

OnabotulinumtoxinA for the Treatment of Major Depressive Disorder: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial in Adult Females

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SUPPLEMENTAL TEXT

Statistical analyses and Sample Size

An in-clinic assessment with the Structured Interview Guide was used to obtain clinic MADRS total score. For the primary analysis, an MMRM with unstructured covariance was used with treatment (onabotA vs placebo), visit (Weeks 3, 6, and 9), treatment-by-visit interaction, and investigator center as fixed effects, and baseline MADRS total score, duration of illness, and number of previous major depressive episodes as covariates. Investigator centers with <10 patients were pooled into 1 small-center group within each dose cohort. Missing patient scores were estimated according to a modified last observation carried forward (mLOCF) imputation method. Secondary ANCOVAs of MADRS total score were made for baseline and change from baseline to Weeks 3, 6, 9, 12, 15, 18, 21, and 24, using the same model as for the primary MMRM analysis with mLOCF imputation, but without repeat measures.

For CGI-S and HAM-D-17 score analyses, by visit-week comparisons of the changes from baseline between treatment groups were done by ANCOVA on the response variable, with the baseline value as covariate, using observed data and no imputation of missing data. The same MMRM model as the primary analysis was used, with appropriate baseline values, but parameters for visit and visit interactions were excluded.

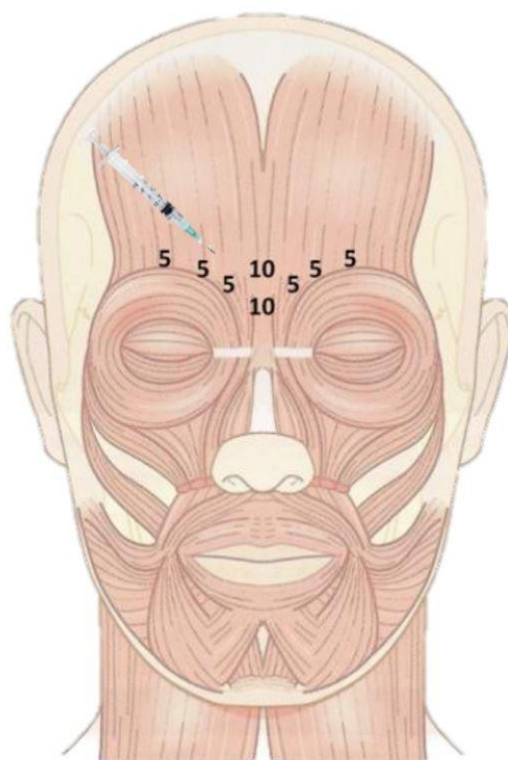
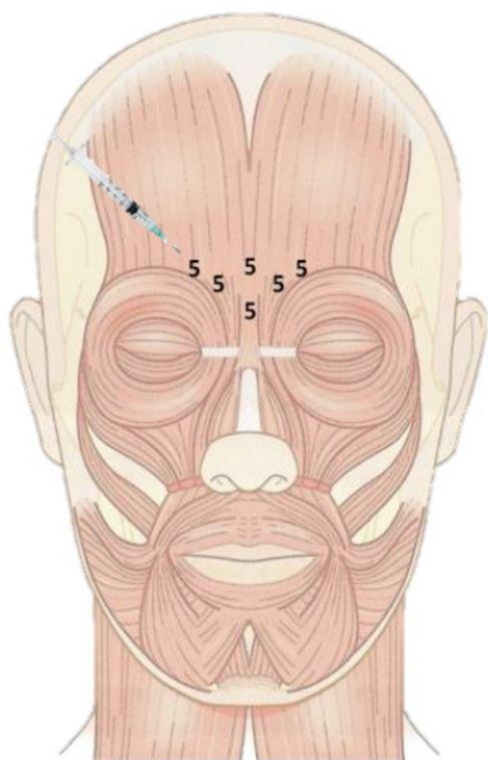
Comparisons of changes from baseline between treatment groups in CSFQ total and subscale scores were performed using a rank ANCOVA with treatment group as a factor and baseline score as covariate by visit at Weeks 6, 12 and 18.

The original sample size of 35 patients per treatment group had sufficient power to detect a 6.0-point difference from baseline to Week 6 MADRS between onabotA and placebo within both cohorts. An independent team performed an unblinded interim analysis of the primary and secondary efficacy variables when enrollment reached ~50% of planned and had observed data for MADRS total scores at Week 6 to determine if the Pocock boundary indicated to complete the study with current patients or enroll to planned sample size, without other implications for the design or conduct of the study. A Pocock nominal alpha boundary level of 0.0294 was used at each of the interim analysis and the final analysis to maintain the overall false positive error level of alpha 0.05. Prior to study completion or unmasking of treatment, the planned total population size was increased from N=140 to N=248 to detect a smaller difference between treatments, which is more consistent with the effect size generally observed with other ADTs.

Supplemental Figure 1. Diagram of injection sites for a) 30 U dose group (6 injection sites), b) 50 U dose group (8 injection sites).

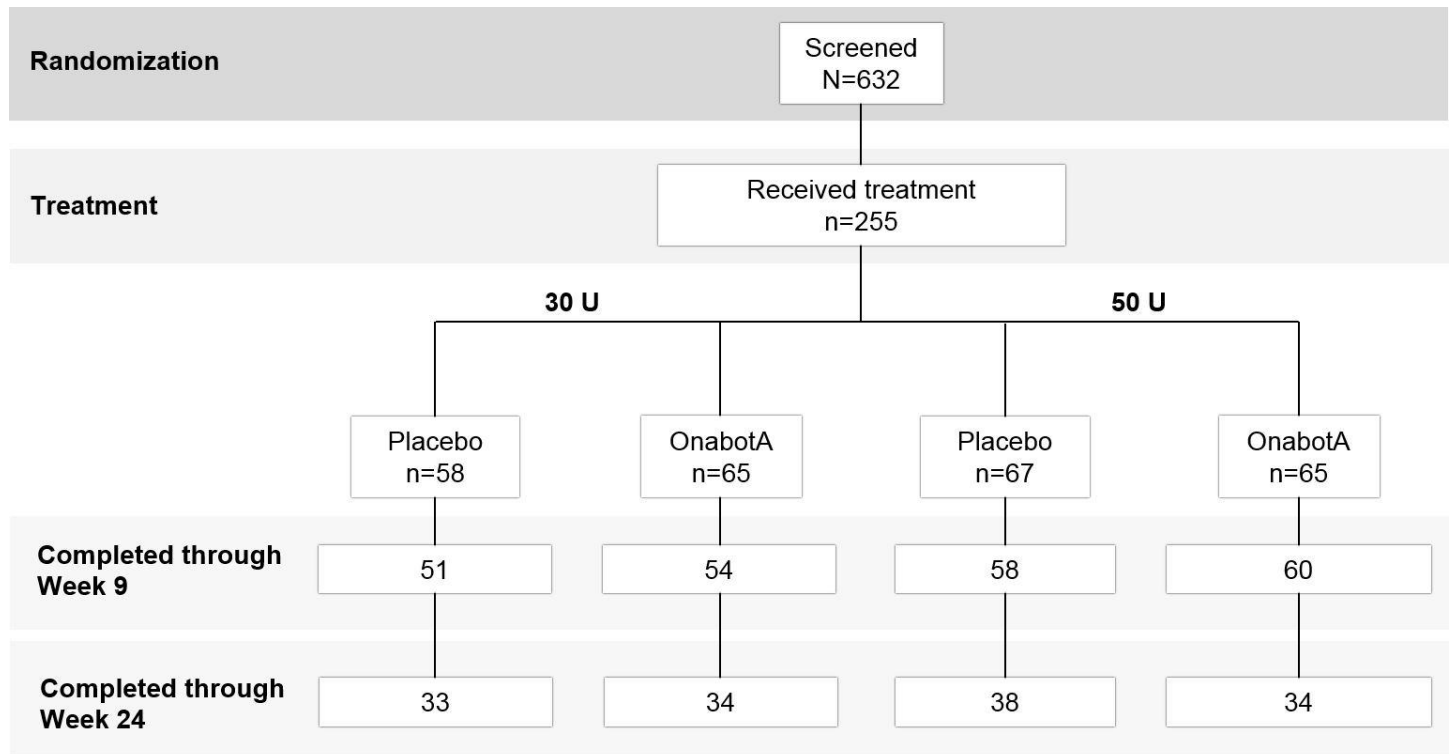
a) 30 U

b) 50 U

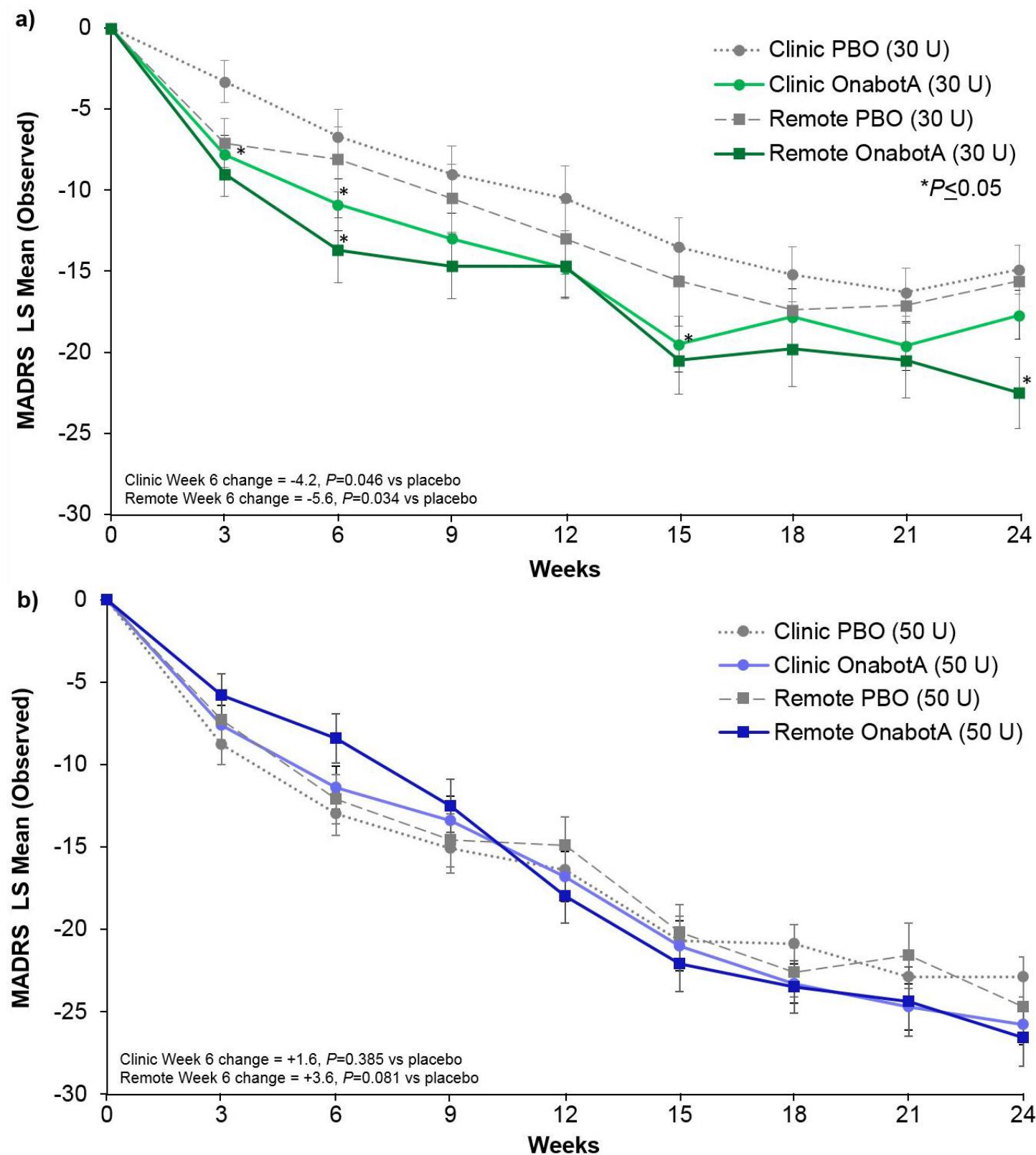


Numbers indicate units (U) of onabotA per injections; all injections were intramuscular except the most lateral corrugator muscle injections in the 50 U group were subcutaneous.

Supplemental Figure 2. Patient disposition (CONSORT diagram)



Supplemental Figure 3. Change from baseline in MADRS total score by visit for remote-rater and in-clinic assessments (observed data, ANCOVA, mITT population) for a) 30 U treatments, b) 50 U treatments.



MADRS, Montgomery-Åsberg Depression Rating Scale; LS, Least squares; ANCOVA, Analysis of covariance; ITT, modified intent-to-treat; U, Units. The data used are 'observed data' (without imputation for missing values), and P-values were obtained from an ANCOVA on the response variable. The model used within each dose cohort included treatment 9onabotA versus placebo) and investigator center as fixed effects, with baseline clinical MADRS total score, duration of illness, and number of previous depression episodes as covariates, each included as continuous rather than categorical variables. Within each dose cohort, sites with fewer than 10 patients were combined into one pseudo-site.

Supplemental Table 1. Reasons for discontinuations

	30 U		50 U	
	OnabotA (n=65)	Placebo (n=59)	OnabotA (n=65)	Placebo (n=69)
Premature discontinuation (n, %)	31 (47.7)	26 (44.1)	31 (47.7)	31 (44.9)
Investigator decision: Relapse	5 (7.7)	8 (13.6)	7 (10.8)	9 (13.0)
Personal reasons	9 (13.8)	4 (6.8)	6 (9.2)	6 (8.7)
Lost to follow-up	5 (7.7)	7 (11.9)	5 (7.7)	4 (5.8)
Lack of efficacy	3 (4.6)	4 (6.8)	7 (10.8)	5 (7.2)
Other	3 (4.6)	3 (5.1)	3 (4.6)	3 (4.3)
Adverse event	3 (4.6)	0	0	1 (1.4)
Investigator decision: other	0	0	3 (4.6)	2 (2.9)
Protocol violation	2 (3.1)	0	0	1 (1.4)
Pregnancy	1 (1.5)	0	0	0

Supplemental Table 2. Baseline characteristics

	30 U		50 U	
	OnabotA (n=65)	Placebo (n=58)	OnabotA (n=65)	Placebo (n=67)
Demographics				
Mean age, years (SD)	43.6 (12.4)	44.7 (11.7)	44.4 (11.9)	42.9 (11.7)
Race, n (%)				
White	42 (64.6)	38 (65.5)	38 (58.5)	32 (47.8)
Black/African-American	14 (21.5)	9 (15.5)	13 (20.0)	18 (26.9)
Asian	2 (3.1)	1 (1.7)	2 (3.1)	2 (3.0)
Hispanic	6 (9.2)	6 (10.3)	8 (12.3)	10 (14.9)
Other	1 (1.5)	4 (6.9)	4 (6.2)	5 (7.5)
Weight (kg), Mean (SD)	77.2 (18.6)	81.7 (22.1)	83.9 (27.7)	83.2 (23.7)
Height (cm), Mean (SD)	164.0 (8.1)	165.4 (7.6)	163.6 (7.6)	162.7 (6.6)
BMI, kg/m ² , Mean (SD)	28.7 (6.6)	29.8 (7.4)	31.3 (9.9)	31.4 (8.7)
Psychiatric History				
Age of MDD onset, years, Mean (SD)	31.3 (13.6)	34.6 (11.5)	32.2 (13.7)	31.8 (13.4)
MDD duration, yrs Mean (SD)	12.3 (11.3)	10.2 (7.5)	12.2 (8.9)	11.1 (9.9)
Mean Current episode duration, wks (SD)	38.2 (37.2)	37.9 (31.1)	50.0 (52.4)	41.9 (31.1)

Supplemental Table 3. Blinding analysis

Rater		30 U		50 U	
		OnabotA (N=65)	Placebo (N=58)	OnabotA (N=65)	Placebo (N=67)
Patient	Strongly/somewhat believed the treatment is real medication, n/N1 (%) ^a	33/50 (66.0)	17/46 (37.0)	42/53 (79.2)	32/59 (54.2)
Clinician	Strongly/somewhat believed the treatment is real medication, n/N1 (%) ^a	23/50 (46.0)	16/46 (34.8)	33/53 (62.3)	33/59 (55.9)
Remote	Strongly/somewhat believed the treatment is real medication, n/N1 (%) ^a	10/40 (25.0)	9/37 (24.3)	11/46 (23.9)	13/53 (24.5)

^an = number of “strongly/somewhat believed the treatment is real medication”; N1 = number of blinding surveys completed

Supplemental Table 4. Additional safety parameters

	Combined OnabotA (n=130)	Combined Placebo (n=125)
Overall suicidal ideation or behavior (C-SSRS, Safety Population), n (%)		
Screening (last 48 weeks)	18 (13.8)	16 (12.8)
Posttreatment period	18 (13.8)	19 (15.2)
CSFQ Total Scores ^a		
Baseline	34.3 (9.88)	34.0 (9.33)
Mean change (SD) Week 6	3.0 (6.79)	2.3 (8.61)
Mean change (SD) Week 12	4.9 (8.47)	4.1 (9.63)
Mean change (SD) Week 18	7.5 (9.97)	5.5 (10.61)

C-SSRS, Columbia-Suicide Severity Rating Scale; CSFQ, Changes in Sexual Functioning Questionnaire.

^aLower CSFQ scores are indicating of decreased sexual desire or functioning