INTERIM ANALYSIS OF A PHASE I CLINICAL TRIAL INVESTIGATING INTRATHECAL ADMINISTRATION OF MESENCHYMAL STEM CELL-NEURAL PROGENITORS IN MULTIPLE SCLEROSIS

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INTRODUCTION

- There is a critical unmet need to develop therapies that enable CNS repair in multiple sclerosis (MS) patients.
- MSC-NPs (mesenchymal stem cell-derived neural progenitors) represent a neural subpopulation of bone marrow-derived MSCs with reduced mesodermal pluripotency and minimized risk of ectopic differentiation.
- In preclinical studies in mouse experimental autoimmune encephalomyelitis (EAE), we established that three doses of MSC-NPs delivered intrathecally (IT) resulted in improved neurological function associated with suppression of local inflammatory response and trophic support for damaged cells at lesion sites.
- The initial clinical experience with autologous MSC-NPs in six MS patients also supported the dosing, safety, feasibility, and potential efficacy of this therapeutic approach.
- In August 2013, the FDA approved the IND application to conduct a phase I safety and tolerability study of autologous intrathecal MSC-NPs in MS.
- The novelty of this cell-based therapeutic approach to treat MS includes:
  - The use of autologous neural progenitors (MSC-NP)
  - Intrathecal route of administration
  - Multiple dosing regimen
  - Use of freshly harvested cells

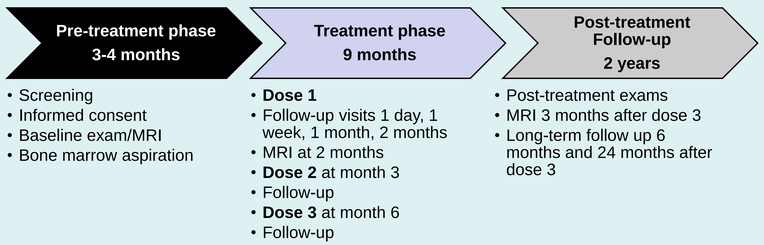
OBJECTIVE

To evaluate safety, tolerability, and preliminary efficacy of intrathecal administrations of autologous MSC-NPs in multiple sclerosis.

DESIGN AND METHODS

Enrollment included 20 MS patients with established disability (EDSS range 3.5 to 8.5) and relatively stable disease as evidenced by less than 1.0 point change in EDSS in the last year, and stable MRI disease burden with no enhancing lesions in the last six months. Autologous MSC-NPs were derived from bone marrow aspirates as previously described and subjected to pre-administration quality testing including sterility, purity, identity, and chromosome stability testing. MSC-NPs were freshly harvested from cell culture and administered intrathecally in three doses of up to 10 million cells per injection, spaced three months apart. Interim safety analysis included adverse event assessments. Interim efficacy analysis included patient self-reporting (QOL questionnaire and physician consults) and neurological exam conducted at screening and at frequent intervals throughout treatment phase. Other clinical parameters such as EDSS, MSFC, MRI, evoked potentials, and urodynamics testing will be conducted during post-treatment followup and thus are not reported here.

Figure 1. Clinical Protocol



RESULTS

Table 1. Patient demographics and dosing

	Patient Code	AGE/ Gender	MS SUBTYPE	EDSS	DISEASE DURATION	DOSE Treatment #1	DOSE Treatment #2	DOSE Treatment #3
1	137JK	35/M	PPMS	8.5	13	10.0×10^6	10.0×10^6	7.8×10^6
2	078ER	34/F	SPMS	7	12	7.0×10^6	9.6×10^6	10.0×10^6
3	092RK	65/M	SPMS	4	14	9.6×10^6	10.0×10^6	
4	121JM	63/F	SPMS	6.5	32	10.0×10^6	9.5×10^6	
5	153RG	27/F	SPMS	5	10	10.0×10^6	10.0×10^6	
6	039JK	61/F	SPMS	7.5	32	9.3×10^6	9.0×10^6	
7	149VG	39/F	SPMS	6	16	7.4×10^6	10.0×10^6	
8	120LL	45/F	SPMS	5.5	11	9.6×10^6		
9	127NH	50/F	SPMS	6	19	8.9×10^6		
10	129AT	52/F	SPMS	7.5	32			
11	168CL	50/M	PPMS	7	10			
12	173KR	51/F	SPMS	6	25			
13	098.2JM	56/M	PPMS	6.5	22			
14	169PR	54/F	SPMS	4.5	13			
15	161SR	59/M	SPMS	3.5	18			
16	165SG	37/F	PPMS	6.5	14			
17	160OC	55/F	SPMS	6	18			
18	190CR	58/M	SPMS	4.5	17			
19	202DM	35/F	SPMS	6.5	20			
20	102CS	52/F	SPMS	6.5	27			
		49 (27-65)	16 SPMS 4 PPMS	6.1 (3.5-8.5)	19 (10-32)	9.1×10^6	9.7×10^6	8.9×10^6

Table 2. Adverse Events

	Patient ID	Treatment 1	Treatment 2	Treatment 3
1	137JK	none	none	none
2	078ER	none	Transient headache	none
3	092RK	none	Transient fever	
4	121JM	Transient headache	Transient headache	
5	153RG	Transient headache	Transient headache	
6	039JK	Spinal headache	Transient headache	
7	149VG	none	none	
8	120LL	Transient headache		
9	127NH	Transient headache		

RESULTS

Table 3. Clinical Results

	Patient ID	Clinical Results
1	137JK	Improved muscle strength in left upper limb, with decrease in EDSS from 8.5 to 8.
2	078ER	No clinical worsening or improvement noted.
3	092RK	Better ambulation, improved endurance, and increased lower limb muscle strength.
4	121JM	Marked bladder function improvement.
5	153RG	Bladder function improvement.
6	039JK	At baseline patient was 0/5 in lower limbs, densely plegic. Movement in right lower limb now 1-2/5 in three muscle groups. Improved bladder function.
7	149VG	Improved endurance and balance. Ambulation transitioned from constant use of cane to occasional use of cane. Improved bladder function.
8	120LL	No clinical worsening or improvement noted.
9	127NH	Improved bladder/bowel function and increased balance and motor function.

Table 4. Summary of Interim Analysis of Phase I Clinical Trial

Summary of safety and tolerability	
# of MS patients who completed 1st MSC-NP administration	**9**
# of MS patients who completed 3 MSC-NP administrations	**2** out of **9**
Incidence of significant adverse events	**0** out of **9**
Incidence of minor adverse events (transient headache and/or fever <100°F)	**6** out of **9** (headache) **1** out of **9** (fever)
Summary of efficacy	
# of patients for which follow-up data is available (self reporting, neuro exam)	**9**
Incidence of clinical worsening in any category	**0** out of **9**
Incidence of QOL improvement (patient self-reporting)	**6** out of **9**
Incidence of improved bladder function (patient self-reporting)	**5** out of **8**
Incidence of cerebellar improvement (cerebellar score)	**0** out of **1**
Incidence of motor strength improvement (neuro exam)	**5** out of **9**

CONCLUSIONS

- The MSC-NP trial is the first of its kind to test intrathecal administration of neural progenitors as a regenerative therapy for MS.
- In the short-term analysis the treatment appears safe and well tolerated.
- Initial efficacy trends are encouraging and suggest possible benefit of this treatment.

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