Double-blind, Placebo- and Active Comparator-Controlled Study in Healthy Males to Assess the Safety, Pharmacokinetics and Pharmacodynamics of 2B3-201

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS). It damages oligodendroglia and axons and may cause paralysis, sensory disturbances, incoordination, visual impairment, and alterations in autonomic and sexual function. Relapses are characterized by periods of acute neurological impairment caused by blood-brain barrier (BBB) breakdown, lymphocyte infiltration in CNS and neuro-inflammation.

MS relapses are most commonly treated with pulse therapy with high dose (1 g) intravenous methylprednisolone (Solu-Medrol®, MP) for 3 to 5 consecutive days (3-5 g total) and is associated with cumbersome side effects. These are acute CNS side effects like mood changes, insomnia, anxiety and even psychosis and other side effects like hyperglycemia, weight gain, and bone loss. Furthermore, the desired anti-inflammatory effect of a single injection of methylprednisolone has a relatively short duration, requiring daily injections for at least 3 consecutive days.

2B3-201 (glutathione PEGylated liposomal methylprednisolone) was designed to enhance the slow and sustained delivery of MP to plasma and brain based on the patented G-Technology®, a novel brain drug delivery technology.

AIM

Primary objective

- Safety, tolerability and pharmacokinetics of 2B3-201, in comparison to MP and placebo

Secondary objectives

- Pharmacodynamic effects of 2B3-201 on a range of CNS functions and hypothalamic-pituitary-adrenal (HPA) axis inhibition, in comparison to MP and placebo
- Effects of 2B3-201 on fasting blood glucose, osteocalcin and lymphocyte count

METHODS

Double-blind, placebo- and active-comparator controlled, cross-over study.

Endpoints

- Safety: Electrocardiography (ECG), blood chemistry and hematology, urinalysis, vital signs, adverse events (AEs)
- Pharmacokinetics
- Neurocart test battery
- Blood pharmacodynamics: Lymphocyte count, fasting blood glucose, ACTH, osteocalcin

2B3-201 and MP cohort and dose algorithm

	Cohort 1	Cohort 2	Cohort 3
2B3-201	150 mg	300 mg	450 mg
MP	1000 mg	300 mg	1000 mg

RESULTS

- 2B3-201 had a similar maximum effect on decrease of ACTH and on increase of fasting glucose as MP in the first 30 hours (Figure 1 and 2, respectively).
- At 7 days the effects on ACTH and fasting glucose in all groups had returned back to baseline.
- Similar results were observed for osteocalcin.

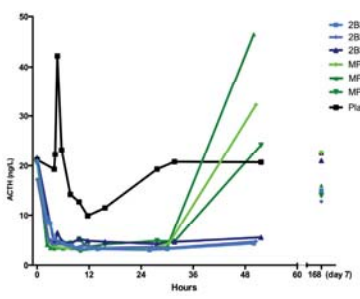

Figure 1: effect on ACTH

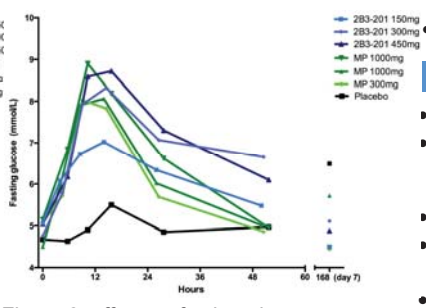

Figure 2: effect on fasting glucose

RESULTS

Safety and tolerability:

- 2B3-201 was shown to be generally well-tolerated and no serious adverse events occurred.
- All 2B3-201 AEs were graded as non serious, mild in intensity and of short duration. 2B3-201 was tested at full therapeutic potential where MP (1 g) was given once instead of on 3-5 consecutive days (3-5 g total).
- Infusion related reactions, also present in other liposomal products, occurred at start of infusion and included symptoms like dyspnea, tachypnea, chest discomfort and back pain. All were mild and transient, disappeared upon infusion speed adjustment and in general did not reoccur after re-start of infusion.
- The NeuroCart test battery results showed no clear effects on CNS functions and no significant differences between 2B3-201 and MP.

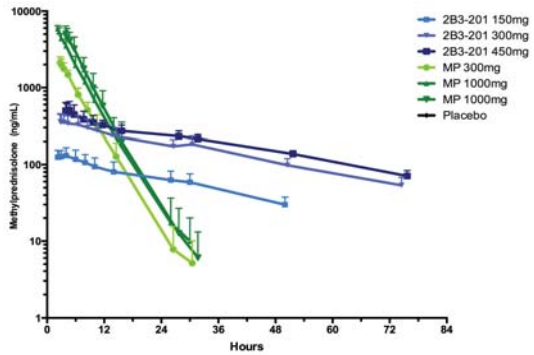

Figure 3: Plasma MP concentration time curves following a single intravenous injection of 2B3-201, MP or placebo

- 2B3-201 is stable and is confined mainly to the vascular fluid volume and the clearance of methylprednisolone from the blood is dependent upon the liposomal carrier. Increase in plasma exposure was dose-proportional.
- 2B3-201 had a tenfold longer plasma elimination half life (t ½ 24 – 29 h) than MP (t ½ 2.4 – 2.7 h) (Figure 3).

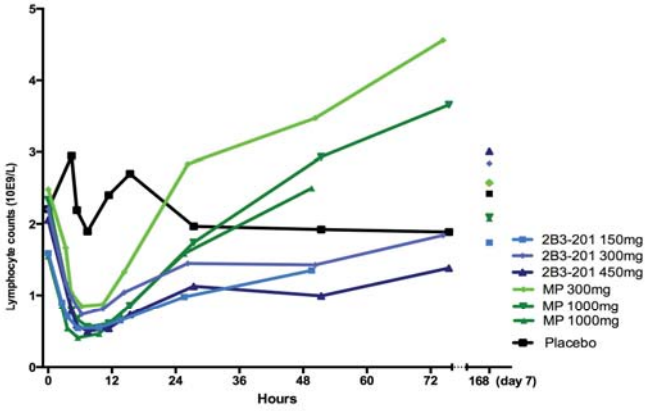

Figure 4: effects on lymphocyte count

- 2B3-201 and MP resulted in a maximum decrease in lymphocyte count in the first 6-12 hours after administration (Figure 4)
- At day 7 the lymphocyte counts of all groups had returned back to baseline.

CONCLUSIONS

- A single administration of 2B3-201 is generally well tolerated at doses up to 450 mg.
- No difference between 2B3-201 and MP in CNS and systemic adverse events. 2B3-201 was tested at full therapeutic potential where MP (1 g) was given once instead of on 3-5 consecutive days (3-5 g total).
- Mild and transient infusion related reactions are the most common AE (78%).
- 2B3-201 has a tenfold longer plasma elimination half-life (t ½ 24 – 29 h) than MP (t ½ 2.4 – 2.7 h).
- Single dose of 2B3-201 has an immunosuppressive effect lasting for at least 3 days (72 hours).

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