DIGNA BIOTECH

# PBGD-conjugate:
## improving hemin efficacy in AIP treatment

- **Acute Intermittent Porphyria** (**AIP**) is a rare metabolic liver disorder resulting from mutations in the porphobilinogen deaminase (PBGD), which encodes for the third enzyme involved in the production of heme.
- Current Standard of Care (SoC) in AIP is **intravenous hemin administration**, which provides exogenous heme for the negative feedback inhibition of ALAS, decreasing further ALA and PBG production.
- Hemin treatment effect is slow and requires 3 or 4 daily infusions. Moreover, **side effects** as headache, thrombophlebitis, hepatosiderosis and decreasing sensitivity should be considered.
- A new molecule **rhPBGD-conjugate** has been developed with the following properties:
  - metabolizes serum PBG.
  - subcutaneous administration.
  - increased half-life in circulation than previous failed approaches rhPBGD (Zymenex A/S).
- **Indication:** combined administration with hemin in AIP acute attacks.

### Scope of the problem

· The SoC for acute attacks is the intravenous administration of hemin (*Normosang*), which restores hepatic heme deficiency and down-regulates stressed hepatic heme biosynthesis.

· A single dose of 250 mg of hemin contains 22.7 mg of iron, and iron overloads are therefore a potential problem in patients treated on numerous occasions. Thus, long-lasting treatment may be considered.

· Hemin administration induces the activity of the key enzyme of heme catabolism, the heme oxygenase, reducing the therapeutic efficacy of hemin administration.

· The effect of low doses of hemin (≤1 mg/kg/body weight) should be further explored as a dose that does not induce heme-oxygenase and reduce iron overload.

### Patient Need Addressed

Low dose hemin treatment combined with our novel molecule rhPBGD-conjugate may maintain the same therapeutic efficacy reducing the time of onset of serum PBG and decreasing the risk of hepatosiderosis and other side effects as the induction of heme-oxigenase.

### Competitive Landscape

New products under development may compete with *Normosang* and reduce its market share:

· Gene therapy, replaces liver transplantation in chronic acute porphyria.

· ALAS-siRNA, represses hepatic ALAS1 but did not restore regulatory heme pool and has no effect on heme precursors accumulated in the serum.

### Product Profile

· The treatment with PBGD-conjugated replacement could be combined with hemin administration increasing the efficacy in the treatment of acute attacks and reducing the elevated toxic precursors accumulation in serum during the first 48 hours post-hemin treatment.

· PBGD-conjugated properties:

· longer half-life in circulation (21.4 fold) than rhPBGD. (Fig. 1) and a single administration ensures protection throughout the acute attack.

· subcutaneous administration ensures quick and long-lasting action (Fig. 2) and may be administered during the time of receipt and preparation of hemin.

· crosses the blood brain barrier (Fig. 3).

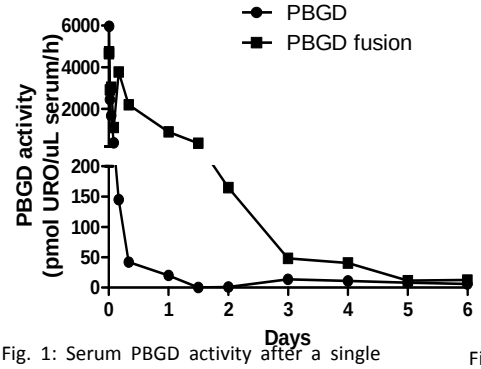


Fig. 1: Serum PBGD activity after a single intravenous administration of 50 µg of rhPBGD-conjugate/mice.

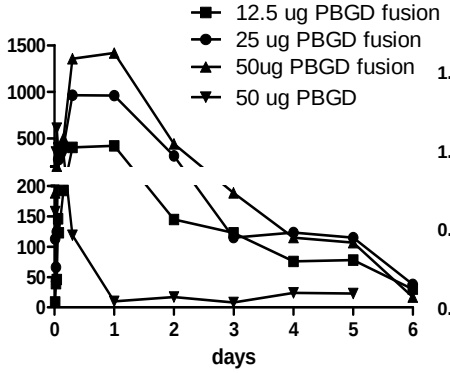


Fig. 2: Serum PBGD activity after single sub-cutaneous administration of rhPBGD or rhPBGD-conjugate.

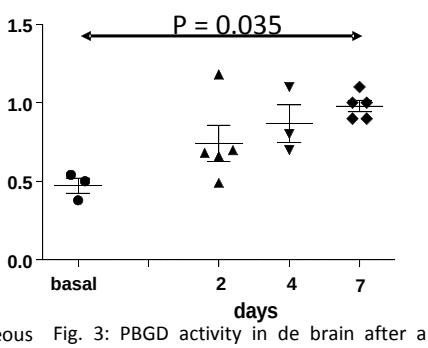


Fig. 3: PBGD activity in de brain after a single administration of 50 ug of rhPBGD conjugate/mice.

### Intellectual Property

Patent application pending in US, EP, and other countries.

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