Glatiramer Acetate Depot (Extended-Release) Phase IIa Study in Patients with Primary Progressive Multiple Sclerosis: Safety and Efficacy

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Background

Primary progressive multiple sclerosis (PPMS) is characterized by continuous neurological decline from symptom onset without early relapses. Glatiramer Acetate (GA) Depot consists of extended-release microspheres containing GA, administered intramuscularly (IM) once every 28 days. In a large placebo-controlled phase III trial in relapsing forms of MS (RMS), GA Depot reduced clinical and radiological activity compared with placebo, with significantly fewer injections than subcutaneous GA. It is hypothesized that GA Depot the IM administration route together with the slow-release formulation may also benefit primary progressive MS (PPMS) patients.

Objective

To assess the safety and efficacy of GA Depot in PPMS patients.

Design/Methods

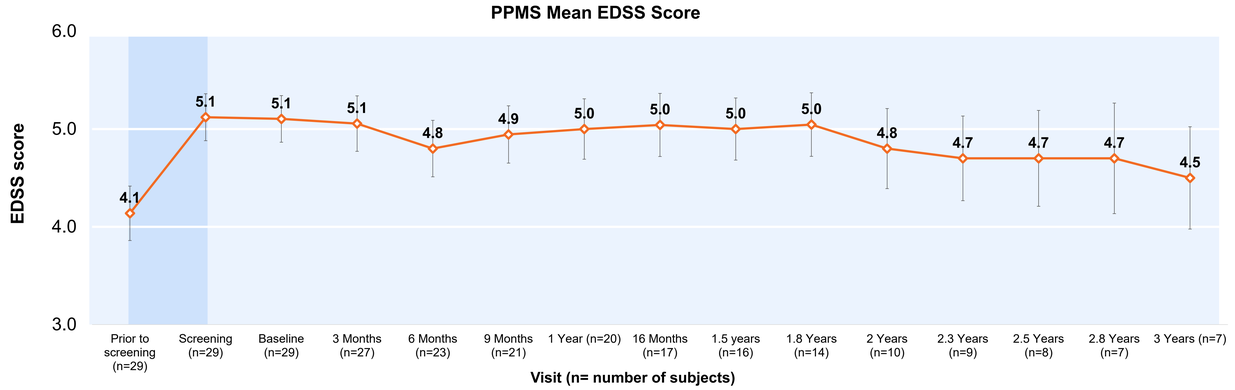
Open-label phase IIa clinical trial in which patients received 25 mg or 40 mg IM GA Depot for up to 3 years (40 mg enrolled first). Key eligibility criteria included: age 18-65, PPMS diagnosis, baseline EDSS 2.0 - 6.5, and EDSS increase in a rate of ≥1 point EDSS in the prior year. Safety was monitored through adverse events (AEs) and laboratory tests. Efficacy was assessed using EDSS, 9-Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW) and MRI volumetric analysis. The analysis also evaluated the proportion of patients with No Evidence of Progression (NEP), a composite score defined as the absence of worsening in EDSS (12-week Confirmed Disability Progression (CDP)), T25FW and 9HPT.

Disclosures: Dr. Ron Milo, Dr. Anda Eilam, Prof. Adi Vaknin-Dambinsky, Dr. Mark Hellmann and Dr. Alla Shifrin, served as site Principal Investigators .Prof. Arnon Karni held a dual role as the study Coordinating PI and site PI. Dr. Hadar Kolb is an external consultant to Mapi Pharma. Dr. Laura Popper, Dr. Nadav Bleich Kimelman, Dr. Shai Rubnov (co-inventor of GA Depot), Ornit Almog and Uri Danon are employed by Mapi Pharma. Ehud Marom, co-inventor of GA Depot, is the founder and CEO of Mapi Pharma.

Results

Thirty PPMS patients (20 received 40 mg, 10 received 25 mg) were treated for up to 3 years. This analysis includes data from patients with different treatment durations due to early study termination. Mean EDSS score remained stable (5.1 at baseline, 4.5 at three years), see Figure 1. Only one patient experienced 12-week CDP, resulting in a CDP-free rate of 96.6%. Additionally, 89.7% of patients, maintained stability in the 9HPT and 79.3% in the T25FW test. Notably, 69.0% exhibited NEP (70.0% in the 25 mg dose group and 68.4% in the 40 mg group), see Table 1. Whole brain volume change from baseline was -0.78% at 1-year (n=19), -1.57% at 2-years (n=8), and -1.99% at 3-years (n=6), see Table 2. Cortical volume change from baseline was -2.09% at 1-year, -2.02% at 2-years, and -1.96% at 3-years. Most AEs (81.6%) were mild: most common (ISRs, asthenia, fever). AEs and injection site reactions (ISRs) rates were numerically lower with 25 mg than with 40 mg (0.19 vs. 0.49 and 0.005 vs. 0.15), respectively. No unexpected AEs were reported. Three SAEs occurred in the 40 mg dose, two unrelated and one possibly related to the study drug. No SAEs occurred in the 25 mg dose.

Figure 1: Mean EDSS Score By Visit – All Subjects



Mean EDSS score is presented prior to study start, baseline and every 3 months thereafter. Data presented as mean ± SE.

Table 1: No Evidence of Progression (NEP)

	GA Depot 40 mg	GA Depot 25 mg	All Subjects
No 12 weeks CDP	19/19 (100%)	9/10 (90%)	28/29 (96.6%)
No 12 weeks confirmed progression in T25FW of ≥20%	14/19 (73.7%)	9/10 (90%)	23/29 (79.3%)
No 12 weeks confirmed progression in 9HPT of ≥20%	17/19 (89.5%)	9/10 (90%)	26/29 (89.7%)
No Evidence of Progression (NEP)	**13/19 (68.4%)**	**7/10 (70%)**	**20/29 (69%)**

Table 2: MRI Volumetric Analysis

Percent of whole brain volume change from baseline (%)	GA Depot 40 mg (n)	GA Depot 25 mg (n)	All subjects (n)
V16 week 52	-0.90 (11)	-0.62 (8)	-0.78 (19)
Visit 28 week 100	-1.39 (6)	-2.09 (2)	-1.57 (8)
EOT visit 40 week 148	-2.14 (5)	-1.25 (1)	-1.99 (6)

Percent of Neocortical volume change from baseline (%)	GA Depot 40 mg (n)	GA Depot 25 mg (n)	All subjects (n)
V16 week 52	-2.57 (11)	-1.33 (7)	-2.09 (18)
Visit 28 week 100	-3.03 (6)	1.02 (2)	-2.02 (8)
EOT visit 40 week 148	-3.30 (5)	4.74 (1)	-1.96 (6)

Conclusions

Treatment with GA Depot was safe and associated with stable clinical disability and radiological outcomes. The 25 mg dose showed improved safety and tolerability compared with the 40 mg dose, while maintaining similar efficacy. These findings support further investigation in a large, multicenter, double-blind phase III study.

Study Supported by: Mapi Pharma Ltd