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Novartis investigational dual bronchodilator significantly improved lung function compared to single bronchodilators in patients with moderate-to-severe COPD in phase III studies

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- - EXPEDITION trial results demonstrated QVA149 (indacaterol/glycopyrronium) met all primary and secondary endpoints(1),(2),(3),(4)
- - Treatment with QVA149 for 12 weeks provided robust dual bronchodilation, with clinically meaningful improvement in lung function compared to single bronchodilators, as well as clinically meaningful improvements in breathlessness and health-related quality of life(1),(2)
- - Additional data presentations showed overall safety and tolerability of QVA149 was similar to its individual components and placebo(5),(6)
- - There is an important need for additional treatments for COPD, which affects nearly 27 million people and is the third leading cause of death in the US(7),(8),(9)

EAST HANOVER, N.J., May 20, 2015 /PRNewswire/ -- Today, Novartis announced for the first time detailed results from its phase III EXPEDITION trial program for QVA149 (indacaterol/glycopyrronium) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). In the US, QVA149 and glycopyrronium (NVA237) are currently investigational. The findings were presented at the American Thoracic Society (ATS) International Conference in Denver, May 15-20.

The EXPEDITION trial program consists of two efficacy studies (FLIGHT 1 & 2) and one safety study (FLIGHT 3). The FLIGHT 1 and 2 studies met their primary endpoints, with QVA149 27.5/12.5 mcg demonstrating statistically significant and clinically meaningful improvements in lung function (FEV_1 AUC_{0-12})* at week 12, compared to its individual components – indacaterol 27.5 mcg and glycopyrronium 12.5 mcg – and placebo, all dosed twice-daily[1,2].

In these studies, QVA149 also demonstrated improvements for all secondary endpoints at week 12[1,2,3,4]. This included the key secondary endpoint of health status, as well as trough FEV_1, peak FEV_1, dyspnea (breathlessness) and reduced use of rescue medication versus the mono-components and placebo[1,2,3,4]. Health status was assessed using the St. George's Respiratory Questionnaire (SGRQ) score – a measure of health-related quality of life – while dyspnea was measured by the Transitional Dyspnea Index (TDI) total score[3,4].

A pooled analysis of FLIGHT 1 and 2 found that QVA149 27.5/12.5 mcg had similar safety outcomes at 12 weeks compared to its mono-components indacaterol 27.5 mcg and glycopyrronium 12.5 mcg, as well as placebo[5]. In FLIGHT 3, the incidence rates of adverse events (AEs) and serious adverse events (SAEs) for QVA149 27.5/12.5 mcg and QVA149 27.5/25 mcg, each given twice daily, were similar to those of once-daily indacaterol 75 mcg over a 52-week treatment period[6].

"Symptom relief is a key objective in the management of COPD," said EXPEDITION investigator Donald

Mahler, MD, Director of Respiratory Services, Valley Regional Hospital, Claremont, NH, and Emeritus Professor of Medicine, Geisel School of Medicine at Dartmouth, NH. "The results we've seen for QVA149 further validate the current GOLD strategy, which recommends that maximizing bronchodilation in patients can further improve lung function, symptoms and health status."

Study Designs

FLIGHT 1 and 2 were 12-week, multi-center, double-blind, parallel-group, placebo- and active-controlled studies that randomized patients (1:1:1:1) to QVA149 27.5/12.5 mcg, indacaterol 27.5 mcg, glycopyrronium 12.5 mcg or placebo, all administered twice daily via the Breezhaler®† device[1,2]. Each study was designed to demonstrate superiority of QVA149 versus indacaterol and glycopyrronium in terms of the primary endpoint of FEV_1 AUC_{0-12}, the standard area under the curve from 0 to 12 hours (AUC_{0-12h}) for FEV_1, at Week 12[1,2].

FLIGHT 3 was a 52-week, multi-center, double-blind, active-controlled safety study that randomized patients (1:1:1) to QVA149 27.5/12.5 mcg twice daily, QVA149 27.5/25 mcg twice daily or indacaterol 75 mcg once daily, delivered via the Breezhaler device[6]. The primary objective was to evaluate the safety and tolerability of twice-daily QVA149 27.5/12.5 mcg and QVA149 27.5/25 mcg versus once-daily indacaterol 75 mcg in terms of adverse event (AE) reporting rates over the 52-week treatment period[6].

Efficacy Findings

In FLIGHT 1, QVA149 improved FEV_1 AUC_{0-12h} at Week 12 compared to indacaterol (least square mean [LSM] treatment difference: 94 mL; $p<0.001$), glycopyrronium (98 mL; $p<0.001$), and placebo (231 mL; $p<0.001$)[1]. QVA149 also demonstrated statistically significant improvement in trough FEV_1 compared to the monocomponents and placebo after 12 weeks of treatment (LSM treatment differences [SE]: 81 mL [20.2] and 110 mL [20.2], 213 mL [20.8], respectively, all $p<0.001$) and peak FEV_1 (LSM treatment difference [SE]: 109 mL [21.1] and 100 mL [21.2], 260 mL [21.6], respectively, all $p<0.001$)[1].

The safety profile of QVA149 was similar to its monocomponents and placebo[1].

In FLIGHT 2, QVA149 demonstrated superior bronchodilation compared to indacaterol, glycopyrronium and placebo: Improvements in FEV_1 AUC_{0-12h} at Week 12 (least square mean [LSM] treatment difference) were 112 mL [18.9], 79 mL [18.9] and 262 mL [19.1], respectively, all $p<0.001$[2]. QVA149 also showed statistically significant improvement in trough FEV_1 compared to indacaterol, glycopyrronium and placebo after 12 weeks of treatment (LSM treatment differences [SE]: 78 mL [19.9], 87 mL [20.0] and 233 mL [20.2], respectively, all $p<0.001$) and peak FEV_1 (LSM treatment difference [SE]: 139 mL [20.3], 86 mL [20.3] and 290 mL [20.5], respectively, all $p<0.001$)[2].

The safety profile of QVA149 was similar to that of its monocomponents and placebo[2].

In separate analyses of FLIGHT 2, QVA149 improved SGRQ score (a measure of Health-Related Quality of Life) compared to indacaterol (LSM treatment difference (SE) [95% CI]: -1.5 (1.07) [-3.6, 0.6], $p=0.158$), glycopyrronium (-1.4 (1.08) [-3.5, 0.7], $p=0.190$) and placebo (-6.4 (1.09) [-8.5, -4.2], $p<0.001$)[3]. A reduction of at least 4 units is considered the minimal clinically important difference (MCID) in SGRQ score. QVA149 also improved TDI score (a measure of breathlessness) vs. indacaterol (LSM treatment difference (SE) [95% CI]: 0.90 (0.26) [0.39, 1.40]), glycopyrronium (1.01 (0.26) [0.50, 1.51]) and placebo (2.03 (0.26) [1.52, 2.54]), all $p<0.001$[4]. The MCID for TDI score is an improvement of the least 1 unit.

Safety Findings

In the pooled safety analysis of the FLIGHT 1 and 2 studies, which included 2,040 patients, the occurrence of

adverse events for QVA149 27.5/12.5 mcg, indacaterol 27.5 mcg, glycopyrronium 12.5 mcg and placebo, all dosed twice daily, was 221 (43.50%), 195 (38.16%), 214 (41.72%) and 219 (43.11%), respectively[5]. The corresponding percentages of patients with serious AEs were 3.15%, 3.52%, 3.90% and 4.13%[5].

The most common adverse reactions (incidence greater than or equal to 2% for QVA149 and higher than placebo) were nasopharyngitis and hypertension. Nasopharyngitis occurred in 21 (4.1%), 13 (2.5%), 12 (2.3%) and 9 (1.8%) patients receiving QVA149 27.5/12.5 mcg, indacaterol 27.5 mcg, glycopyrronium 12.5 mcg and placebo, respectively. Hypertension occurred in 10 (2.0%), 5 (1.0%), 3 (0.6%) and 7 (1.4%) patients receiving QVA149 27.5/12.5 mcg, indacaterol 27.5 mcg, glycopyrronium 12.5 mcg and placebo, respectively[5].

In FLIGHT 3, which included 615 patients, the incidence of AEs for twice-daily QVA149 27.5/12.5 mcg and QVA149 27.5/25 mcg and once-daily indacaterol 75 mcg was 139 (68.1%), 142 (69.6%) and 139 (67.5%), respectively, during the 52-week study period[6]. The corresponding incidence rates for SAEs were 26 (12.7%), 25 (12.3%) and 24 (11.7%), respectively[6]. Discontinuation rates from study treatment in the 3 treatment arms were 2.5%, 3.9% and 5.8%, respectively[6].

COPD worsening (exacerbation) in the twice-daily QVA149 27.5/12.5 mcg and QVA149 27.5/25 mcg and once-daily indacaterol 75 mcg arms was seen in 8 (3.9%), 5 (2.5%) and 10 (4.9%) patients, respectively[6]. In total, 9 deaths were reported in all treatment arms during the study: 1 (0.5%) for QVA149 27.5/12.5 mcg, 3 (1.5%) for QVA149 27.5/25 mcg and 5 (2.4%) for indacaterol 75 mcg. None of the deaths were suspected to be related to the study medication[6]. The incidence of major adverse cardiovascular events (MACE) and/or cardiovascular (CV) deaths was 4 (2.0%), 5 (2.5%) and 3 (1.5%), respectively, in the QVA149 27.5/12.5 mcg, QVA149 27.5/25 mcg and indacaterol 75 mcg treatment arms[6]. The corresponding number of CV deaths were 1 (0.5%), 1 (0.5%) and 3 (1.5%)[6]. The study reported no clinically meaningful differences in laboratory tests, ECG and vital signs[6].

About QVA149

In the US, QVA149 (indacaterol/glycopyrrolate) 27.5/15.6 mcg and one of its components, NVA237 (glycopyrrolate) 15.6 mcg, are currently under review by the FDA as twice-daily therapies for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. QVA149 and NVA237 are administered via the Neohaler® device. The indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg dose strength is equivalent to 27.5/12.5 mcg of indacaterol/ glycopyrronium.

Glycopyrronium bromide was exclusively licensed to Novartis in April 2005 by Vectura and its co-development partner Sosei.

About COPD

COPD is a progressive and life-threatening lung disease that makes it difficult to breathe[11]. Nearly 27 million people in the US are affected by COPD[7]. The disease ranks as the third leading cause of death in the US[8,9] and is a major cause of serious long-term disability[12].

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "investigational," "currently," "objective," "recommends," "can," "under review," or similar terms, or by express or implied discussions regarding potential marketing approvals for QVA149 or NVA237, or regarding potential future revenues from QVA149 or NVA237. 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 QVA149 or NVA237 will be submitted in any additional markets, or approved for sale in any market where they have been submitted, or at any particular time. Nor can there be any guarantee that QVA149 or NVA237 will be commercially successful in the future. In particular, management's expectations regarding QVA149 and NVA237 could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; 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 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

Located in East Hanover, N.J., Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which 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 2014, the Group achieved net sales of USD 58.0 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion, excluding impairment and amortization charges). Novartis Group companies employ approximately 120,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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Novartis Media Relations

Julie Masow	Martin DeBenedetto
Novartis Media Relations	Novartis Division Communications
+1 212 830 2465 (direct)	862-778-7619 (direct)
+1 862 579 8456 (mobile)	973-738-4104 (mobile)
julie.masow@novartis.com	martin.debenedetto@novartis.com

e-mail: us.mediarelations@novartis.com

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* FEV_1 AUC_{0-12} is the repeated measurement over 12 hours of FEV_1 (forced expiratory volume in 1 second), a common measure of lung function.

† In the US, QVA149 and NVA237 are administered via the Neohaler® device.

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2. http://www.novartis.com/
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