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Novartis unveils promising Phase II data for bronchodilator QAB149

QAB149 provides 24-hour bronchodilation with once-daily dosing

San Diego, Calif., May 23, 2005 – Novartis announced today that its development compound indacaterol (QAB149) may provide a new standard for beta₂-agonist therapy in patients with asthma and chronic obstructive pulmonary disease (COPD), according to data presented at the centenary meeting of the American Thoracic Society (ATS). The collective data from Phase II studies show indacaterol provides effective and well-tolerated bronchodilation for up to 24-hours, with convenient once-daily dosing.

“The release of these first clinical data on indacaterol show that it offers significant therapeutic potential for patients with asthma and COPD, either as a single agent or in combination with drugs such as the long-acting anti-muscarinic AD 237, which was recently licensed by Novartis,” said Joerg Reinhardt, Global Head of Development, Novartis Pharma AG. “Tackling respiratory diseases is one of our major priorities for the future, and we have designed an ambitious development program for these and other compounds.”

Results in patients

A randomized, double-blind, dose-ranging study (50, 100, 200, 400 µg or placebo) in 42 patients with intermittent or mild to moderate persistent asthma demonstrated effective 24-hour bronchodilation within five minutes and a favorable safety profile with once-daily dosing. Improvements in efficacy were generally dose-dependent, while safety and tolerability were similar to the effects reported for placebo.ⁱ

“Despite advances in the management of these chronic conditions, the numbers of individuals affected by asthma and COPD are large and growing,” said James Donohue, M.D., Professor of Medicine, Chief, Division of Pulmonary Critical Care, University of North Carolina School of Medicine. “These data show indacaterol has significant therapeutic potential, including single-dose 24-hour control for asthma and COPD patients.”

A further randomized, double-blind, placebo-controlled, parallel-group, multicenter study involving 156 patients aged 13-75 demonstrated that indacaterol was shown to have a favorable cardiovascular safety profile, with no clinically significant effect on ECG measurements, vital signs or laboratory tests commonly affected by long-duration beta₂-agonists. No clinically notable changes occurred in the mean QTc intervals for any treatment group at any time point (calculated using Fridericia’s formula). No clinically or statistically significant changes in serum potassium and blood glucose, or evidence of dose-related increases in adverse events, were detected. In addition, no serious adverse events occurred in any active treatment group.ⁱⁱ

Indacaterol pre-clinical studies

In addition, extensive pre-clinical studies involving indacaterol were also presented, demonstrating that in isolated human bronchi, indacaterol provides effective bronchodilation with a longer duration of action than albuterol and formoterol and an onset of action more rapid than salmeterol and comparable to albuterol. At resting tone, the onset of action of indacaterol (9.2 ± 1.5 min, $n=8$) was not significantly different from that of formoterol (5.8 ± 0.8 min, $n=8$) and albuterol (11.0 ± 3.6 min, $n=8$) but was significantly faster than that of salmeterol (18.0 ± 3.5 min, $n=8$; $p < 0.05$).ⁱⁱⁱ In addition, indacaterol was shown to be a potent β_2 -agonist that, in contrast to salmeterol, does not antagonize the bronchorelaxant effect of a short-acting β_2 -agonist.

Other pre-clinical data demonstrate that indacaterol provides a long duration of action and fast onset *in vitro* and *in vivo* in animals. The risk of tachyphylaxis, or rapidly decreasing response to a drug, was assessed in once-daily intratracheal (IT) dosing of indacaterol compared with formoterol and salmeterol. Animals in the study were then challenged with aerosolized 5-HT ($175 \mu\text{g/mL}$, 1 min) two hours after β_2 -agonist exposure following both single and five daily IT treatments, and bronchoconstriction was quantified by plethysmography. No tachyphylaxis was observed with indacaterol, formoterol or salmeterol.^{iv}

Significant disease burden

COPD incurs a significant burden on the US healthcare system in terms of number of visits and medications prescribed. Among the papers presented at the ATS meeting was an analysis of data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey conducted by a team of researchers from Novartis Pharmaceuticals, Rutgers University and Duke University that assessed the disease burden. Results showed that during 2002, 9.9 million ambulatory visits were made to physician offices, outpatient departments and emergency departments in the US, representing a 50.1% increase from 2001. In addition, the annual rate of visits for COPD across all settings was 34.4 visits per 1,000 persons in the US population.^v

About asthma and COPD

Exploring new treatments for asthma and COPD is critical. Despite a wide range of currently available therapeutic options, respiratory diseases affect millions of patients around the world. For example, asthma affects more than 23 million people in the US and is the sixth most common chronic condition overall.http://www.ncqa.org/somc2001/asthma/somc_2001_asthma.html - en4#en4 In addition, the estimated number of asthma-related deaths is approximately 5,000 per year.^{vi} COPD is presently the fourth leading cause of death worldwide and is expected to become the third leading cause of death by 2020. While COPD death rates are very low under age 45, complications and deaths increase steeply with age.^{vii}

About Novartis

Novartis AG (NYSE: NVS) is a world leader in pharmaceuticals and consumer health. In 2004, the Group's businesses achieved sales of USD 28.2 billion and pro forma net income of USD 5.6 billion. The Group invested approximately USD 4.2 billion in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ about 81,400 people and operate in over 140 countries around the world. For further information please consult <http://www.novartis.com>.

Disclaimer

The foregoing release contains certain forward-looking statements that can be identified by terminology such as "promising", "may provide", "significant therapeutic potential", "for the future", or similar expressions, or by discussions regarding the potential that indacaterol

will be approved for marketing, or regarding any potential revenues from indacaterol. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with indacaterol to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that indacaterol will be approved for sale in any market. In particular, management's expectations regarding commercialization of indacaterol could be affected by, among other things, uncertainties relating to clinical trials; new clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures; as well as other risks and factors referred to in the Company's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. 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.

References

ⁱ Beeh K-M, Schelfout V, Grönke L, Kannies F, Cameron R, van As A. Indacaterol (QAB149): the first once-daily β_2 -agonist with 24-hour bronchodilation. Abstract 1314, poster board number G34.

ⁱⁱ Chuchalin AG, Tsoi AN, Richter K, Arievidh H, Cameron R, Bao W, van As A. Cardiovascular safety of indacaterol (QAB149), a novel 24-hour β_2 -agonist, in patients with asthma. Abstract 1316, poster board number G35.

ⁱⁱⁱ Naline E, Molimard M, Fairhurst R, Trifilieff A, Advenier C. Duration and onset of action of indacaterol (QAB149), a novel 24-hour β_2 -agonist, on the isolated human bronchus. Abstract 1296, poster board number G32.

^{iv} Battram CH, Mok J, Lewis CA. Once-daily administration of indacaterol (QAB149) does not induce tachyphylaxis *in vivo*. Abstract 2569, poster board number G37.

^v Lau H, Valiyeva E, Suh D, Mahajan S. Characteristics of ambulatory care visits for chronic obstructive pulmonary disease in 2002 in a national sample of the US population. Abstract 3636, poster board number J115.

^{vi} http://www.ncqa.org/somc2001/asthma/somc_2001_asthma.html

^{vii} <http://www.thoracic.org/COPD/2/epidemiology.asp>

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