Focus on Eosinophilic Asthma

Eosinophilic asthma (EA), a distinctive phenotype of asthma, is characterized by the increased levels of eosinophils in sputum, blood, and respiratory epithelium, increased disease severity (exacerbations), late onset, and refractoriness to inhaled corticosteroids. Approximately 85% of patients with severe asthma have eosinophilic asthma. EA patients typically present with acute exacerbations, night-time awakening, dyspnea, lung function abnormalities (reduced FEV1), and comorbidities (chronic rhinosinusitis with nasal polyposis).

There are 11 assets in clinical development for EA – 2 (Phase I), 5 (Phase II), 3 (Phase III), and 1 (Pre-registration).

Late-stage Assets with Recent Efficacy Data

Tezepelumab (*TSLP inhibitor, Pre-registration phase, Amgen/AstraZeneca*)

Targets severe asthma patients, irrespective of phenotype. It has demonstrated promising efficacy in the Phase III NAVIGATOR study, in Type 2 as well as non-Type 2 asthma and has the potential to become the SoC to reduce exacerbations for most patients with severe asthma, especially for non-responders to current therapies. Despite its ability to reduce asthma exacerbations, tezepelumab failed to demonstrate a significant reduction of daily maintenance dose of OCS from baseline vs. placebo at week 48 in the Phase III SOURCE study.

Efficacy Data from Phase III NAVIGATOR Study

- Annualized severe asthma exacerbation rate (SAER) at week 52: Tezepelumab + SoC (0.93) vs. placebo + SoC (2.10), rate ratio = 0.44, p<0.001.
- Annualized asthma exacerbations rate (AAER) in patients with blood eosinophil count of <300 cells/microliter at week 52: Tezepelumab + SoC (1.02) vs. placebo + SoC (1.73), rate ratio = 0.59, p<0.001.
- Change from baseline in prebronchodilator FEV1 (forced exhalation volume in 1 second) in liters at week 52: Tezepelumab + SoC (0.23) vs. placebo + SoC (0.09), PSD = 0.13, p<0.001.
- Change from baseline in ACQ-6 (Asthma control questionnaire-6) at week 52: Tezepelumab + SoC (–1.55) vs. placebo + SoC (–1.22), PSD = –0.33, p<0.001.

Efficacy Data from Phase III SOURCE Study

- Categorized percent reduction from baseline in daily maintenance OCS dose while not losing asthma control at week 48 with tezepelumab 210 mg Q4W vs. placebo: odds ratio = 1.28, p=0.43.
- Reduction of annualized asthma exacerbation rate (AAER) at week 48 with tezepelumab 210 mg Q4W vs. placebo: tezepelumab (31%), placebo value not available, p=0.11.

Masitinib (*Tyrosine kinase inhibitor, Phase III, AB Science*)

- Demonstrated encouraging efficacy vs. placebo in a Phase III study:
  - Annualized severe asthma exacerbation rate (SAER): Masitinib (0.34) vs. Placebo (0.48), 35% reduction, p=0.0103.
  - Moderate/severe asthma exacerbation rate at week 60: Masitinib (0.48) vs. Placebo (0.69), 36% reduction, p=0.0014.
  - LS mean change from baseline in FEV1 (forced exhalation volume in 1 second) at week 96: Masitinib (0.0989) vs. Placebo (0.0314), p=0.016.
  - LS mean change from baseline in ACQ (Asthma control questionnaire) at week 96: Masitinib (–0.5369) vs. Placebo (–0.3241), p=0.05.

Depemokimab (*Phase III planned, GSK*)

- A long-acting anti-IL-5, if efficacious, is likely to supplant the currently approved anti-IL-5 therapies.

In the past year, multiple therapies failed in Phase II clinical trials for severe asthma including GB001 (DP2 antagonist, Gossamer Bio/Teijin Pharma); etokimab (IL-33 antagonist, AnaptysBio); and GSK37728473 (IL-33R antagonist, GlaxoSmithKline).

Despite multiple approved therapies for the management of EA, approximately half the patients do not respond to treatment and OCS tapering remains challenging.

Key questions that remain to be answered:

- What is the best way to effectively manage non-responders to currently approved therapies?
- What are the strategies to achieve steroid tapering in patients with oral corticosteroid dependent asthma?
- How can we further reduce the burden of symptoms, repeated hospitalizations, and mortality associated with severe asthma?

Sources: 1. ClinicalTrial.gov; 2. Company Websites

Please contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile.: +44-(0)-752-163-8242
Mobile.: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, INDIA)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel.: 91-124-4313800

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