BOTOX®
onabotulinumtoxinA injection

MOST STUDIED PREVENTIVE TREATMENT APPROVED FOR CHRONIC MIGRAINE[1,*]

A PROVEN option for Chronic Migraine

8 to 9 fewer headache days per month from baseline at week 24 (vs 6 to 7 with placebo)[3]

15 YEARS OF PATIENT IMPACT[2,†]

Studied in two Phase 3, randomized, double-blind, placebo-controlled clinical studies[3]

679 patients in PREEMPT[‡] 1 and 705 patients in PREEMPT 2[3]

The primary endpoint was change from baseline in headache days per month at week 24[3]

Subjects included adult Chronic Migraine patients who, in a 28-day baseline period, had:

- At least **15 headache days**, which lasted **4 hours or more**[3]
- Migraine/probable migraine on at least 50% of their headache days[3]

BOTOX® patient baseline data from PREEMPT trials showed significant headache burden[3-7]

	PREEMPT 1 (n = 341)	**PREEMPT 2** (n = 347)
Headache days/month	20 days	19.9 days
Migraine/probable migraine days/month	19.1 days	19.2 days
Acute medication overuse	66.3%	63.4%
Depression	22.6%	24.8%
Severe HIT-6[§] category scores	94.4%	92.5%

- Patients in PREEMPT trials were not allowed to use concurrent preventive medication

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[*] Based on a literature search for peer-reviewed publications on Chronic Migraine prevention and therapy.

[†] Since FDA approval in October 2010.[2]

[‡] **PREEMPT** = **P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy.

[§] HIT-6 = Headache Impact Test-6.

INDICATION

Chronic Migraine

BOTOX® (onabotulinumtoxinA) for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Limitations of Use

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses.

Please see additional Important Safety Information throughout.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide, or visit www.rxabbvie.com/pdf/botox_pi.pdf

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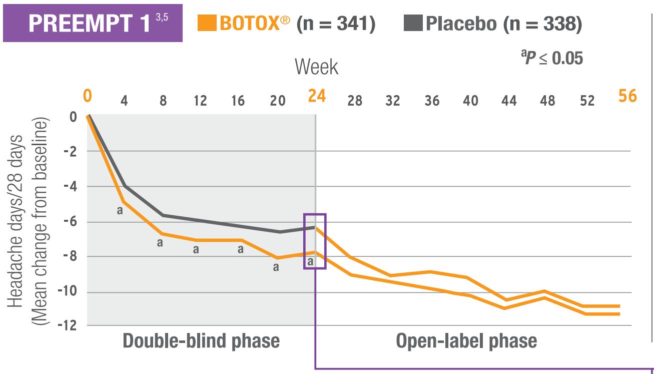
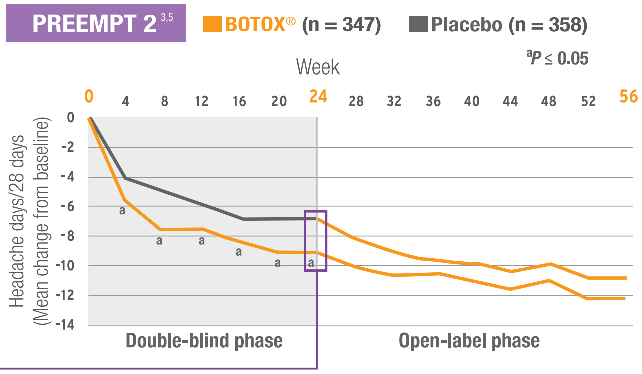
PROVEN efficacy in PREEMPT clinical trials

8 to 9 fewer headache days per month from baseline at week 24 (vs 6 to 7 with placebo)[3]





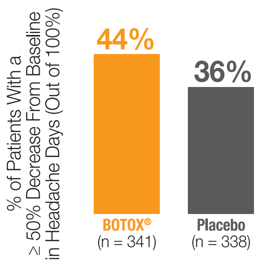
After the primary endpoint was measured at week 24, all patients received BOTOX®[5]

- Statistically significant headache day reductions were observed vs placebo at week 4, which was the first prespecified efficacy evaluation time point; primary endpoint was measured at 24 weeks[5]
- 8 to 9 fewer migraine/probable migraine days per month from baseline at week 24 (vs 6 to 7 with placebo)[3] (secondary endpoint)

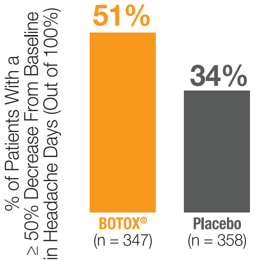
Responder rates for BOTOX® patients in PREEMPT clinical trials

Other endpoint: percentage of patients with a ≥ 50% reduction in headache days from baseline in each month at week 24[8,9]

RESULTS FROM **PREEMPT 1**

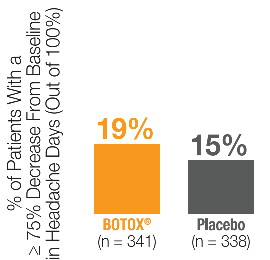


RESULTS FROM **PREEMPT 2**

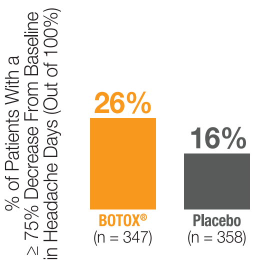


Other endpoint: percentage of patients with a ≥ 75% reduction in headache days from baseline in each month at week 24[8,9]

RESULTS FROM **PREEMPT 1**



RESULTS FROM **PREEMPT 2**



Limitations: The responder rate analyses were prespecified, other endpoints in PREEMPT clinical trials[5] and were not included as part of the hierarchical testing strategy or adjusted for multiplicity. Therefore, treatment differences cannot be regarded as statistically significant.

Study design: PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Subjects included adult Chronic Migraine patients not using any concurrent headache prophylaxis and, during a 28-day baseline period, had ≥ 15 headache days lasting 4 hours or more, with ≥ 50% being migraine/probable migraine. Patients were allowed to use acute headache treatments during the study. Primary time point was 24 weeks. A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache.[3,5]

Start BOTOX® today, delaying treatments delays results

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

BOTOX is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS

Spread of Toxin Effect

See *Boxed Warning*.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for chronic migraine at the labeled dose have been reported.

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

Please see additional Important Safety Information throughout.

BOTOX®
onabotulinumtoxinA injection

Established safety profile in PREEMPT clinical trials at week 24[3,5]

[10]

Most frequently reported adverse reactions*	**BOTOX®** (n = 687)[2]	**Placebo** (n = 692)[2]
Neck pain	9%	3%
Headache	5%	3%
Eyelid ptosis	4%	< 1%
Migraine	4%	3%
Muscular weakness	4%	< 1%
Musculoskeletal stiffness	4%	1%
Bronchitis	3%	2%
Injection-site pain	3%	2%
Musculoskeletal pain	3%	1%
Myalgia	3%	1%
Facial paresis	2%	0%
Hypertension	2%	1%
Muscle spasms	2%	1%

*This does not cover all the possible serious side effects of BOTOX®. Please see the Important Safety Information, including Boxed Warning, and the full Prescribing Information and Medication Guide.

- 4% of BOTOX® patients discontinued pivotal trials due to adverse events (vs 1% for placebo)[3,5]
- Observed treatment-related adverse events were typically mild to moderate in severity.
- Patients were evaluated for adverse reactions at every visit from week 0 through week 24, as shown in the chart above (7 evaluations)[5]
- Patients were also evaluated throughout the open-label phase from week 24 through week 56 (9 evaluations)[5]

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Serious Adverse Reactions With Unapproved Use
Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had preexisting dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently, the causal agent cannot be reliably determined.

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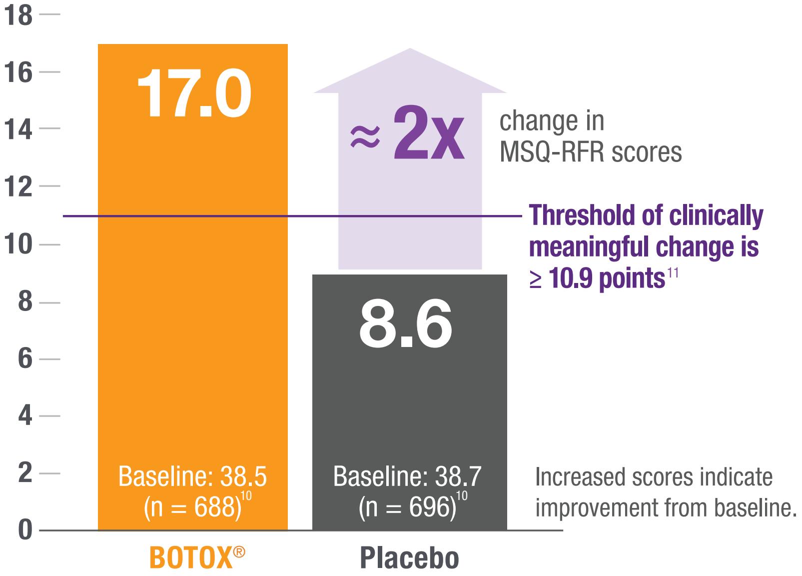
BOTOX® data beyond headache days

MSQ-RFR* measures the degree to which performance of daily work and social activities is limited by migraines

Other endpoint: change from baseline MSQ-RFR score at week 24[10]

Pooled PREEMPT 1 & 2



MSQ-RFR v2.1 is a self-reported outcome instrument that measures the degree to which performance of daily activities is limited by migraine across these concepts[5,12-14]:

- Work Activities
- Relationships
- Focus
- Home Activities
- Social Activities
- Productivity
- Leisure Activities
- Energy Levels

Note: MSQ-RFR v2.1 was measured as a total score and was not designed to assess these components individually.

- ≈ 2x change in MSQ-RFR scores from baseline vs placebo at 24 weeks[11,15,16]
- Threshold of clinically meaningful change (≥ 10.9 points from baseline) was met and surpassed at 17.0 points with BOTOX® vs 8.6 with placebo[11,15,16]

The MSQ-RFR is a valuable tool for assessing the functional impact of migraine in clinical trials[5,12-14]

- The MSQ version 2.1 is a 14-item patient-reported outcome instrument that measures the impact of migraine across 3 domains of a patient's migraine-related quality of life:
  - Role function-restrictive (RFR): 7 items assess how migraines limit daily social and work-related activities
  - Role function-preventive (RFP): 4 items assess how migraines prevent daily social and work-related activities
  - Emotional function (EF): 3 items assess emotions associated with migraine
- All 3 MSQ domains were assessed in the PREEMPT pivotal trials as prespecified other endpoints at week 24. This presentation focuses only on the RFR domain to assess participants' functional limitations attributable to migraine[5]
- Threshold of clinically meaningful change is considered ≥ 10.9 points from baseline.[11]

Limitations: MSQ-RFR change from baseline was a prespecified other endpoint in PREEMPT clinical trials and was not included as part of the hierarchical testing strategy or adjusted for multiplicity. Therefore, treatment differences cannot be regarded as statistically significant.

Study design: PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Subjects included adult Chronic Migraine patients not using any concurrent headache prophylaxis and, during a 28-day baseline period, had ≥ 15 headache days lasting 4 hours or more, with ≥ 50% being migraine/probable migraine. Patients were allowed to use acute headache treatments during the study. Primary time point was 24 weeks. A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache.[3,5]

*MSQ-RFR = **M**igraine **S**pecific **Q**uality-of-Life Questionnaire **R**ole **F**unction-**R**estrictive.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin.

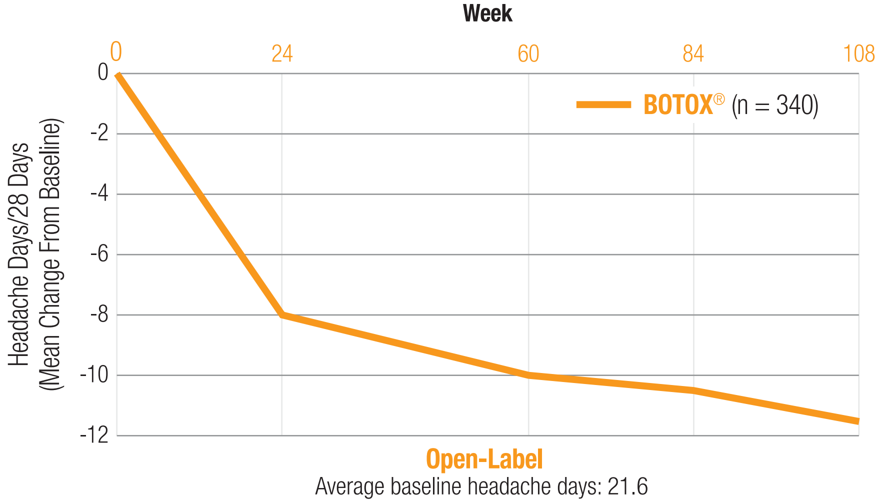
Please see additional Important Safety Information throughout.

Long-term efficacy and safety results from 2-year, open-label COMPEL* trial[17-19]

2 **YEAR TRIAL**

Efficacy consistent with PREEMPT trials over 108 weeks and up to 9 treatments[17-19]

Results from COMPEL[17-19]



- **Data from the subgroup of patients who did not use an oral preventive medication anytime during the study are presented (n = 340)**[19]
- 8.0, 10.0, 10.5, and 11.6 fewer headache days per month from baseline at weeks 24, 60, 84, and 108, respectively[19]
- Adverse events from the COMPEL trial were consistent with those of the PREEMPT 1 and 2 trials[17]
- Adverse events reported in COMPEL were: neck pain, eyelid ptosis, musculoskeletal stiffness, injection-site pain, headache, migraine, muscular weakness, facial paresis, and skin tightness[17]

Limitations: This nonrandomized, 2-year, open-label study has potential for bias due to no placebo or active comparator arm and low persistency rates given the duration.

Considered the established efficacy and safety of BOTOX® for Chronic Migraine and determined it most appropriate to avoid giving patients placebo for the study duration because of the debilitating impact of the disease.[17]

Study design: Open-label study (n = 716) in which enrolled patients received 155 Units of BOTOX® (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles over 12 weeks for 9 treatment cycles [108 weeks]). The primary endpoint was headache-day reduction at week 108. 56% of patients enrolled received all 9 treatments, and 52% received all study treatments and attended the final follow-up visit.[17]

*__COMPEL__ = **C**hronic Migraine **O**nabotulinu**M**toxinA **P**rolonged **E**fficacy open **L**abel.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders (continued)
Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects, including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX (see *Warnings and Precautions*).

Dysphagia and Breathing Difficulties
Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see *Boxed Warning*).

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MOST STUDIED PREVENTIVE TREATMENT APPROVED FOR CHRONIC MIGRAINE[1,*]

15 YEARS OF PATIENT IMPACT[2,†]

*Based on a literature search for peer-reviewed publications on Chronic Migraine prevention and therapy.
†Since FDA approval in October 2010.[2]

Why wait? Deliver BOTOX® today.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS

Adverse reactions to BOTOX for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine vs placebo include, respectively, neck pain (9% vs 3%); headache (5% vs 3%); eyelid ptosis (4% vs <1%); migraine (4% vs 3%); muscular weakness (4% vs <1%); musculoskeletal stiffness (4% vs 1%); bronchitis (3% vs 2%); injection-site pain (3% vs 2%); musculoskeletal pain (3% vs 1%); myalgia (3% vs 1%); facial paresis (2% vs 0%); hypertension (2% vs 1%); and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in study 1 and study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX are discussed in greater detail in *Postmarketing Experience* (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors, including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Co-administration of BOTOX and other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide, or visit www.rxabbvie.com/pdf/botox_pi.pdf

References: 1. Data on file, AbbVie Inc. REF-139816. 2. Data on file, AbbVie Inc. REF-69930. 3. BOTOX®. Prescribing information. AbbVie Inc; 2023. 4. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM, Diener HC. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: analysis of PREEMPT data. *Cephalalgia*. 2019;39(8):945-956. 5. Data on file, AbbVie Inc. REF-89746. 6. Data on file, AbbVie Inc. REF-89970. 7. Data on file, AbbVie Inc. REF-89971. 8. Data on file, AbbVie Inc. REF-96832. 9. Data on file, AbbVie Inc. REF-96833. 10. Data on file, AbbVie Inc. ABVRRTI78987. 11. Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache*. 2007;47:1398-1408. 12. Shibata M, Nakamura T, Ozeki A, Ueda K, Nichols RM. Migraine-Specific Quality-of-Life Questionnaire (MSQ) version 2.1 score improvement in Japanese patients with episodic migraine by galcanezumab treatment: Japan phase 2 study. *J Pain Res*. 2020;13:3531-3538. 13. Speck RM, Shaloub H, Wyrwich KW, et al. Psychometric validation of the Role Function Restrictive Domain of the Migraine Specific Quality-of-Life Questionnaire version 2.1 electronic patient-reported outcome in patients with episodic and chronic migraine. *Headache*. 2019;59:756-774. 14. Bagley CL, Rendas-Baum R, Maglinte GA, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. *Headache*. 2012;52:409-421. 15. Data on file, AbbVie Inc. REF-105090. 16. Data on file, AbbVie Inc. REF-105091. 17. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19(1):1-12. 18. Winner PK, Blumenfeld AM, Eross EJ, et al. Long-term safety and tolerability of onabotulinumtoxinA treatment in patients with chronic migraine: results of the COMPEL study. *Drug Saf*. 2019;42(8):1013-1024. 19. Data on file, AbbVie Inc. REF-96834.

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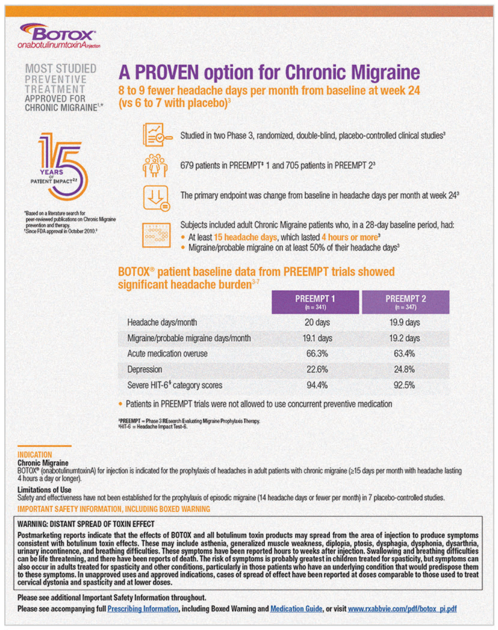

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- Studied in two Phase 3, randomized, double-blind, placebo-controlled clinical studies[3]
- 679 patients in PREEMPT‡ 1 and 705 patients in PREEMPT 2[3]
- The primary endpoint was change from baseline in headache days per month at week 24[3]
- Subjects included adult Chronic Migraine patients who, in a 28-day baseline period, had:
  - At least 15 headache days, which lasted 4 hours or more[3]
  - Migraine/probable migraine on at least 50% of their headache days[3]

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‡PREEMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy.
§HIT-6 = Headache Impact Test-6.

INDICATION

Chronic Migraine

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Established safety profile in PREEMPT clinical trials at week 24[3,5]

Most frequently reported adverse reactions*	BOTOX® (n = 687)[3]	Placebo (n = 692)[3]
Neck pain	9%	3%
Headache	5%	3%
Eyelid ptosis	4%	< 1%
Migraine	4%	3%
Muscular weakness	4%	< 1%
Musculoskeletal stiffness	4%	1%
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Musculoskeletal pain	3%	1%
Myalgia	3%	1%
Facial paresis	2%	0%
Hypertension	2%	1%
Muscle spasms	2%	1%

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- 4% of BOTOX® patients discontinued pivotal trials due to adverse events (vs 1% for placebo)[3,5]
- Observed treatment-related adverse events were typically mild to moderate in severity.
- Patients were evaluated for adverse reactions at every visit from week 0 through week 24, as shown in the chart above (7 evaluations)[5]
- Patients were also evaluated throughout the open-label phase from week 24 through week 56 (9 evaluations)[5]

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Serious Adverse Reactions With Unapproved Use
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Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently, the causal agent cannot be reliably determined.

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PROVEN efficacy in PREEMPT clinical trials

8 to 9 fewer headache days per month from baseline at week 24 (vs 6 to 7 with placebo)[3]

After the primary endpoint was measured at week 24, all patients received BOTOX®[5]

- Statistically significant headache day reductions were observed vs placebo at week 4, which was the first prespecified efficacy evaluation time point; primary endpoint was measured at 24 weeks[5]
- 8 to 9 fewer migraine/probable migraine days per month from baseline at week 24 (vs 6 to 7 with placebo)[3] (secondary endpoint)

Responder rates for BOTOX® patients in PREEMPT clinical trials

Other endpoint: percentage of patients with a ≥ 50% reduction in headache days from baseline in each month at week 24[8,9]

Other endpoint: percentage of patients with a ≥ 75% reduction in headache days from baseline in each month at week 24[8,9]

	RESULTS FROM PREEMPT 1 (≥ 50%)	RESULTS FROM PREEMPT 2 (≥ 50%)	RESULTS FROM PREEMPT 1 (≥ 75%)	RESULTS FROM PREEMPT 2 (≥ 75%)
BOTOX®	44% (n = 341)	51% (n = 347)	19% (n = 341)	26% (n = 347)
Placebo	36% (n = 338)	34% (n = 358)	15% (n = 338)	16% (n = 358)

Limitations: The responder rate analyses were prespecified, other endpoints in PREEMPT clinical trials[5] and were not included as part of the hierarchical testing strategy or adjusted for multiplicity. Therefore, treatment differences cannot be regarded as statistically significant.

Study design: PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Subjects included adult Chronic Migraine patients not using any concurrent headache prophylaxis and, during a 28-day baseline period, had ≥ 15 headache days lasting 4 hours or more, with ≥ 50% being migraine/probable migraine. Patients were allowed to use acute headache treatments during the study. Primary time point was 24 weeks. A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache.[3,5]

Start BOTOX® today, delaying treatments delays results

IMPORTANT SAFETY INFORMATION (continued)
CONTRAINDICATIONS
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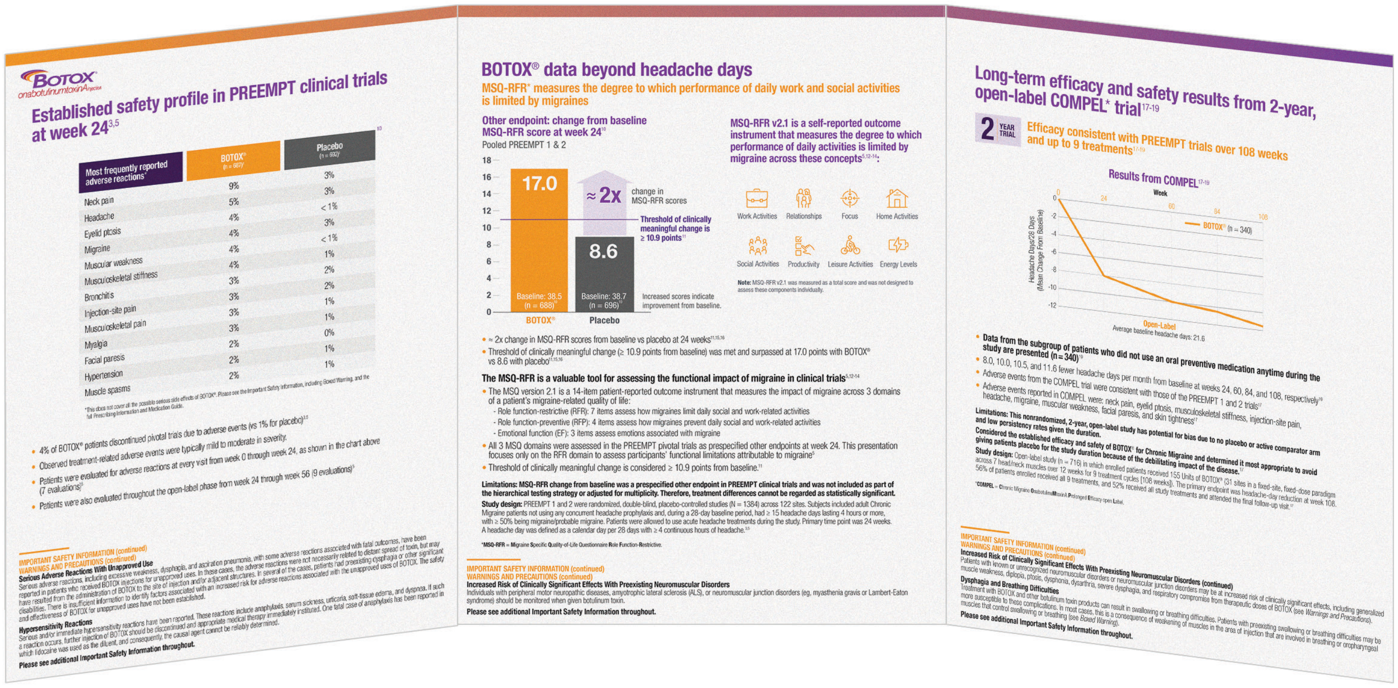
WARNINGS AND PRECAUTIONS
Spread of Toxin Effect
See *Boxed Warning*.
No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for chronic migraine at the labeled dose have been reported.

Lack of Interchangeability Between Botulinum Toxin Products
The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

Please see additional Important Safety Information throughout.

Fully-opened, full spread



Established safety profile in PREEMPT clinical trials at week 24[3,5]

Most frequently reported adverse reactions*	BOTOX® (n = 687)[3]	Placebo (n = 692)[3]
Neck pain	9%	3%
Headache	5%	3%
Eyelid ptosis	4%	< 1%
Migraine	4%	3%
Muscular weakness	4%	< 1%
Musculoskeletal stiffness	4%	1%
Bronchitis	3%	2%
Injection-site pain	3%	2%
Musculoskeletal pain	3%	1%
Myalgia	3%	1%
Facial paresis	2%	0%
Hypertension	2%	1%
Muscle spasms	2%	1%

*This does not cover all the possible serious side effects of BOTOX®. Please see the Important Safety Information, including Boxed Warning, and the full Prescribing Information and Medication Guide.

- 4% of BOTOX® patients discontinued pivotal trials due to adverse events (vs 1% for placebo)[3,5]
- Observed treatment-related adverse events were typically mild to moderate in severity.
- Patients were evaluated for adverse reactions at every visit from week 0 through week 24, as shown in the chart above (7 evaluations)[5]
- Patients were also evaluated throughout the open-label phase from week 24 through week 56 (9 evaluations)[5]

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Serious Adverse Reactions With Unapproved Use
Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had preexisting dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently, the causal agent cannot be reliably determined.

Please see additional Important Safety Information throughout.

BOTOX® data beyond headache days

MSQ-RFR* measures the degree to which performance of daily work and social activities is limited by migraines

Other endpoint: change from baseline MSQ-RFR score at week 24[10]

Pooled PREEMPT 1 & 2

MSQ-RFR v2.1 is a self-reported outcome instrument that measures the degree to which performance of daily activities is limited by migraine across these concepts[5,12-14]:

Work Activities
Relationships
Focus
Home Activities
Social Activities
Productivity
Leisure Activities
Energy Levels

Note: MSQ-RFR v2.1 was measured as a total score and was not designed to assess these components individually.

- ≈ 2x change in MSQ-RFR scores from baseline vs placebo at 24 weeks[11,15,16]
- Threshold of clinically meaningful change (≥ 10.9 points from baseline) was met and surpassed at 17.0 points with BOTOX® vs 8.6 with placebo[11,15,16]

The MSQ-RFR is a valuable tool for assessing the functional impact of migraine in clinical trials[5,12-14]

- The MSQ version 2.1 is a 14-item patient-reported outcome instrument that measures the impact of migraine across 3 domains of a patient's migraine-related quality of life:
  - Role function-restrictive (RFR): 7 items assess how migraines limit daily social and work-related activities
  - Role function-preventive (RFP): 4 items assess how migraines prevent daily social and work-related activities
  - Emotional function (EF): 3 items assess emotions associated with migraine
- All 3 MSQ domains were assessed in the PREEMPT pivotal trials as prespecified other endpoints at week 24. This presentation focuses only on the RFR domain to assess participants' functional limitations attributable to migraine[5]
- Threshold of clinically meaningful change is considered ≥ 10.9 points from baseline.[11]

Limitations: MSQ-RFR change from baseline was a prespecified other endpoint in PREEMPT clinical trials and was not included as part of the hierarchical testing strategy or adjusted for multiplicity. Therefore, treatment differences cannot be regarded as statistically significant.

Study design: PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Subjects included adult Chronic Migraine patients not using any concurrent headache prophylaxis and, during a 28-day baseline period, had ≥ 15 headache days lasting 4 hours or more, with ≥ 50% being migraine/probable migraine. Patients were allowed to use acute headache treatments during the study. Primary time point was 24 weeks. A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache.[3,5]

*MSQ-RFR = Migraine Specific Quality-of-Life Questionnaire Role Function-Restrictive.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin.

Please see additional Important Safety Information throughout.

Long-term efficacy and safety results from 2-year, open-label COMPEL* trial[17-19]

2 YEAR TRIAL

Efficacy consistent with PREEMPT trials over 108 weeks and up to 9 treatments[17-19]

Results from COMPEL[17-19]

Average baseline headache days: 21.6

- **Data from the subgroup of patients who did not use an oral preventive medication anytime during the study are presented (n = 340)[19]**
- 8.0, 10.0, 10.5, and 11.6 fewer headache days per month from baseline at weeks 24, 60, 84, and 108, respectively[19]
- Adverse events from the COMPEL trial were consistent with those of the PREEMPT 1 and 2 trials[17]
- Adverse events reported in COMPEL were: neck pain, eyelid ptosis, musculoskeletal stiffness, injection-site pain, headache, migraine, muscular weakness, facial paresis, and skin tightness[17]

Limitations: This nonrandomized, 2-year, open-label study has potential for bias due to no placebo or active comparator arm and low persistency rates given the duration.

Considered the established efficacy and safety of BOTOX® for Chronic Migraine and determined it most appropriate to avoid giving patients placebo for the study duration because of the debilitating impact of the disease.[17]

Study design: Open-label study (n = 716) in which enrolled patients received 155 Units of BOTOX® (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles over 12 weeks for 9 treatment cycles [108 weeks]). The primary endpoint was headache-day reduction at week 108. 56% of patients enrolled received all 9 treatments, and 52% received all study treatments and attended the final follow-up visit.[17]

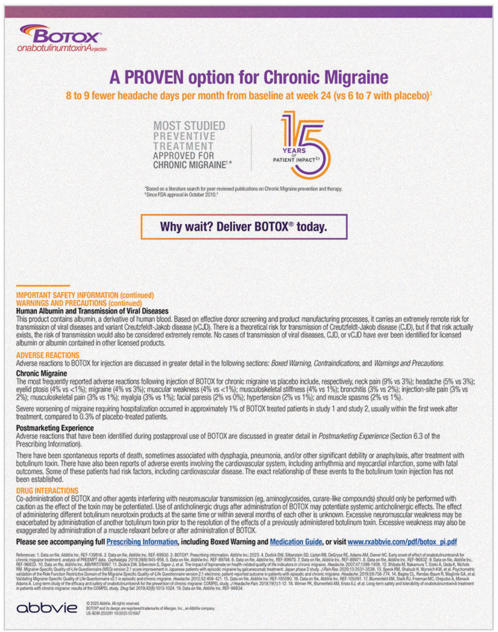
*COMPEL = Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders (continued)
Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects, including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX (see *Warnings and Precautions*).

Dysphagia and Breathing Difficulties
Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see *Boxed Warning*).

Please see additional Important Safety Information throughout.

Back Cover



A PROVEN option for Chronic Migraine

8 to 9 fewer headache days per month from baseline at week 24 (vs 6 to 7 with placebo)[3]

MOST STUDIED PREVENTIVE TREATMENT APPROVED FOR CHRONIC MIGRAINE[1,*]

15 YEARS OF PATIENT IMPACT[2,†]

*Based on a literature search for peer-reviewed publications on Chronic Migraine prevention and therapy.
†Since FDA approval in October 2010.[2]

Why wait? Deliver BOTOX® today.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Human Albumin and Transmission of Viral Diseases
This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS
Adverse reactions to BOTOX for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Chronic Migraine
The most frequently reported adverse reactions following injection of BOTOX for chronic migraine vs placebo include, respectively, neck pain (9% vs 3%); headache (5% vs 3%); eyelid ptosis (4% vs <1%); migraine (4% vs 3%); muscular weakness (4% vs <1%); musculoskeletal stiffness (4% vs 1%); bronchitis (3% vs 2%); injection-site pain (3% vs 2%); musculoskeletal pain (3% vs 1%); myalgia (3% vs 1%); facial paresis (2% vs 0%); hypertension (2% vs 1%); and muscle spasms (2% vs 1%).

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in study 1 and study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Postmarketing Experience
Adverse reactions that have been identified during postapproval use of BOTOX are discussed in greater detail in *Postmarketing Experience* (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors, including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS
Co-administration of BOTOX and other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide, or visit www.rxabbvie.com/pdf/botox_pi.pdf

References: 1. Data on file, AbbVie Inc. REF-139816. 2. Data on file, AbbVie Inc. REF-69930. 3. BOTOX®. Prescribing information. AbbVie Inc; 2023. 4. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM, Diener HC. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: analysis of PREEMPT data. *Cephalalgia*. 2019;39(8):945-956. 5. Data on file, AbbVie Inc. REF-89746. 6. Data on file, AbbVie Inc. REF-89970. 7. Data on file, AbbVie Inc. REF-89971. 8. Data on file, AbbVie Inc. REF-96832. 9. Data on file, AbbVie Inc. REF-96833. 10. Data on file, AbbVie Inc. ABVRRTI78987. 11. Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache*. 2007;47:1398-1408. 12. Shibata M, Nakamura T, Ozeki A, Ueda K, Nichols RM. Migraine-Specific Quality-of-Life Questionnaire (MSQ) version 2.1 score improvement in Japanese patients with episodic migraine by galcanezumab treatment: Japan phase 2 study. *J Pain Res*. 2020;13:3531-3538. 13. Speck RM, Shalhoub H, Wyrwich KW, et al. Psychometric validation of the Role Function Restrictive Domain of the Migraine Specific Quality-of-Life Questionnaire version 2.1 electronic patient-reported outcome in patients with episodic and chronic migraine. *Headache*. 2019;59:756-774. 14. Bagley CL, Rendas-Baum R, Maglinte GA, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. *Headache*. 2012;52:409-421. 15. Data on file, AbbVie Inc. REF-105090. 16. Data on file, AbbVie Inc. REF-105091. 17. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19(1):1-12. 18. Winner PK, Blumenfeld AM, Eross EJ, et al. Long-term safety and tolerability of onabotulinumtoxinA treatment in patients with chronic migraine: results of the COMPEL study. *Drug Saf*. 2019;42(8):1013-1024. 19. Data on file, AbbVie Inc. REF-96834.

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