyrronium), Seebri Breezhaler (glycopyrronium) and Onbrez\textsuperscript{9} Breezhaler\textsuperscript{®}/Arcapta\textsuperscript{®} Neohaler\textsuperscript{®} (indacaterol), which are all indicated as maintenance treatments for COPD patients.

Novartis continues development of respiratory products for delivery via the low resistance Breezhaler\textsuperscript{®} inhalation device, which makes it suitable for patients with different severities of airflow limitation\textsuperscript{8}. The Breezhaler device allows patients to hear, feel and see that they have taken the full dose correctly\textsuperscript{2,8}.

**About COPD**
Chronic obstructive pulmonary disease (COPD) affects an estimated 210 million people worldwide\textsuperscript{9} and is the third leading cause of death\textsuperscript{10}. It is progressive (usually gets worse over time), and can be a life-threatening disease\textsuperscript{9,11}. COPD makes it difficult to breathe, with symptoms that have a destructive impact on patients’ function (i.e. activity limitation, decreased mobility) and quality of life\textsuperscript{9,11}.

**Disclaimer**
The foregoing release contains forward-looking statements that can be identified by words such as “support,” “recommendations,” “should,” “can,” “committed,” “continues,” or similar.
terms, or by express or implied discussions regarding potential new indications or labeling for Ultibro Breezhaler and the other products in the Novartis COPD portfolio, or regarding potential future revenues from Ultibro Breezhaler and the other products in the Novartis COPD portfolio. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Ultibro Breezhaler or the other products in the Novartis COPD portfolio will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Ultibro Breezhaler or the other products in the Novartis COPD portfolio will be commercially successful in the future. In particular, management's expectations regarding Ultibro Breezhaler and the other products in the Novartis COPD portfolio could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2015, the Group achieved net sales of USD 49.4 billion, while R&D throughout the Group amounted to approximately USD 8.9 billion (USD 8.7 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 118,000 full-time equivalent associates. Novartis products are available in approximately 180 countries around the world. For more information, please visit http://www.novartis.com.

Notes
* Long-acting beta2-adrenergic agonist + inhaled corticosteroid (free or fixed-dose combinations)
† Long-acting muscarinic antagonist
‡ Transition dyspnea index (TDI)
§ Short-acting beta agonist and/or short-acting muscarinic antagonist
‘’ Seretide® Accuhaler® (salmeterol/fluticasone) 50 microgram /500 microgram /dose inhalation powder. Seretide and Accuhaler are registered trademarks of the GlaxoSmithKline group of companies

References
3. Vogelmeier C, et al. Once-daily QVA149 provides clinically meaningful improvements in lung function and clinical outcomes versus placebo, indacaterol, glycopyronium, tiotropium and salmeterol/fluticasone in patients with COPD. [ATS abstract 40759; Session C45; Date: May 21, 2013 Time: 8:15 -10:45].
4. Vogelmeier C, et al. Once-daily QVA149 provides clinically meaningful improvements in lung function and clinical outcomes. [ERS 2013 abstract 851178; Session 82; Date: September 8, 2013 Time: 12:50-14:40].

5. Banerji D, et al. Dual bronchodilation with once-daily QVA149 improves dyspnea and health status and reduces symptoms and rescue medication use in patients with COPD: the IGNITE trials. [ERS 2013 abstract 851388; Session 346; Date: September 10, 2013 Time: 8:30-10:30].


---

**Novartis Media Relations**

Central media line: +41 61 324 2200

E-mail: media.relations@novartis.com

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Claudia Paproth
Novartis Pharma Communications
+41 61 696 5556 (direct)
+41 79 560 4713 (mobile)
claudia.paproth@novartis.com

**Novartis Investor Relations**

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central
Samir Shah +41 61 324 7944 Richard Pulik +1 212 830 2448
Pierre-Michel Bringer +41 61 324 1065 Sloan Pavsner +1 212 830 2417
Thomas Hungerbuehler +41 61 324 8425
Isabella Zinck +41 61 324 7188

North America

---

###