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RESEARCH ARTICLE



Long-term safety and efficacy of MBA-P01 for the treatment of glabellar lines: results from a multicenter, repeated-dose, open-label extension study

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ABSTRACT

Purpose: Following the introduction of new type of botulinum toxin (MBA-P01), a recent phase 3 study demonstrated that MBA-P01 showed comparable efficacy and safety to onabotulinumtoxin A for reducing glabellar lines. The primary objective of this study was to evaluate the long-term safety of repeated MBA-P01 administration for the treatment of glabellar lines.

Materials and methods: This multicenter, single-group, repeated-dose, long-term open-label extension study evaluated repeated treatment with MBA-P01 (20U, five treatments over 16 months), with posttreatment evaluation performed up to 52 weeks.

Results: Based on the safety assessment results, no specific irreversible adverse reactions were associated with the safety profile of MBA-P01. Repeated treatment with MBA-P01 was effective for a treatment duration of 3–5 months.

Conclusion: In conclusion, multiple cycles of treatment of glabellar lines with MBA-P01 at a dose of 20U were well tolerated.

Clinical trial registration information: This study is registered in ClinicalTrials.gov (NCT05321979).

ARTICLE HISTORY

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KEYWORDS

Glabellar lines; botulinum toxin; new botulinum toxin (MBA-P01); long-term safety; open-label extension study

Introduction

Facial expressions convey information about one's emotional state and are among the most important factors in interpersonal communications (1–3). However, with age, undesired facial lines may develop owing to repeated contractures of the underlying musculature (4, 5). For example, repeated contraction of the corrugator supercilii, orbicularis oculi, procerus, and depressor supercilii muscles results in glabellar lines, which are cosmetically undesirable and one of the most common causes of negative impressions regarding esthetics (6).

Botulinum toxin Type A (BoNT-A) inhibits the activity of the underlying musculature and is one of the most effective treatments for glabellar lines (7). Although BoNT-A treatment is effective and well tolerated, repeated treatments are required approximately every 3–4 months to maintain this effect. Thus, it is important to thoroughly evaluate the long-term safety and tolerability of BoNT-A in clinical trials to reflect its actual use in clinical practice.

Recently, a new BoNT-A, MBA-P01, was introduced by Numeco Co. Ltd. (Seoul, Korea). MBA-P01 is a *Clostridium* botulinum toxin type A (900 kDa) that consists of the same molecular components as onabotulinumtoxin A (ONA-BoNT-A; Supplementary Table 1) (8). In a recent phase 3 study, MBA-P01 showed efficacy and safety comparable to those of ONA-BoNT-A for reducing glabellar lines. As BoNT-A is generally used repeatedly, the final component of the clinical trial was a large, open-label extension (OLE) study. This

clinical trial was designed to evaluate safety data from an OLE study of suitable participants enrolled after satisfactorily completing the MBA-P01 phase 3 study. The primary objective of this study was to evaluate the long-term safety of repeated administration of MBA-P01 for treatment of glabellar lines.

Materials and methods

Study design and ethics approval

This multicenter, single-group, repeated-dose, long-term open-label extension study evaluated repeated treatment with MBA-P01 (20U, 5 treatments over 16 months); posttreatment evaluation was performed up to 52 weeks. This study was conducted in four different tertiary university hospitals in Republic of Korea. The study was conducted in accordance with the principles of good clinical practice and regulatory requirements. This study was approved by the institutional review board at each center and registered at Clinical Trials. gov (Clinical trial number: NCT05321979).

Participant selection

In this multicenter, OLE trial, 254 participants aged ≥19 years or older who had completed the MBA-P01 phase 3 clinical trial

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(MT14-KR20GBL3090) were included except for those who met the following exclusion criteria:

1. Those planning on receiving treatment with other BoNT-As or filler.
2. Pregnancy or lactation; those who did not agree to contraception through the methods permitted in this clinical trial during the clinical trial period.
3. Those who participated in other clinical trials within 30 days prior to screening and received clinical trial drugs, medical devices, or underwent operations.
4. Any other conditions that could place the participant at risk or jeopardize the objectives of the study.

Detailed inclusion and exclusion criteria for the phase 3 clinical trial are described in [Supplementary Table 2](#).

Treatment

Participants were eligible to receive up to five treatments over a period of 16 months. They were eligible for retreatment ≥ 84 days after the treatment, if they had facial wrinkle scale (FWS) scores of ≥ 2 (moderate) for glabellar lines at maximum glabellar frown. The glabellar line assessment score (FWS) is a validated scoring method, with 0 indicating no wrinkles, 1 indicating mild wrinkles, 2 indicating moderate wrinkles, and 3 indicating severe wrinkles ([Supplementary Table 3](#)).

The total dose of MBA-P01 was fixed (20U) in equally divided amounts at five injection points ([Figure 1](#)): one injection into the procerus muscle, and two injections into the corrugator supercilii muscle (lateral and medial parts) on both the right and left sides.

Outcome measures

The primary outcome measure was safety, specifically incidence, severity, and relationship of MBA-P01 with treatment-emergent adverse events (TEAEs) and serious TEAEs during each treatment and in the overall study.

Safety evaluations were performed every 4 weeks for 52 weeks. Adverse events (AEs), laboratory tests, vital signs, and pregnancy tests were performed after the administration of the

investigational drug. Neutralizing antibody formation tests were also conducted after treatment using a three-step approach to assess the presence of anti-BoNT-A antibodies. This includes screening assay based on a RadioImmunoPrecipitation Assay (RIPA), followed by confirmatory assay based on the competitive, and lastly, the *in vivo* Mouse Protection Assay.

AEs were defined as unintended or harmful signs, symptoms, or diseases. All AEs were coded using the Medical Dictionary for Regulatory Activities software (version 24.0). The investigators evaluated all AEs for their relationship with MBA-P01 (definite, probable, possible, or unrelated) and severity (mild, moderate, or severe). Injection sites were evaluated for edema or erythema, and patients were asked about burning, stinging, or itching at the injection site.

Efficacy assessments/outcomes

Each cycle was defined from the MBA-P01 injection until the next injection. The response rate at frowning was defined as $a \geq 2$ FWS score improvement, with an FWS score of 0 or 1. The response rate at rest was defined as an FWS score of 0 or 1. FWS is a validated scoring method, with 0 indicating no wrinkles, 1 indicating mild wrinkles, 2 indicating moderate wrinkles, and 3 indicating severe wrinkles ([Supplementary Table 3](#)).

1. The response rates at weeks 4, 8, and 12 from baseline in each cycle, based on the investigator's live assessment at frowning and rest.
2. The response rates at weeks 4, 8, and 12 from baseline, based on the participants' improvement assessment at frowning and rest.
3. The participants' satisfaction rates at weeks 4, 8, and 12 from baseline, based on their satisfaction grade. Scores ≥ 5 were considered 'satisfaction'.

Duration of the response defined as the retreatment interval.

Statistical analysis and data presentation

All statistical analyses were performed using SAS[®] version 9.4 (SAS Institute, Cary, NC, USA). A *p*-value < 0.05 was considered significant.

Safety assessment was performed on the safety analysis set (SAS), with an exploratory analysis performed on the exploratory analysis set. Continuous variables were presented as the number of participants, mean, and standard deviation, and median, minimum, and maximum values. Categorical variables were presented as frequencies and percentages. Two-sided 95% confidence intervals were used.

For safety assessment, AEs, including TEAEs, injection site adverse reactions, adverse drug reactions (ADRs), serious AEs (SAEs), and serious ADRs (SADRs), number of test participants, incidence rate, and number of occurrences, were recorded. The TEAEs, ADRs, SAEs, and SADRs were coded according to the System Organ Class (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0; the number of participants, incidence rates, and number of occurrences for each coded adverse reaction were noted.

Results

Patient distribution and characteristics

In the phase 3 trial, 157 and 155 participants in the MBA-P01 and ONA-BoNT-A groups, respectively, completed the study. Among them,

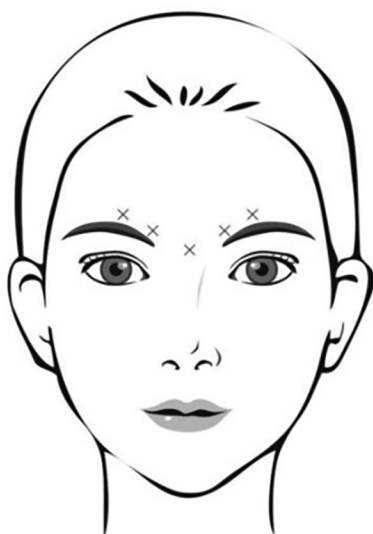


Figure 1. Administration sites of the test product. (a) Middle of the corrugators supercilii muscles. (b) Medial corrugators supercilii muscle. (c) Procerus muscle.

130 and 123 patients from the MBA-P01 and ONA-BoNT-A group, respectively, consented to enrollment in the OLE study ($n=253$). Among the 253 enrolled participants, 240 (94.86%) completed the study. The number of participants who completed each cycle are summarized in [Supplementary Figure 1](#) and [Supplementary Table 4](#).

Among the enrolled participants, three did not receive treatment due to the continuous effect of BoNT-A treatment in the phase 3 trial. One participant withdrew consent before the start of the trial. After excluding these three participants, 249 participants were included in the SAS. The exploratory analysis set included 248 of the 249 participants in the SAS; one participant was excluded because none of the efficacy evaluation variables were measured.

Patient characteristics are summarized in [Table 1](#). The mean age $\pm$ standard deviation was 46.08 ± 9.40 years, and most patients were female ($n=195$, 78.31%).

Exposure to MPA-P01 treatment

For the entire study, the 249 participants received 14,260 units of MPA-P01. The mean number of MPA-P01 treatments administered over the 16-month study period was 2.86.

Safety outcomes

Total AEs included all AEs in the phase 3 trial, as well as in the extension study, that occurred after receiving MBA-P01. As summarized in [Table 2](#), the incidence of TEAEs after the investigational drug administration was 58.63% (146/249, 326 cases), the incidence of ADRs was 2.81% (7/249, 8 cases), the incidence of SAEs was 2.01% (5/249, 6 cases), and the incidence of AEs of special interest (AESIs) was 2.41% (6/249, 7 cases); no SADRs were observed.

On classifying TEAEs by treatment cycle, the incidence of TEAEs in each cycle was 30.12% (75/249, 118 cases) in cycle 1, 30.70% (70/228, 99 cases) in cycle 2, 31.01% (49/158, 75 cases) in cycle 3, 29.85% (20/67, 29 cases) in cycle 4, and 27.27% (3/11, 5 cases) in cycle 5. The incidence of TEAEs was similar for each cycle ([Table 3](#) and [Figure 2](#)).

On classification based on SOC, the most common TEAEs were infections and infestations (30.52% [76/249, 87 cases]), skin and subcutaneous tissue disorders (23.69% [59/249, 91 cases]), and poisoning and procedural complications (6.02% [15/249, 17 cases]) ([Supplementary Table 5](#)). According to the PT criteria, the most common TEAEs were COVID-19 (26.51% [66/249, 66 cases]), acne (21.69% [54/249, 75 cases]), and headache (3.61% [9/249, 10 cases]).

ADRs included eyelid sensory disorders (1.20% [3/249, 3 cases]), injection site reactions (0.8% [2/249, 2 cases]), pruritus (0.4% [1/249, 2 cases]), and erythema (0.4% [1/249, 1 case]). Eyelid sensory disorders were considered AESIs ([Table 4](#)).

Table 1. Demographic and baseline characteristics (safety set).

		Total N=249
Age (years)	N	249
	Mean $\pm$ SD	46.08 $\pm$ 9.40
	Median	45.00
	Min, Max	22.00, 66.00
Age group	19–29 years	12 (4.82%)
	30–39 years	48 (19.28%)
	40–49 years	103 (41.37%)
	50–59 years	63 (25.30%)
	~60 years	23 (9.24%)
Sex	Male	54 (21.69%)
	Female	195 (78.31%)

N, number of safety set; n, number of participants in the category; Min, minimum; Max, maximum; SD, standard deviation.

Most TEAEs with a recorded severity were mild ($n=132$, 53.01%). Only 10 cases (4.02%) of moderate TEAEs and four cases (1.61%) of severe TEAEs were identified. Serious AEs included lumbar spinal stenosis, cholangitis, appendicitis, and osteoarthritis. None of the moderate or severe TEAEs were considered treatment-related.

Ocular AEs

Only three cases of TEAEs categorized as eye disorders have been reported, all of which involved eyelid ptosis ([Table 5](#)). Two cases occurred in Cycle 1 and one in Cycle 3. Treatment-related eyelid ptosis occurred at a frequency of 0.08% (3 events among 3565 injections). All treatment-related ptosis events resolved spontaneously, and none resulted in withdrawal.

Summary of the antibody test

All 246 participants, including six who dropped out of the study, were included in the antibody test ([Table 6](#)). Several participants tested positive in the screening and confirmation assays, but none of the participants showed positive results in the mouse protection assay. Thus, we conclude that the antibody was not detected after the repeated administration of MPA-P01.

Efficacy outcomes

Based on investigator assessments, the overall median duration of response was 143 (range, 50–512) days in cycle 1, 137 (range, 52–340) days in cycle 2, 114 (range, 51–229) days in cycle 3, 96 (range, 51–176) days in cycle 4, and 77 (range, 50–91) days in cycle 5 ([Figure 3](#)).

The results of the response rate at maximum frowning, as assessed by the investigator at 4, 8, and 12 weeks after treatment in each cycle, are shown in [Table 7](#). Overall, the response rate was highest in cycle 1 and slowly decreased over cycle 5. Similar results were seen in the response rate and grade 0 or 1 FWS at rest as assessed by the investigator, as well as the results assessed by the participants. The results of the satisfaction rates answered

Table 2. Summary of adverse events in the entire study (safety set).

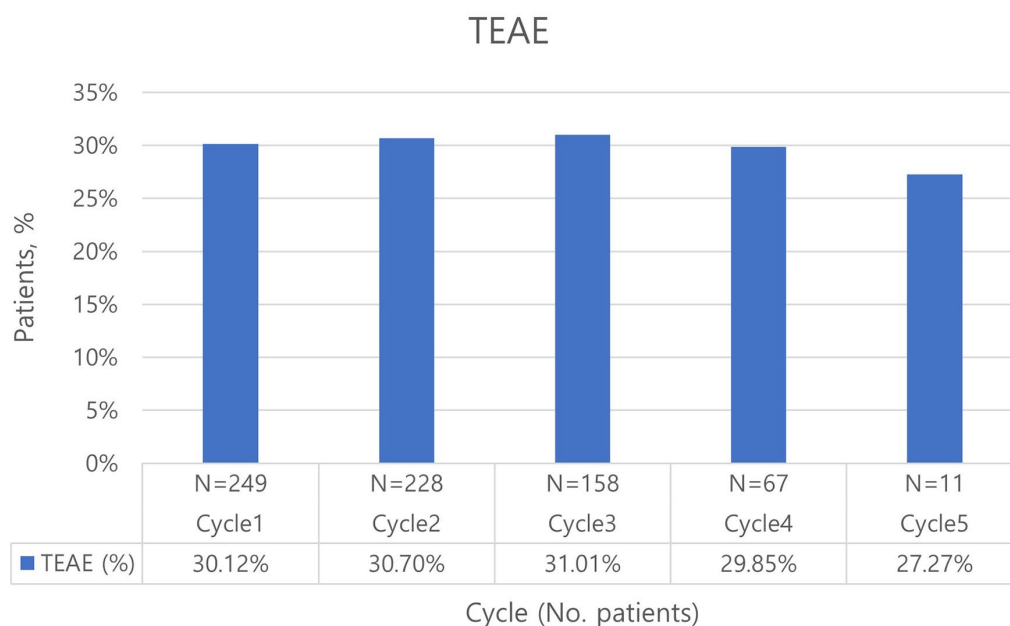
	MBA-P01 N=249 n (%) [case]
TEAEs	146 (58.63%) [326]
ADRs	7 (2.81%) [8]
Eyelid sensory disorder	3 (1.20%) [3]
Injection site reaction	2 (0.80%) [2]
Erythema	1 (0.40%) [1]
Pruritus	1 (0.40%) [2]
SAEs	5 (2.01%) [6]
Arthralgia	1 (0.40%) [1]
Lumbar spinal stenosis	1 (0.40%) [1]
Cholangitis	1 (0.40%) [1]
Appendicitis	1 (0.40%) [1]
Ligament sprain	1 (0.40%) [1]
Ovarian cyst	1 (0.40%) [1]
SADRs	0 (0.00%) [0]
AESIs	6 (2.41%) [7]
Eyelid sensory disorder	3 (1.20%) [3]
Ocular myasthenia	1 (0.40%) [1]
Bell's palsy	1 (0.40%) [1]
Facial paresis	1 (0.40%) [1]
Constipation	1 (0.40%) [1]

ADR, adverse drug reaction; AESI, adverse event of special interest; N, number of safety set; n, number of participants with at least one event in the category; SADR, serious adverse drug reaction; SAEs, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3. Summary of adverse events in each cycle (safety set).

Item	Cycle 1 N=249 n (%) [case]	Cycle 2 N=228 n (%) [case]	Cycle 3 N=158 n (%) [case]	Cycle 4 N=67 n (%) [case]	Cycle 5 N=11 n (%) [case]
TEAE	75 (30.12%) [118]	70 (30.70%) [99]	49 (31.01%) [75]	20 (29.85%) [29]	3 (27.27%) [5]
ADR	5 (2.01%) [5]	0 (0.00%) [0]	1 (0.63%) [1]	1 (1.49%) [2]	0 (0.00%) [0]
	Eyelid sensory disorder 2 (0.80%), [2]		Eyelid sensory disorder 1 (0.63%), [1]	Pruritus 1 (1.49%), [2]	
	Injection site reaction 2 (0.80%), [2]				
SAE	Erythema 1 (0.40%), [1]	1 (0.44%) [1]	3 (1.90%) [4]	0 (0.00%) [0]	0 (0.00%) [0]
	1 (0.40%) [1]		1 (0.63%), [1]		
	Ovarian cyst 1 (0.40%), [1]	Appendicitis 1 (0.44%), [1]	Arthralgia 1 (0.63%), [1]		
			Lumbar spinal stenosis 1 (0.63%), [1]		
			Cholangitis 1 (0.63%), [1]		
			Ligament sprain 1 (0.63%), [1]		
SADR	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]	0 (0.00%) [0]
AESI	4 (1.61%) [5]	0 (0.00%) [0]	2 (1.27%) [2]	0 (0.00%) [0]	0 (0.00%) [0]
	Eyelid sensory disorder 2 (0.80%), [2]		Eyelid sensory disorder 1 (0.63%), [1]		
	Ocular myasthenia 1 (0.40%), [1]		Facial paresis 1 (0.63%), [1]		
	Constipation 1 (0.40%), [1]				
	Bell's palsy 1 (0.40%), [1]				

ADR, adverse drug reaction; AESI, adverse event of special interest; N, number of safety set; n, number of participants with at least one event in the category; SADR, serious adverse drug reaction; SAEs, serious adverse event; TEAE, treatment-emergent adverse event.

**Figure 2.** Incidence of TEAEs per cycle.**Table 4.** Adverse drug reactions in entire study (safety set).

SOC PT	MBA-P01 N=249 n (%) [case]
Total	7 (2.81%) [8]
Eye disorders	3 (1.20%) [3]
Eyelid sensory disorder	3 (1.20%) [3]
General disorders and administration site conditions	2 (0.80%) [2]
Injection site reaction	2 (0.80%) [2]
Skin and subcutaneous tissue disorders	2 (0.80%) [3]
Erythema	1 (0.40%) [1]
Pruritus	1 (0.40%) [2]

Adverse events were coded using MedDRA version 24.0.

N, number of participants in a specific group; n, number of participants in the specific category; SOC, System Organ Class; PT, preferred term; [case], number of cases.

by the participants at 4, 8, and 12 weeks after treatment in each cycle are shown in Figure 4.

Retreatment interval

The retreatment interval was defined as the period from administration of the investigational drug to the next administration. The median intervals were 162, 143, 148, and 67 days for cycles 1, 2, 3, and 4, respectively (Figure 5).

Treatment duration

The duration of treatment effect was defined as the period from the day of drug administration to the point at which the glabellar

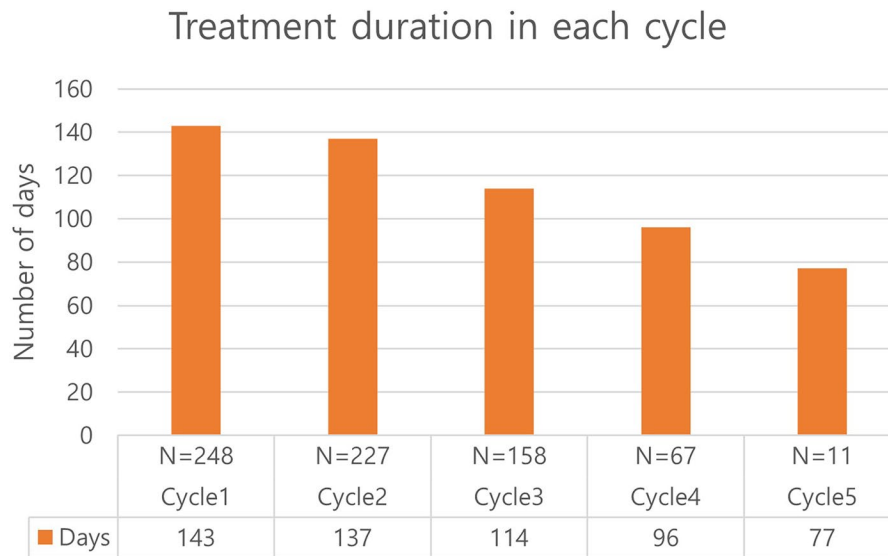
Table 5. Adverse events of special interest related with MBA-P01 (safety set).

PT	SOC	IP administration date	Start date	End date	Outcome	Severity	Causality	Action taken with study treatment	Other action taken	SAE
Eyelid sensory disorder	Eye disorders	2022-03-31 (Cycle 1)	2022-04-11	2022-05-10	Recovered/resolved	Mild	Possible	Dose not changed	N.A	N
Eyelid sensory disorder	Eye disorders	2021-11-10 (Cycle 1)	2021-11-24	2021-12-15	Recovered/resolved	Mild	Possible	N.A	N.A	N
Eyelid sensory disorder	Eye disorders	2022-12-27 (Cycle 3)	2023-01-04	2023-02-03	Recovered/resolved	Mild	Certain	N.A	N.A	N

N.A, not applicable.

Table 6. Summary of antibody test.

Assay (number of samples)	Result	
	Potential positive	Negative
Screening assay (samples)	28	218
Confirmatory assay (samples)	15	13
Mouse protection assay (samples)	0	15

**Figure 3.** Treatment duration (days) in each cycle.**Table 7.** Response rate at maximum frown* assessed by investigator at 4, 8, and 12 weeks after treatment in each cycle (exploratory efficacy set).

Week	Responders	Cycle 1 n (%) N=248	Cycle 2 n (%) N=227	Cycle 3 n (%) N=158	Cycle 4 n (%) N=67	Cycle 5 n (%) N=11
Week 4	n	248	227	158	67	11
	Improved	195 (78.63%)	181 (79.74%)	98 (62.03%)	38 (56.72%)	6 (54.55%)
	Not Improved	53 (21.37%)	46 (20.26%)	60 (37.97%)	29 (43.28%)	5 (45.45%)
	95% CI	(73.00–83.56)	(73.91–84.77)	(53.97–69.62)	(44.04–68.78)	(23.38–83.25)
	3	0 (0.00%)	1 (0.44%)	1 (0.63%)	2 (2.99%)	0 (0.00%)
	2	9 (3.63%)	11 (4.85%)	7 (4.43%)	4 (5.97%)	0 (0.00%)
Week 8	1	68 (27.42%)	55 (24.23%)	59 (37.34%)	30 (44.78%)	7 (63.64%)
	0	171 (68.95%)	160 (70.48%)	91 (57.59%)	31 (46.27%)	4 (36.36%)
	n	247	226	157	67	11
	Improved	147 (59.51%)	111 (49.12%)	43 (27.39%)	13 (19.40%)	1 (9.09%)
	Not Improved	100 (40.49%)	115 (50.88%)	114 (72.61%)	54 (80.60%)	10 (90.91%)
	95% CI	(53.11–65.69)	(42.43–55.83)	(20.58–35.07)	(10.76–30.89)	(0.23–41.28)
Week 12	3	3 (1.21%)	5 (2.21%)	1 (0.64%)	3 (4.48%)	0 (0.00%)
	2	21 (8.50%)	18 (7.96%)	23 (14.65%)	15 (22.39%)	3 (27.27%)
	1	110 (44.53%)	114 (50.44%)	100 (63.69%)	39 (58.21%)	8 (72.73%)
	0	113 (45.75%)	89 (39.38%)	33 (21.02%)	10 (14.93%)	0 (0.00%)
	n	234	195	144	58	11
	Improved	95 (40.60%)	51 (26.15%)	15 (10.42%)	6 (10.34%)	1 (9.09%)
	Not Improved	139 (59.40%)	144 (73.85%)	129 (89.58%)	52 (89.66%)	10 (90.91%)
	95% CI	(34.25–47.19)	(20.14–32.91)	(5.95–16.60)	(3.89–21.17)	(0.23–41.28)
	3	8 (3.42%)	2 (1.03%)	5 (3.47%)	6 (10.34%)	1 (9.09%)
	2	35 (14.96%)	22 (11.28%)	33 (22.92%)	20 (34.48%)	9 (81.82%)
	1	130 (55.56%)	138 (70.77%)	97 (67.36%)	28 (48.28%)	1 (9.09%)
	0	61 (26.07%)	33 (16.92%)	9 (6.25%)	4 (6.90%)	0 (0.00%)

N, number of exploratory efficacy set; n, number of participants in the respective category; FWS, facial wrinkles scale; Week, (week 4, week 8, week 12); 95% CI: 95% confidence interval of improvement rate.

*The response rate at frowning was defined as $a \geq 2$ FWS score improvement, with an FWS score of 0 or 1. FWS is a validated scoring method, with 0 indicating no wrinkles, 1 indicating mild wrinkles, 2 indicating moderate wrinkles, and 3 indicating severe wrinkles and is defined in [Supplementary Table 3](#).

Subject Satisfaction Responder Rate

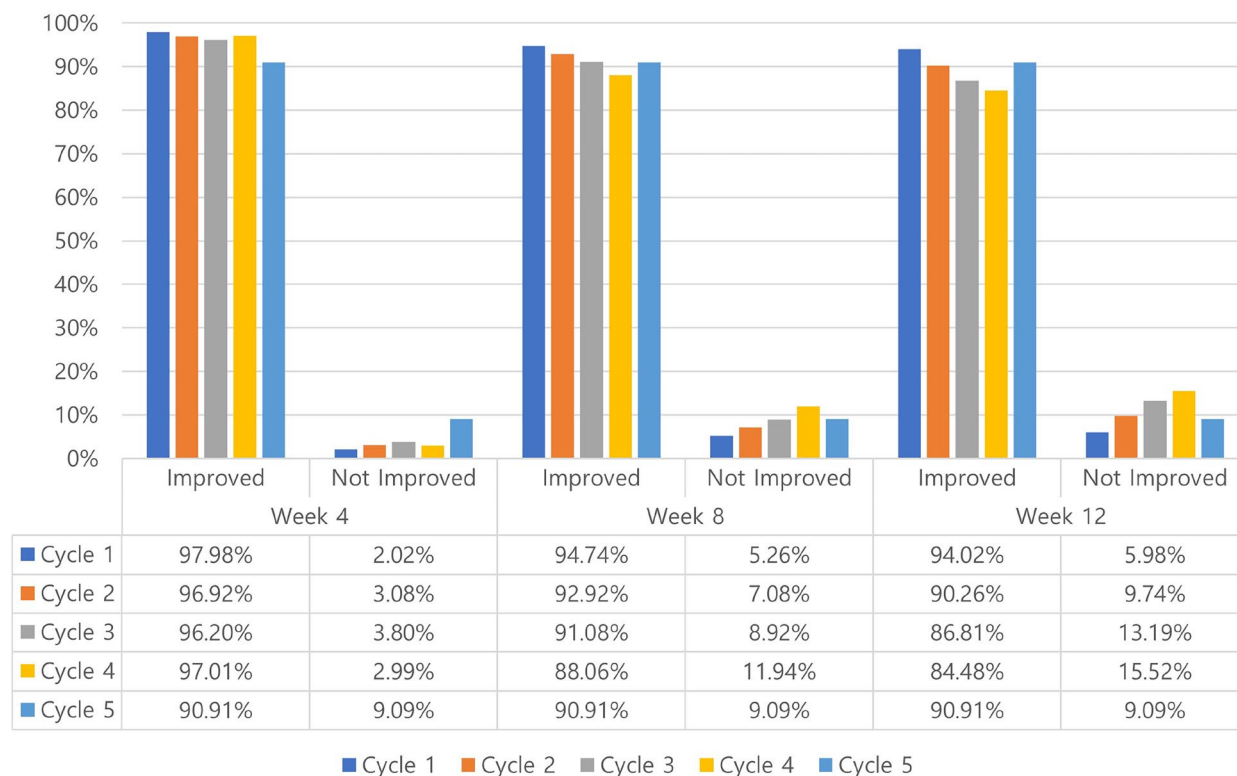


Figure 4. Participants' satisfaction rate at weeks 4, 8 and 12 in each cycle. Scores ≥ 5 were considered 'satisfied'.

Retreatment interval

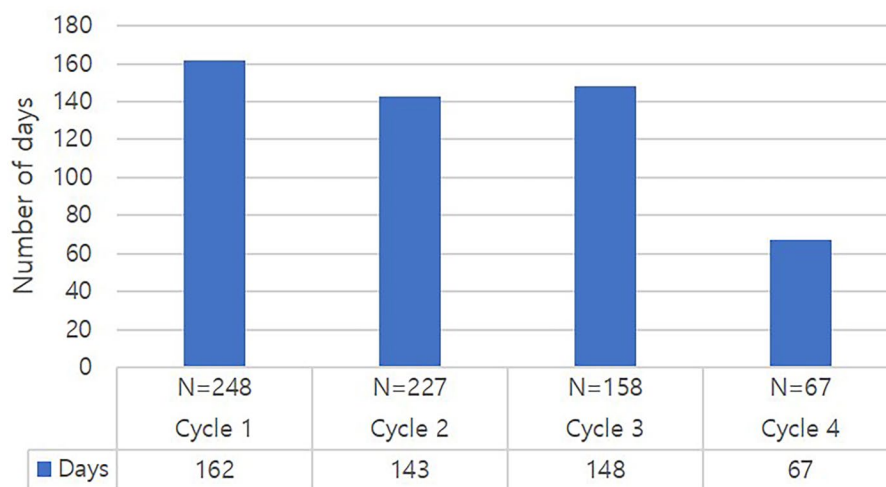


Figure 5. Retreatment interval (days) in each cycle.

wrinkle score evaluated by the investigator deteriorated to moderate (2 points) or severe (3 points). The treatment durations declined with each treatment cycle as they were 143, 137, 114, 96, and 77 days for cycles 1, 2, 3, 4, and 5, respectively.

Discussion

As the safety of an agent used in an esthetic procedure is very important, this OLE was performed at four different centers to

evaluate the long-term safety of repeated administrations of a novel BoNT-A (MBA-P01) in adults presenting with moderate or severe glabellar wrinkles. Additionally, improvements in glabellar wrinkles and patient satisfaction were assessed. In total, 249 participants were included in the SAS and 248 participants were included in the EAS. Overall, long-term treatment with MBA-P01 was well tolerated and effective in patients with moderate to severe glabellar lines. TEAEs were reported by 53.63% of the participants, most of which were mild or moderate and were deemed to have no causal relationship with the investigational drug. Also,

TEAEs had similar incidence in each cycle which suggests that suggests that repeated administration of MBA-P01 does not increase the incidence of side effects.

Only seven participants (2.81%) experienced at least one possible or probable related event; these events were typically eye disorders or injection site reactions. In one participant, one injection site reaction was related to eyebrow lifting after BoNT-A injection, which also occurred in the phase 3 clinical trial when the patient was injected with ONA-BoNT-A. This occurred again in cycle 1 of the OLE after the injection of MBA-P01; however, the patient was satisfied with the treatment and decided to continue until cycle 3. Similarly, in another participant, an injection site reaction related to eyebrow lifting also occurred 2 weeks after the treatment and spontaneously resolved. Eyebrow lifting is one of the most common complications associated with BoNT-A injection for the treatment of forehead wrinkles or glabellar lines; it is usually self-limiting and disappears spontaneously within 3 months without any further treatment.

The most common AESI associated with the investigational drug was eyelid sensory disorder (eyelid ptosis) which occurred in 3 participants (1.20%). This is caused by diffusion of the toxin through the orbital septum fascia to the levator palpebrae superioris, an upper eyelid levator muscle. This is especially common in older adult patients with preexisting lid ptosis or levator function weakness (9). Additionally, eyelid sensory disorders occur more commonly in Asian participants owing to differences in Asian and Caucasian eyelid anatomy and enhanced awareness. In Asians, orbital septum fusion to the levator aponeurosis beneath the superior tarsal border occurs at variable distances, and primary levator aponeurosis insertion in the orbicularis muscle and skin of the upper eyelid occurs closer to the eyelid margin than in Caucasians (10). In a previous study, Cavallini et al. reviewed 35 articles, with over 8000 patients, concluding the rate of eyelid ptosis to be about 2.5% (11–15). In this study, treatment-related eyelid ptosis occurred at a frequency of 0.08% (3 events among 3565 injections), which is significantly lower than the previously reported rate, despite the fact that all patients were Asians. This may be also partly due to the fact that experienced clinicians performed treatment in our study. Furthermore, among the three cases of eyelid ptosis, two cases occurred in cycle 1, and one case occurred in cycle 3. Thus, the incidence of eyelid ptosis did not increase with the number of treatment cycles and all treatment-related events of eyelid ptosis resolved spontaneously.

Headache is also one of the most frequent AE when BoNT-A is administered into the glabellar lines. In a previous meta-analysis, the incidence of headache was approximately 9% of subjects regardless of a causal relationship (16, 17). In this study, headache was not observed despite of repeated treatment of BoNT-A. Additionally, no participants presented antibodies against BoNT-A. In this study, detection of immunogenicity was performed using a sensitive RIPA as a screening assay, and positive samples were confirmed using a competitive RIPA, and all positive samples were further evaluated using a Mouse Protection Assay (18). This is a highly sensitive three-step approach and the results confirmed the absence of induction of neutralizing antibodies despite repeated treatment.

Regarding clinical efficacy, the 2-point composite response is a stringent measure of efficacy that is mandated by the US FDA (19). However, in clinical practice, 'achieving none or mild glabellar line severity (FWS score of 0 or 1)' is more important for the clinicians in describing duration of effect since the return of moderate or severe glabellar lines will likely trigger a patient's desire for re-treatment. Thus, we used a composite primary efficacy outcome, where we defined response rate as ' $a \geq 2$ FWS score improvement, with an FWS score of 0 or 1' at frowning.

The results of our study showed that the response rate decreased from cycles 1 to 5. Similarly, the participants' satisfaction rates were $>97\%$ in cycles 1–4; however, the percent of participants who responded as 'very satisfied' and 'satisfied' gradually decreased over each cycle. Furthermore, the median response duration also decreased from cycles 1 to 5. We believe that this is because the participants were eligible for retreatment ≥ 84 days after the treatment, with FWS scores of ≥ 2 (moderate) for glabellar lines at maximum glabellar frown. Thus, participants whose treatment effect lasted >84 days could not receive retreatment and were excluded from cycles 4 and 5. Also, as the treatment cycle progressed, the proportion of participants with severe glabellar wrinkles decreased, whereas the proportion of participants with moderate glabellar wrinkles increased owing to treatment efficacy. This means that the number of participants whose glabellar wrinkle score could be reduced by >2 points decreased. For this reason, the response rate, which reflects the proportion of participants with $a \geq 2$ -point improvement and grade 0 or 1 FWS, decreased as the cycle progressed. Nonetheless, the proportion of participants with an FWS score of 0 or 1 was $>90\%$ in all cycles.

The treatment durations were 143, 137, 114, 96, and 77 days for cycles 1, 2, 3, 4, and 5, respectively. In a previous study that evaluated the long-term efficacy and safety of Reloxin (Dysport[®]), the treatment durations were around 90 days in cycles 1–3 (20). In that previous study, 50U of Reloxin was injected (10U into each of the five injection sites in the glabellar area), whereas in our study, 20U of MBA-P01 was injected. Nonetheless, the treatment duration of MBA-P01 in cycles 1–4 were all >90 days in our study, indicating the possibility of a longer duration for this investigational product.

The limitations of this study include the fact that the majority of the patients were female and that all patients were Asians. Therefore, further studies with larger sample sizes that includes other ethnic groups are warranted to increase the generalizability of our results. Nonetheless, considering the fact that Asian populations are especially vulnerable to eyelid sensory disorder, which is the most common side effect of BoNT-A treatment for glabellar lines, we believe that the safety results regarding this side effect confirmed in this study can be applied to other ethnic groups.

In conclusion, multiple cycles of treatment with MBA-P01 at a dose of 20U were well tolerated and effective. There was no evidence of cumulative safety issues because the incidence of all TEAEs decreased over time, and only 2.81% of the participants experienced at least one possible or probable TEAE, all of which were mild in severity. Furthermore, regarding the treatment efficacy, repeated treatment of MBA-P01 was shown to be effective, with a treatment duration of 3–5 months. Therefore, this clinical trial demonstrates that MBA-P01 can be safely and effectively used when administered repeatedly to patients who need to improve moderate to severe glabellar wrinkles.

Author contributions

WSK, YWL, CHW, WSL, and BJK involved in the conception and design; HSH and SYC involved in analysis and interpretation of the data; HSH and SYC involved in the drafting of the paper; WSK, YWL, CHW, and WSL involved in revising it critically for intellectual content; all authors involved in the final approval of the version to be published; and that all authors agree to be accountable for all aspects of the work.

Ethical approval

This study was approved by the institutional review board at each center and was ethically conducted according to local laws and

applicable regulations in compliance with the Korea Good Clinical Practice, International Council for Harmonization-Good Clinical Practice, and the Declaration of Helsinki.

Patient consent

The authors obtained written consent from the patients for their photographs and medical information to be published in print and online, and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but were retained by the authors.

Disclosure statement

Wooshun Lee is a registered director of NUMECO Inc. The remaining authors have indicated no significant interest to disclose.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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