Long-term safety and efficacy of MYOBLOC® (rimabotulinumtoxinB) in the treatment of adult sialorrhea

Stuart Isaacson[1], Mark Lew[2], Khashayar Dashtipour,[3] Dilip Chary,[4] Thomas Clinch,[4] Rajesh Pahwa[5]

[1]Parkinson's Disease and Movement Disorder Center, Boca Raton, FL, USA, [2]USC School of Medicine, Los Angeles, CA, USA, [3]Loma Linda University Health System, Schools of Medicine, Loma Linda, CA, USA, [4]US WorldMeds, LLC, Louisville, KY, USA, [5]University of Kansas Medical Center, Kansas City, KS, USA.

INTRODUCTION

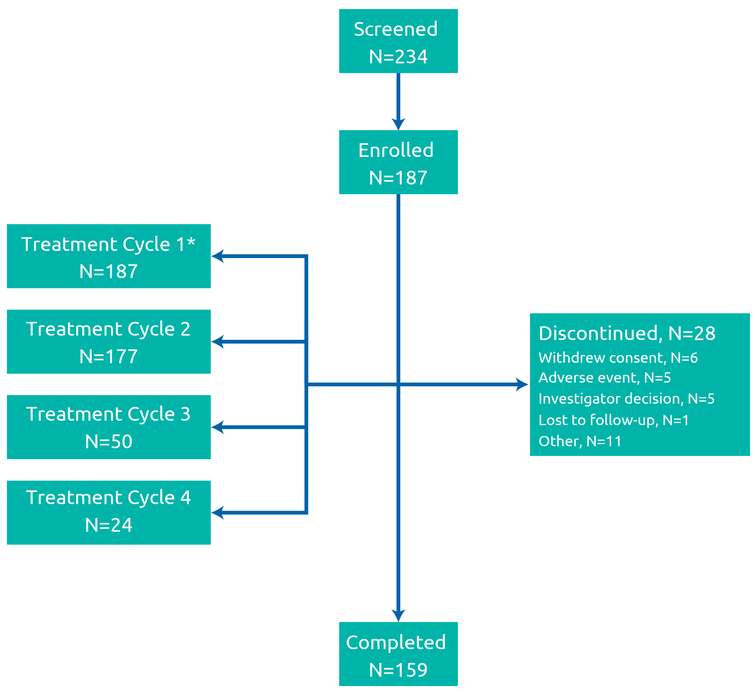
- Sialorrhea (drooling) is a common and often problematic symptom for many patients with neurologic disorders such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and stroke.[1-3]
- When present, sialorrhea often causes social embarrassment, perioral irritation, soiled clothing, swallowing impairment, and poor oral hygiene. Left untreated, pooling of saliva in the oropharynx can lead to respiratory infection and aspiration.[3]
- Local injections of botulinum toxin (BoNT) into the parotid and submandibular salivary glands inhibit saliva production by blocking the release of acetylcholine at the parasympathetic terminals.[4]
- This Phase III study was conducted to assess the safety, tolerability and effectiveness of repeated MYOBLOC (rimabotulinumtoxinB) injections in adults with troublesome sialorrhea over a period of 1 year.

METHODS

- The Optimyst study (NCT02610868) was a Phase III, multicenter, open-label, outpatient study conducted at 40 sites in the US, Ukraine, and Belarus.
- Adult subjects (18-85 years) seeking treatment for troublesome sialorrhea secondary to PD, ALS, stroke and other disorders were recruited. Patients had to have a minimum unstimulated salivary flow rate (USFR) of 0.2 g/min and a minimum Drooling Frequency and Severity Scale (DFSS) score of 4 to be included in the trial.[5]
- All subjects received MYOBLOC (3500 U) on Day 1. Treatment was repeated when the subject returned to clinical baseline status (investigator judgment), with a treatment interval of 11-15 weeks.
- Dose reductions to 2500 U were permitted from cycle 2 for intolerability.

RESULTS

Patient disposition



*Optimyst had rolling admission and was stopped once enough subjects completed the study to meet FDA safety database requirements. Thus, not all patients entered study Treatment Cycles 3 and 4.

Baseline characteristics

Parameter	MYOBLOC 3500 U (N=187)
Male gender; N(%)	129 (69.0)
Age (years); mean (SD)	64.1 (12.2)
Categories; N(%)	
18-64	85 (45.5)
65-74	64 (34.2)
75+	38 (20.3)
Diagnosis	
PD	123 (65.8)
ALS	26 (13.9)
Stroke	7 (3.7)
Cancer	5 (2.7)
Cerebral palsy	4 (2.1)
TBI	3 (1.6)
Other	19 (10.1)
Previous treatment for sialorrhea; N(%)	49 (26.2)
Years since sialorrhea diagnosis; mean (SD)	3.2 (5.1)

Treatment exposure

Parameter	MYOBLOC 3500 U (N=187)
Duration between injections (weeks), mean (SD)	13.4 (1.0)
Duration of exposure (weeks); mean (SD)	31.1 (10.4)
Number of injections; mean (SD)	2.3 (0.8)
Categories; N(%)	
1 injection	10 (5.3)
2 injections	127 (67.9)
3 injections	26 (13.9)
4 injections	24 (12.8)

Safety reporting

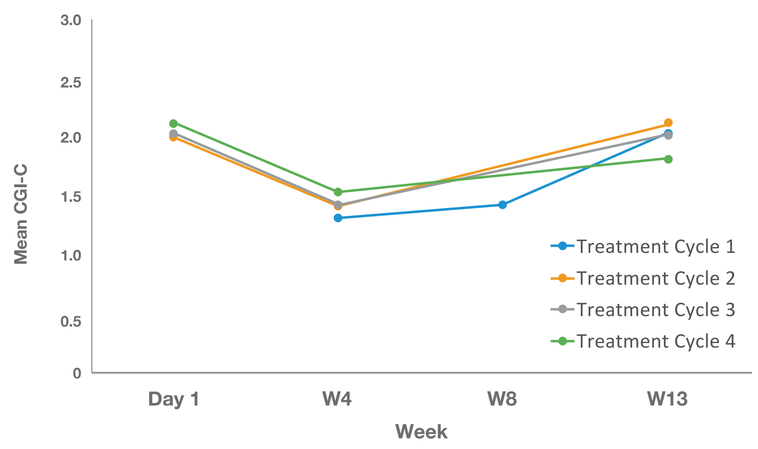
Adverse event	Cycle 1 (N=187)	Cycle 2 (N=177)	Cycle 3 (N=50)	Cycle 4 (N=24)
Total AE	77 (41.2)	70 (39.5)	20 (40.0)	7 (29.2)
Treatment-related AE	42 (22.5)	26 (14.7)	4 (8.0)	2 (8.3)
AE leading to discontinuation	4 (2.1)*	6 (3.4)	2 (4.0)	1 (4.2)
Serious AE	7 (3.7)	14 (7.9)	3 (6.0)	2 (8.3)
Death**	1 (0.5)	4 (2.3)	2 (4.0)	1 (4.2)
Most common AEs (≥5%)				
Dry Mouth	29 (15.5)	10 (5.6)	1 (2.0)	-
Dental caries#	29 (15.5)	17 (9.6)	6 (12.0)	2 (8.3)
Dysphagia	13 (7.0)	-	-	-
Nasopharyngitis	6 (3.2)	-	-	-
Fall	6 (3.2)	3 (1.7)	1 (2.0)	-
Constipation	-	10 (5.6)	-	-

*Only 1 patient discontinued the study due to dry mouth. **8 patients died during the study. All deaths were considered unrelated to study treatment (neoplasm progression N=3, ALS N=3, urosepsis N=1, community acquired pneumonia, N=1). # Subjects underwent scheduled dental exams by a dentist.

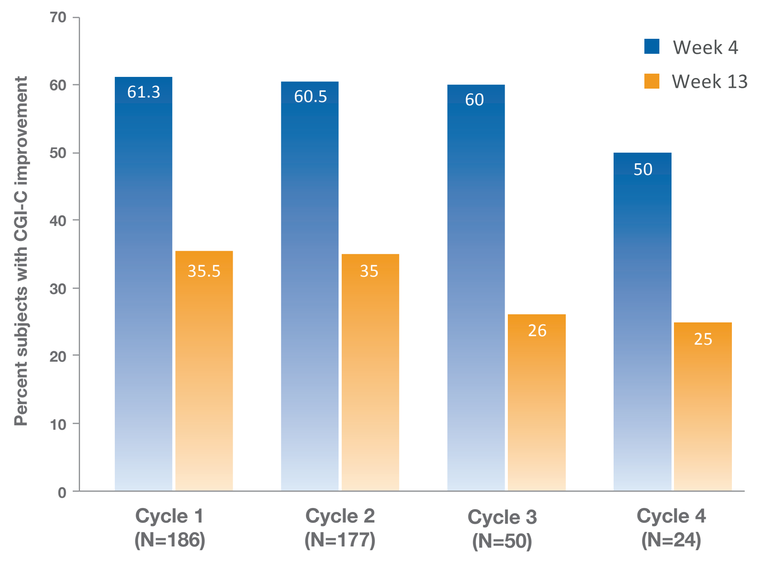
Treatment with MYOBLOC significantly reduced unstimulated salivary flow rate (USFR)

Clinical Global Impression of Change (CGI-C) (a) mean scores (b) percent subjects with improvement

(a)



(b)



1 =Very Much Improved, 2 = Much Improved, 3 = Minimally Improved, 4 = No Change, 5 = Minimally Worse, 6 = Much Worse, and 7 = Very Much Worse. Week 8 assessment performed for Treatment Cycle 1 only.

CONCLUSIONS

- In this Phase III open-label study, long-term, repeat treatment with MYOBLOC for the management of adult sialorrhea was generally well-tolerated.
- Both coprimary measures (objective USFR and subjective CGI-C) were significant at the Week 4 endpoint ($p < 0.0001$)
- The most common adverse events were dry mouth and dental carries. Dry mouth was an expected therapeutic event and only led to discontinuation in one patient.
- The efficacy of repeat treatment was maintained for up to 1 year.

References

1. Newall AR, Orser R, Hunt M. The control of oral secretions in bulbar ALS/MND. J Neurol Sci 1996;139 Suppl:43-44.
2. Kalf JG, de Swart BJ, Borm GF, Bloem BR, Munneke M. Prevalence and definition of drooling in Parkinson's disease: a systematic review. J Neurol 2009;256(9):1391-1396.
3. Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. Am Fam Physician 2004;69(11):2628-2634.
4. Bhidayasiri R, Truong DD. Expanding use of botulinum toxin. J Neurol Sci 2005;235 (1-2):1-9.
5. Wang SL, Zhao ZT, Li J, Zhu XZ, Dong H, Zhang YG. Investigation of the clinical value of total saliva flow rates. Arch Oral Biol 1998;43(1):39-43.

Disclosures

Stuart Isaacson, Khashayar Dashtipour and Rajesh Pahwa were all investigators in the Optimyst study and report fees for consultancy from US WorldMeds LLC. Mark Lew reports fees for consultancy from US WorldMeds, LLC. Dilip Chary and Thomas Clinch are employees of US WorldMeds LLC.

US WorldMeds

PRESENTED AT TOXINS 2019: BASIC SCIENCE AND CLINICAL ASPECTS OF BOTULINUM AND OTHER NEUROTOXINS, 16-19 JANUARY, 2019, COPENHAGEN, DENMARK.