Press release

Hørsholm
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New data from GAP landmark trial confirms GRAZAX® prevents asthma symptoms in children

- **Treatment benefit increased over time. In the two years after treatment completion, the estimated risk of experiencing asthma symptoms nearly halved**
- **Significant improvement in allergic rhinoconjunctivitis symptoms, with benefit sustained two years after end of treatment**
- **Patients showed modified immunological responses to grass pollen, indicating inhibition of disease progression**

ALK (ALKB:DC / OMX: ALK B / AKABY / AKBLF) today presented new data from the *GRAZAX® Asthma Prevention* (GAP) trial with GRAZAX®, ALK's allergy immunotherapy tablet against grass pollen allergy.

The data, presented at the 2016 Annual Congress of the European Academy of Allergy and Clinical Immunology (EAACI) in Vienna, confirms that GRAZAX® can prevent asthma symptoms, as well as offering sustained relief from grass allergy symptoms. Moreover, immunological findings were highly supportive of the disease-modifying nature of the treatment.

The GAP trial is the largest allergy immunotherapy trial ever conducted in children and investigated the effect of GRAZAX® versus placebo on the risk of developing asthma. It involved a three-year treatment phase and a two-year follow-up phase and included 812 children aged 5–12 years at the start of treatment.

New data confirms prevention of asthma symptoms
The detailed analysis of the GAP trial results confirmed that treatment with GRAZAX® prevented asthma symptoms in children:

- GRAZAX® treatment reduced the proportion of patients with asthma symptoms[1] or use of asthma medication[2] when evaluated at end of trial, i.e., two years post treatment (Odds Ratio: 0.66, $p<0.05$)
- GRAZAX® treatment also reduced the proportion of patients experiencing asthma symptoms during the entire five year trial period (Odds Ratio: 0.71, $p<0.05$) with the effect most pronounced during the two year post-treatment period (Odds Ratio: 0.55, $p<0.05$)

In addition, the treatment effect increased with time and was apparent both during the grass pollen season and during winter.

Moreover, the GAP trial demonstrated the efficacy of GRAZAX® on grass allergic rhinoconjunctivitis in children, with benefits persisting for two years after treatment.

[1] Asthma symptoms included wheezing, chest tightness, shortness of breath or cough for more than 10 days.

[2] Asthma medication included short-acting beta-2-agonist (SABA), systemic corticosteroid, inhaled corticosteroid (ICS), leukotriene receptor antagonist (LTRA), long-acting beta-2-agonist (LABA), sustained-release theophylline, or cromolyn sodium.

Inhibition of disease progression
The trial also yielded new data, with the detailed analysis of patients' immunological response supportive of early intervention with GRAZAX®.

Two years after treatment, GRAZAX®-treated children were less IgE sensitised to grass pollen and had lower total IgE, both indicating a reduced allergic response. GRAZAX® patients also had higher grass pollen-specific IgG4 levels, indicating raised immunological tolerance. Meanwhile, the wheal size from the skin prick test using grass allergen – an indicator of the extent of an allergic reaction – was significantly smaller for the GRAZAX® group than for the placebo group.

The continued analysis of data from the GAP landmark trial follows the initial release of top-line data in January 2016. This showed that GRAZAX® treatment significantly reduced the proportion of children experiencing asthma symptoms or using asthma medication, however, there was no detectable effect in terms of time to the first diagnosis of reversible impairment of lung function and the primary endpoint of the trial was therefore not met. The safety and tolerability of GRAZAX® were both favourable and in line with previous studies, with no new or unexpected findings.

Erkka Valovirta, paediatric allergist, Adjunct Professor at the University of Turku, Finland, and principal investigator for the GAP trial, said: *"These results further enhance our understanding of allergic disease and the benefit of GRAZAX® treatment for children whose grass allergy is not well controlled by conventional therapies. For the first time, we also see that, by treating paediatric patients early enough, we can change the trajectory of their immune system development."*

He added: *"The GAP trial provides further evidence that it is possible to reprogramme the allergic immune response. It also suggests there may be benefit in offering early treatment to children in order to minimise the risk of a lifetime of respiratory disease."*

Henrik Jacobi, ALK's Executive Vice President of Research and Development, said: *"We are particularly excited about these new results. They confirm the benefit of GRAZAX® in offering sustained relief from childhood allergic rhinitis both during and after treatment. They also provide the strongest evidence yet for the early use of GRAZAX® in children with moderate-to-severe allergies and who are at risk of developing asthma."*

He continued: *"These insights also reaffirm ALK's position as the leading innovator in allergy treatment and further advance our understanding of the way the human immune system responds to specific allergens."*

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About the GAP trial

The GRAZAX® Asthma Prevention *(GAP) trial was initiated by ALK in 2009 to evaluate the efficacy and safety of the grass allergy immunotherapy tablet (GRAZAX®) in children with allergic rhinoconjunctivitis. The trial was a randomised, parallel-group, double-blind, placebo-controlled, multi-national trial investigating the effect of GRAZAX® compared to placebo on the risk of developing asthma.*

812 children (5-12 years of age) from 101 sites in 11 European countries (Austria, Denmark, Finland, France, Germany, Great Britain, Norway, Poland, Spain, Sweden and Switzerland) were included in the trial. The primary criteria for inclusion in the trial were a clinical relevant history of grass pollen allergic rhinoconjunctivitis having received symptomatic treatment during the two grass pollen seasons prior to treatment start and no medical history or signs of asthma.

The trial consisted of a screening phase, a three-year treatment phase with daily treatment, and a two-year follow-up phase. To rule out asthma before randomisation, two screening visits took place. The purpose of the first screening visit was to investigate the subject eligibility in terms of all inclusion and exclusion criteria. At the second screening visit (placed in the grass pollen season), all subjects were examined according to the pre-specified asthma diagnosis. Subjects with a suspicion of asthma or diagnosed with asthma were per definition screening failures. After the end of the grass pollen season 2010, eligible subjects were randomised to GRAZAX® (N=398) or placebo (N=414) for three consecutive years. The trial continued with double-blinded follow-up for additional two years. Independently of whether asthma was diagnosed or not during the trial, all randomised subjects were to continue in the trial for five years. Subjects experiencing asthma symptoms during the trial were instructed to call the investigator for an unscheduled visit.

The asthma evaluation included four components: asthma physical examination, asthma medical history, asthma medication history, and lung-function tests.

About the European Academy of Allergy and Clinical Immunology (EAACI) Congress

The EAACI Annual Congress is the foremost event of its kind, drawing allergy experts, policy makers and science media from all over the world. Its scientific programme and industry-sponsored sessions provide an important update on the latest research, trends and product launches in allergy treatment. Find more information at www.eaaci2016.com

About ALK

ALK is a research-driven global pharmaceutical company focusing on allergy prevention, diagnosis and treatment. ALK is a world leader in allergy immunotherapy – a treatment of the underlying cause of allergy. The company has approximately 1,900 employees with subsidiaries, production facilities and distributors worldwide. ALK has entered into partnership agreements with MSD (known as Merck (NYSE: MRK) in the USA and Canada), Torii, Abbott and Seqirus (previously bioCSL) to commercialise sublingual allergy immunotherapy tablets in North America, Japan, Russia, Australia and New Zealand, respectively. The company is headquartered in Hørsholm, Denmark, and listed on NASDAQ Copenhagen. Find more information at www.alk.net.