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MEDIA UPDATE

Novartis Phase III IRIDIUM data in Lancet Respiratory Medicine show benefit of Enerzair® Breezhaler® (QVM149), the first-in-class inhaled LABA/LAMA/ICS combination in uncontrolled asthma

- *Once-daily Enerzair® Breezhaler® (QVM149; IND/GLY/MF) was superior to once-daily IND/MF (QMF149) in improving the lung function of patients whose asthma is uncontrolled with LABA/ICS standard-of-care treatment*[1]
- *In secondary analyses, improvements in lung function were observed with high- and medium-dose IND/GLY/MF compared to high-dose Sal/Flu*[1]
- *In other secondary analyses, clinically meaningful reductions in moderate-to-severe (36%) and severe (42%) asthma exacerbation rates were observed with high-dose IND/GLY/MF compared to high-dose Sal/Flu*[1]
- *IND/GLY/MF is approved in EU, Japan and Canada, and is currently under regulatory review in other countries*

Basel, July 10, 2020 — Novartis today announced that full results from the Phase III IRIDIUM study were published in *The Lancet Respiratory Medicine*. The primary endpoint results show that once-daily treatment with high- and medium-dose Enerzair® Breezhaler® (QVM149; indacaterol acetate, glycopyrronium bromide and mometasone furoate [IND/GLY/MF]) demonstrated statistically significant improvements in lung function compared with once-daily QMF149 (indacaterol acetate and mometasone furoate [IND/MF])[1]. The key secondary endpoint was improvement in Asthma Control Questionnaire (ACQ-7) score for IND/GLY/MF versus IND/MF. Although both treatments delivered clinically meaningful improvements in this measure, the key secondary endpoint was not met[1]. In secondary analyses, improvements in lung function and clinically meaningful reductions in moderate-to-severe and severe asthma exacerbation rates were observed with high-dose IND/GLY/MF compared to high-dose salmeterol xinafoate/fluticasone propionate (Sal/Flu)[1].

“The IRIDIUM data show that once-daily treatment with a combination of IND/GLY/MF has the potential to improve lung function and reduce exacerbations in people who continue to experience symptoms despite receiving a LABA/ICS, which is the standard-of-care,” said Professor Huib Kerstjens, Head, Department of Pulmonology at the University Medical Center Groningen. “These data are encouraging because achieving optimal symptom control in asthma remains challenging; at least 45% of patients at GINA steps 4 and 5 remain uncontrolled, which can lead to reduced quality of life, decreased work productivity, and increased emergency or hospital-based medical care.”

The primary endpoint was met, with both high- and medium-doses of IND/GLY/MF demonstrating statistically significant improvement in trough FEV_1 ([0.065 L; p<0.001] and [0.076 L; p<0.001], respectively) compared to the corresponding doses of IND/MF at Week 26[1].

The key secondary endpoint was improvement in ACQ-7 score for IND/GLY/MF versus IND/MF. Both treatments delivered clinically meaningful improvements in this measure of symptoms from baseline at Week 26, but the key secondary endpoint was not met[1].

“At Novartis, we are working to reimagine respiratory treatment by bringing innovative medicines and digital solutions to patients,” said Dominic Brittain, Respiratory Global Program Head, Novartis Pharmaceuticals. “There have been relatively few developments in inhaled asthma treatment options over the last decade, so it’s exciting to see IND/GLY/MF show its potential as a once-daily, fixed-dose combination for the treatment of uncontrolled asthma in this pivotal study.”

In secondary analyses, improvements in lung function (FEV_1) were observed for both doses of IND/GLY/MF versus high-dose Sal/Flu at Week 26 (high-dose [0.119 L; p<0.001]; medium-dose [0.099 L; p<0.001]). Similar FEV_1 improvements were seen across all comparisons at Week 52, indicating the potential long-term benefits of this maintenance medicine. Improvements in post-dose FEV_1 were seen with both doses of IND/GLY/MF as early as five minutes after initial drug administration, versus respective doses of IND/MF and high-dose Sal/Flu (p<0.001), indicating rapid onset of action[1].

In further secondary analyses, substantial reductions in moderate-to-severe (36%; p<0.001) and severe (42%; p<0.001) asthma exacerbation rates were observed for high-dose IND/GLY/MF compared to high-dose Sal/Flu. Reductions in moderate-to-severe (19%; p=0.041) and severe (16%; p=0.117) asthma exacerbation rates were also seen with medium-dose IND/GLY/MF compared with high-dose Sal/Flu[1].

The IRIDIUM study assessed IND/GLY/MF, a once-daily, fixed-dose combination of a long-acting $beta_2$-agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS) in high (150/50/160 µg) and medium (150/50/80 µg) doses versus IND/MF (LABA/ICS) in corresponding high (150/320 µg) and medium (150/160 µg) doses, in asthma patients not adequately controlled on current inhaled therapies, over 52 weeks of active treatment[1].

The overall incidence of adverse events (AEs) and serious adverse events (SAEs) for IND/GLY/MF and IND/MF in the IRIDIUM study were generally low and comparable among treatment groups. Asthma exacerbation was the most commonly reported AE and SAE[1].

To date, medium- and high-doses of IND/GLY/MF have been approved in Japan, and high-dose IND/GLY/MF has been approved in the EU and Canada; these submissions were supported by the IRIDIUM study[1,2]. Additionally, IND/MF has received regulatory approval in the EU and Canada; these submissions were supported by the PALLADIUM study (also published in *The Lancet Respiratory Medicine*)[3]. Further regulatory reviews for both products are currently underway in multiple countries.

In keeping with the Novartis commitment to reduce the environmental impact of our asthma combinations, IND/GLY/MF and IND/MF will both be available in the Breezhaler® device which is hydrofluoroalkane/chlorofluorocarbon (HFA/CFC)-free.

About Uncontrolled Asthma

Asthma affects an estimated 358 million people worldwide and can cause a significant personal, health and financial burden when not adequately controlled[4,5]. Despite current therapy, over 40% of patients with asthma at Global Initiative for Asthma (GINA) Step 3, and

over 45% at GINA Steps 4 and 5 remain uncontrolled[6,7]. Patients with uncontrolled asthma may downplay or underestimate the severity of their disease and are at a higher risk of exacerbation, hospitalization or death[8-10]. Barriers, such as less than optimal adherence, incorrect inhaler technique, treatment mismatch, safety issues with oral corticosteroids and ineligibility for biologics, have created an unmet medical need in asthma[11-14].

About Enerzair Breezhaler in the EU
On July 7, 2020, Novartis announced European Commission (EC) approval of Enerzair Breezhaler (QVM149; IND/GLY/MF) 150/50/160 µg once-daily as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long acting beta$_2$-agonist (LABA) and a high-dose of an inhaled corticosteroid (ICS) who experienced one or more asthma exacerbations in the previous year[2]. This formulation combines the bronchodilation of indacaterol acetate (a LABA) and the antimuscarinic effects of glycopyrronium bromide (a LAMA) with mometasone furoate (ICS) in a precise once-daily formulation, delivered via the dose-confirming Breezhaler device. Glycopyrronium bromide certain use and formulation intellectual property were exclusively licensed to Novartis in April 2005 by Sosei Heptares and Vectura. Mometasone furoate is exclusively licensed to Novartis from a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, for use in IND/GLY/MF (worldwide excluding the US).

IND/GLY/MF will be administered via the dose-confirming Breezhaler device, which enables once-daily inhalation using a single inhaler. IND/GLY/MF is the first asthma treatment in the EU that can be prescribed together with a digital companion; the Propeller Health app and sensor custom-built for the Breezhaler device. The digital companion will provide patients with inhalation confirmation, medication reminders and access to objective data that can be shared with their physician in order to help them make better therapeutic decisions. The sensor for the Breezhaler device was developed by Propeller Health and is a CE marked Medical Device, designed and licensed to Novartis for use with the Breezhaler inhaler worldwide. The sensor includes a microchip, a microphone, Bluetooth capabilities, an antenna and a battery. The sensor does not alter the drug delivery characteristics of the Breezhaler inhaler itself but produces a recording of each administered dose. Based on the patient's recorded medication usage, personalized content is presented within the app to help the patient better self-manage their asthma.

About Atectura® Breezhaler® in the EU
On May 30, 2020, Atectura Breezhaler (QMF149; IND/MF) 150/80 µg, 150/160 µg and 150/320 µg once-daily received European Commission (EC) approval as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with ICS and inhaled short-acting beta$_2$-agonists[15]. IND/MF combines the bronchodilation of indacaterol acetate (a LABA) with the anti-inflammatory mometasone furoate (an ICS) in a precise once-daily formulation, delivered via the dose-confirming Breezhaler device. Mometasone furoate is exclusively licensed to Novartis from a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, for use in IND/MF.

About the PLATINUM Clinical Development Program
The PLATINUM program, having enrolled over 7,500 patients worldwide, is the Novartis Phase III/IIIb clinical development program supporting the development of IND/GLY/MF and IND/MF. It includes four studies: the QUARTZ study, which compared a low-dose of IND/MF with MF alone; the PALLADIUM study, which compared IND/MF with MF and salmeterol xinafoate/fluticasone propionate (Sal/Flu); the IRIDIUM study, which compared IND/GLY/MF with IND/MF and Sal/Flu; and the ARGON study, which compared IND/GLY/MF with a free combination of Sal/Flu plus tiotropium (Tio).

About the IRIDIUM study[1]

IRIDIUM was a Phase III, multicenter, randomized, double-blind, parallel-group study, designed to compare the efficacy and safety of IND/GLY/MF with IND/MF in patients with asthma.

The purpose of the study was to evaluate the efficacy and safety of two different doses of IND/GLY/MF (high: 150/50/160 µg and medium:150/50/80 µg), versus two corresponding IND/MF doses (high: 150/320 µg and medium: 150/160 µg) in patients with uncontrolled asthma, as determined by pulmonary function testing and effects on asthma control.

All patients were required to be symptomatic at screening and to have one or more exacerbations in the previous year, despite being on treatment with medium or high stable doses of LABA/ICS. Approximately 3,092 male and female adult patients with asthma were randomized 1:1:1:1:1 (approximately 618 patients in each of the treatment groups) to receive one of the following treatments:

- IND/GLY/MF 150/50/80 µg (once-daily)
- IND/GLY/MF 150/50/160 µg (once-daily)
- IND/MF 150/160 µg (once-daily)
- IND/MF 150/320 µg (once-daily)
- Sal/Flu 50/500 µg (twice-daily)

The primary objective of this study was to demonstrate superiority of both high-dose IND/GLY/MF versus high-dose IND/MF and medium-dose IND/GLY/MF versus medium-dose IND/MF, all delivered once-daily, in improving trough FEV_1 (volume of air that can be forced out in the first second of expiration approximately 24 hours post-administration of study drug) after 26 weeks of treatment in patients with asthma.

The key secondary objective was to demonstrate the superiority of both doses of IND/GLY/MF versus respective doses of IND/MF, in improving Asthma Control Questionnaire (ACQ-7) score after 26 weeks of treatment in patients with asthma.

Other secondary analyses also included reduction of exacerbation rate, comparing high-dose IND/GLY/MF with high-dose IND/MF and medium-dose IND/GLY/MF with medium-dose IND/MF. Secondary analyses included efficacy comparisons for both doses of IND/GLY/MF compared with Sal/Flu (50/500 µg).

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containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, 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 media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update as a result of new information, future events or otherwise.

About Novartis
Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 145 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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