Safety and tolerability of onabotulinumtoxinA in the treatment of upper facial lines from global registration studies in 5298 participants: A meta-analysis

Mitchell F. Brin, MD,[a,b] Koen De Boulle, MD,[c] Steven Liew, MBBS,[d] Alastair Carruthers, MD,[e] Jean Carruthers, MD,[e] Alexander Rivkin, MD,[f] Yan Wu, MD, PhD,[g] Makoto Kawashima, MD,[h] Irina Yushmanova, MD,[a] Terry I. Boodhoo, MS,[a] and Elisabeth Lee, MPH[a]

Background: Since its discovery as a facial aesthetic treatment >30 years ago, onabotulinumtoxinA has received worldwide approval for dynamic upper facial line treatment.

Objective: Meta-analysis examining the safety of onabotulinumtoxinA for treatment of glabellar lines (GL), crow's feet lines (CFL), and forehead lines (FHL).

Methods: Participants (N = 5298) with moderate to severe GL, CFL, or FHL at maximum contraction received onabotulinumtoxinA or placebo in 1 of 18 registration studies (14 double-blind, placebo-controlled [DBPC]; 1 double-blind; 3 open-label). Adverse events (AEs) were analyzed by descriptive statistics and fixed-effects meta-analysis.

Results: In the overall double-blind placebo-controlled (DBPC) population, AEs were reported in 1443 (42.1%) and 486 (35.8%) participants in the onabotulinumtoxinA (n = 3431) and placebo (n = 1359) groups, respectively. Serious AEs were reported in 54 (1.6%) and 17 (1.3%) participants; 1 (spontaneous abortion) was considered possibly treatment related by the investigator. Using fixed-effects statistical meta-analysis, AEs of interest that were found to be statistically higher for onabotulinumtoxinA than placebo in the DBPC population were eyelid ptosis, eyelid sensory disorder, skin tightness, brow ptosis, eyelid edema, and facial pain ($P \leq .05$).

Limitations: Retrospective, ad hoc analysis.

Conclusion: This meta-analysis confirms the onabotulinumtoxinA safety profile for GL, CFL, and FHL treatment, with no new onabotulinumtoxinA-associated AEs. (JAAD Int 2024;14:4-18.)

From the Allergan Aesthetics, an AbbVie Company, Irvine, California[a]; University of California, Irvine, California[b]; Aalst Dermatology Clinic, Aalst, Belgium[c]; Private Practice, Sydney, NSW, Australia[d]; University of British Columbia, Vancouver, British Columbia, Canada[e]; Private Practice, Los Angeles, California[f]; Peking University First Hospital, Beijing, China[g]; and Tokyo Women's Medical University School of Medicine, Tokyo, Japan.[h]

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Correspondence to: Mitchell F. Brin, MD, Allergan Aesthetics, an AbbVie Company, 2525 Dupont Dr, T2-3, Irvine, CA 92623-9534. E-mail: Mitchell.Brin@Allergan.com.

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INTRODUCTION

Over 30 years ago, onabotulinumtoxinA was found to have potential aesthetic applications in addition to its therapeutic indications.[1-5] Since then, onabotulinumtoxinA efficacy and safety data from aesthetic indication clinical trials have been published in approximately 500 peer-reviewed journal articles.[6] OnabotulinumtoxinA is now approved for upper facial lines, including glabellar lines (GL), crow's feet lines (CFL), and forehead lines (FHL).[6]

A previous meta-analysis by Brin et al[7] examined the safety and tolerability of onabotulinumtoxinA in more than 1600 participants treated for GL and CFL in 9 studies. Adverse events (AEs) associated with onabotulinumtoxinA were generally mild to moderate, and most treatment-related AEs were associated with local pharmacological effect or injection techniques.

This updated meta-analysis examines the onabotulinumtoxinA safety profile using data pooled from 18 studies in 5298 participants treated for GL, CFL, and FHL.

CAPSULE SUMMARY

- This update of a 2009 meta-analysis of the safety and tolerability of onabotulinumtoxinA more than triples the number of participants ($N = 5298$; 18 studies) and includes additional facial aesthetic indications.
- The onabotulinumtoxinA safety profile remained consistent with the product label, and no new signals emerged from the pooled populations.

METHODS

Study selection

Double-blind, placebo-controlled (DBPC), double-blind (DB), and open-label (OL) clinical studies of onabotulinumtoxinA for the treatment of GL, CFL, or FHL, and combinations thereof, were analyzed.[7-23] These registration studies adhered to all regulatory guidelines for product licensure, and were conducted by Allergan (an AbbVie Company) or its business partners. All studies were completed, with databases locked and study reports available. All studies complied with the Declaration of Helsinki, included written informed consent, and were approved by an institutional review board (IRB).

Participants

Enrolled participants had investigator-rated moderate to severe, bilaterally symmetrical GL, CFL, or FHL at maximum contraction (frowning for GL; smiling for CFL; eyebrow elevation for FHL), based on Allergan's validated facial wrinkle scales.

Assessments

Analyses were based on pooled safety populations overall (participants who received ≥1 injection of onabotulinumtoxinA or placebo) and by primary study treatment area (eg, GL, CFL, FHL). Demographic and disposition data were summarized by treatment group, while safety data were analyzed by treatment area, simultaneous treatment areas, and treatment cycle (as applicable). All AEs were classified by Medical Dictionary for Regulatory Activities, Version 21.1 (MedDRA) preferred terms (Table I) and were evaluated for possible distant spread of toxin (PDSOT) beyond the injection site. Subsequent to the present analysis, a preferred term, "Mephisto sign," was introduced into MedDRA. Therefore, in this analysis, where appropriate, some instances of skin tightness were reassessed as a Mephisto sign.

Statistical analysis

AEs were coded using MedDRA 21.1 and summarized using descriptive statistics. A fixed-effects meta-analysis assumes that the studies being analyzed can be considered homogeneous; that is, they all share the same "effect size" (common odds ratio for AEs in this case) and can be combined to estimate it. This assumption can be tested by evaluating the level of heterogeneity among studies being combined. Study heterogeneity was assessed separately for each AE using the Q statistic and I^2 index[24]; AEs with $I^2 \leq 50\%$ were considered homogeneous and could be combined.[25] Incidence data for each homogeneous AE were fitted to fixed-effects meta-analytic models, using both the Peto method and Mantel–Haenszel method with continuity correction proportional to the reciprocal of the relative size of the opposite treatment group.[26] AEs with high heterogeneity were not considered suitable to combine, and were evaluated descriptively by study. Comparisons between onabotulinumtoxinA and placebo were performed for treatment areas individually and

Abbreviations used:

AE:	adverse event
CFL:	crow's feet lines
DB:	double-blind
DBPC:	double-blind placebo-controlled
FHL:	forehead lines
GL:	glabellar lines
MedDRA:	Medical Dictionary for Regulatory Activities
OL:	open label
PDSOT:	possible distant spread of toxin
SAE:	serious adverse event

collectively using the first 90 days of DBPC treatment cycle 1 to ensure comparable exposure across studies. Fisher's exact test was used to compare treatments for areas with only 1 DBPC study (FHL/GL/CFL simultaneously treated) or 2 DBPC studies with the same participants (CFL/GL simultaneously treated). All tests other than those for homogeneity were two-sided and conducted at the 0.05 significance level, with no adjustment for multiplicity as a conservative approach that was deemed appropriate for this safety analysis. SAS version 9.4 (SAS) was used for all statistical analyses.

RESULTS

The analysis included 14 DBPC, 1 DB, and 3 OL registration studies (Table II): 9 studies from the previous meta-analysis (ie, 4 DBPC GL, 3 OL GL, and 2 DBPC CFL studies)[7] and 9 additional studies (ie, 3 DBPC CFL, 2 DBPC CFL/GL, 1 DB CFL/GL, 2 DBPC FHL/GL, and 1 DBPC FHL/GL/CFL).[14-21,23] This report focuses on data pooled from the 14 DBPC studies (DBPC population).[8-10,12,14-23]

Participants

Participants from 14 DBPC studies (N = 4690) were predominantly White (68.7%) or Asian (24.5%) and female (85.9%), with a median (range) age of 47.0 (18.0-85.0) years. Four DBPC studies were conducted in Asia (n = 1083) and 10 in North America/Europe (n = 3607). The total exposure population (N = 4449) was treated for GL only (n = 1269), CFL only (n = 1415), CFL/GL (n = 505), FHL/GL (n = 514), and FHL/GL/CFL (n = 746). Demographics were similar to those previously reported for the DBPC population (Table III).[7]

Adverse events

Descriptive summary. AEs were reported in 42.1% and 35.8% of the onabotulinumtoxinA and placebo groups, respectively, and most commonly (≥2%) were headache, nasopharyngitis, injection site bruising, and upper respiratory tract infection (Table IV). In the onabotulinumtoxinA group, subjects reported the following: eyelid ptosis (1.1%; n = 38), eyelid sensory disorder (<1%; n = 26), eyelid edema (<1%; n = 12). Oral herpes, influenza, and injection site pain were numerically lower in incidence for the onabotulinumtoxinA group versus placebo.

Assessment of homogeneity. Across all treatment areas, 2 events, nasopharyngitis (GL; I^2 = 51.46; P value associated with the Q statistic = 0.103) and upper respiratory tract infection (FHL/GL; I^2 = 65.20; P = .056), had heterogeneity. Study-level treatment group incidence rates for nasopharyngitis varied, ranging from respective onabotulinumtoxinA and placebo incidence rates of 18.9% and 6.1% in 1 study to 3.0% and 6.7% in another study. Similarly, respective incidence rates for upper respiratory tract infection varied, ranging

Table I. MedDRA preferred terms used to evaluate PDSOT

Cardiac disorders	Nervous system disorders
Bradycardia	Bulbar palsy
	Cranial nerve palsies, multiple
Eye Disorders	Cranial nerve paralysis
Accommodation disorder	Dysarthria
Diplopia	Facial paralysis
Extraocular muscle paresis	Facial paresis
Eyelid function disorder	Hyporeflexia
Eyelid ptosis	Hypotonia
Pupillary reflex impaired	Paralysis
Vision blurred	Paresis cranial nerve
	Peripheral nerve palsy
Gastrointestinal Disorders	Peripheral paralysis
Constipation	Speech disorder
Dry mouth	Vocal cord paralysis
Dysphagia	Vocal cord paresis
Ileus paralytic	
	Renal and urinary disorders
Respiratory, thoracic, and mediastinal disorders	Urinary retention
Aspiration	
Diaphragmatic paralysis	Reproductive system and breast disorders
Dysphonia	Pelvic floor muscle weakness
Dyspnea	
Pneumonia aspiration	Infections and infestations
Respiratory arrest	Botulism
Respiratory depression	
Respiratory failure	Musculoskeletal and connective tissue disorders
	Muscular weakness

MedDRA, Medical Dictionary for Regulatory Activities; *PDSOT*, possible distant spread of toxin.

Table II. Study characteristics and number of participants included in meta-analysis of safety of onabotulinumtoxinA for upper facial lines

Indication	Type of study (publication/study completion date)	Location	Dose/treatment, cycles	Duration, wk	DBPC population, *n*		Total exposure population
					OnabotA	Placebo	
GL	DBPC (2002)[8]	North America	20 U 1 cycle	16	203	60	203
	DBPC (2003)[27]	North America	20 U 1 cycle	16	202	70	202
	OL (2004)[11]	North America	20 U 1 cycle	16	0	0	96
	OL/191622-907 (2001)[7]	Japan	20 U 1 cycle	16	0	0	125
	DBPC (2008)[10]	Japan	10 or 20 U 1 cycle	16	90	49	90
	OL (2009)[13]	Japan	10 or 20 U 1 cycle	64	0	0	363
	DBPC (2010)[22]	China	20 U 1 cycle	16	170	57	190
CFL	DBPC (2005)[12]	EU	6-36 U 1 cycle	24	130	32	130
	DBPC/191622-514 (2004)[7]	EU	12-36 U 1 cycle	12	149	48	149
	DBPC (2014)[16,*]	North America/EU	24 U 1 cycle	20	220	224	220
	DBPC (2017)[23,*]	Japan	12 U, 24 U Up to 5 cycles	56	203	97	294
	DBPC (2019)[20,*]	China	24 U 1 cycle	20	316	101	316
CFL and CFL/GL	DBPC (2015)[14,*]	North America/EU	CFL: 24 U GL: 20 U 2 cycles	32	611	306	611
	DBPC (2015)[15,*,†]	North America/EU	CFL: 24 U GL: 20 U 2 cycles	20	100	0	100
CFL/GL	DB (2020)[21,*]	Japan	CFL: 12 U or 24 U + GL: 20 U Up to 5 cycles	56	0	0	100
FHL/GL	DBPC (2016)[17,*]	Canada	FHL: 10 U or 20 U +	24	116	59	116
	DBPC (2017)[18,*]	North America/EU	GL: 20 U 1 cycle FHL: 20 U + GL: 20 U Up to 3 cycles	52	290	100	374
FHL/GL and FHL/GL/CFL	DBPC (2018)[19,*]	North America/EU	FHL: 20 U + GL: 20 U or FHL: 20 U + GL: 20 U + CFL: 24 U Up to 3 cycles	52	318 313	156 156	318 746
Total					3431	1359	4449

CFL, Crow's feet lines; *CFL/GL*, crow's feet lines and glabellar lines combined; *DBPC*, double-blind placebo-controlled; *EU*, European Union; *GL*, glabellar lines; *OL*, open-label; *OnabotA*, onabotulinumtoxinA.

*New studies relative to Brin et al.[7]

†Extension of study 099, with 684 participants (onabotulinumtoxinA, *n* = 588 [including new exposure; *n* = 100]; placebo, *n* = 96).

Table III. Demographics by analysis population and treatment areas

	All DBPC		GL DBPC		CFL DBPC		CFL + GL DBPC		FHL + GL DBPC		FHL + GL + CFL DBPC		All OnabotA
	OnabotA (*N* = 3431)	Placebo (*N* = 1359)	OnabotA (*N* = 665)	Placebo (*N* = 236)	OnabotA (*N* = 1324)	Placebo (*N* = 808)	OnabotA (*N* = 405)	Placebo (*N* = 306)	OnabotA (*N* = 724)	Placebo (*N* = 315)	OnabotA (*N* = 313)	Placebo (*N* = 156)	(*N* = 4449)
Age, y													
Median	47.0	47.0	44.0	46.0	48.0	47.0	50.0	49.0	47.0	47.0	45.0	48.0	47.0
Range	18-85	22-74	22-78	22-69	22-75	22-74	24-85	25-73	18-77	22-73	21-76	22-73	18-85
Sex, *n* (%)													
Female	2953 (86.1)	1163 (85.6)	557 (83.8)	203 (86.0)	1131 (85.4)	681 (84.3)	355 (87.7)	263 (85.9)	626 (86.5)	279 (88.6)	284 (90.7)	140 (89.7)	3860 (86.8)
Male	478 (13.9)	196 (14.4)	108 (16.2)	33 (14.0)	193 (14.6)	127 (15.7)	50 (12.3)	43 (14.1)	98 (13.5)	36 (11.4)	29 (9.3)	16 (10.3)	589 (13.2)
Race, *n* (%)													
White	2379 (69.3)	933 (68.7)	341 (51.3)	107 (45.3)	740 (55.9)	543 (67.2)	358 (88.4)	265 (86.6)	655 (90.5)	283 (89.8)	285 (91.1)	145 (92.9)	2657 (59.7)
Asian	822 (24.0)	329 (24.2)	269 (40.5)	110 (46.6)	529 (40.0)	209 (25.9)	6 (1.5)	6 (2.0)	16 (2.2)	10 (3.2)	2 (0.6)	1 (0.6)	1530 (34.4)
Black	48 (1.4)	24 (1.8)	21 (3.2)	7 (3.0)	12 (0.9)	10 (1.2)	4 (1.0)	2 (0.7)	9 (1.2)	7 (2.2)	2 (0.6)	3 (1.9)	57 (1.3)
Other	182 (5.3)	73 (5.4)	34 (5.1)	12 (5.1)	43 (3.2)	46 (5.7)	37 (9.1)	33 (10.8)	44 (6.1)	15 (4.8)	24 (7.7)	7 (4.5)	205 (4.6)

CFL, Crow's feet lines; *DBPC*, double-blind placebo-controlled; *FHL*, forehead lines; *GL*, glabellar lines; *OnabotA*, onabotulinumtoxinA.

Table IV. Adverse events occurring in ≥1% of participants occurring across all treatment areas (DBPC population)

	GL		CFL		CFL/GL		FHL/GL		FHL/GL/CFL		All	
Preferred term, *n* (%)	**OnabotA *N* = 665**	**Placebo *N* = 236**	**OnabotA *N* = 1324**	**Placebo *N* = 808**	**OnabotA *N* = 405**	**Placebo *N* = 306**	**OnabotA *N* = 724**	**Placebo *N* = 315**	**OnabotA *N* = 313**	**Placebo *N* = 156**	**OnabotA *N* = 3431**	**Placebo *N* = 1359**
Overall	300 (45.1)	94 (39.8)	483 (36.5)	293 (36.3)	210 (51.9)	136 (44.4)	312 (43.1)	99 (31.4)	138 (44.1)	52 (33.3)	1443 (42.1)	486 (35.8)
Headache	75 (11.3)	27 (11.4)	50 (3.8)	31 (3.8)	32 (7.9)	21 (6.9)	62 (8.6)	17 (5.4)	24 (7.7)	8 (5.1)	243 (7.1)	75 (5.5)
Nasopharyngitis	40 (6.0)	14 (5.9)	82 (6.2)	44 (5.4)	29 (7.2)	20 (6.5)	35 (4.8)	10 (3.2)	26 (8.3)	5 (3.2)	212 (6.2)	68 (5.0)
Injection site bruising	2 (0.3)	2 (0.8)	35 (2.6)	16 (2.0)	20 (4.9)	6 (2.0)	37 (5.1)	8 (2.5)	12 (3.8)	5 (3.2)	106 (3.1)	26 (1.9)
Upper RTI	4 (0.6)	2 (0.8)	29 (2.2)	17 (2.1)	16 (4.0)	11 (3.6)	14 (1.9)	5 (1.6)	5 (1.6)	1 (0.6)	68 (2.0)	24 (1.8)
Injection site hematoma	0 (0.0)	0 (0.0)	25 (1.9)	8 (1.0)	14 (3.5)	4 (1.3)	16 (2.2)	3 (1.0)	11 (3.5)	3 (1.9)	66 (1.9)	11 (0.8)
Sinusitis	8 (1.2)	3 (1.3)	14 (1.1)	13 (1.6)	10 (2.5)	7 (2.3)	15 (2.1)	4 (1.3)	6 (1.9)	3 (1.9)	53 (1.5)	20 (1.5)
Influenza	10 (1.5)	1 (0.4)	15 (1.1)	11 (1.4)	5 (1.2)	5 (1.6)	74 (1.0)	5 (1.6)	4 (1.3)	4 (2.6)	41 (1.2)	17 (1.3)
Bronchitis	6 (0.9)	3 (1.3)	16 (1.2)	9 (1.1)	10 (2.5)	6 (2.0)	6 (0.8)	0 (0.0)	2 (0.6)	0 (0.0)	40 (1.2)	12 (0.9)
Eyelid ptosis	16 (2.4)	0 (0.0)	0 (0.0)	1 (0.1)	5 (1.2)	1 (0.3)	15 (2.1)	1 (0.3)	2 (0.6)	1 (0.6)	38 (1.1)	2 (0.1)
Oral herpes	0 (0.0)	1 (0.4)	15 (1.1)	8 (1.0)	4 (1.0)	3 (1.0)	7 (1.0)	6 (1.9)	4 (1.3)	6 (3.8)	30 (0.9)	15 (1.1)
Injection site pain	16 (2.4)	4 (1.7)	4 (0.3)	6 (0.7)	3 (0.7)	3 (1.0)	5 (0.7)	3 (1.0)	0 (0.0)	0 (0.0)	28 (0.8)	13 (1.0)

Included only adverse events with incidence of ≥1% in either treatment group across all treatment areas in the DBPC population.
CFL, Crow's feet lines; *DBPC*, double-blind placebo-controlled; *FHL*, forehead lines; *GL*, glabellar lines; *OnabotA*, onabotulinumtoxinA; *RTI*, respiratory tract infection.

Table V. Adverse events across all treatment areas, filtered by $P \leq .050$ (DBPC population, treatment cycle 1, days 1-90)

Preferred term, *n* (%)	OnabotA (*N* = 3431)	Placebo (*N* = 1359)	*P* value	Treatment group favored
Overall	1136 (33.1)	395 (29.1)	.0103	OnabotA
Eyelid ptosis	34 (1.0)	1 (0.1)	.0024	OnabotA
Eyelid sensory disorder	25 (0.7)	1 (0.1)	.0024	OnabotA
Skin tightness	22 (0.6)	1 (0.1)	.0179	OnabotA
Brow ptosis	20 (0.6)	0	.0098	OnabotA
Diarrhea	7 (0.2)	9 (0.7)	.0054	Placebo
Eyelid edema	12 (0.3)	0	.0214	OnabotA
Facial pain	12 (0.3)	0	.0285	OnabotA
Lower RTI	4 (0.1)	6 (0.4)	.0129	Placebo
Pneumonia	3 (0.1)	5 (0.4)	.0345	Placebo
Rash	2 (0.1)	4 (0.3)	.0276	Placebo
Gastroesophageal reflux disease	1 (0.0)	3 (0.2)	.0357	Placebo
Periodontitis	0	3 (0.2)	.0054	Placebo
Visual impairment	0	2 (0.1)	.0229	Placebo
Adjustment disorder*	0	1 (0.1)	.0438	Placebo
Back injury	0	1 (0.1)	.0443	Placebo
Diabetes mellitus	0	1 (0.1)	.0443	Placebo
Fibromyalgia	0	1 (0.1)	.0443	Placebo
Gastrointestinal infection	0	1 (0.1)	.0438	Placebo
Leiomyoma	0	1 (0.1)	.0443	Placebo
Osteoarthritis	0	1 (0.1)	.0443	Placebo
Petechiae	0	1 (0.1)	.0443	Placebo
Perioral dermatitis	0	1 (0.1)	.0443	Placebo
Varicose vein	0	1 (0.1)	.0443	Placebo
Skin indentation	0	1 (0.1)	.0443	Placebo

Included only statistically significant adverse events ($P \leq .050$) across all treatment areas in the DBPC population. Statistical testing was based on a fixed-effects meta-analysis model using both the Peto method and the Mantel–Haenszel method. The minimum *P* value between the 2 methods is displayed.

DBPC, Double-blind placebo-controlled; *OnabotA*, onabotulinumtoxinA; *RTI*, respiratory tract infection.

*With depressed mood.

from 2.5% and 0.6% in 1 study to 0.3% and 3.0% in another study. The fixed modeling approach may not apply for these 2 events in these treatment areas as there was no consistent pattern related to onabotulinumtoxinA across the individual studies.

Fixed-effects statistical modeling. The meta-analysis statistical modeling method was applied to the DBPC population and GL, CFL, and FHL/GL treatment areas. Model-generated significant AEs were defined as those achieving $P \leq .05$ using either the Peto or Mantel–Haenszel methodologies. Fisher's exact tests were applied to the CFL/GL and FHL/GL/CFL treatment areas. The most common model-generated significant AEs for the DBPC population (all $P < .04$), regardless of treatment group, were eyelid ptosis, eyelid sensory disorder, skin tightness, brow ptosis, diarrhea, eyelid edema, facial pain, lower respiratory tract infection, pneumonia, rash, gastroesophageal reflux disease, periodontitis, and visual impairment (Table V). Considering the objective to describe the safety and tolerability of onabotulinumtoxinA, AEs favoring placebo were excluded following medical review. The remaining model-generated significant AEs (all $P < .03$) were eyelid ptosis, eyelid sensory disorder, skin tightness, brow ptosis, eyelid edema, and facial pain.

An analysis was also performed for each treatment area for any AE and by individual preferred term. This showed a significantly higher overall incidence of AEs reported with onabotulinumtoxinA than placebo for the GL treatment area (Table VI), with similar findings for FHL/GL and FHL/GL/CFL, whereas AEs overall did not significantly differ for CFL and CFL/GL.

From the individual preferred term analysis, AEs favoring onabotulinumtoxinA were eyelid ptosis and eyelid sensory disorder for GL treatment; eyelid edema, injection site hemorrhage, cough, arthropod bite, and injection site paresthesia for CFL; eyelid ptosis, skin tightness, brow ptosis, and head discomfort for FHL/GL; and nasopharyngitis for FHL/GL/CFL (Table VII).

Maximum cycle analysis. The effect of repeated onabotulinumtoxinA treatment was

Table VI. Adverse events across all treatment areas, filtered by $P \leq .050$ across all groups (DBPC population, treatment cycle 1, days 1-90)

	GL		CFL		CFL/GL		FHL/GL		FHL/GL/CFL		All	
Preferred term, *n* (%)	OnabotA *N* = 665	Placebo *N* = 236	OnabotA *N* = 1324	Placebo *N* = 808	OnabotA *N* = 405	Placebo *N* = 306	OnabotA *N* = 724	Placebo *N* = 315	OnabotA *N* = 313	Placebo *N* = 156	OnabotA *N* = 3431	Placebo *N* = 1359
Overall	282 (42.4)	85 (36.0)	NS	NS	NS	NS	273 (37.7)	84 (26.7)	122 (39.0)	45 (28.8)	1136 (33.1)	395 (29.1)
Eyelid ptosis	16 (2.4)	0	NS	NS	NS	NS	15 (2.1)	1 (0.3)	NS	NS	34 (1.0)	1 (0.1)
Eyelid sensory disorder	21 (3.2)	1 (0.4)	NS	NS	NS	NS	NS	NS	NS	NS	25 (0.7)	1 (0.1)
Skin tightness	NS	NS	NS	NS	NS	NS	10 (1.4)	0	NS	NS	22 (0.6)	1 (0.1)
Brow ptosis	NS	NS	NS	NS	NS	NS	11 (1.5)	0	NS	NS	20 (0.6)	0
Eyelid edema	NS	NS	5 (0.4)	0	NS	NS	NS	NS	NS	NS	12 (0.3)	0
Diarrhea	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	7 (0.2)	9 (0.7)
Facial pain	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	12 (0.3)	0
Lower RTI	NS	NS	1 (0.1)	3 (0.4)	NS	NS	NS	NS	NS	NS	4 (0.1)	6 (0.4)
Pneumonia	NS	NS	NS	NS	NS	NS	0	2 (0.6)	NS	NS	3 (0.1)	5 (0.4)
Periodontitis	NS	NS	0	2 (0.2)	NS	NS	NS	NS	NS	NS	0	3 (0.2)
Adjustment disorder*	NS	NS	0	1 (0.1)	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Back injury	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Diabetes mellitus	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Fibromyalgia	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Gastrointestinal infection	NS	NS	0	1 (0.1)	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Leiomyoma	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Osteoarthritis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Petechiae	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Skin indentation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Varicose vein	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Injection site pruritus	2 (0.3)	4 (1.7)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Rash	0	3 (1.3)	NS	NS	NS	NS	NS	NS	NS	NS	2 (0.1)	4 (0.3)
Gastroesophageal reflux disease	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	1 (0.0)	3 (0.2)
Visual impairment	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	2 (0.1)
Perioral dermatitis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	1 (0.1)
Neck pain	0	2 (0.8)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Injection site hemorrhage	NS	NS	8 (0.6)	1 (0.1)	NS	NS	NS	NS	NS	NS	NS	NS
Cough	NS	NS	6 (0.5)	0	NS	NS	NS	NS	NS	NS	NS	NS
Arthropod bite	NS	NS	4 (0.3)	0	NS	NS	NS	NS	NS	NS	NS	NS
Injection site paresthesia	NS	NS	4 (0.3)	0	NS	NS	NS	NS	NS	NS	NS	NS
Upper RTI	NS	NS	NS	NS	NS	NS	N/A	N/A	NS	NS	NS	NS
Dermatitis	NS	NS	0	3 (0.4)	NS	NS	NS	NS	NS	NS	NS	NS
Vision blurred	NS	NS	0	3 (0.4)	NS	NS	NS	NS	NS	NS	NS	NS
Dermatitis contact	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Eye pain	NS	NS	0	2 (0.2)	NS	NS	NS	NS	NS	NS	NS	NS
Large intestine polyp	NS	NS	0	1 (0.1)	NS	NS	NS	NS	NS	NS	NS	NS

Continued

Table VI. Cont'd

Preferred term, *n* (%)	GL		CFL		CFL/GL		FHL/GL		FHL/GL/CFL		All	
	OnabotA *N* = 665	Placebo *N* = 236	OnabotA *N* = 1324	Placebo *N* = 808	OnabotA *N* = 405	Placebo *N* = 306	OnabotA *N* = 724	Placebo *N* = 315	OnabotA *N* = 313	Placebo *N* = 156	OnabotA *N* = 3431	Placebo *N* = 1359
Toothache	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Oral herpes	NS	NS	NS	NS	NS	NS	NS	NS	2 (0.6)	5 (3.2)	NS	NS
Head discomfort	NS	NS	NS	NS	NS	NS	10 (1.4)	0	NS	NS	NS	NS
Nasopharyngitis	N/A	N/A	NS	NS	NS	NS	NS	NS	22 (7.0)	3 (1.9)	NS	NS

Included only statistically significant adverse events ($P \leq .050$) across all treatment areas in the DBPC population. For overall DBPC population, GL, CFL, and FHL/GL treatment areas, statistical testing was based on a fixed-effects meta-analysis model using both the Peto method and the Mantel–Haenszel method. The minimum *P* value between the 2 methods was used. For GL/CFL and FHL/GL/CFL treatment areas, statistical testing was based on Fisher's exact tests.

CFL, Crow's feet lines; *DBPC*, double-blind placebo-controlled; *FHL*, forehead lines; *GL*, glabellar lines; *N/A*, not applicable; *NS*, not significant; *OnabotA*, onabotulinumtoxinA, *RTI*, respiratory tract infection.

*With depressed mood.

assessed in the population (N = 142) who received onabotulinumtoxinA for CFL (n = 82) or GL (n = 60) across 5 possible treatment cycles. The AEs most commonly associated with onabotulinumtoxinA injection (injection site pruritus, eyelid sensory disorder, eyelid ptosis) decreased between the first and fifth cycles (Table VIII). Overall, there was a trend toward reduced AEs with repeated onabotulinumtoxinA treatment.

Characterization of onabotulinumtoxinA model–generated significant AEs

AEs of interest in onabotulinumtoxinA-treated participants, including eyelid ptosis, eyelid sensory disorder, skin tightness, brow ptosis, eyelid edema, and facial pain, occurred in the first 90 days of treatment cycle 1 for the DBPC population and were of mild to moderate severity (Table VII). Most occurred within the first week and generally resolved within a few weeks of treatment.

Eyelid ptosis. There were 37 cases of eyelid ptosis in 34 participants (1.0%), described verbatim as, for example, "eyelid ptosis," "drooping upper eyelid-bilateral," and "bilateral heavy eyelid." Thirty (81.1%) were mild in severity; the remainder were moderate. Most (81.1%) were reported within 14 days of treatment with a median onset of 9 days. Almost half (48.6%) of the cases resolved within 28 days of onset. The median duration was 28 days.

Eyelid sensory disorder. Twenty-five cases of eyelid sensory disorder were reported in 25 participants (0.7%); verbatim terms included "heavy feeling eyelids" and "feeling of impaired lid function." All were mild except for 1 of moderate severity. Most (88.0%) were reported within 14 days of treatment. Median onset was 4 days; 60% resolved within 28 days of onset. The median duration was 15 days.

Skin tightness. Twenty-two cases of skin tightness were reported in 22 participants (0.6%); verbatim descriptions included "tight feeling at forehead," "forehead skin tightness," and "raised lateral superciliary arch." Twenty (90.9%) were mild in severity; the rest were moderate. All but 1 case (95.5%) were reported within 14 days of treatment; median onset was 4.5 days. One case resolved within 24 hours, and 13 (59.1%) resolved within 28 days of onset. The median duration was 19 days.

Brow ptosis. Twenty cases of eyebrow ptosis were reported in 20 participants (0.6%); verbatim descriptions included "feeling of brow heaviness," "eyebrow ptosis," and "heavy brow." Three (15.0%) were moderate in severity, 1 had a missing severity, and the remainder were mild. All but 1 case (95%) were reported within 14 days of treatment; median

Table VII. Adverse events across all treatment areas, filtered by $P \leq .050$ and occurring more frequently in onabotulinumtoxinA than in placebo across all groups (DBPC population, treatment cycle 1, days 1-90)

	GL		CFL		CFL/GL		FHL/GL		FHL/GL/CFL		All	
Preferred term, *n* (%)	**OnabotA *N* = 665**	**Placebo *N* = 236**	**OnabotA *N* = 1324**	**Placebo *N* = 808**	**OnabotA *N* = 405**	**Placebo *N* = 306**	**OnabotA *N* = 724**	**Placebo *N* = 315**	**OnabotA *N* = 313**	**Placebo *N* = 156**	**OnabotA *N* = 3431**	**Placebo *N* = 1359**
Overall	282 (42.4)	85 (36.0)	NS	NS	NS	NS	273 (37.7)	84 (26.7)	122 (39.0)	45 (28.8)	1136 (33.1)	395 (29.1)
Eyelid ptosis	16 (2.4)	0	NS	NS	NS	NS	15 (2.1)	1 (0.3)	NS	NS	34 (1.0)	1 (0.1)
Eyelid sensory disorder	21 (3.2)	1 (0.4)	NS	NS	NS	NS	NS	NS	NS	NS	25 (0.7)	1 (0.1)
Skin tightness	NS	NS	NS	NS	NS	NS	10 (1.4)	0	NS	NS	22 (0.6)	1 (0.1)
Brow ptosis	NS	NS	NS	NS	NS	NS	11 (1.5)	0	NS	NS	20 (0.6)	0
Eyelid edema	NS	NS	5 (0.4)	0	NS	NS	NS	NS	NS	NS	12 (0.3)	0
Facial pain	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	12 (0.3)	0
Injection site hemorrhage	NS	NS	8 (0.6)	1 (0.1)	NS	NS	NS	NS	NS	NS	NS	NS
Cough	NS	NS	6 (0.5)	0	NS	NS	NS	NS	NS	NS	NS	NS
Arthropod bite	NS	NS	4 (0.3)	0	NS	NS	NS	NS	NS	NS	NS	NS
Injection site paresthesia	NS	NS	4 (0.3)	0	NS	NS	NS	NS	NS	NS	NS	NS
Head discomfort	NS	NS	NS	NS	NS	NS	10 (1.4)	0	NS	NS	NS	NS
Nasopharyngitis	N/A	N/A	NS	NS	NS	NS	NS	NS	22 (7.0)	3 (1.9)	NS	NS

Included only statistically significant adverse events ($P \leq .050$) and occurring more frequently in the onabotulinumtoxinA treatment group across all treatment areas in the DBPC population. Statistical testing was based on a fixed-effects meta-analysis model using both the Peto method and the Mantel−Haenszel method. The minimum *P* value between the 2 methods was used.
CFL, Crow's feet lines; *DBPC*, double-blind placebo-controlled; *FHL*, forehead lines; *GL*, glabellar lines; *N/A*, not applicable; *NS*, not significant; *OnabotA*, onabotulinumtoxinA.

Table VIII. Adverse events by cycle occurring in ≥2 participants in the OnabotA group: maximum cycle analysis per treatment area

	OnabotA: GL (*n* = 60)					OnabotA: CFL (*n* = 82)				
Preferred term, *n* (%)	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**
Overall	28 (46.7)	21 (35.0)	27 (45.0)	27 (45.0)	14 (23.3)	16 (19.5)	16 (19.5)	27 (32.9)	18 (22.0)	8 (9.8)
Nasopharyngitis	5 (8.3)	11 (18.3)	11 (18.3)	10 (16.7)	1 (1.7)	4 (4.9)	5 (6.1)	11 (13.4)	3 (3.7)	1 (1.2)
Injection site pruritus	5 (8.3)	1 (1.7)	0	0	0	1 (1.2)	0	0	0	0
Eyelid ptosis	3 (5.0)	0	1 (1.7)	0	0	0	0	0	1 (1.2)	1 (1.2)
Eyelid sensory disorder	2 (3.3)	1 (1.7)	0	1 (1.7)	0	1 (1.2)	1 (1.2)	0	0	0
Headache	2 (3.3)	2 (3.3)	0	0	1 (1.7)	1 (1.2)	1 (1.2)	0	0	0
Back pain	2 (3.3)	0	1 (1.7)	1 (1.7)	1 (1.7)	0	0	1 (1.2)	2 (2.4)	0
Blood creatine phosphokinase	0	0	3 (5.0)	0	0	0	0	0	0	0
Influenza	0	0	1 (1.7)	2 (3.3)	0	0	0	0	1 (1.2)	0
Seasonal allergy	0	0	1 (1.7)	3 (5.0)	0	0	0	0	0	0
Injection site hemorrhage	0	0	0	0	0	2 (2.4)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Upper respiratory tract inflammation	2 (3.3)	1 (1.7)	0	0	0	0	1 (1.2)	0	1 (1.2)	0
Abdominal pain upper	1 (1.7)	0	2 (3.3)	0	0	0	0	0	0	0
Purpura	0	0	0	0	0	0	0	2 (2.4)	3 (3.7)	1 (1.2)
Xeroderma	0	0	0	0	0	0	0	2 (2.4)	0	0
Blood cholesterol increased	0	0	0	0	2 (3.3)	0	0	0	0	0
Eczema	0	1 (1.7)	0	2 (3.3)	0	0	0	1 (1.2)	0	0
Rash	1 (1.7)	0	0	0	2 (3.3)	0	0	0	0	0

OnabotA, OnabotulinumtoxinA.

onset was 6 days. Forty percent of the cases resolved within 28 days, and 1 resolved within 24 hours. The median duration was 44 days.

Eyelid edema. Thirteen cases of eyelid edema were reported in 12 participants (0.3%); verbatim descriptions included "eyelid edema," "palpebral edema right and left not at the site of injection," and "lymphoedema lower eye lids both sides, not injection." All were mild in severity. Eleven cases (84.6%) were reported within 14 days of treatment; median onset was 5.0 days. Nine cases (69.2%) resolved within 28 days of onset. The median duration was 14 days.

Facial pain. Twelve cases of facial pain, all mild, were reported in 12 participants (0.3%); verbatim descriptions included "discomfort between brows," "tenderness in glabella area," and "pain at forehead." Ten cases (83.3%; median onset, 1 day) were reported within 2 weeks of treatment. Two cases occurred at days 29 and 52 after treatment. All cases resolved within 8 days, with a median duration of 2 days.

Serious AEs (SAEs)

SAEs were reported in 54 (1.6%) and 17 (1.3%) of the onabotulinumtoxinA and placebo groups, respectively (Table IX). Only 1 (spontaneous abortion) was considered possibly treatment related. The subject had a negative pregnancy test before receiving a single treatment of onabotulinumtoxinA for CFL. Nineteen days after treatment, the patient reported a possible pregnancy, confirmed to be twins by a gynecologist 2 days later. Within 1 week later, the patient spontaneously expelled 1 fetus and the second was subsequently medically removed due to lack of viability.

PDSOT

A detailed medical review of AE reports containing ≥1 MedDRA term used to analyze PDSOT (Table I) revealed no relation to distant spread of toxin. All AEs reviewed were confirmed to be consistent with known local spread events associated with the treatment area.

DISCUSSION

This updated meta-analysis expands on the safety data previously reported for onabotulinumtoxinA for GL and CFL,[7] more than tripling the number of participants and reporting on additional facial aesthetic indications. The onabotulinumtoxinA safety profile for facial aesthetic indications remained consistent with the product label, and no new signals emerged from pooling populations. At approved onabotulinumtoxinA doses, local AEs and

Table IX. Serious adverse events occurring in ≥2 participants across all treatment areas (DBPC population, by treatment area)

	GL		CFL		CFL/GL		FHL/GL		FHL/GL/CFL		All	
Preferred term, *n* (%)	**OnabotA *N* = 665**	**Placebo *N* = 236**	**OnabotA *N* = 1324**	**Placebo *N* = 808**	**OnabotA *N* = 405**	**Placebo *N* = 306**	**OnabotA *N* = 724**	**Placebo *N* = 315**	**OnabotA *N* = 313**	**Placebo *N* = 156**	**OnabotA *N* = 3431**	**Placebo *N* = 1359**
Overall	10 (1.5)	2 (0.8)	18 (1.4)	12 (1.5)	11 (2.7)	7 (2.3)	10 (1.4)	3 (1.0)	5 (1.6)	2 (1.3)	54 (1.6)	17 (1.3)
Basal cell carcinoma	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)	0 (0.0)
Breast cancer	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Intervertebral disc protrusion	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Overdose*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

Included only serious adverse events occurring in ≥2 participants in either treatment group across all treatment areas in the DBPC population.
CFL, Crow's feet lines; *DBPC*, double-blind placebo-controlled; *FHL*, forehead lines; *GL*, glabellar lines; *onabotA*, onabotulinumtoxinA.
*Overdose of alcohol, gabapentin, and zopiclone (*n* = 1) and of alcohol and co-codamol 30/500 (*n* = 1).

incidences were relevant to the treatment area, and maximum cycle analysis did not indicate increased risk from greater cumulative dose across multiple areas. Moreover, both repeat and long-term treatment (ie, >12 months) did not affect the AE risk over time (Table VIII).

This meta-analysis expands current knowledge of the safety and tolerability of onabotulinumtoxinA in the context of aesthetic treatment of upper facial lines, which generally uses lower and less-frequent dosing compared with therapeutic indications such as adult upper limb spasticity.[28,29] Accepted statistical methods were used to confirm the relevance of existing AEs. Descriptive statistics showed that among the most common AEs favoring onabotulinumtoxinA, 2 were likely procedure related (injection site bruising and injection site hematoma). When fixed-effects statistical modeling was applied to the pooled AEs of the DBPC population across all treatment areas, 24 individual AEs were identified statistically. These AEs statistically favored either onabotulinumtoxinA (n = 6) or placebo (n = 18) (Table V). However, most occurred in very low numbers, especially in the placebo group, where 12 of the 18 AEs were reported in 1 or 2 subjects across all treatment areas. Upon medical review, the 12 AEs were not considered clinically meaningful but rather a consequence of the fixed-effects model used to evaluate significance between onabotulinumtoxinA and placebo in the pooled incidence of each AE. The disproportionately small ratio of patients receiving placebo versus onabotulinumtoxinA may have also influenced this statistical outcome.

When the analysis was performed by individual preferred term for each treatment area, significant AEs favoring onabotulinumtoxinA for at least 1 treatment area were eyelid ptosis, eyelid sensory disorder, eyelid edema, skin tightness, brow ptosis, facial pain, injection site hemorrhage, cough, arthropod bite, injection site paresthesia, head discomfort, and nasopharyngitis. After medical review excluded AEs unrelated to treatment, the remaining model-generated significant AEs (all $P < .03$) were eyelid ptosis, eyelid sensory disorder, skin tightness, brow ptosis, eyelid edema, and facial pain (Table VII). Of these AEs, only eyelid ptosis was identified as having a frequency of at least 1% in the descriptive statistical analysis (Table IV). Furthermore, all had been previously associated with onabotulinumtoxinA upper facial line treatments and none were deemed related to PDSOT.

The prior analysis of GL studies had revealed 3 AEs with a significantly higher incidence in onabotulinumtoxinA-treated subjects: eyelid ptosis, eyelid sensory disorder, and eyelid edema.[7] With the inclusion of additional safety results from CFL and FHL studies in the present analysis, eyebrow ptosis, facial pain, and skin tightness were also revealed as significant AEs associated with onabotulinumtoxinA treatment. When analyzed by treatment area, eyelid ptosis and eyelid sensory disorder were significant AEs favoring onabotulinumtoxinA with GL treatment; eyelid ptosis, skin tightness, and brow ptosis were associated with FHL/GL; eyelid edema was significant for CFL; and facial pain showed no significance in any single treatment area but was significantly higher than placebo in the pooled DBPC population. These AEs are expected local effects to the muscle groups injected for each treatment area.

One AE of spontaneous abortion was considered possibly treatment related by the investigator. It involved a twin pregnancy and occurred early in the first trimester in a subject with no known past pregnancy. Spontaneous abortion and fetal defects have been reported with onabotulinumtoxinA treatment.[30,31] A recent 29-year retrospective study of the Allergan safety database reviewed the pregnancy outcomes of 397 mothers worldwide, a majority of whom (n = 202 of the 242 pregnancies where dosage was reported) were exposed to <200 U of onabotulinumtoxinA during or within 3 months prior to pregnancy.[31] Of the 195 pregnancies that were recorded prospectively, 77.2% resulted in live births. The incidence of fetal loss due to spontaneous abortion was 16.2%. The prevalence of these outcomes was consistent with rates reported in the general population, where spontaneous abortion is expected to occur in approximately 20% of known pregnancies in the U.S.[32]

Strengths of this study are that the analysis is based on prospective, longitudinal data drawn from 5298 participants, 4449 of whom were treated with onabotulinumtoxinA in upper facial areas in DBPC clinical studies. These were conducted for product registrations; thus, they were robust in scope and quality. In addition, the clinical studies analyzed were conducted using accepted meta-analytic methods and had a high degree of homogeneity as assessed by the Q statistic and I^2 index.

Study limitations include clinical trial design whereby the safety data analyzed are primarily based on studies lasting a year or less and excluding patients with severe medical disease. In addition, whereas the fixed-effects modeling method provides an additional means for detecting significant AEs, medical review is necessary to contextualize these events in practice.

CONCLUSIONS

This meta-analysis of safety data from 5298 participants confirmed the safety and tolerability of onabotulinumtoxinA for dynamic upper facial lines treatment (GL, CFL, and FHL), using accepted statistical methodologies. The AEs were generally mild to moderate in severity, and treatment-related AEs represented local pharmacologic or injection-associated responses. No new safety signals emerged from the pooled populations.

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Conflicts of interest

MF Brin, I Yushmanova, TI Boodhoo, and E Lee are employees of Allergan Aesthetics, an AbbVie Company, and may hold AbbVie stock. K De Boulle serves as a consultant and member of speaker boards for Allergan Aesthetics, an AbbVie Company, Laboratoires Genevrier, and IBSA. S Liew reports no conflicts. A Carruthers and J Carruthers serve as consultants and investigators for Allergan Aesthetics, an AbbVie Company, Alphaeon, Merz Aesthetics, Revance, and Zeltig. A Rivkin serves as a consultant and investigator for Allergan Aesthetics, an AbbVie Company, and Merz Aesthetics. Y Wu has served as an investigator for Allergan Aesthetics, an AbbVie Company. M Kawashima has no conflicts to disclose. The authors did not receive honoraria or any other form of compensation for authorship or other activities related to the preparation or submission of this manuscript.

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