OnabotulinumtoxinA for the treatment of major depressive disorder: a phase 2 randomized, double-blind, placebo-controlled trial in adult females

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This 24-week double-blind placebo-controlled multicenter randomized phase 2 trial evaluated efficacy and safety of onabotulinumtoxinA (onabotA; BOTOX) vs. placebo for major depressive disorder (MDD) [NCT02116361]. Primary endpoint was the change in Montgomery-Åsberg Depression Rating Scale (MADRS); secondary endpoints were Clinical Global Impressions-Severity and 17-item Hamilton Depression Rating Scale at week 6. A total of 255 adult females were treated. OnabotA 30 U approached significance compared to placebo on MADRS (mixed-effect model repeated measures least-squares mean difference: −3.7; $P = 0.053$) and reached significance [least-squares mean differences: −3.6 to −4.2; $P < 0.05$ (two-sided)] at weeks 3 and 9. Secondary endpoints were also significant at several time points. At week 6, onabotA 50 U did not separate from placebo in any parameters. OnabotA was generally well-tolerated: the only treatment-emergent adverse events reported in ≥5% in either onabotA group, and more than matching placebo were headache, upper respiratory infection, and eyelid ptosis. OnabotA 30 U, administered in a standardized injection pattern in a single session, had a consistent efficacy signal across multiple depression symptom scales for 12 or more weeks. OnabotA 30 U/placebo MADRS differences of (observed ANCOVA) ≥4.0 points (up to week 15) and ≥2.0 points (weeks 18–24) agree with the 2-point change threshold considered clinically relevant in MDD. OnabotA is a local therapy and is not commonly associated with systemic effects of conventional antidepressants and may represent a novel treatment option for MDD. *Int Clin Psychopharmacol* 35: 19–28 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Major depressive disorder (MDD) is a common chronic condition (Kessler *et al*., 2003) that can lead to substantial disability and high economic cost (Merikangas *et al*., 2007; Baldessarini *et al*., 2017). Despite estimations that antidepressant treatments (ADTs) were prescribed to ~12% of adults (≥20 years old) and ~23% of women 40–65 years old in the United States from 2005 to 2008 (Kit *et al*., 2012), patients with MDD frequently lack adequate response to standard ADTs (Fava, 2003). In the STAR*D study, approximately two-thirds of patients with MDD failed to achieve depression remission following initial treatment with a selective serotonin reuptake inhibitor. Those who did not enter remission began a second treatment step from the following options: switching to another ADT, augmentation with an additional ADT or cognitive therapy, or cognitive therapy alone. Of those who completed a second treatment step, only 31% achieved remission (Rush *et al*., 2006; Warden *et al*., 2007). This lack of adequate response after multiple treatment steps is of clinical interest because patients with MDD are less likely to respond and more likely to relapse as treatment steps are added (Warden *et al*., 2007), indicating a need for additional, novel treatment options for MDD.

In addition to issues involving inadequate response and rates of remission, standard oral ADTs are associated with multiple sexual and gastrointestinal adverse events (AEs), which can result in decreased adherence, increased discontinuation, and potential relapses (Pollack, 1987; Remick *et al*., 1989; Baldessarini and Marsh, 1990; Clayton and McGarvey, 2006). In fact, AEs are a leading cause of discontinuation in the first few months of ADT (Demyttenaere *et al*., 2001). Therefore, a nonsystemic treatment option providing relief from depressive symptoms not associated with systemic AEs would be of

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high clinical value. A nonsystemic intervention would also lower the risk of drug–drug interactions, which are of particular concern in patients with MDD due to the high prevalence of psychiatric comorbidities that have been reported to exceed 35% (Thaipisuttikul *et al.*, 2014). A treatment that is effective, after each exposure, for multiple months is also useful to support increased adherence due to less frequent dosing (Medic *et al.*, 2013).

Local injections of onabotulinumtoxinA (BOTOX; onabotA) result in muscle relaxation through a multistep process that includes binding to nerve terminals, internalization, and cleaving SNAP-25 (synaptosomal-associated protein-25 kD), one of the SNARE (soluble NSF-attachment protein receptor) proteins critical for synaptic vesicle fusion to the inner surface of the cellular membrane (Rossetto *et al.*, 2014). Impacted synaptic vesicles can neither release their neurotransmitter contents into the synaptic cleft (e.g. acetylcholine from motor neurons; CGRP from sensory neurons) nor undergo SNARE-mediated delivery of receptors or ion channels carried as vesicular cargo into neuronal membranes (e.g. TRPV1 and P2X3 in nociceptors) (Burstein *et al.*, 2014).

Previous studies indicate a single session of therapeutic injections of onabotulinumtoxinA into facial muscles in the glabellar region may represent a novel, well-tolerated treatment option for MDD (Finzi and Wasserman, 2006; Wollmer *et al.*, 2012; Magid *et al.*, 2014, Finzi and Rosenthal, 2014). OnabotA corrugator and procerus injections have an acceptable record of safety (Brin *et al.*, 2009), and in the published MDD trials, the only common treatment-emergent AEs were temporary and local to the treatment site (headache and injection site irritation) (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014). The results of these studies indicated onabotA may produce antidepressive effects lasting several months following a single-treatment session, which may increase treatment adherence compared to daily medication. The objective of this Phase 2 study was to evaluate the efficacy, safety, and duration of effect of a single-treatment session of onabotA compared to placebo for the treatment of MDD in adult females (NCT02116361).

Methods

This study was conducted from April 2014 to December 2016 at 32 sites in the United States in compliance with ICH-E6 Good Clinical Practice guidelines, and the protocol was approved by Institutional Review Boards at each study center. All patients provided written informed consent. OnabotA is not labeled for MDD by the FDA and is still under investigation.

Study design

This was a 24-week multicenter randomized, double-blind placebo-controlled 2-dose cohort parallel-group study of 30 units (U) and 50 U onabotA in outpatient female patients with MDD. Two different injection paradigms were tested to evaluate the antidepressant effects of differential dosing of onabotA to the procerus and corrugator muscles. The total dosage (30 U or 50 U) was divided into six or eight glabellar injections, respectively (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/ICP/A66*). All injections were intramuscular (IM) except the most lateral corrugator subcutaneous injections of the 50 U dosing paradigm. All injections were 0.1 mL containing 5 U of study drug except those given in the procerus muscle (0.2 mL, 10 U of study drug) in the 50 U cohort.

Participating sites were randomized before study initiation to administer only one dose cohort during the trial (i.e. 30 U sites or 50 U sites), due to the treatment paradigms having a different number of injections depending on dose. Patients were screened 7–14 days before randomization, and all injections were administered in a single-treatment session at baseline (Day 1). Randomization occurred 1:1:2 to onbotA 30 U, onabotA 50 U or placebo using blocks within strata and center [30 U onabotA vs. 30 U placebo (1:1), or 50 U onabotA vs. 50 U placebo (1:1)].

Patients

The present Phase 2 study only included female patients, and the rationale for this was three-fold: an attempt to reproduce the previous studies of onabotA for MDD, which enrolled a predominantly female population (77–93% of total patients) (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014; Magid *et al.*, 2014); an effort to keep the study design streamlined since there were two doses each with matching placebo being investigated because previous MDD studies utilized higher doses in males (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014; Magid *et al.*, 2014); and the higher prevalence of MDD in females, which have nearly twice the rate of 12-month prevalence compared to males (Hasin *et al.*, 2018).

Adult females (18–65 years) with moderate to severe MDD (single episode or recurrent) who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000) based on the Mini International Neuropsychiatric Interview (MINI) were eligible for inclusion (Sheehan *et al.*, 1997). Patients were in a current major depressive episode lasting ≥4 weeks, and had a 17-item Hamilton Depression Rating Scale [HAMD-17] (Hamilton, 1960) score ≥ 18 and Clinical Global Impressions – Severity (CGI-S) subscale score ≥ 4 (Bridge *et al.*, 2007).

Patients were excluded if they met any of the following criteria: taking concurrent ADTs or herbal/homeopathic remedies targeting depressive symptoms (within 2 weeks); had any prior treatment with intravenous ketamine, electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or deep-brain

stimulation; any depot antipsychotic (within 12 weeks), or dermal filler injected into forehead (within 48 weeks), acupuncture to forehead muscles (within 4 weeks); or had any prior treatment or immunization to botulinum toxin; investigator-judged failure to adequately respond to ≥2 ADTs of different drug classes (any previous depressive episodes) or use of psychotropic drugs after screening; any medical condition that exposed patients to undue risk of significant AEs; a DSM-IV-TR diagnosis of any axis I disorder (non-MDD), except for stabilized generalized or social anxiety disorders or specific phobias not requiring treatment or were not the primary focus of treatment within 24 weeks; or any drug or alcohol abuse (within 12 weeks) or dependency (within 24 weeks); or a suicide risk. Intermittent or unstable use of cognitive behavioral therapy or interpersonal psychotherapy was prohibited, but a stable therapy paradigm that was established ≥12 weeks before screening and maintained throughout the study was allowed.

Study treatment

Study medication (onabotA) consisted of 100 U of *Clostridium botulinum* toxin type A, 0.5 mg of human albumin, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative. One Unit corresponds to the calculated median lethal intraperitoneal dose (LD_{50}) in mice. Placebo contained 0.9% sodium chloride in an identical form, and reconstitution procedures for placebo or onabotA were identical. Reconstituted study medication that was not administered immediately was kept in the vial (stored 2–8°C), and vials not used within 4 h were discarded.

Each study center only had access to one dosage of onabotA with matching placebo, and study centers were randomized before site initiation. At baseline (Day 1), eligible patients were randomized (1:1) to onabotA 30 U or matching placebo (30 U sites), or onabotA 50 U or matching placebo (50 U sites) using randomized blocks within strata within center. Patients were stratified according to duration of their current major depressive episode (<24 weeks vs. ≥24 weeks). Study medication was labeled with medication kit numbers, and an automated response system provided the site with the medication kit number(s), which assigned treatment groups for each randomized patient.

Of the two dose-injection paradigms evaluated, the 30 U dose group was similar to the injection paradigm used in previous studies, which demonstrated that depressive symptoms were reduced following onabotA 29 U treatments in the glabellar region (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014). The 50 U dose group received an increased dose (by two-fold) in the procerus, which was based on the strong procerus response reported in the most common glabellar activation patterns (Almeida *et al.*, 2010; de Almeida *et al.*, 2012), and the rationale that this would more effectively relax corrugator muscles and maximize disruption of the neural feedback circuitry potentially involved in depression. A total dose of onabotA 15 U into the corrugator muscles for the 50 U group was chosen in an effort to achieve complete abolishment of corrugator muscle activity with this dose and injection paradigm (Pribitkin *et al.*, 1997).

Blinding

To maintain study blinding, an independent drug reconstitution was assigned at each site for study drug preparation. Due to the potential cosmetic effects of study treatment, remote telephone raters performed the same efficacy assessments as clinic staff without direct patient contact. To evaluate blinding, the patient, investigator, and remote-rater were separately asked to indicate which treatment they believe was received (blinding index) at study exit.

Assessments

After randomization and treatment, a safety follow-up telephone call was conducted at week 2, and in-clinic and remote raters efficacy assessments were conducted at weeks 3, 6, 9, 12, 15, 18, and 21. For the primary efficacy variable, Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total scores, clinician-rated assessments were conducted before the remote-rater assessments to control for potential sequence effects.

Starting from week 9, relapse was defined as a responder with a MADRS total score ≥18 or CGI-S score ≥4 or judged by the investigator at week 12 or later, and those patients were required to exit the study. Patients were also discontinued if they required concomitant medication treatment for depression or a change in their cognitive therapy regimen (from screening) at any time during the study.

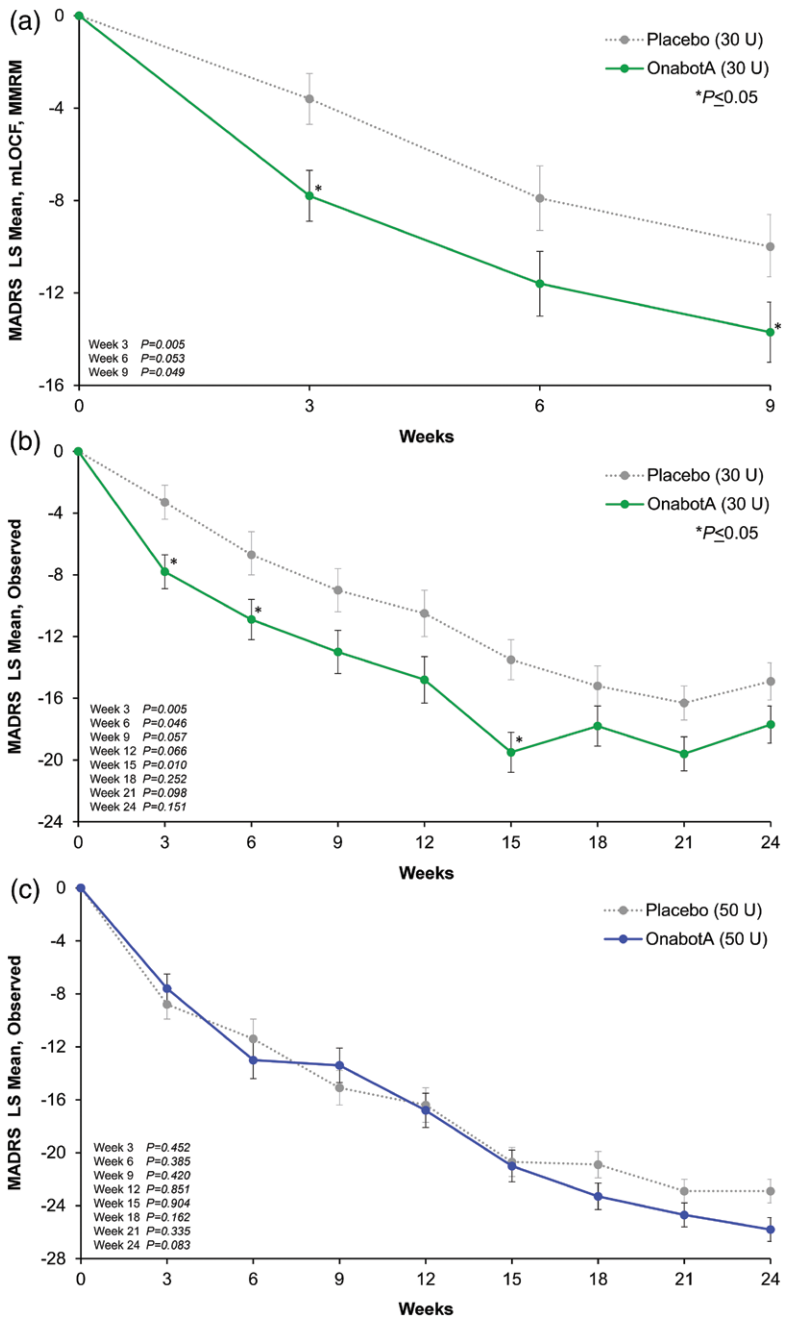
Efficacy parameters

Primary efficacy was assessed by MADRS total score changes at week 6 from baseline for each treatment group (onabotA 30 U or 50 U) compared to matching placebo using a mixed-effect model for repeated measures (MMRM) with unstructured covariance. Secondary efficacy parameters included changes in clinician-rated CGI-S and HAMD-17 total scores, which were analyzed by analyses of covariance (ANCOVA). Statistical analyses and determination of sample size are discussed in the Supplementary text, Supplemental digital content 1, *http://links.lww.com/ICP/A66*.

Safety

Physical examinations, clinical laboratory tests (hematology, chemistry, urinalysis), urine pregnancy tests (females of childbearing potential), and monitoring of AEs, vital signs, and suicide risk [patient and clinic Columbia-Suicide Severity Rating Scale (C-SSRS)] (Posner *et al.*,

Fig. 1



Change from baseline in MADRS total score for (a) mLOCF[a] MMRM[b] clinic visits centered around week 6 for 30 U, and observed data ANCOVA, modified intent-to-treat for (b) 30 U treatments and (c) 50 U treatments. [a]mLOCF was used to impute missing values for follow-up visits. [b]The MMRM model used for combined dose cohort included treatment (BOTOX vs. placebo), visit (weeks 3, 6, and 9), treatment-by-visit interaction, dose cohort (30U vs. 50U), and investigator center as fixed effects; baseline clinic MADRS total score, duration of illness, and number of previous depression episodes as covariates; and patient was included as a random effect. The same model with dose cohort excluded was used for each dose cohort. Within each dose cohort, sites with fewer than 10 patients were combined into one pseudo-site. The '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 (onabotA vs. placebo) and investigator center as fixed effects, with baseline clinic 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. ANCOVA, analysis of covariance; MADRS, Montgomery-Åsberg Depression Rating Scale; LS, least squares, mLOCF, modified last observation carried forward; MMRM, mixed-model repeated measures; U, units; mITT, modified intent-to-treat.

2011) were conducted. The female clinical version of the Changes in Sexual Functioning Questionnaire Short Form 14-item Version (CSFQ SF-14) (Clayton et al., 1997a, 1997b) was administered.

Results

Patient disposition and characteristics

The modified intent-to-treat (mITT) population consisted of 255 patients who received treatment and were randomized as follows: onabotA 30 U (n = 65), 50 U (n = 65), or matching placebo [30 U (n = 58) and 50 U (n = 67)]. Of the mITT population, 220 completed through week 9 and 139 completed through week 24 (Supplementary Fig. 2, Supplemental digital content 1, *http://links.lww.com/ICP/A66*). Premature discontinuation rates were comparable for combined placebo (44.5%) and combined onabotA (47.7%) patients. Per-protocol exit (relapse at or after week 12) rates were onabotA 30 U (7.7%) and matching placebo (13.6%); onabotA 50 U (10.8%) and matching placebo (13.0%). Overall the discontinuation reasons and rates were similar among groups (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/ICP/A66*). Patient baseline characteristics are summarized in Supplementary Table 2 (Supplemental digital content 1, *http://links.lww.com/ICP/A66*) and overall were generally comparable across treatment groups.

Efficacy assessments

Primary

OnabotA 30 U approached statistical significance at the primary endpoint [$P = 0.053$; MMRM, mLOCF, week 6; least-squares mean difference (LSMD)= –3.7] (Fig. 1a), but the symptom improvement was significant [at level $P < 0.05$ (two-sided)] at weeks 3 and 9 (Table 1). In weeks 3–9, onabotA 30 U effect sizes were 0.348–0.521. For the ANCOVA (observed data), LSMDs from baseline to week 15 ranged from –4.0 to –5.9 but leveled off from weeks 18–21 (Fig. 1b). Prevalence of missing assessments at week 12 makes statistical comparisons after this timepoint descriptive and should be interpreted with caution. Additionally, the study design and requirement for patients to exit in the event of relapse may have positively selected for those who responded well to treatment after week 12.

OnabotA 50 U did not separate from placebo for 15 weeks following treatment (observed data, ANCOVA), but changes appeared numerically better than placebo in weeks 18–24 (Fig. 1c). Remote-rater MADRS results were similar to the trends observed in the in-clinic scores. In the onabotA 30 U group, improvement was greater with onabotA treatment compared to placebo at every visit and at week 6 treatment difference = –5.6 ($P = 0.034$) (Supplementary Fig. 3a, Supplemental digital content 1, *http://links.lww.com/ICP/A66*]. OnabotA 50 U did not separate from placebo or appear numerically improved until week 12 in the remote-rater results (Supplementary Fig. 3b, Supplemental digital content 1, *http://links.lww.com/ICP/A66*).

Secondary

Treatment with onabotA 30 U consistently reduced CGI-S scores from baseline to week 24 (Fig. 2a), and reached significance at $P < 0.05$ (two-sided) for weeks 3 (observed data, ANCOVA; LSMD: –0.4; $P = 0.046$), week 6 (–0.5; $P = 0.036$), week 12 (–0.5; $P = 0.050$), week 15 (–0.8; $P = 0.004$), and week 21 (–0.5; $P = 0.046$). Similar to the primary efficacy variable, onabotA 50 U did not show significant treatment/placebo differences from baseline through week 15 in CGI-S scores changes (Fig. 2b), but did demonstrate a numerically greater symptom improvement compared to placebo, which became evident in weeks 18–24 (but as previously stated, these data should be interpreted with caution). OnabotA 30 U numerically reduced HAMD-17 total scores (observed data, ANCOVA) compared to placebo from baseline

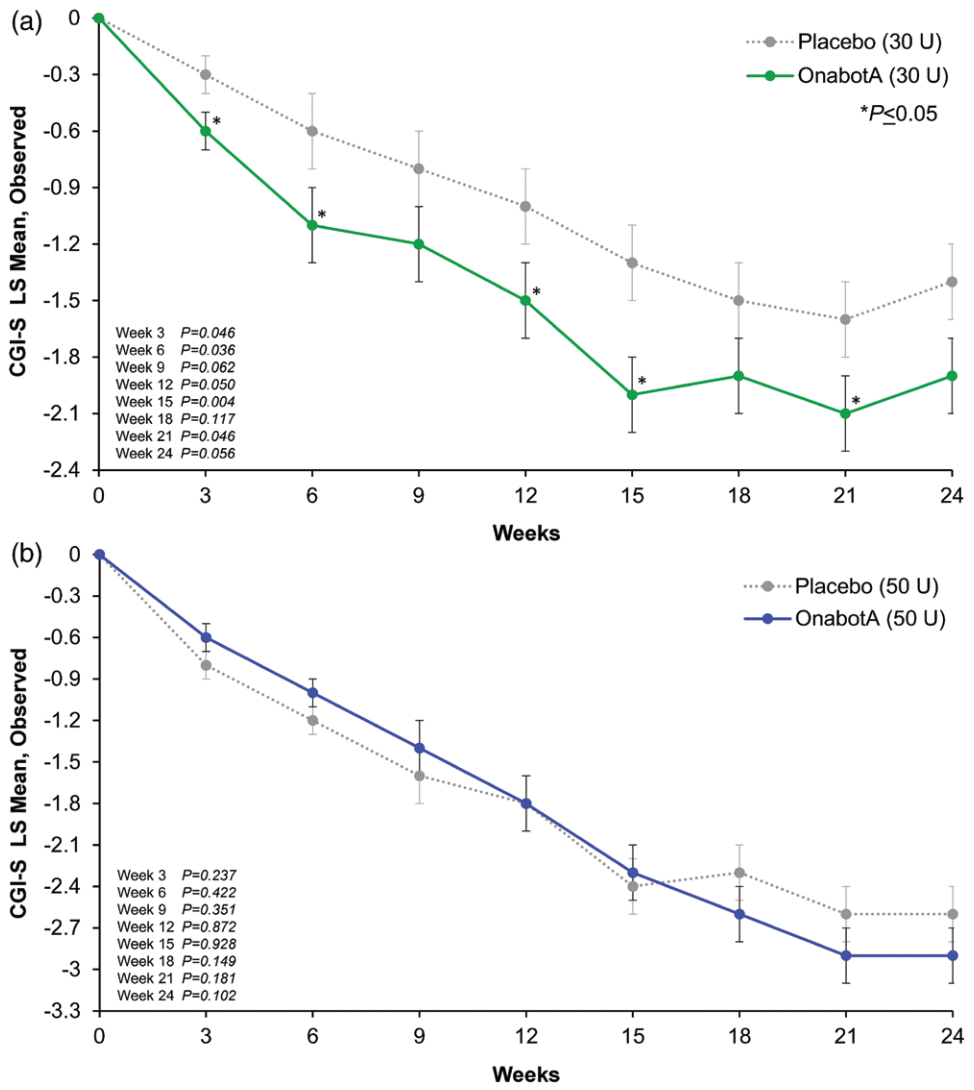
Table 1 Change from baseline to week 6 in Clinic Montgomery-Åsberg Depression Rating Scale total score (modified last observation carried forward, mixed-model repeated measures[a], modified intent-to-treat population)

	30 U		50 U	
	OnabotA (n = 65)	Placebo (n = 58)	OnabotA (n = 65)	Placebo (n = 67)
MADRS total score (MMRM)				
Mean (SD) at baseline	32.0 (4.12)	31.4 (3.99)	32.0 (4.44)	32.4 (5.34)
Mean (SD) at week 3	23.1 (9.74)	26.8 (7.35)	23.8 (8.70)	22.9 (9.01)
Change from baseline LS mean (SE)	−7.8 (1.1)	−3.6 (1.1)	−7.8 (1.1)	−8.8 (1.1)
LSMD (*P* value)	−4.2 (0.005)		1.1 (0.491)	
Mean (SD) at week 6	19.3 (11.79)	22.4 (9.68)	20.1 (9.38)	18.8 (10.06)
Change from baseline LS mean (SE)	−11.6 (1.4)	−7.9 (1.4)	−11.5 (1.2)	−12.9 (1.2)
LSMD (*P* value)	−3.7 (0.053)		1.3 (0.424)	
Mean (SD) at week 9	17.2 (10.42)	20.3 (9.67)	17.9 (9.95)	17.3 (10.89)
Change from baseline LS mean (SE)	−13.7 (1.3)	−10.0 (1.4)	−13.7 (1.3)	−14.4 (1.3)
LSMD (*P* value)	−3.6 (0.049)		0.7 (0.695)	

LS, least squares; LSMD, least-squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; mLOCF, modified last observation carried forward; MMRM, mixed-model repeated measures; U, units.

[a]The MMRM model used for combined dose cohort included treatment (OnabotA vs. placebo), visit (weeks 3, 6, and 9), treatment-by-visit interaction, dose cohort (30 U vs. 50 U), and investigator center as fixed effects; baseline clinic MADRS total score, duration of illness, and number of previous depression episodes as covariates; and patient was included as a random effect. The same model with dose cohort excluded was used for comparison within each dose cohort. Within each dose cohort, sites with fewer than 10 patients were combined into one pseudo-site.

Fig. 2



Change from baseline in CGI-S score (observed data, ANCOVA, mITT population) for (a) 30 U and (b) 50 U treatments. 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 (onabotA vs. placebo) and investigator center as fixed effects, with baseline clinic CGI-S 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. ANCOVA, analysis of covariance; CGI-S, clinical global impressions-severity; LS, least squares; mITT, modified intent-to-treat; U, unit.

to week 12, but statistical significance at level $P < 0.05$ (two-sided) was only reached at week 15 ($P = 0.032$), and the differences leveled off from weeks 18–24 (Fig. 3a). Treatment with onabotA 50 U did not reduce HAMD-17 total scores (improve depressive symptoms) compared to placebo from baseline to week 15, but a numerically greater depressive symptom reduction vs. placebo was observed from weeks 18–24 (Fig. 3b).

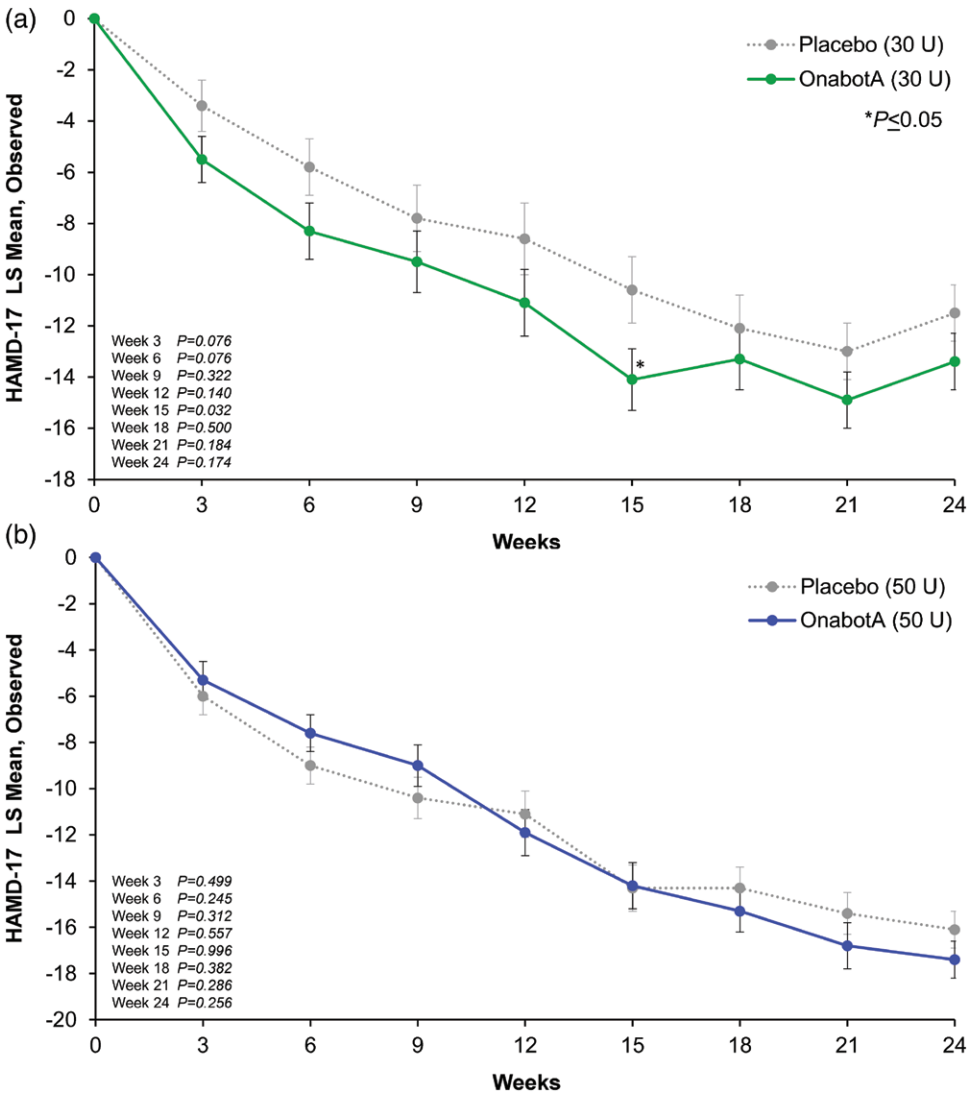
Additional

Few patients were withdrawn from the study due to rescue interventions, and these rates were similar between the onabotA groups (n = 2; 1.5%) and placebo groups (n = 3; 2.4%). Blinding assessment results are presented in Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/ICP/A66*; the highest proportion of patients who believed their treatment was real medication was in the onabotA 50 U group. Clinician and remote raters consistently showed lower frequencies of belief their onabotA patients received onabotA compared to patients.

Safety assessments

Mean durations to study exit were 131.7 and 129.4 days, for combined onabotA and placebo groups, respectively. Common AEs are summarized in Table 2. The

Fig. 3



Change from baseline in HAMD-17 score (observed data, ANCOVA, mITT population) for (a) 30 U, (b) 50 U treatments. 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 (onabotA vs. placebo) and investigator center as fixed effects, with baseline clinic HAMD-17 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. ANCOVA, analysis of covariance; HAMD-17, 17-item Hamilton Depression Rating Scale; LS, least squares; mITT, modified intent-to-treat; U, units.

only treatment-emergent AE that occurred in ≥10% of patients in any group was headache; eyelid ptosis and upper respiratory tract infection were the only AEs occurring in ≥5% in any onabotA group and greater than the placebo group. Although eyelid ptosis is a known local effect of onabotA injections, headache may be related to the procedure, as the incidence was similar for onabotA and placebo in the pooled 30 U and 50 U groups in the current study (onabotA, 15.4%; pbo, 15.2%), as well as in registration GL studies (Brin *et al.*, 2009). Most AEs were considered unrelated to treatment, comparable across treatment groups, and consistent with previously published trials using a similar injection paradigm in both patients with MDD and nondepressed populations (Brin *et al.*, 2009; Wollmer *et al.*, 2012). Reported rates of systemic AEs, including gastrointestinal effects, were low, generally balanced across treatment groups, and did not include any sexual side effects. Additionally, suicide risk and sexual functioning (measured with the C-SSRS and CSFQ scales, respectively) rates were similar among treatment groups (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/ICP/A66*).

Table 2 Summary of adverse events occurring in ≥2% of patients in either onabotA groups (safety population)

	30 U		50 U	
Preferred term	OnabotA (n = 65)	Placebo (n = 58)	OnabotA (n = 65)	Placebo (n = 67)
Overall; n (%)	32 (49.2)	23 (39.7)	39 (60.0)	38 (56.7)
Headache	9 (13.8)	4 (6.9)	11 (16.9)	15 (22.4)
Upper respiratory infection	3 (4.6)	1 (1.7)	4 (6.2)	3 (4.5)
Nasopharyngitis	2 (3.1)	3 (5.2)	3 (4.6)	6 (9.0)
Influenza	3 (4.6)	1 (1.7)	2 (3.1)	0
Sinusitis	4 (6.2)	4 (6.9)	0	0
Urinary tract infection	0	1 (1.7)	3 (4.6)	0
Eyelid ptosis	4 (6.2)	0	2 (3.1)	0
Back pain	1 (1.5)	1 (1.7)	3 (4.6)	2 (3.0)
Insomnia	1 (1.5)	1 (1.7)	2 (3.1)	1 (1.5)
Diarrhoea	2 (3.1)	2 (3.4)	1 (1.5)	3 (4.5)
Skin tightness	1 (1.5)	0	2 (3.1)	0
Blood pressure increased	0	0	2 (3.1)	0
Oropharyngeal pain	0	0	2 (3.1)	0

Discussion

Following a single-treatment session, neither onabotA 30 U nor 50 U demonstrated statistically significant superiority over placebo at the primary endpoint, but onabotA 30 U showed consistent numerical improvement in depressive symptoms compared to placebo up to week 15 with statistical separation from placebo for MADRS changes at weeks 3 and 9. OnabotA 30 U/placebo MADRS differences (observed, ANCOVA) of ≥4.0 points (up to week 15) and ≥2.0 points (weeks 18–24) agree with the 2-point MADRS change threshold generally considered clinically relevant in MDD trials (Montgomery and Moller, 2009). OnabotA 30 U effect sizes from weeks 3–9 ranged from 0.348 to 0.521 and were comparable to those observed in oral ADTs (Turner *et al.*, 2008). Treatment with onabotA 30 U significantly [at level $P < 0.05$ (two-sided)] reduced CGI-S scores compared to placebo at each visit from week 3–21, except at weeks 9 and 18. Numerical decreases in both CGI-S scores and HAMD-17 total scores with 30 U onabotA treatment compared to placebo were observed through the end of the study. These results indicate that a single-treatment session with onabotA 30 U may have long-acting effects on depression symptoms up to 18 weeks post-treatment, which may increase adherence compared to treatments administered daily or weekly.

Treatment with onabotA 50 U did not improve depressive symptoms in the primary or second efficacy assessments. This lack of superiority to placebo may be partially attributed to high placebo response, which was considerably higher than the 30 U matching placebo response. Possible reasons for the heightened placebo response in the 50 U matching group include a greater number of injections, which is consistent with more invasive procedures corresponding to greater placebo response, possible differences in sites that administered the 50 U dose vs. 30 U dose, and potentially heightened expectations of results if patients were aware that the typical dose given in the glabellar region for cosmetic purposes was lower and at fewer injection sites. Notwithstanding the potentially clinically meaningful differences in onabotA 30 U and 50 U dose efficacy results at later timepoints, these results should be viewed with caution to prevent overinterpretation as a pharmacologic effect in MDD, given the enriched population and lack of separation between onabotA 50 U and matching placebo before required patient discontinuation in the case of lack of response at week 12. It should be noted that the results presented herein correspond to onabotA, a specific formulation of botulinum neurotoxin type A. Different formulations of botulinum neurotoxin type A have distinct safety and efficacy profiles and clinical doses expressed in units are not interchangeable from one botulinum toxin product to another.

Previous investigator-initiated trials of onabotA for MDD treatment indicated statistically significant improvement in depressive symptoms compared to placebo (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014, Magid *et al.*, 2014). Key differences in the designs of the present and previous trials exist, which may explain the lack of significant changes observed with onabotA 30 U treatment in some measures and/or timepoints. The present study had the largest sample population to date for an onabotA MDD trial, investigated only female patients, did not select for prior ADT resistance, or allow concomitant use of additional ADTs. A previous study of onabotA effects on MDD indicated that the antidepressive effects persisted for at least 24 weeks (Magid *et al.*, 2014), which exceeds the duration of cosmetic effects on glabellar lines (approximately 12–16 weeks). This led investigators to hypothesize the efficacy in reducing depressive symptoms was not completely related or attributed to the paralytic effects, and the results presented herein agree with this hypothesis.

One potential theory for the reduction of depressive symptoms with onabotA treatment is the 'facial feedback hypothesis', which states that expressive behavior can alter emotional states, likely through afferent sensory modulation (Izard, 1990, McIntosh, 1996). Corrugator muscles, which are activated during negative emotions

(e.g. fear, anger, and sadness) (Ekman and Friesen, 1978), are relatively over-reactive in patients with depressive disorders (Schwartz *et al.*, 1976). Imaging studies have shown that when subjects, without a history of psychiatric illness, mimicked angry expressions, they demonstrated decreased left amygdala activity after treatment with botulinum toxin in the glabellar region in addition to reduced functional coupling between left amygdala and dorsal brainstem (Hennenlotter *et al.*, 2009). The decreased activity may be attributed to the reduction in motor nerve activity associated with dynamic facial expressions and/or proprioceptive sensory input following local treatment. Furthermore, facial somatic sensory afferents synapse in the descending trigeminal nucleus with monosynaptic connections to amygdala (Burstein and Potrebic, 1993), hypothalamus (Malick and Burstein, 1998), nucleus accumbens (Burstein and Giesler, 1989), and thalamus (Burstein *et al.*, 1990), suggesting a pathway for facial afferents to directly influence limbic networks.

Limitations of this study included a relatively small sample size in each treatment group, lack of generalizability to male patients, and the study design, which effectively created two parallel studies with different treatment sites and different investigators. The exploratory and descriptive nature of data after week 12, because of the decreased number of observed values due to high attrition rates, partially due to the study design that required relapsed patients to exit, thereby positively selecting responders, is also a noted limitation. To prevent compromising of blinding by drawing attention to the neuromuscular effects of onabotA treatment, this trial did not assess any correlations between muscle contraction or effect on facial muscles, and efficacy in treating MDD.

The results presented herein are preliminary and thus require further assessment. The onabotA 30 U drug/placebo differences exceeding those generally considered clinically relevant supports moving forward to the next phase of clinical development. Future studies should consider assessment of efficacy of MDD treatment in males and mixed gender populations and its use as an adjunctive treatment to standard ADTs. The efficacy in treatment-resistant patient populations, those with known adherence issues, or sensitivity to AEs related to oral ADTs may also be informative because of the unmet treatment needs in these groups. Elucidating the potential role for this treatment in the management of MDD is important because of its many advantages, including low reported systemic adverse effects, particularly those seen with standard oral ADTs (e.g. sexual dysfunction and gastrointestinal), established safety profile, and the potential for increased compliance compared to daily oral medications because of the long-lasting effects of a single-treatment session. The limited drug/drug interactions of the local onabotA treatment allow it to be used with medications for comorbid conditions or as an adjunctive treatment with conventional ADTs.

OnabotA 30 U consistently reduced depressive symptoms throughout the 24-week observational period following a single-therapeutic session. Both onabotA treatments were well tolerated with most AEs similar to placebo and consistent with previously reported data for comparable doses in both depressed (Wollmer *et al.*, 2012; Finzi and Rosenthal, 2014; Magid *et al.*, 2014) and nondepressed patients (Brin *et al.*, 2009). Additionally, headache and eyelid ptosis were temporary, local to the treatment site, and well tolerated as reported in previous onabotA trials with facial injections, including chronic migraine (Brin *et al.*, 2009; Diener *et al.*, 2014). OnabotA is a nonsystemic intervention with relatively low incidence gastrointestinal and no sexual side effects reported, which may offer safety and tolerability advantages compared to currently available ADTs. The long-lasting effects of a single-injection session may increase treatment adherence compared with the use of a daily oral ADT. A Phase 3 clinical trial is planned for the further assessment of botulinum toxin type A as a treatment for MDD.

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