Press Release, January 12, 2021

Meta-analysis updated with DIAGNODE-2 results provides further support for a precision medicine approach using Diamyd®

The large scale meta-analysis, previously published in August 2020, based on data from Phase III and Phase II trials in Europe and in the United States with the type 1 diabetes vaccine Diamyd® (GAD/alum), has been updated with data from the recenly announced (Sep 2020) European Phase IIb trial DIAGNODE-2. This meta-analysis comprises data from 627 individual patients and provides further support for a positive and statistically significant dose-dependent treatment response on the preservation of endogenous insulin production in individuals with type 1 diabetes that carry the HLA DR3-DQ2 haplotype.

The meta-analysis also shows that the efficacy of Diamyd® treatment does not appear to be affected by glycemic status (HbA1c and insulin dose) at baseline and that intralymphatic administration is superior to subcutaneous administration in individuals carrying the HLA DR3-DQ2 haplotype. Positive trends were seen on all evaluated secondary effect parameters (change in HbA1c, insulin dose and insulin adjusted HbA1c) in individuals that carry the DR3-DQ2 haplotype with best support for intralymphatic administration.

"It is comforting to see that this analysis further supports our development focus on treating the genetically defined patient population by the intralymphatic administration route," said Ulf Hannelius, CEO of Diamyd Medical. "This analysis also supports the robustness of the treatment when taking into account individual differences in blood glucose and insulin dose at baseline, further strengthening the evidence base for the antigen-specific immunotherapy Diamyd. A larger well-powered trial in the genetically selected patient population should have a high likelihood of reaching both primary and secondary endpoints."

HLA and dose influence the effect of Diamyd®

The large-scale meta-analysis, announced in December 2019 and published in Diabetologia in August 2020, was updated with data from the European Phase IIb trial DIAGNODE-2. DIAGNODE-2, where the topline results were announced in September 2020, did not reach the primary endpoint in the full patient population but showed a statistically significant treatment effect in a prespecified patient population positive for the HLA DR3-DQ2 haplotype.

Encompassing data from 627 individuals with a recent diagnosis of type 1 diabetes, the meta-analysis shows, in line with the original meta-analysis and the DIAGNODE-2 results, that the HLA genotype of the individual significantly influenced the effect of Diamyd® treatment.

A statistically highly significant treatment effect on the preservation of endogenous insulin production was observed in individuals positive for HLA DR3-DQ2, a group encompassing approximately 50% of all analyzed individuals. Within this group, individuals treated with three or four doses of Diamyd® retained on average 49% ($p<0.0001$) more of their insulin production at 15 months from study start comparered to placebo treated individuals in the same group. Individuals who were simultaneously negative for the HLA DR4-DQ8 haplotype, approximately 25% of all analyzed individuals, and treated with three or four doses of Diamyd®, appeared to receive the most benefit from Diamyd®, with approximately 85% ($p<0.0001$) more retained endogenous insulin production compared to placebo treated individuals in the same group.

Lower HbA1c (-4.74 mmol/mol, approximately -9%), insulin use (-0.044 IU/kg body weight per day, approximately -9%) and insulin-adjusted HbA1c (-0.48, approximately -5.5%) were also seen in the individuals positive for HLA DR3-DQ2 treated with three or four doses of Diamyd® compared to placebo treated individuals in the same group. Statistical significance in this smaller subgroup of patients was reached for HbA1c but not the other secondary endpoints after adjusting for multiple testing.

The updated analysis also shows, in line with the original meta-analysis, that individuals negative for HLA DR3-DQ2 did not seem to benefit from Diamyd® via the treatment regimens evaluated to date, highlighting the importance of a precision medicine approach in antigen-specific immunotherapy.

Intralymphatic administration superior to subcutaneous administration
To evaluate whether intralymphatic administration is superior to subcutaneous delivery, an analysis based on data from individuals treated with three subcutaenous injections was compared to data from individuals treated with three intralymphatic injections. The analysis indicated that there is a more than a 98% probability that three intralymphatic injections of low doses of antigen provide a superior effect on preserving endogenous insulin production compared to three higher doses of subcutaneous injections in individuals positive for HLA DR3-DQ2.

The analysis also indicates that the probability of a superior effect of intralymphatic injections compared to subcutaneous injections regarding secondary effect parameters is 99% for HbA1c, 43% for insulin dose and 79% for insulin adjusted HbA1c.

No benefit of intralymphatic injections over subcutaneous was observed in individuals negative for HLA DR3-DQ2.

The results support the notion that the effect of an antigen is enhanced when directly targeting superficial lymphnodes, especially when targeting individuals that carry a specific HLA haplotype. Additionally, while previous data also shows a stronger immune response following intralymphatic injections compared to subcutaneous, the use of a lower dose decreases the individual exposure and provides manufacturing advantages compared to the higher dose used for subcutaneous administration.

The effect of Diamyd® is independent of glycemic status at baseline
It is known that individuals recently-diagnosed with type 1 diabetes can vary significantly in their glycemic status, in other words their blood glucose values and insulin dose, when entering a trial and that the effect of some disease-modifying therapies evaluated in individuals with type 1 diabetes may be influenced by this.

When the current analysis was adjusted for hese variables, no negative influence was observed on the effect of Diamyd®, indicating that the effect of Diamyd® is robust against potential differences at baseline in HbA1c and insulin dose.

About HLA
Human Leukocyte Antigen (HLA) molecules make up protein complexes that display short sequences of proteins (peptides) on professional antigen-presenting cells to other immune cells, most prominently T lymphocytes, and are critical in mediating host defense responses and immune tolerance. HLA DR3-DQ2 and DR4-DQ8 constitute sets of associated HLA gene variants and are both known to confer high risk of developing type 1 diabetes. DR3-DQ2 has previously been associated with autoimmunity to GAD while DR4-DQ8 has been associated with autoimmunity to insulin.

About intralymphatic administration
The purpose of administering directly into the lymph node is to, in a safe and simple manner, increase the effect of antigen-specific immunotherapy, a therapy based on the use of endogenous substances to reprogram the body's immune system in autoimmune diseases. Antigen-specific intralymphatic immunotherapy (AS-ILIT) differs from the traditional method where antigen is injected under the skin and then transported by immune cells to the lymph nodes. Instead, the injection is made directly into a lymph node, where the immune cells are trained regarding the need to respond to a particiular antigen From there, the cells spread through the body, including to the pancreas where the reprogrammed cells are intended to create a changed response to the autoimmune attack on the insulin-producing beta cells. Intralymphatic administration has previously been evaluated in the allergy field where it has been shown to result in a stronger clinical and immunological effect. Here, several trials have shown that very small amounts of allergen administered directly into the lymph node provide the same effect and safety as significantly higher amounts of allergen injected under the skin for a prolonged period of treatment. DIAGNODE-1, that reported top-line results in December 2019, is the first clinical trial to evaluate the administration route in an autoimmune disease. DIAGNODE-1 has paved the way for the double-blind and placebo-controlled trial DIAGNODE-2 that reported topline results in September 2020.

About Diamyd Medical
Diamyd Medical develops therapies for type 1 diabetes. The diabetes vaccine Diamyd® is an antigen-specific immunotherapy for the preservation of endogenous insulin production. Significant results have been shown in a genetically predefined patient group in a large-scale metaanalysis as well as in the Company’s European Phase IIb

trial DIAGNODE-2, where the diabetes vaccine was administered directly into a lymph node in children and young adults with recently diagnosed type 1 diabetes. A new facility for vaccine manufacturing is being set up in Umeå for the manufacture of recombinant GAD65, the active ingredient in the therapeutic diabetes vaccine Diamyd®. Diamyd Medical also develops the GABA-based investigational drug Remygen® as a therapy for regeneration of endogenous insulin production and to improve hormonal response to hypoglycaemia. An investigator-initiated Remygen® trial in patients living with type 1 diabetes for more than five years is ongoing at Uppsala University Hospital. Diamyd Medical is one of the major shareholders in the stem cell company NextCell Pharma AB.

Diamyd Medical's B-share is traded on Nasdaq First North Growth Market under the ticker DMYD B. FNCA Sweden AB is the Company's Certified Adviser; phone: +46 8-528 00 399, e-mail: info@fnca.se

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