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An Assessment of Sex and Gender Considerations in Migraine Calcitonin Gene Related Peptide Clinical Trials

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Highlights:

- Clinical trial guidelines recommend the use of sex-based subpopulation analyses when reporting results.
- Participants in migraine clinical trials of CGRP-targeting medications were predominantly identified as female or women and results were not stratified by sex/gender.
- Integration of sex/gender considerations in migraine research design will contribute to better care.

Abstract:

Background: Published guidelines for conducting clinical trials for migraine therapeutics recommend recruiting participants based on disease epidemiology and including sex/gender-based subpopulation analyses. These recommendations aim to improve the quality and generalizability of migraine clinical trials. The aim of this study was to summarize participant demographics in migraine clinical trials for FDA-approved calcitonin gene related peptide (CGRP)-targeting drugs (receptor antagonists; gepants, CGRP peptide or receptor monoclonal antibodies; mAbs) and assess the use of sex/gender- based subpopulation analyses in these studies.

Methods: We conducted a review of industry-sponsored migraine clinical trials for FDA-approved CGRP-targeting medications. Demographic data (sex and/or gender) from Phase II or III trials were abstracted and the use of sex/gender-based analyses were recorded.

Results: Fourteen trials of gepants were included in this analysis. Participants that were identified as females or women were more likely to participate in these trials (87.0 ± 2.2%). Twenty-four trials of CGRP mAbs were reviewed. These studies also reported that participants were predominantly identified as female or women (84.9 ± 2.3%) None of the clinical trials reviewed reported sex/gender-based analyses of their results.

Conclusions: This study suggests that men are underrepresented in migraine CGRP clinical trials. Greater attention to sex and gender is needed in migraine clinical trial design so that they better align with current recommendations made by headache societies and regulatory agencies.

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Introduction:

To better understand migraine etiology and ensure optimal care for all individuals with migraine, consistent consideration of sex and gender in clinical research is paramount. Sex commonly refers to biological attributes including physical and physiological characteristics, whereas gender is a social construct that defines the roles, behaviours, expressions, and identities of individuals (1). These categories are often assumed rather than clearly defined and operationalized within research studies, which can oversimplify the identities of research participants and the interrelation of sex and gender (2). The recent evolution of sex and gender concepts in medicine has led to conflation of these terms in migraine research, limiting our understanding of sex versus gender, their relative contributions, and their interactions with migraine. For example, there is a high prevalence and burden of migraine in women, (3) (4, 5). but men with migraine are underdiagnosed and less likely to seek medical care (4, 6). This can contribute to skewed participation observed in clinical trials and suboptimal pain management (6, 7). The degree to which sex/gender contribute to this disparity is unclear but it highlights important clinical differences in migraine care which must be further explored by embedding sex/gender considerations in research.

To promote best practice in clinical trial design, guidelines have been published by national and international headache societies and regulatory bodies(8-13). The International Headache Society (IHS) published its first guidance document over 30 years ago and has since published increasingly detailed guides for conducting pharmacological clinical trials for both acute and preventative medications (8, 14-18). These documents aim to inform researchers and pharmaceutical companies on innovations in clinical trial design and migraine pathophysiology to ultimately “improve the quality of controlled clinical trials in migraine" (8). A recommendation to enroll male and female participants in line with the sex ratio observed epidemiologically was published in the first guideline in 1991. The FDA published guidelines for conducting clinical trials for acute migraine management (2018) and preventative migraine therapeutics (2023) which included recommendations for the inclusion of sex- based subpopulation analyses of results (11, 13). Despite these published guidelines for inclusivity in clinical trial design from national headache societies and regulatory agencies, a recent review

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suggested that the adoption of inclusive practices has not been widespread in migraine research (19, 20).

Development of medications that target calcitonin gene-related peptide (CGRP) and its receptor have changed the pharmacological management of migraine. In 2018, the FDA approved the first anti-CGRP agent, Erenumab, a monoclonal antibody (mAb) against the CGRP receptor that has shown excellent efficacy for migraine prophylaxis (21). An additional three mAbs have since received regulatory approval as preventative agents (fremanezumab, galcanezumab, and eptinezumab), which act by binding directly to CGRP itself to prevent subsequent CGRP-receptor activation (22-24). Small molecule antagonists of the CGRP receptor (gepants) have emerged as effective acute and prophylactic treatments for migraine. Four gepants are currently approved by the FDA: atogepant, ubrogepant, rimegapnt, and zavegepant (25-28). While these CGRP-targeting medications are used clinically (29), a recent study has uncovered a sex-difference in the efficacy of gepants and highlighted the importance of considering sex/gender- subpopulations when carrying out clinical analysis (7).

The aim of this study was to explore the demographic composition of participants in migraine clinical trials for FDA-approved CGRP-targeting drugs (gepants, mAbs) and assess the inclusion of sex/gender-based subpopulation analyses in these trials.

Methods:

Participant demographics and inclusion of sex/gender- based subpopulation analyses were examined in clinical trials of FDA-approved CGRP-targeting medications. Covidence software was utilized to conduct the study. Relevant papers were identified using PubMed to access the National Library of Medicine's MEDLINE database, and the National Institute of Health's Clinical Trials registry (https://clinicaltrials.gov/). Using PubMed, the following search terms were used to identify relevant articles: "Migraine + Clinical Trial + [Gepant drug name or mAb drug name]" with additional filters applied: Full text, Clinical Trial, Phase II, Clinical Trial, Phase III, Adult: 19+ years, English. Manual searches on clinicaltrials.gov to identify clinical trial numbers for all FDA-approved gepants and CGRP mAbs were also conducted and associated publications identified. Articles identified using these search parameters were

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imported into Covidence and duplicate entries were removed. Both authors (MO and JD) first independently screened study abstracts followed by full text articles to ensure publications were appropriately aligned with our predefined eligibility criteria (Supplementary Table 1). Our screening criteria included industry-funded Phase II or III clinical trials for FDA-approved CGRP-targeting therapeutics. Studies must have been conducted with adult participants only, have included a United States study site, included an outcome of therapeutic efficacy, and be published in English. Studies that did not include a site in the United States were excluded because the goal of this review was to assess the alignment with FDA and IHS guidelines. Only studies that contained primary data were assessed; *post-hoc* analyses of previously published studies or extension trials were excluded from the review. Any conflicts that arose between authors during the screening process were resolved by consensus.

Participant demographics and the inclusion of sex/gender- based data analysis was extracted from all relevant articles. Data were grouped according to the therapeutic class studied, *i.e.*, gepant trials and CGRP mAb trials. Within the reported participant demographic data, we examined whether the sex or gender of participants were published. Using these data, we calculated the percentage of participants in each study that identified as female or women; groups that have traditionally been primarily represented in migraine clinical trials. The examined studies did not define sex or gender or describe how this data was collected, therefore we have reported the data using language that is consistent with the published trials. To assess the use of sex/gender -based analysis, the results and discussion of each manuscript were reviewed for stratification of data that could be used to address whether subpopulations (based on sex/gender) responded differently to trial therapeutics. For each category of data collected, descriptive statistics were reported using either mean values (with ranges) or proportions.

The goal of this study was to describe study demographics and examine the use of sex/gender-based data analysis, rather than to summarize the findings of CGRP-clinical trials, Therefore, we did not assess the quality of studies included in this analysis.

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Results:

In total, 140 papers were identified using the search methods described and imported into Covidence for further analysis. Following removal of duplicate studies, abstract screening was conducted on 136 articles. Ninety-four studies were excluded based on the predefined eligibility criteria via abstract screening. Forty-two studies were then reviewed for relevance with an additional four being removed due to ineligible study design or setting. In total, 38 studies were included in data extraction, encompassing both gepants and CGRP-targeting mAbs as summarised in Figure 1.

Fourteen Phase II or III clinical trials of gepants, published between 2016 and 2023, were included in this study (Table 1). The average number of participants in the examined trials was 1047 ± 346 (range: 480-1581). All studies reported on either the sex or gender of enrolled participants, with the majority reporting sex using female/male (12 studies) rather than gender. Study participants were predominantly identified as female or women (87.0 ± 2.2%). None of the data collected in these trials were evaluated using sex/gender-based subpopulation analysis to examine potential differences in efficacy between groups.

An additional 24 studies were included in our analysis of CGRP mAb clinical trials, published between 2015 and 2022 (Table 2). These studies included on average 690 ± 401 participants (range: 163-1890). All trials reported the sex or gender of participants, with 84.9 ± 2.3% identifying as female or women. Most studies examined reported sex using female/male (19 studies) rather than reporting gender titles. Like the gepant clinical trials, the data reported in mAbs studies were not analyzed for sex/gender differences.

Discussion:

Our examination of gepant and CGRP mAb clinical trials published between 2015 - 2023 revealed that industry-sponsored trials commonly report the sex or gender of study participants, abiding by recommendations from the IHS and FDA. However, these studies did not provide sex/gender-based subpopulation analyses of results. Our results are consistent with prior reviews

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of migraine clinical trials (19, 20) and highlight an opportunity to improve integration of sex and gender in migraine research.

Sex or gender of study participants were reported for all 38 studies examined. Participants in these trials were more likely to be identified as female or women, in line with previously reported findings (19, 20). A 2017 systematic review of minority representation in migraine clinical trials published between 2011-2016 reported that individuals identifying as women represented approximately 80% of participants (19), which is similar to our findings. The authors of that study called for improvement in minority representation in migraine clinical trials and better representation of migraine epidemiology in clinical trial participants; however, our review shows that these numbers have remained consistent. Although guidelines for migraine clinical trials recommend an enrollment of participants that reflects the sex ratio observed in epidemiological studies (16-18), data reported here confirm that female participation in clinical trials overestimates disease epidemiology and thus underpowers studies to determine potential sex-differences in drug efficacy.

Regarding CGRP activity in migraine, both clinical and preclinical investigations have revealed sexually dimorphic results confirming the need to study the effects of CGRP-targeting drugs in all sexes in clinical trials. Clinically, elevated levels of circulating CGRP have been measured in women compared to men, with concentrations increasing further during menstruation (30, 31). Treating migraine with sumatriptan also reduces plasma CGRP levels in women, while in men, changes in CGRP levels are inconclusive with this treatment (32). These early clinical studies suggest a potentially sexually dimorphic involvement of the CGRP pathway in migraine. Additional evidence has been generated in pre-clinical studies where application of CGRP to the dura or spinal cord produces larger nociceptive responses in female animals compared to males (33, 34). This heightened response may be mediated, in part, by higher expression of CGRP receptor proteins in the spinal trigeminal nucleus of female animals (35). Similarly, treatment with both CGRP antagonists or a CGRP-sequestering mAb has also been shown to produce greater anti-nociceptive responses in female animals compared to males (33).

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Despite the reported sex differences in CGRP physiology, sex/gender-based consideration was omitted in all clinical trials described in this review. A recent subpopulation analysis of clinical trial data has uncovered sex-specific responses to CGRP-modulating drugs. Porreca *et al*. evaluated clinical trial data in FDA New Drug Applications of gepants and CGRP mAbs and identified sex-differences in response to acute and preventative therapy that were not previously reported (7). The authors examined separately the primary endpoints for acute migraine treatment (ubrogepant, rimegepant, and zavegapent) and preventative treatment (erenumab, fremanezumab, galcanezumab, eptinezumab, and atogepant), stratified by sex for both categories. Evaluating acute treatments, they found that a higher proportion of females reported 2-hour pain-freedom (9.5% (CI: 7.4 to 11.6, n = 2595)) compared to males (2.8% (CI: −2.5 to 8.2, n = 422)). While acute treatment effects were significant in females, no significant effect was observed in males treated with gepants. Analysis of preventative treatments did not reveal significant differences in primary endpoints between males and females in either episodic or chronic migraine patients; however, the study was underpowered to determine population effects due to low male participation in the trials (17.3%). These findings are supported by two additional post-hoc analyses for fremanezumab and eptinezumab which reported similar responses between sexes (36, 37). A further observational study evaluated sex differences with the use of erenumab (38). The authors did not demonstrate significant differences in efficacy or adverse events at 12-weeks in a multi-site retrospective review; however, men only made up 18.2% of the study population. These studies further highlight the importance of conducting sex/gender -based analysis in clinical trials and ensuring study enrollment will provide investigators with sufficient power to conduct these important analyses.

Challenges exist when performing sex/gender analysis in migraine clinical trials. For example, women are more likely to be recruited in clinical trials given differences in diagnosis and care. Additionally, as eligibility criteria often include previous use of acute or preventative migraine therapeutics, gender-differences in medication use (6, 39, 40) may preclude men from participating in Phase II/III clinical trials. Given these potential barriers to recruiting eligible men with migraine, ensuring statistical power to detect differences based on sex/gender may be difficult. To examine the inclusion of sex and gender considerations in clinical trial data that supported regulatory approval of gepants and CGRP mAbs, Phase II and III clinical trials were

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included in this review. While these trials offer important insight into adherence to migraine clinical trial guidelines, additional studies including *post-hoc* analyses and systematic reviews are often more appropriately powered to reveal subpopulation differences. As discussed previously, *post-hoc* analyses of CGRP mAb trials have investigated sex/gender differences and contributed to our understanding of treatment efficacy (36, 37). Phase IV clinical trials and observational pragmatic trials also commonly contain a more diverse population and thus should be considered along with Phase II and III regulatory trials to guide clinical decision-making.

An integration of sex/gender in migraine clinical trials will contribute to better understanding of migraine pathophysiology and treatment approaches. Recommendations in other clinical areas can be adopted in migraine research (2, 41, 42), including clearly defining sex and gender to prevent assumptions and conflation of these terms (43). While it is common to overlook subpopulation analysis in clinical research, in part due to a lack of observed differences, this practice hinders future analyses and interpretation of findings. Reporting stratified results by sex/gender in clinical trials, even when underpowered, will allow for sex/gender-based considerations in systematic reviews or meta-analyses which may be better powered to detect sex/gender effects (41, 42). The terms sex and gender represent distinct but interrelated constructs, and difficulty arises when attempting to distinguish between them in clinical trials (43). Unless research studies have been specifically designed to investigate an influence of biological sex (*e.g.* sex hormones) or gender identity (*e.g.* familial roles/responsibilities) on an outcome (the response to a migraine therapy), the use of the term "sex/gender" is more appropriate to acknowledge the interrelationship between these concepts in study results (2) (41). Embedding these simple approaches into migraine study designs may help fill knowledge gaps and develop tailored treatment approaches for the entire migraine population.

Conclusion:

Migraine is a highly prevalent and debilitating condition that affects a considerable proportion of the general population worldwide. The recent development of CGRP-targeting therapies provides a migraine specific therapeutic option with multiple major clinical trials

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supporting their use. A review of gepant and CGRP mAb clinical trials has revealed that participants in these trials predominantly identify as females or women and thatmen/males are likely underrepresented in clinical trials of CGRP-targeted therapeutics for migraine headache. These findings highlight the need to diversify recruitment for migraine studies as recommended by the IHS and FDA in line with migraine epidemiology (14-16, 19) (11, 13). Although all the trials reported the sex or gender of participants in line with recommendations, sex/gender-based subpopulation analyses of results were not common. Ongoing efforts to better align with clinical trial guidelines and integration of sex/gender analyses will strengthen the quality of migraine research and contribute to better care for migraine patients globally.

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Author contribution:

Research Project Conception: MO and JD, Data collection: MO and JD, Manuscript writing and editing: MO and JD.

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MO has no competing interests to declare. JD has received funding from Abbvie for participation on an Advisory board and providing a lecture.

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Table 1: Summary of Demographic Information Reported in Industry-Sponsored, Phase II/III Clinical Trials of FDA-approved Gepants.

Author, year	Intervention	Trial Phase	N	Sex or Gender Data Reported	Sex/Gender-Based Analysis	% Sample Female or Women
Voss, 2016(25)	Ubrelvy (Ubrogepant)	2b	640	Yes	No	87.3
Lipton, 2019(44)	Ubrelvy (Ubrogepant)	3	1465	Yes	No	89.9
Dodick, 2019(45)	Ubrelvy (Ubrogepant)	3	1436	Yes	No	88.2
Dodick, 2023(46)	Ubrelvy (Ubrogepant)	3	480	Yes	No	87.7
Lipton, 2019(27)	Nurtec (Rimegepant)	3	1072	Yes	No	88.7
Croop, 2021(47)	Nurtec (Rimegepant)	2/3	741	Yes	No	82.7
Croop, 2019(48)	Nurtec (Rimegepant)	3	1351	Yes	No	84.9
Goadsby, 2020(49)	Qulipta (Atogepant)	2b/3	825	Yes	No	86.5
Ailani, 2021(26)	Qulipta (Atogepant)	3	902	Yes	No	88.8
Ashina, 2023(50)	Qulipta (Atogepant)	3	1260	Yes	No	88.2
Lipton, 2023(51)	Qulipta (Atogepant)	3	873	Yes	No	88.5
Pozo-Rosich, 2023(52)	Qulipta (Atogepant)	3	773	Yes	No	87.5
Croop, 2022(28)	Zavzpret (Zavegepant)	2/3	1581	Yes	No	85.5
Lipton, 2023(53)	Zavzpret (Zavegepant)	3	1269	Yes	No	82.9

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Table 2: Summary of Demographic Information Reported in Industry-Sponsored, Phase II/III Clinical Trials of FDA-approved CGRP Monoclonal Antibodies.

Author, year	Intervention	Trial Phase	N	Sex or Gender Data Reported	Sex/Gender Based Analysis	% Sample Female or Women
Bigal, 2015(54)	Ajovy (fremanezumab)	2b	297	Yes	No	87.9
Bigal 2015(55)	Ajovy (fremanezumab)	2b	263	Yes	No	86.3
Silberstein, 2017(22)	Ajovy (fremanezumab)	3	1130	Yes	No	87.7
Dodick, 2018(56)	Ajovy (fremanezumab)	3	875	Yes	No	84.8
Ferrari, 2019(57)	Ajovy (fremanezumab)	3b	838	Yes	No	83.5
Goadsby, 2020 (58)	Ajovy (fremanezumab)	3	1890	Yes	No	87.0
Sun, 2016(21)	Aimovig (erenumab)	2	483	Yes	No	80.5
Tepper, 2017(59)	Aimovig (erenumab)	2	667	Yes	No	82.8
Goadsby, 2017(60)	Aimovig (erenumab)	3	955	Yes	No	85.2
Dodick, 2018(61)	Aimovig (erenumab)	3	577	Yes	No	85.3
Reuter, 2018(62)	Aimovig (erenumab)	3b	246	Yes	No	81.3
Dodick, 2014(24)	Emgality (Erenumab)	2	217	Yes	No	84.8

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Skljarevski, 2018(63)	Emgality (galcanezumab)	2b	410	Yes	No	82.9
Skljarevski, 2018(64)	Emgality (galcanezumab)	3	915	Yes	No	85.4
Stauffer, 2018(65)	Emgality (galcanezumab)	3	858	Yes	No	83.7
Detke, 2018(66)	Emgality (galcanezumab)	3	1113	Yes	No	85.0
Camporeale, 2018(67)	Emgality (galcanezumab)	3	270	Yes	No	82.6
Mulleners, 2020(68)	Emgality (galcanezumab)	3b	462	Yes	No	85.9
Dodick, 2014(23)	Vyepti (eptinezumab)	2	163	Yes	No	81.6
Dodick, 2019(69)	Vyepti (eptinezumab)	2b	616	Yes	No	86.9
Ashina, 2020(70)	Vyepti (eptinezumab)	3	888	Yes	No	84.3
Lipton, 2020(71)	Vyepti (eptinezumab)	3	1072	Yes	No	88.2
Winner, 2021(72)	Vyepti (eptinezumab)	3	480	Yes	No	84.0
Ashina, 2022(73)	Vyepti (eptinezumab)	3b	890	Yes	No	89.9

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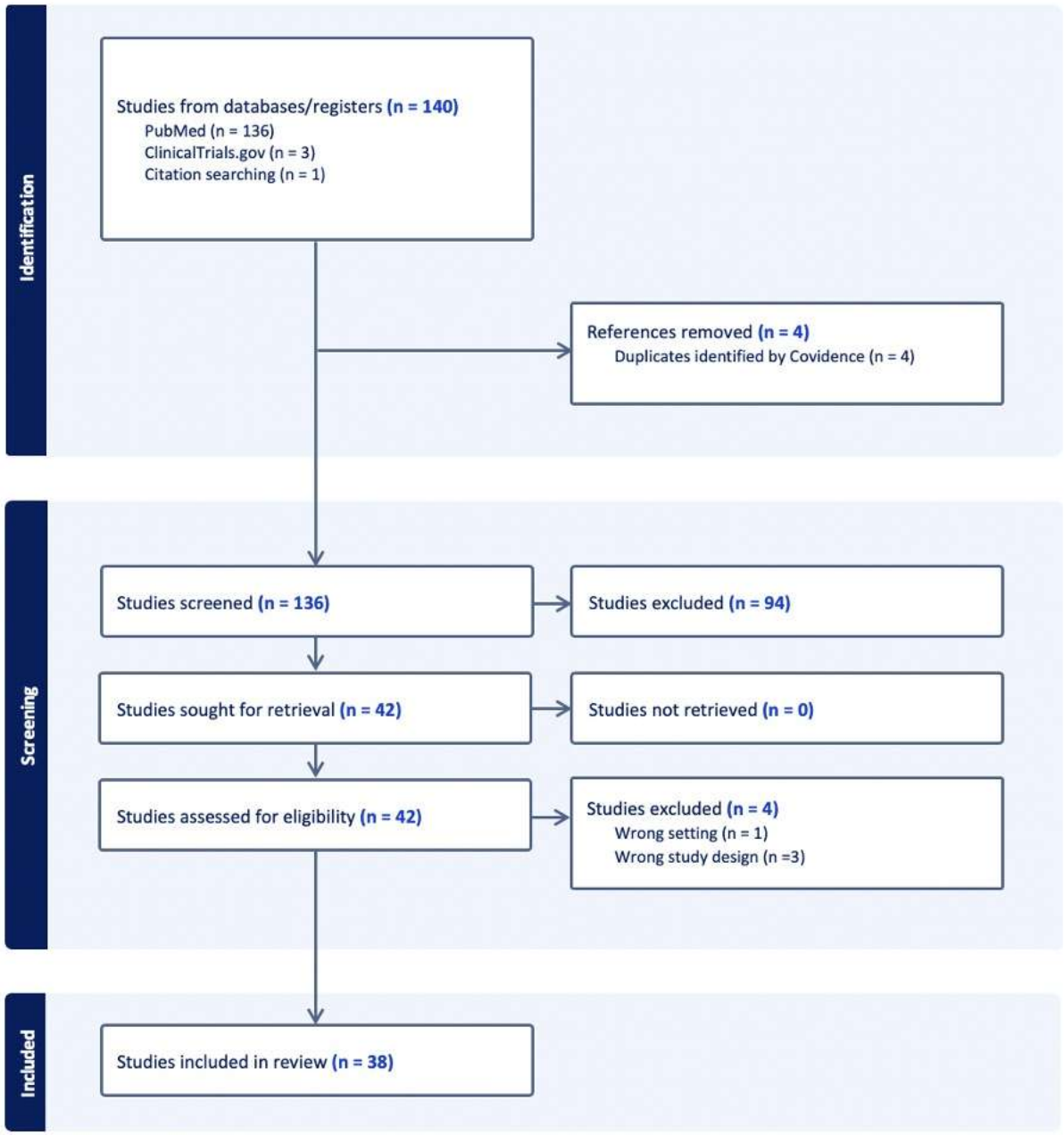

Figure 1: Identification and Review Process of Industry-funded, Phase II/III Clinical Trials of CGRP-Targeting Medications.

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