Identification of Neurorestorative Biomarkers in Patients With Relapsing Forms of Multiple Sclerosis

Adam Ziemann[1]

[1]AbbVie Inc., North Chicago, Illinois, USA

Presented at the International Society for CNS Clinical Trials and Methodology (ISCTM) 2019 • Washington, DC, USA • 19 – 21 February 2019

INTRODUCTION

- The multiple sclerosis (MS) research community requires identification of fluid and imaging biomarkers to accelerate trial execution and refine patient selection.
- MS patients have an urgent need for therapies that can reverse neurologic disability; none currently exist.
- MS patients exhibit upregulation of repulsive guidance molecule A (RGMa), a molecule that inhibits axonal growth and myelination, oligodendroglial regeneration, and functional recovery after trauma or inflammation.[1,2]
- Elezanumab is a fully humanized monoclonal antibody directed against RGMa that promotes axon regeneration, neuroprotection, remyelination, and immune modulation in several MS-relevant preclinical models.[3,4]
- Several previously identified neurorestoration biomarkers have the potential to respond to elezanumab.

OBJECTIVE

- The purpose of this study was to evaluate the effects of multiple elezanumab doses on potential MS neurorestoration biomarkers.

METHODS

STUDY DESIGN

- This study was a phase 1, double-blind, placebo-controlled, randomized, escalating multiple-dose study that enrolled patients at 3 sites in the United States.
- The study lasted 29 weeks and consisted of the following periods:
  - Screening (4 weeks),
  - Treatment (12 weeks), and
  - Follow-up (13 weeks).
- Patients received 4 monthly doses. Three dose levels were studied serially. Each dose level was intended to consist of 5 active and 2 placebo patients. At each dose level, patients were randomized to receive either active treatment or placebo.
- Patients off immunotherapy (n=8) or receiving the following concomitant immunomodulatory medications were allowed: beta-interferon (n=1), glatiramer acetate (n=6), or oral immunomodulatory MS therapies (n=5).

TREATMENT

- Elezanumab doses were given intravenously every 4 weeks for a total of 4 doses, with a loading dose of double the maintenance dose given on day 1.
- Maintenance elezanumab doses were 150 mg, 600 mg, and 1800 mg in groups 1, 2, and 3, respectively. The placebo group received a matching volume intravenous (IV) infusion over a 2-hour period.

ASSESSMENTS

Safety

- The number and percentage of patients reporting treatment-emergent adverse events (TEAEs) were recorded. Clinical laboratory tests, vital sign measurements, neurological and physical examinations, and electrocardiography were conducted and assessed.

Pharmacokinetics and Biomarker Analysis

- Cerebral spinal fluid (CSF) was collected by lumbar puncture on days –1 and 113 to determine elezanumab exposure, CSF interactions with RGMa, and effects on potentially relevant markers such as CSF IL-10 and neurofilament light chain (NF-L), using validated assays.

Additional Assessments

- Expanded Disability Status Scale (EDSS) scores were calculated at screening, days –1, 29, 57, 85, 176, and on subject discontinuation.
- Conventional magnetic resonance imaging (MRI) variables included:
  - Number of new gadolinium (Gd+) T1 lesions across day 57 and day 113, and
  - Number and volume of new or newly enlarging T2 hyperintense lesions at day 113.

RESULTS

- Baseline demographics and disease characteristics of the 20 enrolled patients are shown in **Table 1**.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic		Patients, n (%)			
			Elezanumab		
		Placebo n=5	150 mg n=5	600 mg n=5	1800 mg n=5
Age, years	Mean (SD)	50.4 (9.40)	48.4 (8.96)	47.8 (11.08)	45.2 (9.09)
Sex	Male	1 (20)	2 (40)	1 (20)	4 (80)
	Female	4 (80)	3 (60)	4 (80)	1 (20)
Race	Black	1 (20)	—	3 (60)	3 (60)
	Multirace	1 (20)	—	—	—
	White	3 (60)	5 (100)	2 (40)	2 (40)
Multiple sclerosis type	Secondary progressive	—	1 (20)	—	1 (20)
	Relapsing-remitting	5 (100)	4 (80)	5 (100)	4 (80)
Relapses in the past year, n	Mean (SD)	0.2 (0.45)	0.8 (1.30)	0.2 (0.45)	0.4 (0.89)
	Range	0 – 1	0 – 3	0 – 1	0 – 2
Baseline EDSS Score	Mean (SD)	3.4 (1.08)	2.3 (1.10)	3.9 (1.64)	4.8 (1.10)
	Median (range)	4.0 (1.5 – 4.0)	2.0 (1.0 – 4.0)	4.0 (1.5 – 6.0)	4.0 (4.0 – 6.0)

SAFETY

- The most common TEAE reported was headache (26.7% of all patients; **Table 2**).
- None of the TEAEs led to discontinuation of elezanumab.

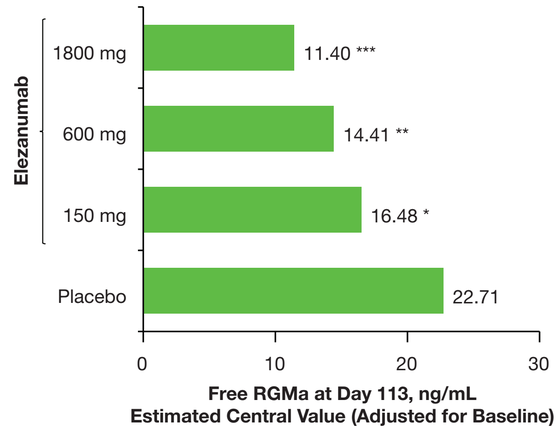
Table 2. Overall Treatment-Emergent Adverse Events

Preferred Term	Patients, n (%)			
		Elezanumab		
	Placebo n=5	150 mg n=5	600 mg n=5	1800 mg n=5
Any TEAEs	4 (80)	5 (100)	3 (60)	5 (100)
Blood and Lymphatic System Disorders				
Iron deficiency anemia	1 (20)	0	0	0
Gastrointestinal Disorders				
Gastroesophageal reflux disease	0	0	0	1 (20)
General Disorders and Administration				
Injury associated with device	0	0	0	1 (20)
Infections				
Bacterial vaginosis	1 (20)	0	0	0
Pyuria	0	1 (20)	0	0
Upper respiratory tract infection	1 (20)	0	0	0
Urinary tract infection	1 (20)	0	1 (20)	1 (20)
Viral upper respiratory tract infection	0	1 (20)	0	0
Injury, Poisoning, and Procedural Complications				
Infusion-related reaction	1 (20)	0	0	1 (20)
Muscle strain	0	1 (20)	0	0
Post lumbar puncture syndrome	1 (20)	1 (20)	1 (20)	1 (20)
Skin abrasion	0	0	0	1 (20)
Musculoskeletal and Connective Tissue Disorders				
Back pain	0	0	0	1 (20)
Limb discomfort	0	0	0	1 (20)
Pain in extremity	1 (20)	1 (20)	0	0
Pain in jaw	1 (20)	0	0	0
Nervous System Disorders				
Headache	1 (20)	2 (40)	1 (20)	1 (20)
Mental impairment	0	1 (20)	0	0
Multiple sclerosis relapse	2 (40)	0	1 (20)	0
Presyncope	1 (20)	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	0	1 (20)	0	0
Rhinorrhea	0	0	0	1 (20)
Skin and Subcutaneous Tissue Disorders				
Rash	0	1 (20)	0	0
Scab	0	0	0	1 (20)
Vascular Disorders				
Hot Flush	1 (20)	0	0	0

TEAE = treatment-emergent adverse event.

- For CSF evaluations, there were 13 subjects with RGMa concentration measurements at both baseline and at day 113. On day 113, free soluble RGMa decreased with increasing doses of elezanumab (**Figure 1**).

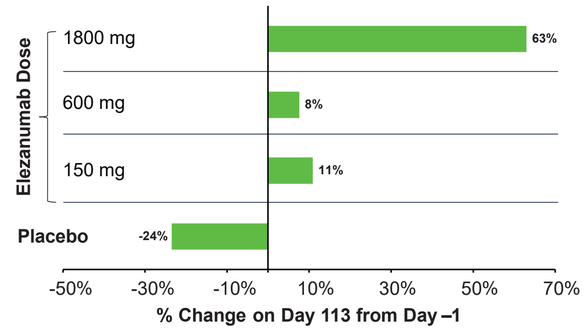
Figure 1. Free RGMa in Cerebral Spinal Fluid



*P < .05; **P < .001; ***P < .0001.
Estimates and tests were done in an analysis of covariance (4 groups) on log transformed data. Tests were 1 sided for free RGMa, all t tests with 8 degrees of freedom. Estimated central value is the back transformation of the adjusted mean from the analysis of covariance for the transformed data.
RGMa = repulsive guidance molecule A.

- Interleukin-10 also increased in a dose-dependent manner in the CSF following elezanumab administration compared with placebo (**Figure 2**).

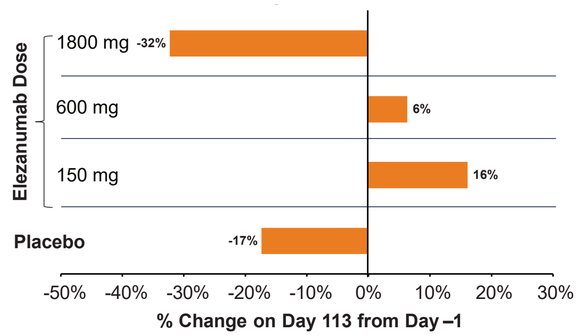
Figure 2. Percent Change from Baseline in CSF IL-10 Levels by Dosing Group



Lower limit of quantitation = 0.0210 pg/mL; limit of detection = 0.0038 pg/mL; CSF = cerebral spinal fluid; IL-10 = interleukin 10.

- NF-L levels were modulated in CSF after elezanumab treatment, depending on the dose (**Figure 3**).

Figure 3. Percent Change from Baseline in CSF NF-L Levels by Dosing Group



NF-L = neurofilament light chain.

- From baseline through the end of the follow-up period, most patients did not change by more than 1 EDSS point following treatment, and no drug or dose-dependent improvement or worsening was observed, as anticipated given the study size and duration.
- There were only 1 or 2 patients in each group who experienced an increase in the number of new Gd+ T1 lesions or new or newly enlarging hyperintense T2 lesions (**Tables 3** and **4**).

Table 3. New Gd+ T1 Lesions

Treatment Group	Patients, n	Number of Patients with Gd+ T1 Lesions at:	
		Screening	Day 113
Placebo	4	1	1
150 mg	5	0	1
600 mg	5	1	1
1800 mg	4	1	1

Table 4. New or Newly Enlarging Hyperintense T2 Lesions

Treatment Group	Patients, n	Number of Patients with New or Newly Enlarging Hyperintense T2 Lesions at Day 113
Placebo	4	1
150 mg	5	2
600 mg	5	1
1800 mg	4	2

CONCLUSIONS

- IL-10 and NF-L levels were assessed.
- Evidence of target binding was demonstrated through reduction in soluble RGMa.
- No effect on traditional MRI was demonstrated, though myelin and axonal-specific imaging may be informative in subsequent development.
- These data will aide phase 2 interim and exploratory efficacy analyses.

REFERENCES

1. Demicheva E, et al. *Cell Reports*. 2015;10:1887–1898.
2. Muramatsu R, et al. *Nat Med*. 2011;17:488–495.
3. Cree BAC, et al. *Mult Scler J*. 2016;22(S3):400–705. Poster #1209.
4. Mueller BK, et al. *Mult Scler J*. 2015;21(S11):76–653. Poster #582.

DISCLOSURES & ACKNOWLEDGEMENTS

This study was funded by AbbVie, Inc. AbbVie participated in the study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving this poster for presentation. **AZ** is an employee of AbbVie and owns stock and/or stock options.

Scan QR code to download an electronic version of this poster.

QR code expiration: February 28, 2019