SUPPLEMENTARY MATERIALS

Supplementary Table 1A. Population, Intervention, Comparator, Outcomes, and Setting/Study Design.

	INCLUSION CRITERIA	
POPULATION	Adult patients with chronic and unspecified migraine	
INTERVENTION	OnabotulinumtoxinA (Botox)	
COMPARATORS	• Eptinezumab • Fremanezumab • Galcanezumab • Erenumab • Amitriptyline • Nortriptyline • Doxepin • Atenolol • Propranolol • Nadolol • Metoprolol Timolol	• Gabapentin • Topiramate • Flunarizine • Divalproex sodium • Valproate sodium • Valproic acid • Candesartan • Pizotyline • Venlafaxine • Duloxetine

OUTCOMES	**Effectiveness outcomes** • Response rates (headache days, as per various definitions and time points) • ≥30% reduction in headache days • ≥50% reduction in headache days • ≥75% reduction in headache days • ≥2-fold increase in headache-free days • Response rates (migraine days, as per various definitions and time points) • ≥30% reduction in migraine days • ≥50% reduction in migraine days • ≥75% reduction in migraine days • Monthly migraine days (MMD) (including change in migraine days from baseline) • Monthly headache days (MHD) (including change in headache days from baseline) • Frequency of moderate or severe headache days	• Health utility (EuroQol 5 Dimensions [EQ-5D], Short Form-12 [SF-12], SF-36) • Comorbid anxiety or depression as per various scales (e.g. Patient Health Questionnaire-9 [PHQ-9], General Anxiety Disorder-7 [GAD-7], Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory [BDI]) • Sleep quality • Change in concomitant preventive medication use • Change in concomitant acute medication use from baseline (e.g. monthly acute medication days/month) • Concomitant non-opioid analgesic use • Concomitant opioid use • Adherence (as assessed at various time points) • Persistence (as assessed at various time points) • Patient satisfaction with treatment **Safety outcomes** • Any TEAEs • Any serious TEAEs • Treatment-related TEAEs

	• Headache or migraine severity/intensity[&] • Headache or migraine duration • Headache impact test-6 (HIT-6) • Migraine-Specific Quality of Life (MSQ) score • Migraine Disability Assessment (MIDAS) score	• Common TEAEs (TEAEs occurring in >2% of patients). **Tolerability outcomes** • Withdrawals/discontinuations due to any reason • Withdrawals/discontinuations due to TEAEs • Withdrawals/discontinuations due to lack of effectiveness • Withdrawals/discontinuations due to lost to follow-up • Withdrawals/discontinuations due to death • Withdrawals/discontinuations due to any other reasons
STUDY DESIGN	Studies identified between January 1, 2010 and January 30, 2021, assessing any pharmacologic agents (with or without a comparator group) for the preventive treatment of chronic migraine; observational study designs (excluding case reports, case series and Phase 4 non-randomized controlled trials); sample size ≥40 and follow-up period reported	

[&]In most studies, headache severity was assessed using a numeric scale or VAS or pain intensity score. In some study abstracts, this may not have been defined.

TEAE: treatment-emergent adverse event; VAS: visual analog scale.

Supplementary Table 1B. Search strategy.

Search strategy for Embase/Medline (using embase.com conducted on 11th Feb 2020.			
No.	Query	Results	Facet
1	'migraine'/exp	64,515	**Disease facet**
2	'migraine':ab,ti OR 'migrainous headache':ab,ti OR 'hemicrania':ab,ti OR 'status hemicranicus':ab,ti OR ‘chronic migraine’:ab,ti	51,823	
3	#1 OR #2	70,396	
4	'observational study'/exp OR 'survey'/exp OR 'electronic health record'/exp OR 'medical record review'/exp OR 'pragmatic trial'/exp OR 'real world data'/exp OR 'real world evidence'/exp OR 'clinical practice'/exp OR 'cross-sectional study'/exp OR 'registry'/exp OR 'register':ab,ti OR 'registries':ab,ti OR 'cohort analysis'/exp	4,187,180	**Study design facet**

	OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'case control study'/exp OR ((case* NEXT/1 control*):ti,ab) OR cohort*:ab,ti OR ((('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti) OR 'retrospective study'/exp		
5	observational:ab,ti OR 'observational study':ab,ti OR survey:ab,ti OR database:ab,ti OR 'insurance claim':ab,ti OR 'electronic health record':ab,ti OR 'electronic medical record':ab,ti OR 'chart review':ab,ti OR 'cross sectional':ab,ti OR 'pragmatic trial':ab,ti OR 'real world':ab,ti OR 'real life':ab,ti OR 'non-interventional':ab,ti OR 'clinical practice':ab,ti	2,025,089	
6	(#4 OR #5) NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	5,040,598	
7	#3 AND #6	16,302	
8	**#3 AND #6 AND [2010-2020]/py**	**12,269**	**Final**

Search strategy for Cochrane library conducted on 6th Mar 2020.			
No.	Query	Results	Facet
1	MeSH descriptor: [Migraine Disorders] explode all trees	2548	**Disease facet**
2	('migraine':ab,ti OR 'migrainous headache':ab,ti OR 'hemicrania':ab,ti OR 'status hemicranicus':ab,ti OR ‘chronic migraine’):ti,ab,kw	6405	
3	#1 OR #2	6510	
4	(Observational study OR cross-sectional OR cohort study OR case-control study):ti,ab,kw	75311	**Study design facet**
5	(prospective study Or retrospective study OR registry OR longitudinal study):ti,ab,kw	213102	
6	(survey OR electronic medical record OR chart review OR real world data):ti,ab,kw	32946	
7	#4 OR #5 OR #6	284863	

8	#3 AND #7	865	
9	#8 with Cochrane Library publication date from Jan 2010 to Mar 2020, in Cochrane Reviews and Trials	**393**	**Final**
Search strategy for updated Embase/Medline search(using embase.com) conducted on 20th Jan 2021.			
No.	Query	Results	Facet
1	exp migraine/ or exp Migraine Disorders/	93,456	**Disease facet**
2	(migrainous headache or migraine or hemicrania or status hemicranicus or chronic migraine).ti,ab.	88,901	
3	#1 OR #2	112,200	
4	exp observational study/ or exp Observational Studies as Topic/ or exp Health Care Surveys/ or exp health care survey/ or exp Health Surveys/ or exp health survey/ or exp Electronic Health Records/ or exp electronic health record/ or exp "medical record review"/ or exp pragmatic trial/ or exp Pragmatic Clinical Trial/ or exp Pragmatic Clinical Trials as Topic/	8,322,962	**Study design facet**

	or exp real world data/ or exp real world evidence/ or exp clinical practice/ or exp cross-sectional study/ or exp Cross-Sectional Studies/ or exp registries/ or exp register/ or (register or registries).ti,ab. or exp cohort analysis/ or exp Cohort Studies/ or exp longitudinal study/ or exp longitudinal studies/ or exp prospective study/ or exp prospective studies/ or exp follow up/ or exp Follow-Up Studies/ or exp case control study/ or exp Case-Control Studies/ or (case* adj1 control*).ti,ab. or cohort*.ti,ab. or (('follow up' or followup) adj1 (study or studies)).ti,ab. or exp retrospective study/ or exp Retrospective Studies/		
5	(observational or 'observational study' or survey or database or 'insurance claim' or 'electronic health record' or 'electronic medical record or 'chart review' or 'cross sectional or 'pragmatic trial or 'real world' or 'real life or 'non-interventional or 'clinical practice').ti,ab.	3,818,272	
6	4 or 5	10,252,176	

7	editorial/	1,218,489	
8	letter/	2,213,403	
9	note/ or Lecture Note/	788,301	
10	7 or 8 or 9	4,218,384	
11	6 not 10	9,906,355	
12	3 and 11	28,163	Limit to date
13	from 12 keep 1-18682	18,682	
14	limit 13 to dd=20200201-20210120 [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	738	
15	from 12 keep 18683-28163	9,481	
16	limit 15 to ed=20200201-20210120 [Limit not valid in Embase; records were retained]	595	

17	14 or 16	1,333	
18	remove duplicates from 17	1,302	
19	limit 12 to yr="2020-Current"	2,697	
20	19 not 18	1,873	
21	remove duplicates from 20	1,426	
22	from 21 keep 1286-1426	141	
23	18 or 22	1,443	
24	**remove duplicates from 23**	**1,345**	**Final**
Search strategy for Cochrane library conducted on 20th Jan 2021			
No.	Query	Results	Facet
1	MeSH descriptor: [Migraine Disorders] explode all trees	2,672	**Disease facet**

2	('migraine' OR 'migrainous headache' OR 'hemicrania' OR 'status hemicranicus' OR ‘chronic migraine’):ti,ab,kw	7,519	
3	#1 OR #2	7,519	
4	(Observational study OR cross sectional OR cohort study OR case control study):ti,ab,kw	93,892	**Study design facet**
5	(prospective study Or retrospective study OR registry OR longitudinal study):ti,ab,kw	227,419	
6	(survey OR electronic medical record OR chart review OR real world data):ti,ab,kw	36,595	
7	#4 OR #5 OR #6	314,258	
8	#3 AND #7	1,047	
9	#3 AND #7 with Cochrane Library publication date Between Mar 2020 and Jan 2021, in Cochrane Reviews, Trials	**100**	**Final**

Supplementary Table 2. Newcastle–Ottawa Scale for cohort and case–control studies.

Study question	Points
Cohort studies	
Selection • Representativeness of the exposed cohort (1 point) • Selection of the non-exposed cohort (1 point) • Ascertainment of exposure (1 point) • Demonstration that outcome of interest was not present at start of study (1 point)	
Comparability • Comparability of cohorts on the basis of the design or analysis (2 points)	
Outcome • Assessment of outcome (1 point) • Was follow-up long enough for outcomes to occur? (1 point) • Adequacy of follow-up of cohorts (1 point)	
Case–control studies	
Selection	

Study question	Points
• Adequacy of the case definition (1 point) • Representativeness of cases (1 point) • Selection of controls (1 point) • Definition of controls (1 point)	
Comparability • Comparability of cases and controls (2 points)	
Exposure • Assessment of exposure (1 point) • Same method of ascertainment for cases and controls (1 point) • Non-response rate (1 point)	

Cohort studies were graded from 0 (poorest quality) to 9 (highest quality).

Supplementary Table 3. Baseline clinical characteristics of patients enrolled in the included studies.

Study name	Sample size	Age, years, mean (±SD)	Age of CM onset, years, mean (±SD)	Female, n (%)	CM duration years, mean (±SD) or median* (range: min-max)	Headache days/ month, mean (±SD) or median* (range: min-max)	Migraine days/ month, mean (±SD) or median* (range: min-max)	Prior treatment status	Prior acute/ preventive med use, n (%)	Number of failed meds	Comorbidities, n (%)
Alpuente 2019	578 [$$]	N/R	N/R	N/R	N/R	26.9 (4.8)	N/R	Unknown	N/R	N/R	N/R
Ahmed 2015 (Hull migraine study)	972	45.0 (14.0–96.0)*	M: 17.0	693 (81.4)	4.0 (range: 0.5–67.0)	N/R	N/R	Previously treated	448 (52.6)/N/R	≥3	N/R
Ahmed 2019 (REPOSE)	633	45.4 (±11.7)	M: 18.2 (±9.9)	540 (85.3)	5.6 (±8.0)	20.6 (±5.4)	N/R	Previously treated	534 (84.4)/ 402 (63.5)	N/R	N/R
Alessiani 2018	54	N/R	N/R	N/R	N/R	~25.5	N/R	Unknown	~20.6[$]/N/R	N/R	N/R
Andreou 2018	200	46.0 (±11.9)	N/R	158 (79.0)	5.9 (±5.0)	24.0 (18.0-30.0)*	13.0 (9.0- 19.0)*	Previously treated	89 (46.0)/N/R	N/R	N/R
Aydinlar 2017	190	39.3 (±10.2)	N/R	167 (87.9)	3.0 (range: 1.0–10.0)*	15.0 (12.0–25.0)*	N/R	Previously treated	190 (100.0)°	N/R	N/R
Belvís 2018	90	N/R	N/R	N/R	N/R	N/R	N/R	Unknown	N/R	N/R	N/R
Boudreau 2020a,b (PREDICT)	184	45.0	N/R	156 (84.8)	N/R	20.9 (±6.7)	N/R	Treatment naïve	N/R	N/R	N/R
Butera 2016	44	50.0 (range:	N/R	37 (82.2)	Mean 14.0 (range: 1.0– 32.0)	25.2 (±6.3)	19.6 (±9.6)	Previously treated	N/R/16 (36.0)	N/R	N/R

		22.0–76.0)									
Caronna 2018	139	47.3 (±11.4)	M: 17.3 (±11.1)	115 (82.7)	9.3 (±9.0)	27.3 (±4.7)	13.4 (±8.1)	Previously treated	139 (100.0)/N/R	≥1	•Anxiety: 96 (69.1) •Depression: 62 (44.9) •Fibromyalgia: 24 (17.4) •CFS: 14 (10.1) •Sleeping disorders: 44 (32.4)
Corbelli 2019	195	•R: 47.8 (±14.1) •Partial-R: 46.9 (±11.9) •Non-R: 45.5 (±13.6) •Dropout: 49.4 (±9.7)""	N/R	160 (82.1)	N/R	24.2 (±5.6)	N/R	Previously treated	N/R	N/R	N/R
d'Onofrio 2020	40[&]	48.6 (±11.1)	N/R	23 (76.6)	25.7 (±12.3)	19.3 (±5.9)	23.0 (±8.9) ^	Previously treated	18.2 (6.3) [$]/N/R	N/R	N/R
de Tommaso 2019	99	46.1 (±13.7)	N/R	85 (85.9)	M: 23.5 (±12.1)	24.8 (±5.5)	N/R	Previously treated	90 (90.9)/N/R	N/R	N/R
Dominguez 2018	725	46.8 (±12.0)	N/R	622 (85.8)	20.4 (±18.7)	21.8 (±6.4)	13.8 (±7.0)	Previously treated	N/R/398 (54.9)	N/R	•Depression: 250 (34.5)

											•Fibromyalgia: 94 (13.0) •Any[§§]: 231 (31.9)
Dikmen 2018	180	40.4 (±10.5)	N/R	159 (88.3)	M: 12.0 (±9.1)	18.9 (±5.5)	N/R	Previously treated	46 (25.5)/N/R	N/R	N/R
Eren 2020	49	43.7 (±12.9)	N/R	45(92.0)	M: 23.4 (±12.3)	24.1 (±5.6)	N/R	Treatment naïve	N/R	N/R	N/R
Gandolfi 2019	40	46.7 (±13.7)	• Pre-ado: 11.0 (±27.5) [∞] • Ado: 13.0 (±32.5) [∞] • Adult: 16.0 (±40) [∞]	37 (92.5)	N/R	N/R	N/R	Previously treated	14 (35)/ 24 (60.0)	≥1	Any: 24 (60.0)
Gonzalez-Martinez 2020	112	43.0 (±11.0)	43.3 (±11.1)	100 (89.3)	2.4 (±3.5)	N/R	N/R	Previously treated	83 (74.1)/N/R	N/R	Anxiety: 66 (58.9)
Garcia-Azorín 2018	49	43.8	M: 19.1	45 (91.8)	3.2	N/R	N/R	Unknown	N/R	N/R	N/R
Guerzoni 2017	90	45.2 (±10.1)	N/R	76 (84.4)	N/R	1.0 (±0.2) [+++]	N/R	Previously treated	N/R/90 (100.0)	≥3	N/R
Grazzi 2016	53	N/R	N/R	N/R	N/R	19.9 (±13.1)	N/R	Previously treated	17.4 (5.6) [$]/N/R	N/R	N/R
Grazzi 2015	66	N/R	N/R	N/R	N/R	21.7 (±6.8) [$$]	22.4 (±6.5) [$$]	Previously treated	N/R	N/R	N/R
Kennedy 2017	120	N/R	N/R	N/R	N/R	N/R	N/R	Unknown	N/R	N/R	N/R

Lee 2016	70	48.0 (±13.6) [R] (n = 42)	N/R	60 (85.7)	N/R	25.9 (±6.0)	N/R	Both	34 (48.6)/N/R	N/R	•Anxiety: 6 (8.5) •Depression: 10 (14.2) •Any[^^]: 4 (5.7)
Lin 2014	94	47.6 (±13.6)	N/R	79 (84.0)	8.1 (±8.3)	23.9 (±8.1)	N/R	Previously treated	18 (19.1)/94 (100.0)	≥2	N/R
Navarrete Perez 2017	117	41.0 (±11.7)	N/R	102 (87.2)	N/R	N/R	N/R	Unknown	N/R	N/R	N/R
Negro 2016	143 (onabotA 195 IU)	44.9 (±12.7)	N/R	114 (79.7)	9.3 (±5.1)	22.2 (±4.9)	21.6 (±4.8)	Previously treated	143 (100.0)	N/R	N/R
	132 (onabotA 155 IU)	43.2 (±13.5)	N/R	108 (81.8)	10.2 (±4.8)	22.3 (±4.1)	21.4 (±4.3)	Previously treated	132 (100.0)	N/R	N/R
Ornello 2020	115	50 (44.5–54.0)*	N/R	97 (84.3)	5.2 (range: 2.0–12.0)*	Non-R: 30 (range: 30–30)* Anytime R: 30 (range: 24–30)* Sustained-R: 25 (range: 21.5–30.0)*	N/R	Previously treated	89 (77.4)/N/R	N/R	Hypertension: 29 (25.2)
Pedraza 2015	52	42.8 (±12.7)	M: 16.8 (7.8)	44 (84.6)	N/R	23.4 (±6.3)	13.9 (±7.3)	Previously treated	43 (82.7)/52 (100.0)	N/R	N/R
Quintas 2019	193	41.4 (±11.06)	18.09 (±9.4) [+];	168 (87.0)	3.6 (±4.9)	22.3 (±6.1)	11.5 (±7.2) [+]; 11.5 (±6.5) [++]	Treatment naïve	132 (68.4)/N/R	N/R	N/R

		[+]; 42.02 (±11.5) [++]	18.6 (±9.3) [++]								
Romoli 2017	56	45.7	N/R	45 (79.7)	N/R	23.3 (±5.7) at cycle 1	18.5 at cycle 1	Both	40 (71.4)/N/R at cycle 1	N/R	N/R
Russo 2016	52	48.7 (±12.9)	38.2 (12.1)	46 (88.5)	9.9 (±7.6)	N/R	N/R	Previously treated	46 (88.5)/N/R	N/R	N/R
Santoro 2020	109	48.1 (±13.5)	N/R	82 (75.2)	11.7 (±9.8)	25.5 (±5.8)	N/R	Previously treated	N/R/47 (43.1)	N/R	N/R
Stark 2019	211	44.6 (±12.5)	N/R	187 (88.6)	14.5 (±12.3)	25.2 (±5.3)	15.3 (±7.9)	Previously treated	129 (61.1)/ N/R	N/R	•Anxiety: 17 (8.0) •Depression: 23 (11.0)
Sanz 2018	69	43.2 (±15.2)	N/R	61 (88.4)	N/R	20.6 (±8.5)	N/R	Both	N/R/57 (82.6)	≥3	Anxiety: 14 (20.3)
Sarchielli 2017	56	45.7 (±6.5)	N/R	47 (83.9)	7.9 (±4.3)	23.1 (±6.3)	18.9 (±5.6)	Previously treated	2.6 (0.5) [$]	≥2	N/R
Torres-Ferrus 2020	395	46.7 (±12.6)	N/R	336 (85.1)	10.5 (±9.9)	26.5 (±5.2)	N/R	Treatment naïve	378 (95.7)/N/R	N/R	N/R
Taddei-Allen 2019	21 (CGRP)	47.0	N/R	15 (71.0)	N/R	N/R	N/R	Unknown	N/R	N/R	N/R
	21 (onabotA)	47.0	N/R	19 (90.0)	N/R	N/R	N/R	Unknown	N/R	N/R	N/R
Vernieri 2019	115	Roma center: 51.6 (±10.3);	N/R	95 (82.6)	N/R	Roma center, 21.2 (±6.7); Milano center: 20.2 (±6.2)	N/R	Previously treated	115 (100.0)/N/R	≥2	N/R

		Milano center: 51.0 (±8.2)									
Velasco-Juanes 2018	70	48.9 (±12.4)	38.8 (±14.0)	61 (87.1)	N/R	25.8 (±14.6)	N/R	Previously treated	39 (55.7)/ 70.0 (100.0)	≥3	N/R

CGRP: calcitonin gene-related peptide; CFS: chronic fatigue syndrome; CM: chronic migraine; IU: international units; M: chronic or episodic migraine not specified; N/R: not reported; onabotA: onabotulinumtoxinA; R: responders; SD: standard deviation; VAS: visual analog scale.

Note: [^]Mean (SD) days with headache/migraine per 30-day period; *Median (range); °Both preventive and acute medications; [$]Mean (SD) of acute medication used; [$$]Data available only for group of 20 patients who completed the treatment; [^^]Hypo- and hyperthyroidism: [+]Wearing off responders; [++]Full-length responder; [+++]Headache index after one onabotulinumtoxinA injection; [§]Migraine pain severity; [~]Values are N (%); [§§]Includes hypertension, heart disease, gastrointestinal disease, lung disease, and skin disturbances; [&]Patients characteristics were reported only for 30 patients; [R]Responders; [“”]Patients’ age at the end phase 1; [&]In most studies, headache severity was assessed using a numeric scale or VAS or pain intensity score.

[1]Corresponds to headache days/month at baseline; [2]The number of episodes of moderate–severe acute headache longer than 4 hours (or shorter if treated with symptomatic medications).

Supplementary Table 4. Baseline HRQoL and disability level of patients enrolled in the included studies which measured the outcomes.

Study name	Baseline HIT-6 score	Baseline MSQ domain or total score	Baseline MIDAS score
	Mean (±SD) [SE] or median		
Ahmed 2015a	68.9 (±4.3)	N/R	N/R
Ahmed 2019	N/R	Role-function restrictive: 36.2 (±17.8) Role-function preventive: 50.2 (±22.8) Emotional function: 42.4 (±25.6)	N/R
Alpuente 2019a	N/R	N/R	86.4 (±71.3)
Andreou 2018	70.0 (65.0-72.0)	N/R	N/R
Aydinlar 2017	N/R	N/R	57 [N=89] ^
Barbanti 2020b	N/R	N/R	N/R
Barbanti 2019a	69.2 (±6.8)	N/R	N/R

Boudreau 2018	N/R	Role-function restrictive 36.7 (SD N/R) Role-function preventive 51.4 (SD N/R) Emotional function 38.0 (SD N/R)	N/R
Butera 2016	65.6 (±8.2)	N/R	117.3 (±94.8)
Caronna 2018a	N/R	N/R	80.4 (±67.5)
de Tommaso 2019	N/R	N/R	63.4 (±61.8)
Dominguez 2018a	N/R	N/R	35.9 (±29.6)
d'Onofrio 2020	62.9 (±11.1)	N/R	55.3 (±26.1)
Gandolfi 2019	61.62 (±8.42)	N/R	Total: 65.67 (±61.12) HF: 39.37 (±24.91) PI: 6.37 (±1.61)
Guerzoni 2017	65.1 (±6.2)	N/R	N/R
Grazzi 2015	65.4 (±7.5)	N/R	79.8 (±57.9)
Jenkins 2019	66	N/R	N/R

Kennedy 2017	N/R	N/R	N/R
Lambru 2020	ERE: 67.6 (±0.4)	N/R	N/R
	ERE-MOH: 66.7 (±1)	N/R	N/R
	ERE-nMOH: 66.7 (±1)	N/R	N/R
Lambru 2016	69.1	N/R	N/R
Lee 2016	68.2 (±5.7)	N/R	N/R
Lin 2014	N/R	N/R	60^
Naprienko 2020	OBT-A: 61.2 (SD N/R)	N/R	N/R
	TPM: 62.0 (SD N/R)	N/R	N/R
Negro 2016	OBT-A 155 U: 68.9 (±4.3)	N/R	N/R
	OBT-A 195 U: 67.9 (±4.2)	N/R	N/R
Ornello 2020a	65.0 (60-69)	N/R	87.5 (42.5- 123.5) ^
Russo 2016	N/R	N/R	71.7 (±43.4)
Russo 2020	N/R	N/R	108.1 [±11.2]

Stark 2019	68.2 (SD or SE N/R)	All domains (total score): 62.7 [±7.5]	N/R
Sarchielli 2017	72.1 (±6.0)	N/R	N/R
Talbot 2021	66.9 (±9.4)	N/R	N/R
Velasco-Juanes 2018	69.2 (±6.1)	N/R	N/R
Vernieri 2019	N/R	N/R	72.0^(interquartile N/R)
Yalinay Dikmen 2018	N/R	N/R	53.3 (±26.6)
Zyloney 2020	N/R	N/R	62 (SD N/R)

CI: confidence interval; CM: chronic migraine; ERE: erenumab; GAL: galcanezumab; HIT: headache impact test; MOH: medication overuse; nMOH: non-medication overuse; MIDAS: Migraine Disability Assessment; MSQ: Migraine-Specific Quality of Life; N/R: not reported; OBT-A: onabotulinumtoxinA; SD: standard deviation; SE: standard error; TPM: topiramate.

^Median (inter-quartile) values

Supplementary Table 5. Treatment characteristics and designs of the included studies.

Study name	Sample size	OnabotA dose (IU)	Frequency (weeks)	Protocol	Duration (months) [N of cycles]
Ahmed 2015	972	155	N/R	PREEMPT	N/R [5,745]
Ahmed 2019	633	155–195[&]	Every 12	FTP	N/R
Alpuente 2019	N/R	N/R	Quarterly	PREEMPT	24
Alessiani 2018	54	N/R	N/R	PREEMPT	N/R
Andreou 2018	97	155	N/R	FSFD	N/R
	103	177[++]	N/R	FTP	N/R
Aydinlar 2017	190	N/R	Every 12	• FSFD • FTP	≥6 [2]
Belvís 2018	90	N/R	N/R	PREEMPT	N/R
Boudreau 2020	184	171 (18)[$]	13.2 (1.8)[$]	Canadian product monograph	24 [7]
Butera 2016	44	N/R	Every 12	PREEMPT	N/R
Corbelli 2019	195	155–195	Every 12	N/R	12 [4]
Caronna 2018	139	155	• At baseline	PREEMPT	N/R [2]

Study name	Sample size	OnabotA dose (IU)	Frequency (weeks)	Protocol	Duration (months) [N of cycles]
			• At 12		
d'Onofrio 2020	40	155	• At baseline • At 12 • At 24	PREEMPT	N/R [3]
de Tommaso 2019	99	155–195	• Every 12 (1st year • Every 12 or 16 (2nd year)	In 31–39 peri-cranial sites	24
Dikmen 2018	180	155	Quarterly (1st year) (all patients received ≥1 dose)	PREEMPT	N/R [≥1]
Dominguez 2018	725	N/R	Every 12	PREEMPT	12 [4]
Eren 2020	49	155	N/R	PREEMPT	N/R
Gandolfi 2019	40	N/R	N/R	PREEMPT	N/R [3]
Garcia-Azorín 2018	49	N/R	N/R	Spanish national guidelines	N/R
Gonzalez-Martinez 2020	112	155–195	Every 12 or 15	N/R	N/R [≥2]

Study name	Sample size	OnabotA dose (IU)	Frequency (weeks)	Protocol	Duration (months) [N of cycles]
Grazzi 2016	53	155	Every 12	PREEMPT	12
Grazzi 2015	66	155 (5 IU/site)	Every 12	In 31 sites	12 [5]
Guerzoni 2017	90	155	Every 12	PREEMPT	N/R
Kennedy 2017	120	N/R	N/R	PREEMPT	N/R [5]
Lee 2016	70	N/R	Every 12	PREEMPT	N/R
Lin 2014	94	75 or 100	N/R	In 21 sites	June 2008–July 2010
		155	N/R	PREEMPT	From August 2010
Navarrete Perez 2017	117	N/R	N/R	N/R	N/R [2]
Negro 2016	143	195	N/R	PREEMPT	N/R
	132	155	N/R	PREEMPT	N/R
Ornello 2020	115	155 (± 40)	Every 12	• FSFD • FTP	15 [5]
Pedraza 2015	52	N/R	N/R	PREEMPT (no additional injections in the first two sessions)	N/R

Study name	Sample size	OnabotA dose (IU)	Frequency (weeks)	Protocol	Duration (months) [N of cycles]
Quintas 2019	193	155	N/R	PREEMPT	N/R
	31°°	195	N/R	FTP	N/R
Romoli 2017	56	N/R	N/R	N/R	Non-responders to cycle 1: N/R [5]
Russo 2016	52	N/R	Every 12	PREEMPT	N/R
Santoro 2020	109	155–195	Every 12 (± 10 d)	PREEMPT (CM patients received detoxification with betamethasone for 6 d, and after 15 d patients were advised to take a max of 2 IU/week of NSAIDs)	N/R
Sanz 2018	69	155	Every 12 or 24	PREEMPT	16
Sarchielli 2017	56	195”	Every 12 (±1)	PREEMPT (7 specific head/neck muscle areas)	N/R [5]
Stark 2019	211	155 (±40)	N/R	• FSFD (31 sites)	N/R [4 (2–11)]*

Study name	Sample size	OnabotA dose (IU)	Frequency (weeks)	Protocol	Duration (months) [N of cycles]
				• FTP	
Taddei-Allen 2019	21	N/R	N/R	N/R	N/R
	21	N/R	N/R	N/R	N/R
Torres-Ferrus 2020	395	N/R	N/R	PREEMPT	N/R [2]
Velasco-Juanes 2018	70	70–155	N/R	• PREEMPT • Posterior cervical • Bilaterally into the frontal, glabellar, and temporal muscle	N/R
Vernieri 2019	115	N/R	Every 12	PREEMPT	[≥4]

CM: chronic migraine; CGRP: calcitonin gene-related peptide; d: days; FTP: follow the pain; FSFD: fixed sites fixed dose; max: maximum; N: number; N/R: not reported; NSAID: non-steroidal anti-inflammatory drug; PREEMPT: Phase 3 Research Evaluating Migraine Prophylaxis Therapy; IU: international units.

[$]Mean (standard deviation); *Median (range); [^]Erenumab, galcanezumab, fremanezumab; [++]Average dose; °°Out of 193, 31 (68.9%) patients received 195 U at the second procedure; [&]OnabotulinumtoxinA 155 U, with discretion to administer an additional 40 U over 8 injection sites according to the follow-the-pain strategy to a maximum total dose of 195 U; “Total dose administrated was 195.

Supplementary Figure 1. Distribution of studies by country (N = 44).