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Safety and efficacy of MT10107 in post-stroke upper limb spasticity treatment

A phase I randomized controlled trial

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Abstract

Background: Botulinum toxin type A injection is widely used treatment option for the treatment of upper limb spasticity in stroke patients. The purpose of this study was to explore the safety and efficacy of MT10107, a new botulinum toxin type A, in patients with post-stroke upper limb spasticity.

Methods: A prospective, randomized, double-blind, active drug-controlled, multi-center, phase I clinical trial. Thirty patients with post-stroke upper limb spasticity were received either MT10107 or onabotulinumtoxinA. Primary endpoint was change of modified Ashworth scale (MAS) score for wrist flexor from baseline to week 4. The secondary endpoints were changes of MAS scores for elbow and finger flexors, response rate, Disability Assessment Scale (DAS), and global assessment of treatment. The safety endpoints such as adverse events, vital signs, physical examination, and laboratory test were evaluated. The outcome measures were evaluated from baseline to week 4.

Results: The primary endpoints were −1.07 ± 0.70 and −1.23 ± 0.56 for the MT10107 and onabotulinumtoxinA groups, respectively. The intergroup difference of change between the 2 groups was 0.17 (95% confidence interval −0.31 to 0.64, P = .5769). In secondary endpoints, both groups showed a significant improvement in both MAS and DAS. There was no significant between-group difference in all secondary endpoints and safety measures.

Conclusion: The safety and efficacy of MT10107 showed no significant difference compared to onabotulinumtoxinA in post-stroke upper limb spasticity treatment.

Abbreviations: ADR = adverse drug reaction, AE = adverse event, BoNT-A = botulinum toxin type A, DAS = disability assessment scale, FAS = full analysis set, IP = investigational product, MAS = modified Ashworth scale, PPS = per-protocol set.

Keywords: botulinum toxins, muscle spasticity, safety, stroke, upper extremity

1. Introduction

Upper limb spasticity is a condition associated with pain or discomfort in the upper limbs that interfere with daily activities such as dressing and hygiene, thereby decreasing the patient's quality of life.[1–7] Upper limb spasticity is reported in approximately 38% of patients after stroke in the United States, and it could also result from several different conditions such as traumatic brain injury or damage to upper motor neurons.[8] Currently, there are numerous treatment options for post-stroke upper limb spasticity, but botulinum toxin type A (BoNT-A) injection is the first choice and well-tolerated treatment option for the treatment of focal spasticity.[4,9,10]

Medytox Inc. has developed a new BoNT-A product, MT10107 (Coretox®), utilized with 150-kDa neurotoxin excluding hemagglutinin and nontoxic non-hemagglutinin (complexing proteins), human serum albumin. OnabotulinumtoxinA (Botox®; Allergan Inc, Irvine, CA), abobotulinumtoxinA (Dysport®; Ipsen Ltd, Slough, Berkshire, UK), and incobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) are globally available BoNT-A products, but incobotulinumtoxinA is the only product that is free from

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complexing proteins. The presence of complexing protein could cause treatment failure as it increases the risk of neutralizing antibody formation against BoNT-A.[11,12] Furthermore, most of the BoNT-A preparation such as onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA contains HSA as a stabilizer. The use of HSA is controversial due to some safety concerns such as viral and prion transmission.[13,14] MT10107 is the only product on the market free from both HSA and complexing protein, which contains methionine, polysorbate 20, and sucrose as stabilizers. However, MT10107 has not been demonstrated for the treatment of post-stroke spasticity. Therefore, this study was designed to explore the safety and efficacy of MT10107, compared to onabotulinumtoxinA in the treatment of post-stroke upper limb spasticity.

2. Methods

2.1. Ethics statement

This study was approved by Institutional Review Boards of participating institutions, and was registered on clinicaltrials.gov. This trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before the study's enrollment. The sponsor (Medytox Inc., Republic of Korea) developed the protocol as this was a sponsored study. However, the research process, writing manuscript, and submission were handled by the investigators.

2.2. Study design

This study was a prospective, randomized, double-blinded, active drug-controlled, multi-center, Phase I clinical trial that was conducted between July and September 2017 in 5 university hospitals. The efficacy and safety endpoints were assessed at 4 weeks after administration.

2.3. Participants

The inclusion criteria were as follows: age ≥ 19 years; ≥ 6 months since the last stroke; focal spasticity of ≥ 2 points on modified Ashworth scale (MAS) for wrist flexor and ≥ 1 point in either of MAS for elbow or finger flexor; and acquisition of written informed consent. The exclusion criteria were as follows[3,6,7]: neuromuscular disorders; history within 4 months of screening or planned (during study period) treatment with phenol, alcohol, or botulinum toxin injection, tendon lengthening, or surgery in the target limb; fixed joint/muscle contracture, which was defined as severely limiting the range of motion; severe atrophy in the target limb; concurrent treatment with intrathecal baclofen; subjects who have a bleeding tendency or taking anti-coagulant agents; dysphagia or breathing difficulties; known allergy or sensitivity to study medication or its components; females who are pregnant, lactating, or planning to become pregnant during the study period, or females of childbearing potential not using a reliable means of contraception; subjects who are not eligible for this study at the discretion of the investigator; and changes in physical, occupational, or splinting therapy on the target limb, and muscle relaxants and/or benzodiazepine medication within a month before screening or any change in plans for the therapies during the study period. If the therapies (physical, occupational, or splinting therapy) or drugs have been used stably for at least a month before screening with no plans for a shift in the therapeutic regimens, then the subject was not excluded.

2.4. Procedures

Eligible subjects were randomized by using iMedidata Balance, and were dynamically allocated to either MT10107 or onabotulinumtoxinA group in a 1:1 ratio by an independent statistician. This study was a double-blind test, so both physicians and subjects were kept blind during the study period. Subject numbers were managed only by screening numbers, which were kept in sealed envelopes, and the blinding was not canceled unless it was necessary to unblind because of the subject's safety. Randomized subjects received a single injection of investigational products (IP), MT10107 (100 U), and onabotulinumtoxinA (100 U) of up to a maximum of 360 U. The IPs were reconstituted with 4.0 ml of sterile 0.9% sodium chloride solution, and the reconstitution was performed by the pharmacists who had no interactions with neither subjects nor investigators.

Target muscles and the injection dose were determined according to the investigator's examination and judgment based on Table 1, and the injection was administered under the guidance of electromyography or ultrasonography by skilled physicians. The wrist flexors, flexor carpi radialis, and flexor carpi ulnaris were always treated. Finger flexors, flexor digitorum profundus and flexor digitorum sublimis, elbow flexor, biceps brachii were only treated when MAS score was >1.

2.5. Efficacy measures

The primary endpoint was the change in the MAS score of wrist flexor at week 4 compared to baseline. The secondary endpoints included: change in MAS score of the elbow or finger flexor at week 4 compared to baseline; the response rate of all treated muscles at week 4, where the responder is defined as at least 1-point decrease in MAS after treatment; change in Disability Assessment Scale (DAS) score of predefined functional domains at week 4 compared to baseline; and investigator- and subject-rated global assessment score at week 4.

MAS, a scale used to assess the severity of muscle spasticity, is a 6-point scale with scores of 0, 1, 1+, 2, 3, and 4, where 1 + category was converted to 1.5 during the statistical analysis.[15] DAS is a scale that measures functional disability for patients with upper limb spasticity after stroke with valuable reliability.[16] At baseline, the subjects selected 1 of 4 areas of functional disabilities – hygiene, dressing, limb position, and pain – as their principal treatment target with the help of investigator. The investigator will assess pre-selected functional disability by using the 4-point DAS ranging from 0 (no disability) to 3 (severe disability).[16,17] The global assessment of treatment was used by both the investigator and the subjects to evaluate the treatment benefit by using a 7-point Likert scale. The higher the score, the higher the treatment benefit.

2.6. Safety measures

For the safety measures, all incidences of adverse events (AE), adverse drug reactions (ADR), and serious adverse events were monitored throughout the study. Vital signs and physical examinations were conducted in every visit, and laboratory tests were performed only at screening and end of trial visit. All the safety measures were compared between the 2 groups.

2.7. Statistical analysis

The analyses of the data were performed on the full analysis set (FAS), per-protocol set (PPS), and safety set population. The FAS that most closely resembles the intent-to-treat population was the primary analysis set for the efficacy assessment. It included all randomized subjects with at least 1 evaluation of efficacy endpoints. The PPS was used as a supportive analysis to FAS and included subjects from FAS without major protocol deviations. The safety set included all subjects with 1 or more safety assessments after IP administration.

Table 1

Injection doses and sites of botulinum toxin type A.

Target muscle	Recommended injection dose (U)	Number of injection sites	MT10107 group	OnabotulinumtoxinA group	*P* value
Wrist flexors					
FCR	15–60	1–2			
n			15	15	
Mean ± SD			54.00 ± 7.37	54.00 ± 6.32	.9083*
Median [IQR]			60.00 [40.00, 60.00]	50.00 [40.00, 60.00]	
FCU	10–50	1–2			
n			15	15	
Mean ± SD			46.67 ± 7.24	46.33 ± 7.19	.7578*
Median [IQR]			50.00 [30.00, 50.00]	50.00 [25.00, 50.00]	
Elbow flexor					
BB	100–200	Up to 4			
n			15	15	
Mean ± SD			130.7 ± 33.05	122.7 ± 39.77	.7402*
Median [IQR]			150.0 [80.00, 200.0]	150.0 [50.00, 165.0]	
Finger flexors					
FDP	15–50	1–2			
n			11	12	
Mean ± SD			50.00 ± 0.00	49.17 ± 8.75	1.0000*
Median [IQR]			50.00 [50.00, 50.00]	50.00 [25.00, 65.00]	
FDS	15–50	1–2			
n			14	15	
Mean ± SD			47.14 ± 7.26	48.00 ± 8.62	.9754*
Median [IQR]			50.00 [30.00, 50.00]	50.00 [25.00, 65.00]	
Total	Up to 360				
n			15	15	
Mean ± SD			312.0 ± 59.31	310.3 ± 62.58	.9299*
Median [IQR]			310.0 [180.0, 360.0]	350.0 [200.0, 360.0]	

BB = biceps brachii, FCR = flexor carpi radials, FCU = flexor carpi ulnaris, FDP = flexor digitorum profundus, FDS = flexor digitorum sublimis, IQR = interquartile range.
*Wilcoxon rank-sum test.

Statistical analysis was performed using a 2-sided test at a significance level of 0.05. The continuous variables of demographics and baseline characteristics were analyzed using either a 2-sample *t* test or Wilcoxon rank-sum test depending on the result of the normality test. For categorical data, the chi-square test or Fisher's exact was used. The following methods were used to analyze the primary endpoint and the MAS and DAS outcomes of secondary endpoints. Depending on the result of the normality test, a 2-sample *t* test or Wilcoxon's rank-sum test was used for intergroup analysis and paired *t* test or Wilcoxon's sign-rank test was used for intragroup analysis. For other secondary endpoints such as the response rate and global assessment analysis, Fisher's exact test or Pearson's chi-square test was used in evaluating the intergroup differences.

The following statistical methods were used to evaluate the safety endpoints. For the incidence of AE and ADR after treatment, the chi-square test or Fisher's exact test was used for intergroup analysis. Intergroup differences of physical examinations, vital signs, and laboratory tests were analyzed using a paired *t* test or Wilcoxon's rank-sum test for continuous variables. For categorical variables, Fisher's exact test or Pearson's chi-square test was used. Intragroup differences were analyzed by using McNemar's test for categorical variables, and the paired *t* test or Wilcoxon's sign-rank test was used depending on the result of the normality test for continuous variables.

3. Results

3.1. Demographic and baseline characteristics

Among the initially screened 34 subjects, 30 subjects were randomized into the MT10107 (n = 15) and onabotulinumtoxinA (n = 15) groups (Fig. 1). Safety set and FAS population included all randomized subjects, but 1 subject from the onabotulinumtoxinA group was excluded from the PPS population because of major protocol deviation, "out of visit window."

Table 2 shows a summary of the demographics and baseline characteristics of the randomized subjects. The intergroup difference in demographic and baseline characteristics was not statistically significant in the FAS population.

3.2. Primary and secondary outcomes

The outcomes shown in this section is based on the FAS population. For primary endpoint analysis, the changes in MAS of wrist flexor at week 4 compared to baseline was −1.07 ± 0.70 and − 1.23 ± 0.56 in MT10107 and onabotulinumtoxinA groups, respectively ($P < .05$, Table 3). The intergroup difference in change between the 2 groups was not statistically significant ($P = .5769$), with a 95% 2-sided confidence interval of −0.31 to 0.64.

All randomized 30 subjects have received treatment on their elbow flexor in addition to the wrist flexors (Table 3). In total, 29 subjects (14 and 15 subjects in MT10107 and onabotulinumtoxinA groups, respectively) received finger flexors treatment in addition to the wrist and elbow flexors. The changes in MAS of elbow flexor at week 4 compared to baseline were −0.70 ± 0.84 and −0.60 ± 0.69 in MT10107 and onabotulinumtoxinA groups, respectively, and the changes in MAS of finger flexor were −0.96 ± 0.57 and −1.10 ± 0.57 in MT10107 and onabotulinumtoxinA groups, respectively, which showed a statistically significant decrease in both groups ($P < .05$). The intergroup difference for the change in the elbow and finger flexor at week 4 from baseline was not statistically significant ($P = .5208$ and $P = .9327$, respectively).

The response rates of subjects treated for wrist flexors at week 4 were 86.67% (13/15 subjects) and 93.33% (14/15 subjects) for MT10107 and onabotulinumtoxinA groups, respectively (Table 3). For elbow flexor, the response rates were 73.33% (11/15 subjects) and 60.00% (9/15 subjects) for MT10107 and onabotulinumtoxinA group, respectively. Finally, the response rates of finger flexors were 85.71% (12/15 subjects) and

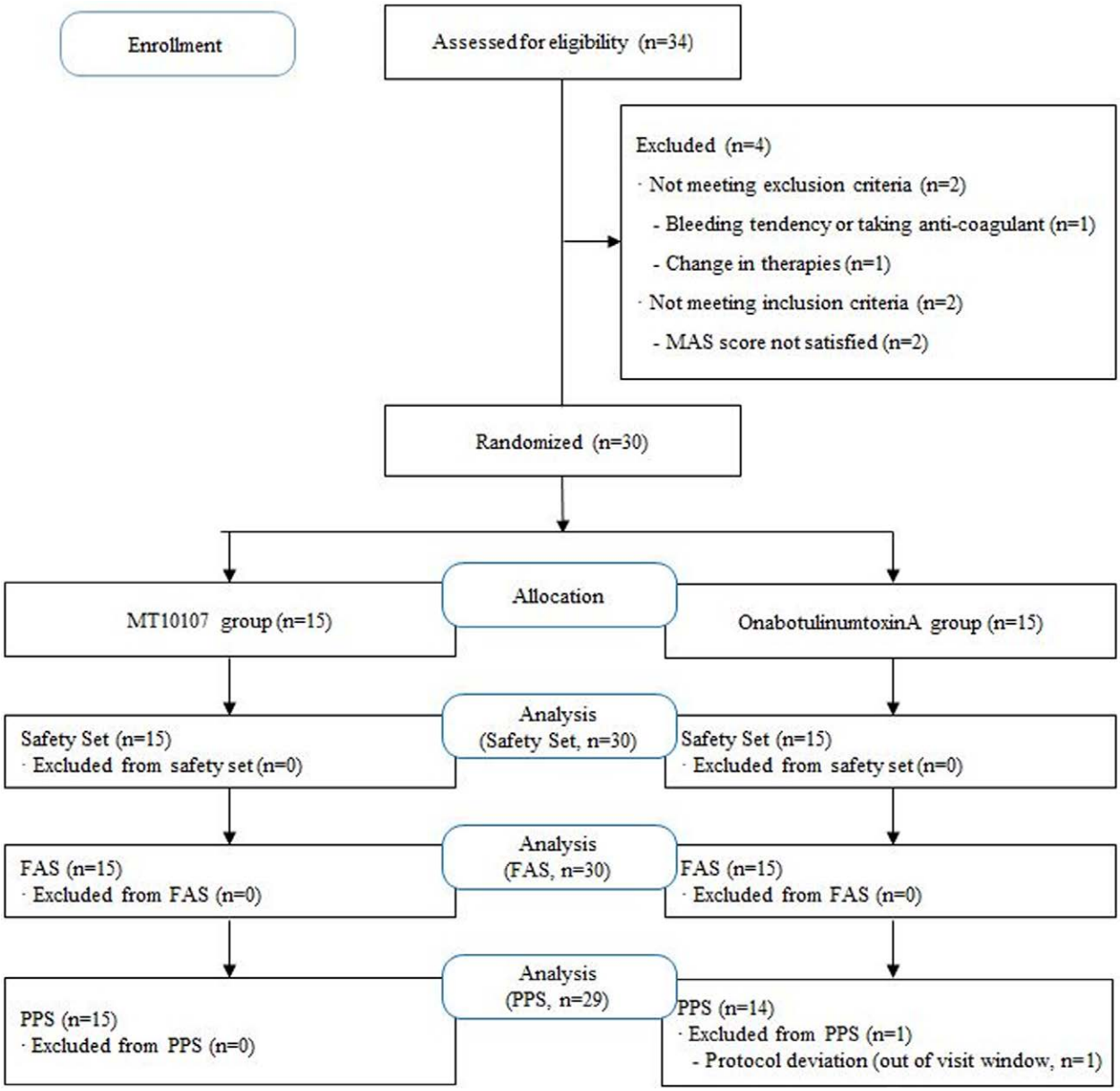

Figure 1. Flowchart of the study. FAS = full analysis set, PPS = per protocol set.

Table 2

Demographics and baseline characteristics of patients.

	MT10107 group (n = 15)	OnabotulinumtoxinA group (n = 15)	*P* value
Age (yrs)	58.00 ± 14.42	60.80 ± 10.96	.5542*
Sex, n (%)			
Men	10 (66.67%)	13 (86.67%)	.3898†
Women	5 (33.33%)	2 (13.33%)	
Duration from stroke (years)	10.23 ± 5.41	10.29 ± 7.27	.9800*
Concomitant therapies, n (%)			
Yes	4 (26.67%)	5 (33.33%)	1.0000†
No	11 (73.33%)	10 (66.67%)	

*Two-sample *t* test.
†Fisher's exact test.

Table 3

Changes in spasticity of all muscles measured by modified Ashworth scale, response rate, disability assessment scale, and global assessment of treatment from full analysis set.

Outcome			MT10107 group	OnabotulinumtoxinA group	95% CI	*P* value*
Modified Ashworth scale						
Wrist flexor		n	15	15		
	Baseline	Mean ± SD	2.33 ± 0.49	2.33 ± 0.49	(–0.36, 0.36)	1.0000†
		Median [IQR]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]		
	Week 4	Mean ± SD	1.27 ± 0.75	1.10 ± 0.60	(–0.34, 0.68)	.3574†
		Median [IQR]	1.00 [0.00, 3.00]	1.00 [0.00, 2.00]		
	Change	Mean ± SD	–1.07 ± 0.70	–1.23 ± 0.56	(–0.31, 0.64)	.5769†
		Median [IQR]	–1.00 [–2.00, 0.00]	–1.00 [–2.00, 0.00]		
		P value‡	0.0000§	0.0001‖		
Elbow flexor		n	15	15		
	Baseline	Mean ± SD	1.80 ± 0.80	1.97 ± 1.08		.9318†
		Median [IQR]	1.50 [1.00, 4.00]	2.00 [1.00, 4.00]		
	Week 4	Mean ± SD	1.10 ± 0.69	1.37 ± 0.88		.8209†
		Median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 4.00]		
	Change	Mean ± SD	–0.70 ± 0.84	–0.60 ± 0.69		.5208†
		Median [IQR]	–0.50 [–3.00, 0.50]	–0.50 [–2.50, 0.00]		
		P value‡	0.0039‖	0.0039‖		
Finger flexor		n	14	15		
	Baseline	Mean ± SD	2.39 ± 0.56	2.60 ± 0.74		.3591†
		Median [IQR]	2.00 [1.50, 3.00]	3.00 [1.00, 4.00]		
	Week 4	Mean ± SD	1.43 ± 0.39	1.50 ± 0.46		.6936†
		Median [IQR]	1.50 [1.00, 2.00]	1.50 [1.00, 2.00]		
	Change	Mean ± SD	–0.96 ± 0.57	–1.10 ± 0.57		
		Median [IQR]	–1.00 [-2.00, 0.00]	–1.00 [–2.00, 0.00]		
		P value‡	0.0000§	0.0001‖		.9327†
Response rate						
Wrist flexor	n		15	15		
	Responder, n (%)		13 (86.67)	14 (93.33)		1.0000¶
Elbow flexor	n		15	15		
	Responder, n (%)		11 (73.33)	9 (60.00)		.4386#
Finger flexor	n		14	15		
	Responder, n (%)		12 (85.71)	14 (93.33)		.5977¶
Disability assessment scale						
Dressing		n	4	6		
	Baseline	Mean ± SD	2.50 ± 1.00	2.17 ± 0.41		.3458†
		Median [IQR]	3.00 [1.00, 3.00]	2.00 [2.00, 3.00]		
	Week 4	Mean ± SD	1.50 ± 0.58	1.67 ± 0.82		.9062†
		Median [IQR]	1.50 [1.00, 2.00]	1.50 [1.00,3.00]		
	Change	Mean ± SD	–1.00 ± 0.82	–0.50 ± 0.55		.5050†
		Median [IQR]	–1.00 [–2.00, 0.00]	–0.50 [–1.00, 0.00]		
		P value‡	0.0917§	0.2500‖		
Hygiene		n	1	1		
	Baseline	Mean ± SD	2.00 ± 0	3.00 ± 0		
		Median [IQR]	2.00 [2.00, 2.00]	3.00 [3.00, 3.00]		
	Week 4	Mean ± SD	1.00 ± 0	2.00 ± 0		
		Median [IQR]	1.00 [1.00, 1.00]	2.00 [2.00,2.00]		
	Change	Mean ± SD	–1.00 ± 0	–1.00 ± 0		
		Median [IQR]	–1.00 [–1.00, –1.00]	–1.00 [–1.00, –1.00]		
		P value‡	1.0000‖	1.0000‖		
Limb position		n	10	8		
	Baseline	Mean ± SD	2.30 ± 0.48	2.25 ± 0.71		1.0000†
		Median [IQR]	2.00 [2.00, 3.00]	2.00 [1.00, 3.00]		
	Week 4	Mean ± SD	1.60 ± 0.84	1.38 ± 0.52		.7198†
		Median [IQR]	1.00 [1.00, 3.00]	1.00 [1.00, 2.00]		
	Change	Mean ± SD	–0.70 ± 0.48	–0.88 ± 0.35		1.0000†
		Median [IQR]	–1.00 [–1.00, 0.00]	–1.00 [–1.00, 0.00]		
		P value‡	0.0156‖	0.0156‖		
Global assessment	Investigator	n	15	15		
		Mean ± SD	5.27 ± 1.58	5.73 ± 0.70		.7440†
		Responder, n (%)	11 (73.33)	14 (93.33)		.3295¶
		Very satisfied, n (%)	2(13.33)	1 (6.67)		.5534¶
		Satisfied,n (%)	8(53.33)	10 (66.67)		
		Slightly satisfied, n (%)	1(6.67)	3 (20.00)		
		Neutral, n (%)	2(13.33)	1 (6.67)		
		Slightly dissatisfied, n (%)	0(0.00)	0 (0.00)		
		Dissatisfied, n (%)	2(13.33)	0 (0.00)		
		Very dissatisfied, n (%)	0(0.00)	0 (0.00)		

(*Continued*)

Table 3

(*Continued*)

Outcome			MT10107 group	OnabotulinumtoxinA group	95% CI	*P* value*
	Subject/caregiver	n	15	15		
		Mean ± SD	5.27 ± 1.16	4.80 ± 1.57		.4610†
		Responder, n (%)	11 (73.33)	9 (60.00)		.4386#
		Very satisfied, n (%)	2 (13.33)	2 (13.33)		.9735¶
		Satisfied,n (%)	5 (33.33)	3 (20.00)		
		Slightly satisfied, n (%)	4 (26.67)	4 (26.67)		
		Neutral, n (%)	3 (20.00)	4 (26.67)		
		Slightly dissatisfied, n (%)	1 (6.67)	1 (6.67)		
		Dissatisfied, n (%)	0 (0.00)	0 (0.00)		
		Very dissatisfied, n (%)	0 (0.00)	1 (6.67)		

IQR = interquartile range.
*Intergroup analysis.
†Wilcoxon rank-sum test.
‡Intragroup analysis.
§Paired *t* test.
||Wilcoxon signed-rank test.
¶Fisher's exact test.
#Pearson's chi-square test.

93.33% (14/15 subjects) for MT10107 and onabotulinumtoxinA groups, respectively. There was no statistically significant difference in the response rate of all muscles between the groups at week 4 ($P > .05$).

The changes in DAS score of dressing, hygiene, and upper limb position at week 4 compared to baseline were -1.00 ± 0.82, -1.00 ± 0, and -0.70 ± 0.48 in the MT10107 group and -0.50 ± 0.55, -1.00 ± 0, and -0.88 ± 0.35 in the onabotulinumtoxinA group, respectively (Table 3). The change in the DAS score of all predefined functional domains at week 4 compared to baseline was statistically significant for both groups ($P < .05$). The intergroup difference for the change in DAS score for "dressing" and "upper limb position" was not statistically significant ($P = .5050$ and $P = 1.0000$, respectively). For "hygiene," only 1 subject per group was involved, so the intergroup difference was not analyzed.

Table 3 shows the results of the global assessment of treatment assessed by the investigator and subject/caregiver for overall treatment benefit at week 4. If the investigator- and the subject/caregiver-reported outcome was greater than 5 (slightly satisfied), then the treatment benefit was considered as improved. In the investigator-rated global assessment, 73.33% (11/15 subjects) and 93.33% (14/15 subjects) of subjects were considered to be improved in MT10107 and onabotulinumtoxinA groups, respectively. In the subject/caregiver-rated global assessment, 73.33% (11/15 subjects) and 60.00% (9/15 subjects) were considered to be improved in MT10107 and onabotulinumtoxinA groups, respectively. No statistically significant intergroup differences in the result of global assessment were found ($P > .05$).

In all primary and secondary outcomes, the PPS population showed similar results as the FAS population (data not shown).

3.3. Injection dose

The mean total injection doses from MT10107 and onabotulinumtoxinA groups were 312.0 ± 59.31 U and 310.3 ± 62.58 U, respectively (Table 1). All subjects received treatment on all 3 muscles except for 1 subject that did not receive treatment on finger flexors. The intergroup differences in total dose and dose per muscle were not statistically significant ($P > .05$).

3.4. Safety assessment

In the safety set population (n = 30), 3 subjects experienced 3 AE (Table 4). Two cases were "dyspepsia" and "rash" (each with 6.67%, 1/15 subject) from the MT10107 group, 3.4. and the third case was "pain in extremity" (6.67%, 1/15 subject) from onabotulinumtoxinA group. "Rash" was further identified as ADR, and there was no serious adverse event. The intergroup differences in the incidences of AE and ADR were not statistically significant ($P = 1.0000$ and $P = 1.0000$, respectively).

MT10107 group showed no significant changes in all safety assessments such as vital signs, physical examinations, and laboratory tests after the treatment, and the intergroup differences were not significant.

4. Discussion

The results of this study suggested that the efficacy of MT10107 was comparable to onabotulinumtoxinA in the treatment of upper limb spasticity after stroke. MAS was used in this study as the primary endpoint measure for its reliability in evaluating the severity of upper limb spasticity.[18,19] Week 4 was used as the primary and secondary endpoints assessment timing as the BoNT-A effect optimizes around at week 4 after treatment.[19] According to Phase I pharmacodynamic study of MT10107, the largest percent reduction (%) of compound muscle action potential M-wave amplitude measured in extensor digitorum brevis was around at week 4 compared to baseline,[12] thereby supporting the assessment timing of this study. The intergroup differences on all safety endpoints were statistically insignificant, reinforcing the safety of MT10107 up to a maximum of 360 U.

The results of this study were consistent with the results of previous BoNT-A studies on post-stroke upper limb spasticity. OnabotulinumtoxinA has shown its efficacy and safety in the treatment of post-stroke upper limb spasticity when assessed by MAS, DAS, and global assessment.[2,17,20–23] AbobotulinumtoxinA[19,24,25] and incobotulinumtoxinA[3,26,27] have also shown their efficacy and safety in the treatment of post-stroke upper limb spasticity by using similar assessment measures as this study. Additionally, several new BoNT-A such as Neuronox (Medytox Inc., Cheongju, Republic of Korea), Nabota (Daewoong Pharmaceutical, Seoul, Korea), and letibotulinumtoxin A (Botulax®; Hugel Inc., Chuncheon, Korea) producers have conducted their pivotal studies for post-stroke upper limb spasticity with similar study design.[5–7] These studies used MAS, DAS, Care Burden Scale, and global assessments at weeks 4, 8, and 12 to confirm their non-inferiority compared to a comparator, onabotulinumtoxinA. The MAS, DAS, and global assessment scores of these studies were also consistent with the result of this study.

Table 4

Adverse events and adverse drug reactions.

	System organ class	Preferred term	MT10107 group (n = 15) n (%), [case]	OnabotulinumtoxinA group (n = 15) n (%), [case]	*P* value
Adverse events	Gastrointestinal disorders	Dyspepsia	1 (6.67), [1]	0 (0.00), [0]	
	Skin and subcutaneous tissue disorders	Rash	1 (6.67), [1]	0 (0.00), [0]	
	Musculoskeletal and connective tissue disorders	Pain in extremity	0 (0.00), [0]	1 (6.67), [1]	
	Total		2 (13.33), [2]	1 (6.67), [1]	1.0000*
Adverse drug reactions	Skin and subcutaneous tissue disorders	Rash	1 (6.67), [1]	0 (0.00), [0]	
	Total		1 (6.67), [1]	0 (0.00), [0]	1.0000*

*Fisher's exact test.

In the global assessment, no statistically significant intergroup differences were observed. In the OnabotulinumtoxinA group, the responders of investigator-rated global assessment and subject/caregiver-rated global assessment were 90% and 60%, respectively, which showed a large difference. However, the mean scores of investigator-rated global assessment and subject/caregiver-rated global assessment were 5.73 ± 0.70 and 4.80 ± 1.57, respectively, which did not show a considerable difference between the 2 assessments. The investigator-rated global assessment was higher than the subject/caregiver-rated global assessment possibly because the investigator focused on improving spasticity, whereas the subject and caregiver focused on functional impairment. In previous studies, global assessment scores measured by physicians are also higher than those measured by patients/caregivers.[5,6]

The analysis of covariance was performed to adjust the variables that could affect the primary outcome. The disease duration since stroke onset was adjusted as it could affect the treatment effect due to secondary changes in the muscles and joints. The adjusted result showed no statistically significant intergroup differences. Additionally, the severity of the MAS of wrist flexor at baseline was adjusted by analysis of covariance, and the intergroup differences were also not statistically significant (data not shown).

4.1. Study limitations

This study is not without limitations. First, the sample size of this study was kept minimal as the study was designed to explore the safety and efficacy of MT10107 in the treatment of upper limb spasticity. Second, the study duration was too short for capturing the long-term safety and efficacy of MT10107. The benefits or adverse effects did not differ between the MT10107 and onabotulinumtoxinA treatment groups. The results of this study were insufficient to support the benefit of HSA as a stabilizer in MT10107, which could require long-term data points. A long-term study of phase II or phase III was planned to evaluate long-term efficacy and long-term safety, including potential treatment failure and long-term side effects. However, MT10107 is cheaper than onabotulinumtoxinA; therefore, MT10107 may have an advantage. Finally, the formation of BoNT-A–neutralizing antibodies before and after treatment was not investigated.

5. Conclusions

In conclusion, this study demonstrated the safety of MT10107 in the treatment of post-stroke upper limb spasticity. In terms of efficacy, MT10107 demonstrated a comparable effectiveness to onabotulinumtoxinA. Further investigation with a larger sample is necessary to evaluate the efficacy and safety of MT10107 in the treatment of post-stroke upper limb spasticity.

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Author contributions

MHC designed the study. MHC, YJK, SUL, DYK, and NJP conducted the experiments and acquired the data for the study. JKL and MHC interpreted the data. JKL drafted the manuscript. JKL and MHC revised the manuscript. The authors read and approved the final manuscript.

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