



Utilization and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine from an observational study in Europe

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Abstract

Objective: To examine treatment utilization patterns and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine in routine clinical practice.

Background: Clinical trials support onabotulinumtoxinA for the prophylaxis of headache in patients with chronic migraine, but real-world data are limited.

Design/methods: A prospective, observational, post-authorization study in adult patients with chronic migraine treated with onabotulinumtoxinA. Data were collected at the first study injection and approximately every three months for ≤ 52 weeks for utilization and ≤ 64 weeks for safety data, and summarized using descriptive statistics.

Results: Eighty-five physicians (81% neurologists) at 58 practices in the United Kingdom, Germany, Spain, and Sweden participated and recruited 1160 patients (84.2% female, median age 46.6 years). At baseline, 85.8% of patients had physician diagnoses of chronic migraine/transformed migraine and reported an average of 11.3 (SD = 6.9) severe headache days per 28 days; 50.6% had previously used onabotulinumtoxinA for chronic migraine. A total of 4017 study treatments were observed. The median number of injection sites ($n = 31$) and total dose (155 U) were consistent across all treatment sessions, with a median 13.7 weeks observed between sessions. At least one treatment-related adverse event was reported by 291 patients (25.1%); the most frequently reported treatment-related adverse event was neck pain (4.4%). Most patients (74.4%) were satisfied/extremely satisfied with onabotulinumtoxinA treatment.

Conclusions: Patient demographics/characteristics are consistent with published data on the chronic migraine population. Utilization of onabotulinumtoxinA treatment for chronic migraine appears to be consistent with the Summary of Product Characteristics and published PREEMPT injection paradigm. No new safety signals were identified.

Keywords

Chronic headache, utilization, adverse events, safety, PREEMPT paradigm

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Introduction

The pharmacologic management of chronic migraine, defined as headache occurring on at least 15 days per month for >3 months in which headache with features of migraine occur on ≥ 8 days per month (1), includes acute treatment of headaches as well as preventive therapies to reduce the frequency of headaches and related migraine disability (2). Chronic migraine has been estimated to affect approximately 1.4% to 2.2% of the population globally (3), with rates of 0.4% to 2.0% reported for German populations depending on how strictly the criteria for chronic migraine were applied (4). As chronic migraine is often associated with substantial disability, functional impairment, and decreased quality of life (5,6), and in many cases may be associated with medication overuse (7), it is important that any treatment is both effective and well tolerated.

The efficacy and safety of onabotulinumtoxinA has been demonstrated in the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials (8,9). In a pooled analysis of four double-blind placebo-controlled trials, onabotulinumtoxinA was safe and well tolerated, with 3.4% of patients discontinuing treatment with onabotulinumtoxinA due to an adverse event (10). Serious adverse events occurred in 5.4% of patients receiving onabotulinumtoxinA and 3.0% of those receiving placebo. Consistent with the known tolerability profile of onabotulinumtoxinA, the most frequently reported adverse events in the pooled analysis were musculoskeletal in origin and were comparable to the known adverse events associated with onabotulinumtoxinA when used in other indications.

OnabotulinumtoxinA is approved for the prophylaxis of headache in adults with chronic migraine (10,11). There are limited data on the utilization and safety of onabotulinumtoxinA for chronic migraine in a clinical setting. Therefore, the goal of this study was to monitor the utilization practices and describe the safety profile of onabotulinumtoxinA for chronic migraine headache prophylaxis in routine clinical practice settings in Europe as part of post-authorization regulatory commitments.

Methods

Study design/physician recruitment

This was a prospective, observational, multinational European study (NCT01432379). The study protocol was reviewed and approved by the relevant ethics committees in each country. Physicians were recruited for the study in the United Kingdom, Germany, Sweden, and Spain, primarily through attendance at training sessions on the administration of

onabotulinumtoxinA for the management of chronic migraine educational meetings.

Patient recruitment was targeted to begin 12 months after regulatory approval in each country, with the first recruitment in the United Kingdom on September 9, 2011. The recruitment period was 27 months in the United Kingdom, 16 months in Germany, and 14 months in Spain and Sweden. Patients were followed up for up to 64 weeks after the baseline treatment, with the last follow-up visit scheduled for approximately 12 weeks after the final study treatment session at 48 to 52 weeks. The total duration of the study from the first patient enrollment through to the final follow-up visit for the last patient was 43 months in the United Kingdom, 31 months in Germany, 27 months in Sweden, and 28 months in Spain. The last patient's final follow-up visit was conducted in Spain on April 18, 2015.

Study population

The study population consisted of patients receiving onabotulinumtoxinA therapy for chronic migraine, recruited by their participating physicians. Patients were adults aged 18 years and older with a new or established physician diagnosis of chronic migraine. All patients were being treated for chronic migraine headache in routine practice, and could have been new to treatment with onabotulinumtoxinA for chronic migraine (treatment naïve) or could have been previously treated with onabotulinumtoxinA (non-naïve). The decision to initiate or continue treatment was independent of the patients' enrollment in the study. Written informed consent was provided by all participating patients.

OnabotulinumtoxinA exposure

Patients were administered onabotulinumtoxinA in routine clinical practice for the treatment of chronic migraine. Although participating physicians were provided with the Summary of Product Characteristics, the study protocol did not mandate the treatment paradigm or frequency of administration as outlined in the Summary of Product Characteristics. The intent of the study was to observe treatment utilization and safety in real-world clinical practice with no study intervention.

According to the Summary of Product Characteristics, the recommended dose of onabotulinumtoxinA is 155 U, up to a maximum dose of 195 U, administered intramuscularly using a 30-gauge, 0.5 in needle as 0.1 mL (5 U) injections into 31 to 39 sites, every 12 weeks (12). The injections are recommended to be divided across seven specific head

and neck muscle areas (i.e. frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, and cervical paraspinal muscle group) and are recommended to be injected bilaterally with the exception of the procerus, which requires one midline injection. In the case of predominant pain location(s), additional injections can be administered in up to three specific muscle areas (i.e. occipitalis, temporalis, and trapezius) (12).

Data sources and measurement

Practice and physician characteristics were collected at baseline via a questionnaire that captured details including practice type and characteristics, physician experience, and number of patients seen. Patient demographics and clinical characteristics were also collected at baseline. Medical and migraine-related history at baseline was captured from the patient's medical record. Treatment utilization information was collected at every treatment session for up to 52 weeks and included details on onabotulinumtoxinA dose, number and location of injections, and needle size. Detailed information on any adverse events and specific adverse events of special interest, including worsening of migraine and intractable migraine, reported by patients and occurring during or between treatment sessions, was collected throughout the study period. Information pertaining to dysphagia was also collected. A final follow-up visit was conducted approximately 12 weeks after the final treatment session and collected data on adverse events that occurred after the final treatment session in addition to patient reported overall satisfaction with onabotulinumtoxinA treatment, measured by a single question using a five-point scale from extremely satisfied to extremely dissatisfied.

Study size

This study was not designed for hypothesis testing; therefore, no formal power calculations were performed. The number of patients was chosen based on a practical basis in conjunction with the ability to detect rates of adverse events similar to those in phase 3 trials undertaken previously. With agreement from the Medicines and Health Product regulatory agents in the United Kingdom and the Irish Medicines Board, the final overall study enrollment was targeted at 900 patients, which targeted 320–350 in the United Kingdom, 250–280 in Germany, 200–210 in Sweden, and 70–125 in Spain.

Statistical analysis

Data were summarized using descriptive statistics and stratified by country and prior onabotulinumtoxinA

use. As the analysis was descriptive in nature, statistical inference was not performed. Any missing data were excluded from the analysis. Safety data were summarized using terminology from the Medical Dictionary for Regulatory Activities (MedDRA version 17.1). For each system organ class and preferred term, the number and percentage of patients who experienced adverse events were tabulated. Patients experiencing more than one adverse event were counted only once at each MedDRA level. Incidence rates of adverse events were calculated as the number of new events occurring during the study period divided by the person-time at risk and displayed with 95% exact Poisson confidence intervals.

The analysis population for physicians included the principal investigator at each site and any additional physicians/healthcare professionals administering injections to study patients at that site. The analysis population for patients included all patients enrolled in the study who completed at least one onabotulinumtoxinA treatment session.

Results

Practice site and physician characteristics

A total of 97 physicians completed the site feasibility questionnaire and 85 physicians at 58 sites participated in the study (Figure 1). There were 19 physicians from 16 practice sites in the United Kingdom, 39 physicians from 19 sites in Germany, 14 physicians from 12 sites in Sweden, and 13 physicians from 11 sites in Spain. Among participating sites, 71.4% were specialty-based practices (specialty practice, 32.1%; headache specialty, 26.8%; headache/pain clinic, 12.5%), 50.0% were hospital-based practices or based in hospital outpatient

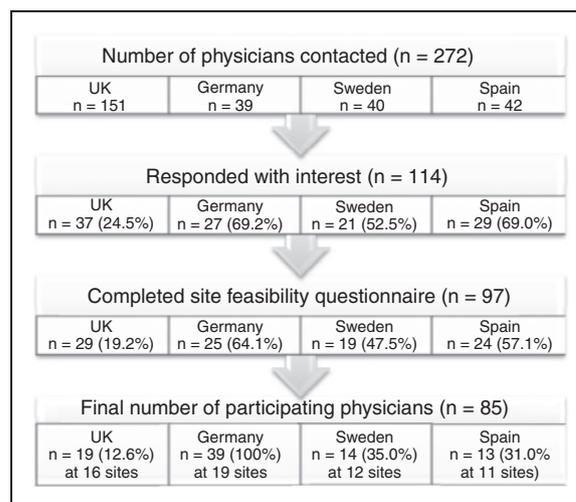


Figure 1. Overview of physician recruitment by country.

clinics, and 21.4% were general practice or ambulatory care practices (Figure 2). Practice characteristics varied across countries, with specialty practice more common in Sweden, and general practice/ambulatory care settings more common in Germany and Spain (Supplementary Figure 1).

Approximately 75% of the practices saw ≥ 11 patients with chronic migraine in the three months prior to the study. The majority of the participating physicians were identified as neurologists (81.2%; Figure 2); 75 participating physicians (88.2%) had previous experience treating patients with onabotulinumtoxinA for chronic migraine. The average number of years the physicians were licensed was 18.5 (SD, 9.4) years. The majority of physicians

(67, 78.8%) had attended onabotulinumtoxinA training for chronic migraine and 75 (88.2%) had previously prescribed onabotulinumtoxinA for chronic migraine. Considerable inter-country variability was observed from a mean (SD) of 21.4 (22.6) patients treated per physician in Germany to 222.7 (299.0) patients treated in Spain

Patient characteristics

A total of 1168 patients enrolled in the study, and 1160 completed at least one treatment session (the analysis patient population). Of these, 783 (67.5%) patients completed the entire 52-week observation period and final interview (Figure 3). A total of 346 (29.8%)

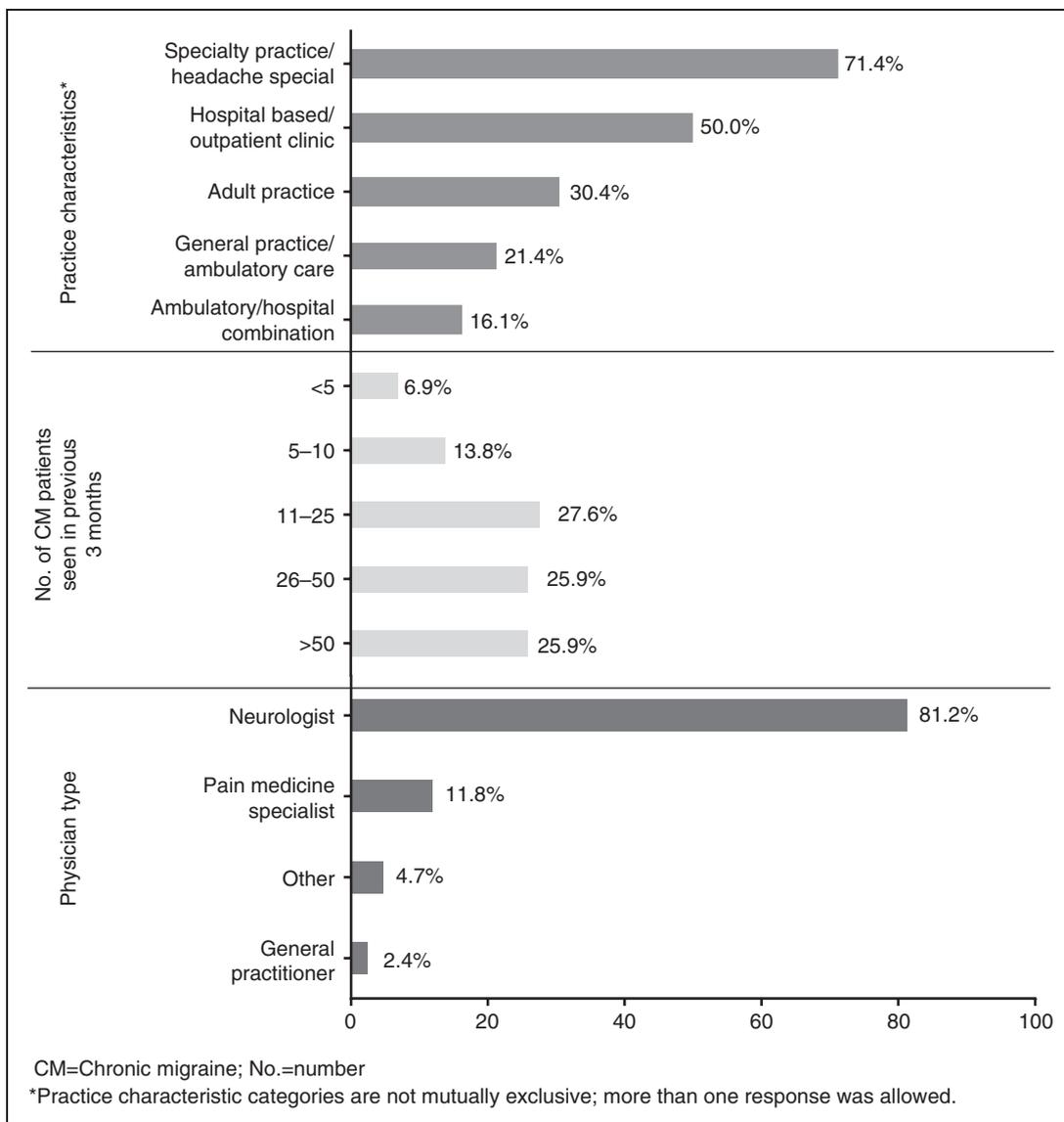


Figure 2. Baseline practice and physician characteristics.

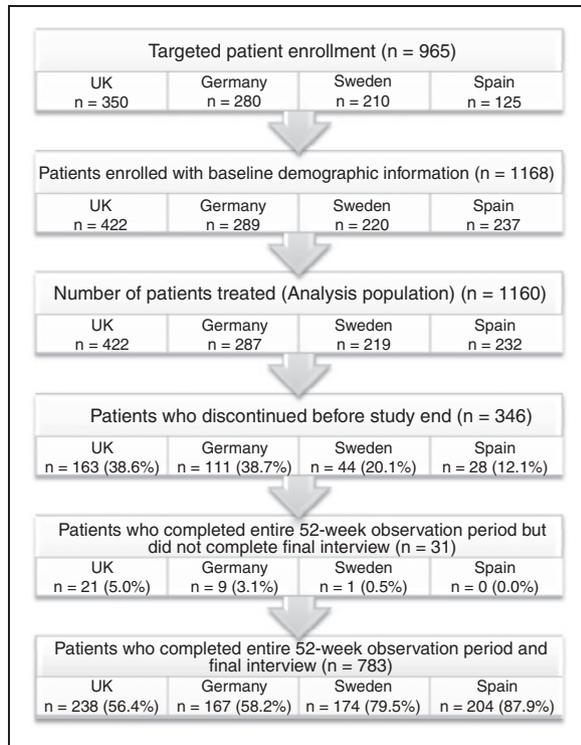


Figure 3. Patient enrollment and disposition.

patients were treated for less than the maximum 52-week observation period; of these, 34 patients were lost to follow-up. Of the 312 patients who provided a reason for discontinuing treatment, the most common reason was lack of efficacy (n = 164, 14.1% of the analysis population; Table 1).

Patients in the analysis population were on average 46.6 (SD, 11.8) years of age, primarily female, and white (Table 2). Based on the patient's medical records, 85.8% of patients had a history of chronic migraine or transformed migraine diagnoses, 51.6% had a documented diagnosis of migraine, and 24.7% had a documented diagnosis of medication overuse. At baseline, in a usual month (defined as 28 days) patients reported experiencing an average 7.7 (SD, 6.9) headache-free days, 9.0 (SD, 6.5) days with headache of mild pain intensity, and 11.3 (SD, 6.9) days with headache of severe pain intensity. Most patients were receiving acute or preventive headache medications at baseline, with nearly half (43.9%) indicating being on ≥ 1 acute and ≥ 1 preventive treatment. In addition, half of the patients (n = 587, 50.6%) indicated having used onabotulinumtoxinA treatment for chronic migraine in the past. Patient characteristics at baseline were similar in the treatment-naïve subgroup (Table 2).

Table 1. Reasons for discontinuing OnabotulinumtoxinA treatment prior to completing 52-week observation period.

	UK (n = 422)	Germany (n = 287)	Sweden (n = 219)	Spain (n = 232)	Overall (N = 1160)
Discontinued study	163 (38.6)	111 (38.7)	44 (20.1)	28 (12.1)	346 (29.8)
Reasons for discontinuation, n (%) [*]					
Lack of efficacy [†]	77 (18.2)	55 (19.2)	18 (8.2)	14 (6.0)	164 (14.1)
Other [‡]	25 (5.9)	13 (4.5)	15 (6.8)	3 (1.3)	56 (4.8)
Side effect/other health problem	22 (5.2)	11 (3.8)	4 (1.8)	2 (0.9)	39 (3.4)
Lost to follow-up	18 (4.3)	12 (4.2)	1 (0.4)	3 (1.3)	34 (2.9)
Treatment successful/migraines subsided [†]	17 (4.0)	9 (3.1)	1 (0.4)	1 (0.4)	28 (2.4)
Treatment too expensive	14 (3.3)	2 (0.7)	1 (0.4)	2 (0.9)	19 (1.6)
Inconvenient to come in for treatment visits	6 (1.4)	8 (2.8)	4 (1.8)	0 (0.0)	18 (1.5)
Injections too painful	6 (1.4)	10 (3.5)	1 (0.4)	0 (0.0)	17 (1.5)
Concerned about risks	3 (0.7)	6 (2.1)	1 (0.4)	2 (0.9)	12 (1.0)
Injections took too much time	0 (0.0)	3 (1.0)	2 (0.9)	1 (0.4)	6 (0.5)

^{*}More than one response was allowed; categories are not mutually exclusive; 312 patients provided ≥ 1 reason why treatment was discontinued and 34 patients were lost to follow-up.

[†]"Lack of efficacy" and "Treatment successful/migraines subsided" were categories determined from manual review of the *Other* category free-text responses, provided by 238 patients.

[‡]UK: Nine patients reported they were getting or seeking treatment on the National Health Service program; four reported they were no longer eligible for treatment based on the NICE guidelines; three reported a pregnancy; two reported adverse effects; two moved away or transferred to another physician; one reported travel distance was too far; one reported treatment was ineffective; one was deceased; two reported other reasons; Germany: Four patients reported travel distance was too far; three reported a pregnancy; two reported adverse effects; one moved away or transferred to another physician; three reported other reasons; Sweden: Two patients moved away or transferred to another physician; one reported adverse effects; one reported a pregnancy; and 11 reported unknown or other reasons; Spain: one patient reported adverse effects; one moved away or transferred to another physician; one was deceased.

Table 2. Baseline patient demographics and clinical characteristics of overall analysis population and treatment-naïve patients.

	Treatment-naïve population (n = 556)*	Overall analysis population (N = 1160)
Mean (SD) age, years	46.3 (11.97)	46.6 (11.8)
Min, max	20, 79	19, 79
Female, n (%)	449 (80.8)	977 (84.2)
White [†] , n (%)	542 (97.5)	1134 (97.8)
Mean (SD) BMI, kg/m ²	25.2 (4.8)	25.4 (5.1)
Min, max	16, 44	15, 55
Headache diagnosis history [‡] , n (%)		
Chronic migraine or transformed migraine	470 (84.5)	995 (85.8)
Migraine	298 (53.6)	599 (51.6)
Medication overuse ^{**}	143 (25.7)	286 (24.7)
Tension headache	76 (13.7)	165 (14.2)
Chronic daily headache	49 (8.8)	116 (10.0)
Chronic tension-type headache	22 (4.0)	52 (4.5)
Intractable/refractory migraine/headache	13 (2.3)	47 (4.1)
Menstrual headache/migraine	21 (3.8)	43 (3.7)
Cluster headache	14 (2.5)	27 (2.3)
Stress headache	14 (2.5)	26 (2.2)
New daily persistent headache	2 (0.4)	8 (0.7)
Sinus headache	4 (0.7)	8 (0.7)
Hemicrania continua	3 (0.5)	6 (0.5)
Other	21 (3.8)	40 (3.4)
Baseline headache medication(s) [†]		
Acute, n (%)		
0	82 (14.7)	155 (13.4)
1	208 (37.4)	436 (37.6)
2	152 (27.3)	323 (27.8)
≥3	114 (20.5)	246 (21.2)
Preventive, n (%)		
0	277 (49.8)	564 (48.6)
1	172 (30.9)	338 (29.1)
2	75 (13.5)	187 (16.1)
≥3	32 (5.8)	71 (6.1)
Acute and preventive, n (%)		
At least one acute and at least one preventive	235 (42.3)	509 (43.9)
Unknown	6 (1.1)	12 (1.0)

*Treatment-naïve patients had not received onabotulinumtoxinA for the treatment of chronic migraine prior to the study.

[†]White is defined differently by country: United Kingdom, white includes English, Welsh, Scottish, Irish, British, Gypsy or Irish Traveler, or any other white background; Germany, white includes white/Caucasian.

[‡]Includes all headache diagnoses included in the patient's medical record; more than one response allowed; categories are not mutually exclusive.

**Includes any diagnosis of medication overuse headache, rebound headache, or medication/analgesic overuse.

OnabotulinumtoxinA utilization

A total of 4017 onabotulinumtoxinA treatment sessions were administered to patients throughout the course of the study, with up to seven treatment sessions per patient. Because only one patient (in Sweden) received a seventh treatment, data are presented on six treatment sessions (Table 3). The median total number of sites injected for each side (right and left) across muscle areas and across all treatment sessions was 15 sites, with one site on the midline also injected (median total number of sites injected was 31 for all treatment cycles 1 to 5). The median total dose of onabotulinumtoxinA administered across all treatment sessions was 75 U for each side (right and left) and 5 U in the midline (combined median total dose of 155 U). The median injection sites and doses were similar across all countries and were the same for treatment-naïve patients as for the overall analysis population (Supplementary Table 1). The majority of injections were administered using a 0.5 in/1.25 cm needle length. The muscle areas injected across treatment sessions were consistent, with the majority of physicians injecting the seven recommended muscle areas (Table 4). The muscle areas injected were similar for the treatment-naïve subgroup (Supplementary Table 2). The average number of weeks between treatment sessions was 14.3 (SD, 3.19) weeks and ranged between 6.0 and 51.4 weeks, with the average time between treatment sessions generally decreasing slightly with each subsequent treatment session (Figure 4).

For the purposes of the study, a deviation from the treatment paradigm recommended in the Summary of Product Characteristics was defined as a dose of <155 U or >195 U, injection of <31 or >39 sites, a dosing interval of <11 or >13 weeks, or use of a needle of length other than 1.25 cm (0.5 in) or 2.5 cm (1 in) for any treatment session; there could be more than one reason for deviation from the recommended label treatment paradigm. If a patient received a treatment with any of these characteristics at any time during the study period, the patient was classified as “deviated” regardless of other treatment sessions.

Overall, 1045 (90.1%) patients in the study were observed to have ≥1 treatment deviation. Patients in the United Kingdom were least likely to receive treatment that deviated from the recommended label treatment paradigm (80.1%) and those in Spain were most likely to do so (99.1%; Supplementary Table 3). The majority of the deviations documented were deviations from the recommended dosage schedule, with 844 (72.8%) patients receiving treatment at an interval greater than 13 weeks. In review of treatment deviations during the study, where ≥1 deviation was reported over the course of up to six treatment sessions, nearly half of the patients (n = 480, 41.4%) were administered a

Table 3. OnabotulinumtoxinA treatment utilization characteristics stratified by treatment session.

	Treatment 1 (n = 1160)	Treatment 2 (n = 1034)	Treatment 3 (n = 885)	Treatment 4 (n = 712)	Treatment 5 (n = 210)	Treatment 6 (n = 15)
Total number of sites injected across muscle areas						
Right side, n	1160	1034	884	711	210	15
Median	15	15	15	15	15	15
Min, max	5, 30	4, 29	4, 34	4, 30	4, 30	12, 17
Left side, n	1160	1034	884	711	210	15
Median	15	15	15	15	15	15
Min, max	5, 30	3, 26	3, 34	4, 32	4, 32	12, 22
Midline*, n	1095	977	834	680	198	15
Median	1	1	1	1	1	1
Min, max	1, 6	1, 6	1, 5	1, 4	1, 4	1, 3
Total dose across muscle areas						
Right side, n	1160	1034	884	711	210	15
Median	75	75	75	75	75	75
Min, max	30, 146	25, 145	20, 162	20, 146	20, 146	30, 131
Left side, n	1160	1034	884	711	210	15
Median	75	75	75	75	75	75
Min, max	30, 160	6, 175	6, 180	20, 180	20, 180	30, 116
Midline*, n	1095	977	835	681	198	15
Median	5	5	5	5	5	5
Min, max	3, 30	3, 30	3, 120	3, 150	3, 25	5, 25
Needle length ^{†,‡} , n (%)						
0.5 in / 1.25 cm	850 (73.3)	798 (77.2)	672 (75.9)	546 (76.7)	163 (77.6)	10 (66.7)
1.0 in / 2.5 cm	111 (9.6)	76 (7.4)	82 (9.3)	67 (9.4)	45 (21.4)	0 (0.0)
Other	279 (23.8)	221 (21.4)	186 (21.0)	147 (20.6)	37 (17.6)	5 (33.3)

*Includes only procerus and "other" midline muscle areas.

[†]More than one response allowed; categories are not mutually exclusive.

[‡]Sweden, Germany, and Spain have needles 1.25 cm and 2.5 cm in length; United Kingdom has needle lengths of 0.5 inch and 1 inch.

dose < 155 U during at least one treatment session. A total of 54 (4.7%) patients received a dose > 195 U during at least one treatment session; however, 626 (54.0%) patients did not have any dose deviations at any treatment session (i.e. received between 155 U and 195 U). A third of the patients (n = 362, 31.2%) received onabotulinumtoxinA into < 31 sites during at least one treatment session, and a quarter (n = 299, 25.8%) were injected with a needle length outside of recommendations.

Adverse events

A total of 478 (41.2%) patients reported ≥ 1 adverse event during the study for an overall incidence rate of 53.8 per 1000 patient months (95% CI, 49.0–58.8; Table 5). The incidence of reported adverse events was lowest in Spain (31.8 per 1000 patient months [95% CI, 24.9–40.1]) and Sweden (45.7 [95% CI, 36.5–56.4]) and highest in Germany (65.3 [95% CI 54.3–77.9]) and the United Kingdom (68.8 (95% CI, 59.5–79.1)). Treatment-related

adverse events were reported by 291 (25.1%) patients, resulting in an overall incidence rate of 27.9 per 1000 patient months (95% CI, 24.7–31.2) that varied from 9.9 per 1000 patient months (95% CI, 6.4–14.5) in Spain to 42.1 per 1000 patient months (95% CI 35.3–49.7) in the United Kingdom. OnabotulinumtoxinA treatment was stopped due to a treatment-related adverse event in 51 (4.4%) of patients (Table 5). A serious adverse event was reported by 61 (5.3%) patients and 1 (0.1%) patient reported a treatment-related serious adverse event (worsening of migraine). Fatal adverse events were reported in two (0.2%) patients (one patient with myocardial infarction and one patient with metastatic lung neoplasm); neither was considered related to treatment. Of the 54 patients who received > 195 U during ≥ 1 treatment session, 22 (40.7%) patients reported ≥ 1 adverse event. The adverse event rate in this population was consistent with the total study population. Overall, the percentage of patients reporting ≥ 1 adverse event declined with each subsequent treatment session, with 311/1160

Table 4. Muscle areas injected with onabotulinumtoxinA stratified by treatment session.

Muscle areas injected, n (%)*	Treatment 1 (n = 1160)	Treatment 2 (n = 1034)	Treatment 3 (n = 885)	Treatment 4 (n = 712)	Treatment 5 (n = 210)	Treatment 6 (n = 15)
Right side						
Frontalis	1154 (99.5)	1027 (99.3)	876 (99.0)	704 (98.9)	208 (99.0)	15 (100)
Corrugator	1131 (97.5)	1006 (97.3)	872 (98.5)	701 (98.5)	206 (98.1)	15 (100)
Occipitalis	1128 (97.2)	1011 (97.8)	870 (98.3)	703 (98.7)	204 (97.1)	15 (100)
Temporalis	1155 (99.6)	1031 (99.7)	878 (99.2)	706 (99.2)	207 (98.6)	15 (100)
Trapezius	1129 (97.3)	1008 (97.5)	864 (97.6)	697 (97.9)	205 (97.6)	15 (100)
Cervical paraspinal	1091 (94.1)	960 (92.8)	820 (92.7)	655 (92.0)	196 (93.3)	15 (100)
Masseter	4 (0.3)	12 (1.2)	18 (2.0)	8 (1.1)	3 (1.4)	1 (6.7)
Other	129 (11.1)	123 (11.9)	103 (11.6)	91 (12.8)	44 (21.0)	4 (26.7)
Left side						
Frontalis	1154 (99.5)	1027 (99.3)	876 (99.0)	705 (99.0)	208 (99.0)	15 (100)
Corrugator	1130 (97.4)	1005 (97.2)	872 (98.5)	701 (98.5)	206 (98.1)	15 (100)
Occipitalis	1128 (97.2)	994 (96.1)	859 (97.1)	703 (98.7)	204 (97.1)	15 (100)
Temporalis	1154 (99.5)	1014 (98.1)	868 (98.1)	707 (99.3)	207 (98.6)	15 (100)
Trapezius	1129 (97.3)	993 (96.0)	854 (96.5)	697 (97.9)	205 (97.6)	15 (100)
Cervical paraspinal	1091 (94.1)	944 (91.3)	810 (91.5)	655 (92.0)	196 (93.3)	15 (100)
Masseter	4 (0.3)	12 (1.2)	18 (2.0)	8 (1.1)	3 (1.4)	1 (6.7)
Other	131 (11.3)	123 (11.9)	101 (11.4)	89 (12.5)	46 (21.9)	5 (33.3)
Midline						
Procerus	1095 (94.4)	977 (94.5)	834 (94.2)	680 (95.5)	198 (94.3)	15 (100)
Other	18 (1.6)	19 (1.8)	11 (1.2)	10 (1.4)	3 (1.4)	1 (6.7)

*More than one response allowed; categories are not mutually exclusive.

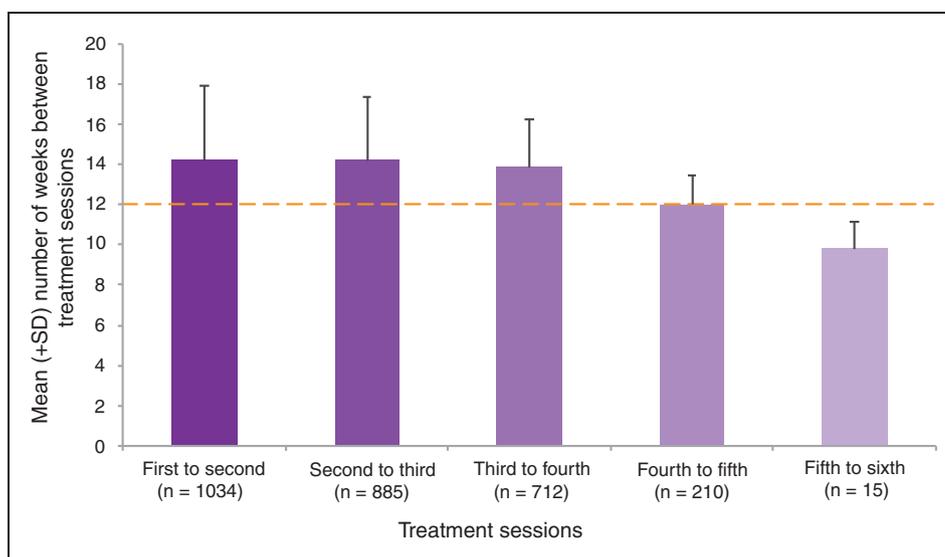


Figure 4. Mean (SD) time between onabotulinumtoxinA treatment sessions. Dotted line indicates recommended treatment interval of 12 weeks between treatment sessions. Descriptive statistics only were undertaken, and there were no intergroup tests of statistical significance performed.

Table 5. Summary of adverse events and treatment-related adverse events.

	UK (n = 422)	Germany (n = 287)	Sweden (n = 219)	Spain (n = 232)	All patients (n = 1160)
Patients with ≥ 1 adverse event, n (%)	197 (46.7)	123 (42.9)	86 (39.3)	72 (31.0)	478 (41.2)
Incidence per 1000 patient months (95% CI)	68.8 (59.5–79.1)	65.3 (54.3–77.9)	45.7 (36.5–56.4)	31.8 (24.9–40.1)	53.8 (49.0–58.8)
Serious adverse events, n (%)	20 (4.7)	16 (5.6)	16 (7.3)	9 (3.9)	61 (5.3)
Treatment discontinued due to adverse events, n (%)	27 (6.4)	16 (5.6)	5 (2.3)	3 (1.3)	51 (4.4)
Special interest adverse events, n (%)					
Worsening of migraine	41 (9.7)	19 (6.6)	12 (5.5)	29 (12.5)	101 (8.7)
Intractable migraine	2 (0.5)	8 (2.8)	2 (0.9)	8 (3.4)	20 (1.7)
Hypersensitivity	11 (2.6)	1 (0.3)	4 (1.8)	1 (0.4)	17 (1.5)
Dysphagia	3 (0.7)	1 (0.3)	0 (0.0)	1 (0.4)	5 (0.4)
Fatal adverse events, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.2)
Treatment-related adverse events					
Patients with ≥ 1 treatment-related adverse events, n (%)	138 (32.7)	88 (30.7)	39 (17.8)	26 (11.2)	291 (25.1)
Incidence per 1000 patient months (95% CI)	42.1 (35.3–49.7)	40.2 (32.3–49.6)	16.7 (11.8–22.8)	9.9 (6.4–14.5)	27.9 (24.7–31.2)
Serious treatment-related adverse events, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Special interest treatment-related adverse events, n (%)					
Worsening of migraine	28 (6.6)	10 (3.5)	7 (3.2)	1 (0.4)	46 (4.0)
Intractable migraine	0 (0.0)	3 (1.0)	0 (0.0)	2 (0.9)	5 (0.4)
Hypersensitivity	7 (1.7)	0 (0.0)	2 (0.9)	1 (0.4)	10 (0.9)
Dysphagia	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Fatal treatment-related adverse events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Treatment-naïve patients have not previously received onabotulinumtoxinA for the treatment of chronic migraine.

(26.8%) patients reporting ≥ 1 adverse event at treatment session 1 and 39/210 (18.6%) patients doing so by treatment session 5.

For the adverse events of special interest, worsening of migraine occurred most frequently (101 of 1160 patients, 8.7%) and was considered serious in six (0.5%) patients. The highest percentage of patients reporting ≥ 1 worsening of migraine event was observed in Spain (12.5%) and the lowest in Sweden (5.5%). Intractable migraine occurred in 20 (1.7%) patients, and was considered serious in three (0.3%) patients. Hypersensitivity reactions, none of which were serious, occurred in 17 (1.5%) patients and dysphagia in five (0.4%). The most commonly reported treatment-related adverse event of special interest was worsening of migraine (n = 46, 4.0%). All other treatment-related adverse events of special interest were reported in < 1% of the study population (Table 5).

The most commonly reported treatment-related adverse event was neck pain (n = 51, 4.4%; Table 6).

Table 6. Treatment-related adverse events reported by $\geq 1\%$ of the treatment-naïve or overall analysis population.

Adverse event, n (%)	Treatment-naïve patients (n = 556)*	Overall (n = 1160)
Neck pain	30 (5.4)	51 (4.4)
Eyelid ptosis	24 (4.3)	47 (4.1)
Muscular weakness	16 (2.9)	31 (2.7)
Headache	14 (2.5)	26 (2.2)
Musculoskeletal stiffness	14 (2.5)	23 (2.0)
Migraine	12 (2.2)	34 (2.9)
Facial paresis	7 (1.3)	15 (1.3)
Facial spasm	7 (1.3)	11 (0.9)
Myalgia	7 (1.3)	11 (0.9)
Pruritus	7 (1.3)	7 (0.6)
Musculoskeletal pain	6 (1.1)	10 (0.9)

*Treatment-naïve patients have not previously received onabotulinumtoxinA for the treatment of chronic migraine.

The proportion of patients reporting ≥ 1 adverse events and treatment-related adverse events observed in the treatment-naïve population were similar to those observed in the overall study population (Table 6).

Patient satisfaction with treatment

Overall, 1090 patients responded to the treatment satisfaction question during the final interview ($n = 783$ for those completing 52 weeks of treatment and $n = 307$ for those treated for less than 52 weeks). The majority of patients (74.4%) expressed satisfaction (extremely satisfied/satisfied) with onabotulinumtoxinA treatment for chronic migraine (Figure 5a). Patient-reported satisfaction differed by country; the proportion of patients extremely satisfied/satisfied was lowest in Germany

(61.3%) and highest in Spain (86.0%). Patient-reported satisfaction differed according to whether patients completed the entire 52-week observation period (90.1% [705/783] extremely satisfied/satisfied) or were treated for less than 52 weeks (34.5% [106/307] extremely satisfied/satisfied) (Figure 5a). Satisfaction among patients who had previously received onabotulinumtoxinA treatment was higher than the satisfaction observed with treatment-naïve patients (Figure 5b). Among those who were treatment-naïve, 338 of 519 (65.1%) were extremely satisfied/satisfied with treatment. The proportion of patients reporting satisfaction with treatment was lower among treatment-naïve patients who were treated for less than the 52-week study period (46/183, 25.1%) than among those who were treated for the full 52 weeks (292/336, 86.9%).

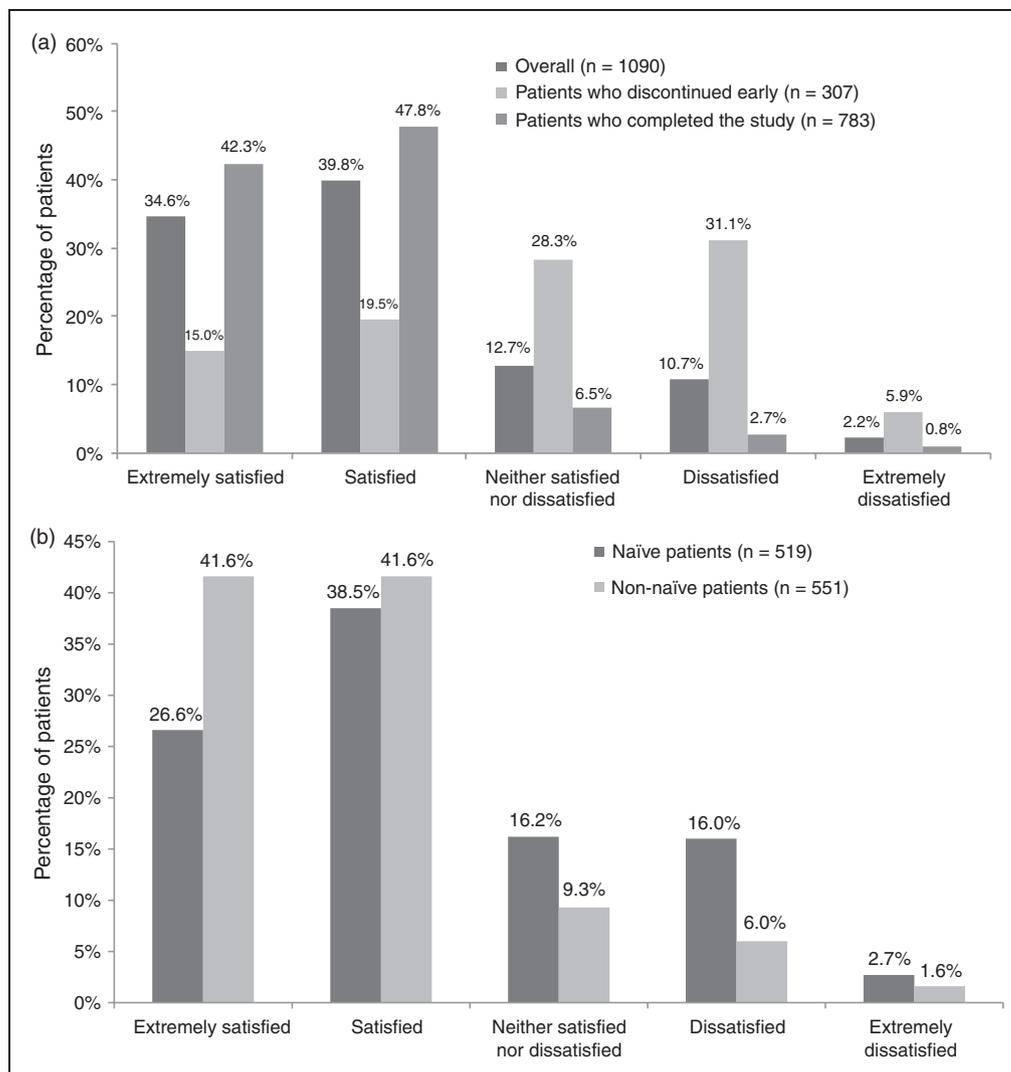


Figure 5. Patient-reported satisfaction with onabotulinumtoxinA treatment for chronic migraine: (a) Overall population stratified by study disposition; (b) stratified by onabotulinumtoxinA treatment history ($n = 1070$). Data on prior use of onabotulinumtoxinA for chronic migraine were available for 1136 patients out of the 1160 patients in the analysis population.

Discussion

The safety and efficacy of onabotulinumtoxinA has been established in controlled trials (8,9); however, real-world data in an actual clinical setting are limited. This study examined the utilization patterns and safety of onabotulinumtoxinA in a routine clinical setting. As such, efficacy and effectiveness were not specifically examined. Consistent with other published studies of chronic migraine, the majority of patients in the study had a diagnosis of chronic migraine at their baseline visit (6,10,13–16). Although other diagnoses were also recorded, it is likely that migraine and chronic migraine diagnoses overlapped, in addition to tension-type headache and medication overuse headache. Overall, patient demographics and clinical characteristics align with typical chronic migraine characteristics; therefore, this study was successful in enrolling and observing chronic migraine patients in a real-world setting.

The doses and muscle areas injected were generally consistent across treatment sessions and with the Summary of Product Characteristics and PREEMPT injection guidelines (12,17). Approximately half of the patients received the recommended 155 U to 195 U dose during all their treatment sessions. Of those treatments that deviated from the recommended paradigm, the majority (72.8%) deviated due to longer treatment intervals (i.e. > 13 weeks between treatments). Although approximately 41% of patients received doses < 155 U, this may be an artifact of packaging restrictions for onabotulinumtoxinA (availability of 50 U, 100 U, or 200 U vials only). Indeed 205 patients (17.7%) received exactly 150 U of onabotulinumtoxinA in ≥ 1 treatment session. As this was an observational study of routine clinical practice in which the treatment schedule was not specified and instead depended on physicians' judgment and patient preferences, variability in treatment intervals is to be expected.

Adverse events were consistent with the product label and with the results from the PREEMPT trials (8,9,12,18). The percentage of patients reporting ≥ 1 adverse event was generally lower than that reported from previous pooled registration studies (41.2% vs 72.9%) (10), but the percentage of patients with ≥ 1 serious adverse event was similar (5.3% vs. 5.4%) (10). A reported adverse event rate in a clinical practice setting lower than that reported in a controlled study environment is in line with the expectation that adverse event reporting would be less stringent in an observational study than in a clinical trial. The observed findings also suggest that patients or physicians could have tended to under-report non-serious adverse events.

Although the overall incidence of adverse events was lower in our observational study, the nature of the most frequently reported adverse events was similar to that

reported in clinical trials and included neck pain, muscular weakness, headache, facial paresis and musculoskeletal stiffness.

In general, the adverse event incidence rate decreased with each subsequent treatment session, a finding also reported by Diener et al. in a pooled analysis of PREEMPT trials (10). It is likely that the reduction in adverse events reflects the fact that patients experiencing fewer benefits and experiencing adverse events discontinued treatment sooner than those with higher perceived benefit and greater tolerability. The observation that many patients with adverse events continued treatment with onabotulinumtoxinA suggests that these patients experienced a degree of satisfaction/benefit with treatment that outweighed the reported adverse event.

Adverse events associated with potential distant spread of toxin were also assessed, using a conservative approach where all potential cases were counted. No new or unexpected findings were reported from this assessment.

Although the evaluation of efficacy data was not the objective of this observational study, results of the one question on patient-reported satisfaction obtained during the final follow-up interview revealed an overall high level of patient satisfaction by those patients who completed the entire 52-week observational period and attended the final interview. In a post hoc analysis stratified by prior treatment status, the subgroup of patients who had previously received onabotulinumtoxinA for chronic migraine reported higher satisfaction (83.6% of those using onabotulinumtoxinA in the previous six months were extremely satisfied or satisfied) than the treatment-naïve subgroup of patients (65.1% were extremely satisfied or satisfied). It should be noted that patients in these subgroups had a varying number of treatment cycles; typically, at least two to three treatment cycles repeated every 12 weeks are required to determine responsiveness to onabotulinumtoxinA in patients with chronic migraine (19). Because stratification by prior treatment status was a post hoc analysis, these results should be interpreted with caution. Treatment-naïve patients may provide a more accurate "real-world" indication of satisfaction for people new to treatment with onabotulinumtoxinA.

This study is not without its limitations. The design of this study allowed for the observation of onabotulinumtoxinA utilization in actual clinical practice from a diverse sample of physicians and practices, which may increase the generalizability of the data. However, the majority of the physicians were specialists with prior experience with onabotulinumtoxinA for chronic migraine; therefore, the data may more closely reflect results from specialists who have previously

treated patients with onabotulinumtoxinA in the countries studied than clinicians new to using the therapy. In addition, the study population included both patients who were treatment-naïve and those who had previously used onabotulinumtoxinA for chronic migraine. These two groups can have a different safety experience. It has been shown that for many therapeutic products, the rate at which adverse events occur varies with time, with increased risk occurring early after the initiation of therapy (20). As the study was initiated so soon after market authorization approval in each of the participating countries, it was unexpected that > 50% of patients would have previously received onabotulinumtoxinA for chronic migraine. As a result of this unexpected finding, we stratified safety results on prior use of onabotulinumtoxinA in a post hoc analysis. Those who had used onabotulinumtoxinA within the six months before the study also had a lower incidence rate per 1000 person-months of discontinuation of treatment due to an adverse event (2.4, 95% CI, 1.3–4.0) than did the treatment-naïve subgroup (5.2, 95% CI, 3.6–7.4). Again, due to the post hoc nature of this analysis, these results must be interpreted with caution.

Those patients who had experienced positive results and tolerable adverse events after prior treatment with onabotulinumtoxinA would be more likely to be treated than patients who either experienced poor clinical outcomes or intolerable adverse events. Patients who were treatment-naïve therefore arguably provide data

that may be more generalizable to new users of onabotulinumtoxinA in a real-world clinical setting. However, a real-world setting would likely include a mix of patients (naïve and non-naïve); hence, to observe utilization in a routine clinical practice, we included a mix of patients in our study. Finally, with regards to safety data, the observed adverse events and incidence rate of adverse events were consistent with the Summary of Product Characteristics and previously published results.

Overall, this study captured utilization and safety data from a large population of chronic migraine patients treated primarily in headache or pain specialty clinics or at hospital based practices across four countries in Europe, providing a comprehensive look at real-world practices of onabotulinumtoxinA for the prophylactic treatment of chronic migraine in these practice settings.

To our knowledge, this is the largest observational study to date examining utilization and safety of onabotulinumtoxinA for chronic migraine in actual clinical practice. Results from this study indicate that real-world utilization of onabotulinumtoxinA for chronic migraine appears to be consistent with the recommendations in the Summary of Product Characteristics and the published PREEMPT injection paradigm. No new safety signals were identified in this study, and the data continue to support the favorable safety profile of onabotulinumtoxinA for chronic migraine headache prophylaxis.

Clinical implications

- Results from this study indicate that real-world utilization of onabotulinumtoxinA for chronic migraine appears to be consistent with the recommendations in the Summary of Product Characteristics and the published PREEMPT injection paradigm.
- No new safety signals were identified in this study, and the data continue to support the favorable safety and tolerability profile of onabotulinumtoxinA for chronic migraine headache prophylaxis.
- The majority of patients reported they were satisfied or extremely satisfied with onabotulinumtoxinA treatment for chronic migraine.
- This study was able to capture utilization and safety data from a large population of chronic migraine patients across four countries in Europe, providing a comprehensive look at real-world practices of onabotulinumtoxinA for the prophylactic treatment of chronic migraine.

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Author contributions

Manjit Matharu, Julio Pascual, Ingela Nilsson Remahl, and Andreas Straube conducted the study as principal investigators at their respective sites/countries and provided input, review, and edits to the manuscript content. Arlene Lum sponsored the study, provided oversight and management for the study, presented study updates routinely to the DSMB, and provided input, review, and edits to the manuscript content. Gudarz Davar sponsored the study, provided oversight for the study, and provided input, review, and edits to the manuscript content. Dawn Odom was the lead author for the Statistical Analysis Plan, conducted analyses to produce tables and listings, and provided input, review, and edits to the manuscript content. Lee Bennett led the conduct of and provided quality oversight to all analyses, analyzed the data and produced tables and listings, provided input to the study report, and provided input, review, and edits to the manuscript content. Christina Proctor analyzed the data and produced tables and listings, provided input to the study report, and provided input, review, and edits to the manuscript content. Lia Gutierrez participated in the study design; co-authored the study protocol and data collection forms; led the production of content for physician training; was lead author for the study safety plan; managed and monitored all aspects of data collection and management, site recruitment, site management, and site monitoring; was co-author of progress reports and the study report; and provided input, review, and edits to the manuscript content. Elizabeth Andrews participated in the study design, co-authored the study protocol and data collection forms, provided senior consultation for all aspects of the study, performed senior review for all study deliverables and reports, and provided input, review, and edits to the manuscript content. Catherine Johannes participated in the study design; co-authored the study protocol and data collection forms; provided oversight for all aspects of the study conduct; co-authored the statistical analysis plan, recruitment plan, progress reports, and study report; and provided input, review, and edits to the manuscript content.

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