Recombinant PBGD-conjugate: A rapid & efficent therapy for acute attacks

- **Acute Intermittent Porphyria (AIP)** is a rare metabolic liver disorder caused by reduced activity of hepatic porphobilinogen deaminase (PBGD). The dominant clinical feature is the acute neurovisceral attack induced under conditions leading to increased hepatic heme demand and associated to high production of potentially neurotoxic porphyrin precursors (ALA & PBG).

- Current Standard of Care (SoC) in AIP is **intravenous hemin administration**, which provides exogenous heme for the negative feedback inhibition of ALAS, generating a slow decrease of ALA and PBG accumulation.

- A new molecule **rhPBGD-conjugate** (CM-1349) has been developed with the following properties:
  - metabolizes serum PBG: subcutaneous administration ensures quick (minutes) and long-lasting action (five days).
  - crosses the blood brain barrier, helping to detoxify PBG metabolites accumulated in the central nervous system.
  - targeting to the liver: extends the protection against the acute attacks for one month.

**Scope of the problem**
- The intravenous administration of hemin (**Normosang**) restores hepatic heme deficiency and down-regulates stressed hepatic heme biosynthesis. However, its effect is slow and requires 3 or 4 daily infusions and chronic use is associated with side effects as headache, thrombophlebitis, hepatosiderosis and reduction of the therapeutic efficacy over time.
- Recently, Alnylam Pharmaceuticals developed a novel therapeutic for AIP based on interfering RNAi-mediated silencing of hepatic hepatic heme biosynthesis. This technology has the disadvantage that generates a durable blockage (more than 40 days) of the hepatic heme synthesis and any demand of heme will not be supplied. This could modify excretion of hydrophobic and toxic compounds and increase the sensitivity to drug and other triggering factors associated to acute attacks.

**Patient Need Addressed**
An efficient therapy for acute attacks should act in the three compartments involved in the acute attack: i) It must lead to a rapid and sustained reduction in serum PBG and ALA; ii) it must be able to cross the blood brain barrier and protect the brain from neurotoxic precursors accumulated in the plasma during the acute attack and iii) it must restore the regulatory heme pool in the liver.

**Product Profile of PBGD-conjugate:**
- A single administration of PBGD-conjugate ensures quick and long-lasting action (Fig. 1) reducing the time of onset of serum PBG accumulation and ensures protection throughout the acute attack for 1 week.
- Crosses the blood brain barrier
- Liver targeting after a single PBGD-conjugate injection extended the protection against 4 consecutive induced biochemical attacks (up to 1 month post-injection) as measured by reducing both PBG excretion (Fig. 2) and pain (Fig.3).

**Intell ectual Property**  WO2009150284. Conjugates for the administration of biologically active compounds (licensed to Digna Biotech).

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