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Characterizing Prodrome (Premonitory Phase) in Migraine

Results From the PRODROME Trial Screening Period

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Abstract

Background and Objective

Limited data are available describing the frequency, severity, and consistency of prodromal symptoms followed by headache. This analysis of the PRODROME trial screening period characterized prodromal symptoms in people with migraine, including the most common symptoms and their severity, and the frequency and consistency with which prodromal symptoms were followed by headache.

Methods

PRODROME was a multicenter, randomized, double-blind, placebo-controlled, crossover trial conducted in the United States that enrolled adults with 2–8 migraine attacks per month who stated they could identify prodromal symptoms that were reliably followed by a headache. The trial included a 60-day screening period designed to test the predictive validity of "qualifying prodrome events" before the onset of headache. Participants used an eDiary to report qualifying prodrome events, defined as prodromal symptoms whereby the participant was confident a headache would follow within 1–6 hours. This analysis evaluated common prodromal symptoms and their severity, time from prodrome onset to headache onset, and the percentage of participants who identified prodromal symptoms that were followed by a headache ≥75% of the time over the 60-day screening period.

Results

A total of 920 participants entered eDiary data, with a mean of 5.2 qualifying prodrome events during the 60-day screening period. A total of 4,802 qualifying prodrome events were recorded. The most common prodromal symptoms identified were sensitivity to light (57.2%; 2,748/4,802), fatigue (50.1%; 2,408/4,802), neck pain (41.9%; 2,013/4,802), sensitivity to sound (33.9%; 1,630/4,802), either difficulty thinking or concentrating (30.0%; 1,442/4,802), and dizziness (27.8%; 1,333/4,802). Of all qualifying prodrome events reported, 81.5% (3,913/4,802) were followed by headache of any intensity within 1–6 hours. For each participant, a mean of 84.4% of their qualifying prodrome events were followed by a headache within 1–6 hours, with 76.9% of participants identifying qualifying prodrome events that were followed by headache within 1–6 hours ≥75% of the time.

Discussion

Participants were able to identify migraine attacks in which prodromal symptoms were reliably followed by a headache within 1–6 hours. These findings suggest the potential for initiating treatment during the prodrome to prevent headache.

Trial Registration Information

ClinicalTrials.gov NCT04492020. Submitted: July 27, 2020; First patient enrolled: August 21, 2020. clinicaltrials.gov/study/NCT04492020.

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Introduction

The migraine attack consists of up to 4 phases: prodrome (premonitory phase), aura, headache, and postdrome.[1] Although most migraine research and management strategies have focused on the headache phase, the prodrome is of substantial interest because it is the earliest phase of the migraine attack. It may provide insights into the pathophysiology of migraine attack initiation and serve as a warning of the impending migraine headache.[2-4] Furthermore, results from the PRODROME trial show that the prodrome is an opportunity for treating the migraine attack with acute therapy.[5] The PRODROME trial demonstrated that for individuals with migraine who could accurately and consistently identify prodromal symptoms followed by headache within 1–6 hours, ubrogepant treatment during the prodrome can prevent or reduce the severity of the impending headache and migraine attack-related disability. Within 24 hours following treatment during qualifying prodrome events, a headache of moderate/severe intensity was absent for 45.5% of ubrogepant-treated events compared with 28.6% of placebo-treated events ($p < 0.001$). The absence of moderate/severe intensity headache within 48 hours, ability to function normally over 24 hours, and headache of any intensity within 24 hours were achieved following a significantly greater number of ubrogepant-treated events compared with placebo-treated events ($p < 0.001$ for all comparisons).

Previous literature provides a wide range of estimates on the prevalence and duration of prodromal symptoms before headache onset.[4,6,7] There are limited published data on the severity of prodromal symptoms, functional disability during the prodrome phase, and the frequency and consistency of prodromal symptoms being followed by headache.[5] The objective of this analysis of the PRODROME trial screening period was to characterize prodromal symptoms in a large cohort of people with migraine over many prodrome events, including the most common symptoms and their severity, the frequency and consistency with which self-identified prodromal symptoms are followed by headache, and time to onset of headache following prodromal symptoms.

Methods

PRODROME was a multicenter, randomized, double-blind, placebo-controlled, phase 3 crossover trial conducted in the United States. Briefly, the trial included a 60-day screening period and a double-blind treatment period that could be up to 60 days. Methods and primary results from the double-blind treatment period have been previously described.[5] This report focuses on data collected only during the screening period before study treatment was administered.

Participants

Eligible participants were 18–75 years of age with at least a 1-year history of migraine with or without aura diagnosed according to the International Classification of Headache Disorders, 3rd Edition, and a history of 2–8 migraine attacks per month with moderate to severe headache in each of the 3 months before screening. At the initial screening visit (visit 1), participants completed a comprehensive interview to confirm the diagnosis of migraine and evaluate their eligibility based on investigation of prodromal symptoms (eTable 1). Participants were asked if they experience any warning signs (prodromal symptoms) that lead them to believe that a headache will follow and how often a headache indeed occurs within 1–6 hours after they experience prodromal symptoms. During this structured interview, in addition to the prodromal symptoms spontaneously verbalized by the participant, a checklist of 29 potential prodromal symptoms was reviewed to assess whether the participant routinely experienced each symptom before headache onset, and if so, how long before headache onset each symptom typically occurred. The identified symptoms were preprogrammed into the eDiary for convenience. If the participant experienced a symptom not previously identified, they still had the ability to choose and add the symptom on their eDiary. A maximum of 6 symptoms could be preprogrammed into the eDiary. Participants were asked, "After experiencing your prodrome symptoms, how reliably does a headache occur within 1 to 6 hours?" Based on this evaluation of participant history, the investigators determined whether each participant routinely experienced prodromal symptom(s) that are reliably followed (≥75% of the time) by a headache within 1–6 hours. Participants who exhibited this reliability and met all other eligibility criteria were able to proceed into the 60-day screening period. Participants were excluded from further participation if they did not experience prodromal symptoms reliably followed by headache within 1–6 hours per the interview, if they had chronic migraine, had difficulty distinguishing migraine from tension-type headache or other headache type, or overused acute medications for migraine. Participants were also excluded if they had prior exposure to a calcitonin gene-related peptide–targeted monoclonal antibody within 3 months before screening visit 1. Although participants were permitted to use oral gepants before study enrollment, use of oral gepants was prohibited for the duration of the study.

Eligible participants entered the screening period and were instructed to record all "qualifying prodrome events" in their eDiary for the next 60 days. A "qualifying prodrome event" was an event with prodromal symptoms meeting all of the following 5 criteria: (1) headache was not currently present; (2) the participant had not experienced a headache in the previous 48 hours; (3) acute treatment(s) for headache had not been taken in the previous 48 hours; (4) the participant was confident that a headache would follow within 1–6 hours; and (5) the participant was able to complete the eDiary for at least the next 8 hours.

At the time of a qualifying prodrome event, the participant recorded the absence or presence of each candidate preprogrammed prodromal symptom and if present, the intensity (mild, moderate, or severe), and the presence or absence of aura. Following the completion of their initial eDiary entry, participants were asked to complete eDiary assessments at 1, 2, 3, 4, 6, 8, 24, and 48 hours to record the

presence or absence of headache and the presence or absence of prodromal symptoms. If a headache occurred at any time between prespecified assessment times, participants were instructed to record headache onset at the time of occurrence once per event using the eDiary. During the screening period, participants were instructed to not take acute medication during the prodrome phase. Participants were allowed to take rescue medication if a headache of any intensity developed following a qualifying prodrome event.

Statistical Analysis

All qualifying prodrome events recorded during the screening period were analyzed. The number of qualifying prodrome events per participant was summarized as a discrete variable and categories of <3, 3, 4, 5–8, 9–16, and >16 qualifying prodrome events over the 60-day screening period. The frequency of prodromal symptoms was summarized as the percentage of all qualifying prodrome events in which the given prodromal symptom was present. The consistency of prodrome symptoms across qualifying events was assessed using the prevalence rate. The prevalence of individual prodromal symptoms was calculated for each participant based on the number of qualifying prodrome events with a given symptom divided by the number of qualifying prodrome events recorded in the eDiary. Kaplan-Meier curves for time to onset of a headache of any intensity and moderate to severe intensity were generated using all prodrome events. For each participant, the positive prodrome rate of prodrome events was calculated based on the denominator of the number of qualifying prodrome events and the numerator of the number of positive prodrome events. This rate was summarized as a continuous variable and as categories of <25%, ≥25% to <50%, ≥50% to <75%, ≥75% to <100%, and 100%.

The study protocol and statistical analysis plan were previously published.[5]

Standard Protocol Approvals, Registrations, and Participant Consents

This trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice. Participants provided written informed consent before trial entry. An independent ethics committee or institutional review board at each site approved the protocol and any written information provided to participants. PRODROME is registered at ClinicalTrials.gov: NCT04492020.

Data Availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: vivli.org/ourmember/abbvie/ then select "Home."

Results

Participants

From August 21, 2020, through February 16, 2022, a total of 1087 participants at 75 sites in the United States participated in the screening period of the PRODROME trial. The mean (SD) age of all screened participants was 42.0 (12.9) years, and 85.6% were female (Table 1). A total of 920 (84.6%) of 1,087 participants met all initial eligibility criteria at visit 1 and recorded at least 1 qualifying prodrome event during the screening period. The reasons for discontinuation during the screening period without entering eDiary data were initial screen failure (i.e., did not meet eligibility criteria) at visit 1

Table 1 Baseline Demographics

	Total (N = 1,087)
Age, mean (SD), y	42.0 (12.9)
Sex, n (%)	
Male	156 (14.4)
Female	931 (85.6)
Race, n (%)	
White	911 (83.8)
Black or African American	129 (11.9)
Asian	24 (2.2)
American Indian or Alaska Native	4 (0.4)
Native Hawaiian or Other Pacific Islander	3 (0.3)
Multiple[a]	14 (1.3)
Missing	2 (0.2)
Ethnicity, n (%)	
Hispanic	87 (8.0)
Non-Hispanic	997 (91.7)
Missing	3 (0.3)
Body mass index, mean (SD), kg/m²	28.5 (5.5)

[a] Participants who reported multiple races are included only in the multiple category.

(n = 142), lost to follow-up (n = 7), and withdrawal of participant (n = 18). Additional details on screening period completions and discontinuations are shown in eFigure 1.

Qualifying Prodrome Events

Across the full 60-day screening period, a total of 4,802 qualifying prodrome events were recorded, with a mean (SD) of 5.2 (3.4) qualifying prodrome events recorded per participant (Table 2). The proportion of participants who recorded between 3 and 16 qualifying prodrome events was 79.0% (727/920; Table 2). Fewer than 3 qualifying prodrome events were recorded by 20.0% (184/920) of participants with exactly 1 qualifying prodrome event reported by 107 participants. More than 16 qualifying prodrome events were recorded by 1.0% (9/920) of participants. Of those who reported between 3 and 16 qualifying prodrome events, which was an inclusion criterion to continue in the study, a total of 518 participants met all inclusion criteria and were randomized to the double-blind treatment period.

Prodromal Symptoms

The most common prodromal symptoms recorded during the screening period relative to all qualifying prodrome events were sensitivity to light (57.2%; 2,748/4,802), fatigue (50.1%; 2,408/4,802), neck pain (41.9%; 2,013/4,802), sensitivity to sound (33.9%; 1,630/4,802), dizziness (27.8%; 1,333/4,802), irritability (26.4%; 1,269/4,802), nausea (23.1%; 1,110/4,802), difficulty concentrating (20.8%; 999/4,802), muscle pain (19.4%; 931/4,802), and blurred vision (14.7%; 708/4,802) (Table 3). The prodromal symptoms of difficulty concentrating and difficulty thinking were assessed separately in the screening symptom checklist (eTable 1).

Table 2 Summary of Qualifying Prodrome Events Recorded in the 60-Day Screening Period

	All screened participants (N = 1,087)
Participants who recorded eDiary data, n (%)	920 (84.6)
Mean (SD) number of qualifying prodrome events per participant	5.2 (3.4)
Median (Q1, Q3) number of qualifying prodrome events per participant	5.0 (3.0, 7.0)
Number of qualifying prodrome events recorded by a participant	
<3	184 (20.0)
3	126 (13.7)
4	134 (14.6)
5–8	351 (38.2)
9–16	116 (12.6)
>16	9 (1.0)

When evaluated together, a total of 30.0% (1,442/4,802) of qualifying prodrome events included at least one of these cognitive symptoms (difficulty concentrating or difficulty thinking), with 5.0% (238/4,802) of qualifying prodrome events including both symptoms.

The full list of recorded prodromal symptoms and the reported intensity of each prodromal symptom are presented in eTable 2. Among the top 5 most recorded prodromal symptoms, between 29.8% and 56.1% were reported as moderate or severe in intensity by the participant. Neck pain and fatigue showed the highest rates of moderate or severe intensity (56.1% [1,130/2,013] and 53.2% [1,280/2,408], respectively).

Consistency of Prodromal Symptoms

Prodromal symptoms were consistently experienced across all qualifying prodrome events recorded by individual participants. For example, participants who reported sensitivity to light during at least 1 qualifying prodrome event experienced sensitivity to light, on average, during 87.2% (SD: 21.4%) of their qualifying prodrome events. In addition, participants who reported fatigue experienced fatigue, on average, during 92.0% (SD: 17.7%) of their qualifying prodrome events. Consistency results, including the mean prevalence rates, for common prodromal symptoms are presented in Table 4.

Occurrence of Headache Following Qualifying Prodrome Events

Of 4,802 qualifying prodrome events, 81.5% (3,913) were followed by headache of any intensity within 1–6 hours (Figure 1). The percentage of qualifying prodrome events that were followed by headache in more than 6 but less than 24 hours was 4.5% (217/4,802). A total of 0.8% (39/4,802) of qualifying prodrome events were followed by headache at more than 24 hours. Similar results were observed for time to onset of headaches of moderate or severe intensity, with 68.3% (3,281/4,802) of qualifying prodrome events followed by a headache of moderate or severe intensity within 1–6 hours (Figure 2).

Looking at within-participant data, the mean percentage of qualifying prodrome events followed by headache of any intensity 1–6 hours after prodrome onset was 84.4% and the median was 100% (Table 5). A total of 76.9% (701/911) of screened participants with available data identified qualifying prodrome events that were followed by a headache within 1–6 hours at least 75% of the time. Only 7.8% (71/911) of participants identified qualifying prodrome events that were followed by a headache within 1–6 hours less than 50% of the time.

Discussion

This analysis of data from the screening period of the PRODROME trial demonstrates that many people with migraine can

Table 3 Summary of Common Prodromal Symptoms (≥10%) in the 60-Day Screening Period

Prodromal symptom, n (%)	Total qualifying prodrome events (N = 4,802)
Sensitivity to light	2,748 (57.2)
Mild	1,654 (60.2)
Moderate	896 (32.6)
Severe	198 (7.2)
Fatigue[a]	2,408 (50.1)
Mild	1,128 (46.8)
Moderate	1,013 (42.1)
Severe	267 (11.1)
Neck pain[b]	2,013 (41.9)
Mild	883 (43.9)
Moderate	906 (45.0)
Severe	224 (11.1)
Sensitivity to sound	1,630 (33.9)
Mild	950 (58.3)
Moderate	553 (33.9)
Severe	127 (7.8)
Dizziness[c]	1,333 (27.8)
Mild	936 (70.2)
Moderate	346 (26.0)
Severe	51 (3.8)
Irritable	1,269 (26.4)
Mild	733 (57.8)
Moderate	422 (33.3)
Severe	114 (9.0)
Nausea	1,110 (23.1)
Mild	743 (66.9)
Moderate	294 (26.5)
Severe	73 (6.6)
Difficulty concentrating	999 (20.8)
Mild	589 (59.0)
Moderate	331 (33.1)
Severe	79 (7.9)
Muscle pain/aching	931 (19.4)
Mild	483 (51.9)
Moderate	381 (40.9)
Severe	67 (7.2)
Blurred vision	708 (14.7)
Mild	457 (64.5)
Moderate	209 (29.5)
Severe	42 (5.9)
Difficulty thinking	681 (14.2)
Mild	440 (64.6)
Moderate	205 (30.1)
Severe	36 (5.3)
Yawning	612 (12.7)
Mild	374 (61.1)
Moderate	185 (30.2)
Severe	53 (8.7)
Other	509 (10.6)
Mild	286 (56.2)
Moderate	193 (37.9)
Severe	30 (5.9)
Sensitive to smell	490 (10.2)
Mild	306 (62.4)
Moderate	151 (30.8)
Severe	33 (6.7)

Prodromal symptoms identified at baseline are symptoms reported by participants at the beginning of qualifying prodrome events. Participants were able to report up to 6 prodromal symptoms.
[a] Represents tired/sleepy/fatigue category in the eDiary.
[b] Represents neck pain/stiff neck category in the eDiary.
[c] Represents dizziness/lightheaded/vertigo/imbalance category in the eDiary.

self-identify prodromal symptoms that are followed by a headache within 1–6 hours. Of the 1087 participants who entered the screening period, 47.7% completed the screening period and were randomized to the double-blind treatment period. The most common prodromal symptoms were sensitivity to light (57.2%), fatigue (50.1%), neck pain (41.9%), sensitivity to sound (33.9%), dizziness (27.8%), and mood and cognitive symptoms (irritability 26.4%, difficulty concentrating 20.8%, and difficulty thinking 14.2%). These prodromal symptoms were most commonly of mild intensity but were of moderate or severe intensity over one-third of the time. Neck pain and fatigue each were reported as moderate or severe intensity over half of the time. Qualifying prodrome events were reliably followed by headache within 1–6 hours: 81.5% of qualifying prodrome events were followed by headache within 1–6 hours, and 76.9% of participants had their qualifying prodrome events

Table 4 Consistency of Common Prodromal Symptoms[a]

Prodromal symptom, mean prevalence rate (SD)	All screened participants (N = 1,087)
Sensitivity to light	87.2 (21.4)
Fatigue[b]	92.0 (17.7)
Neck pain[c]	92.5 (16.4)
Sensitivity to sound	83.6 (23.6)
Dizziness[d]	77.0 (28.3)
Difficulty concentrating	86.8 (21.0)
Difficulty thinking	83.5 (21.5)

[a] Individual prodrome symptom prevalence rates based on the denominator of the number of qualifying prodrome events and the numerator of the numbers of qualifying prodrome events preceded with this symptom.
[b] Represents tired/sleepy/fatigue category in the eDiary.
[c] Represents neck pain/stiff neck category in the eDiary.
[d] Represents dizziness/lightheaded/vertigo/imbalance category in the eDiary.

followed by headache within 1–6 hours at least 75% of the time. These results generated from 4,802 qualifying prodrome events add substantially to our preexisting knowledge about the symptomatology, severity, timing, and reliability of self-identified symptoms during the prodrome phase of the migraine attack. Furthermore, results suggest that the outcomes of the PRODROME trial, which demonstrated efficacy of ubrogepant when administered during the prodrome phase, are applicable to people with migraine who can identify prodromal symptoms that are reliably followed by headache.

Previously published studies have provided estimates on the frequency of prodrome and individual prodromal symptoms.[7,8] A systematic review and meta-analysis of studies published through May 2022 found a pooled estimate of 29% for having at least 1 prodromal symptom among those with migraine in population-based studies and 66% in clinic-based studies.[7] Substantial between-study heterogeneity and risk of bias led the authors to suggest cautious interpretation of these results. The meta-analysis included 11 clinic-based studies to calculate the most common prodromal symptoms, which were fatigue (49%), neck stiffness (46%), mood change (37%), concentration difficulties (30%), nausea (29%), photophobia (29%), phonophobia (26%), yawning (22%), depressive symptoms (19%), irritability (16%), and food craving (11%).[3,4,9-19] Since the publication of that meta-analysis, additional data about prodrome from the Chronic Migraine Epidemiology and Outcomes Study have been presented.[8] Among the 12,810 people with episodic (91.2% of the sample) or chronic migraine who answered questions about prodrome, 84.3% reported having at least 1 preheadache symptom and 56.7% reported having at least 1 preheadache symptom that warned them about their impending headache. Preheadache warning symptoms most reported were neck pain or stiffness (51.2% of 6129 individuals reported this symptom), vision problems (49.2%), dizziness or lightheadedness (41.3%), difficulty

Figure 1 Kaplan-Meier Plot of Time to Onset of a Headache of Any Intensity for All Prodrome Events in the Screening Period

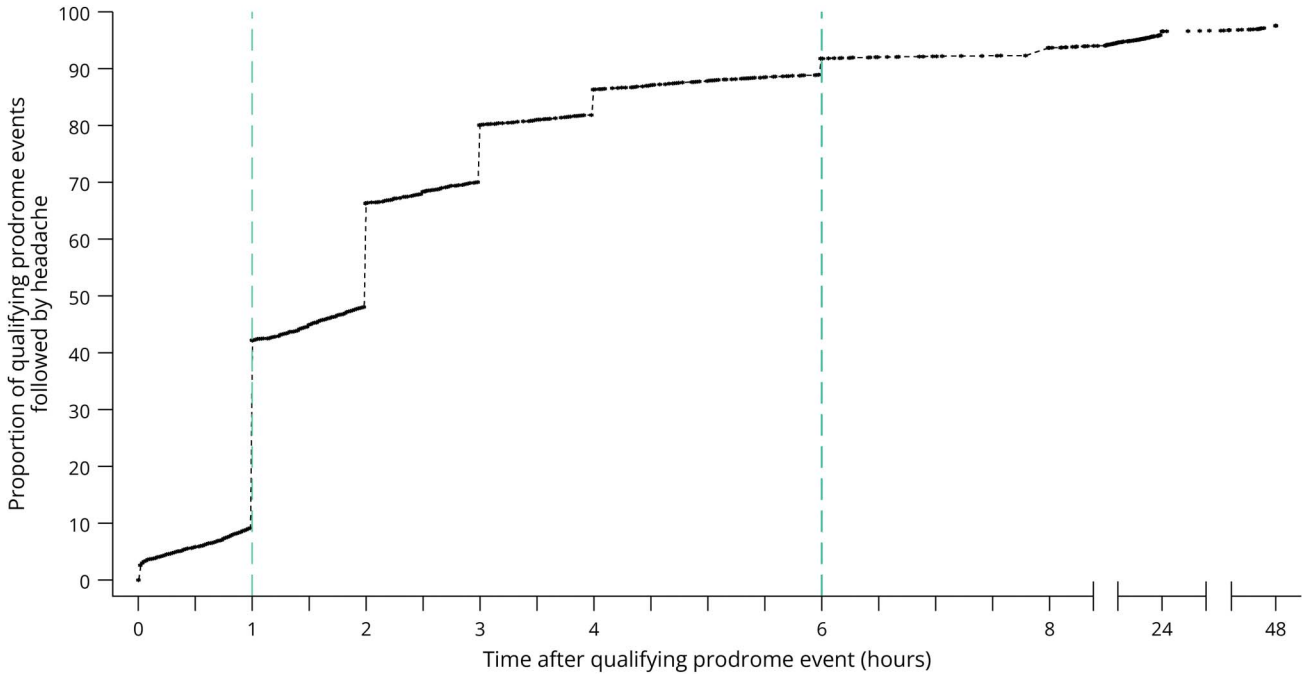
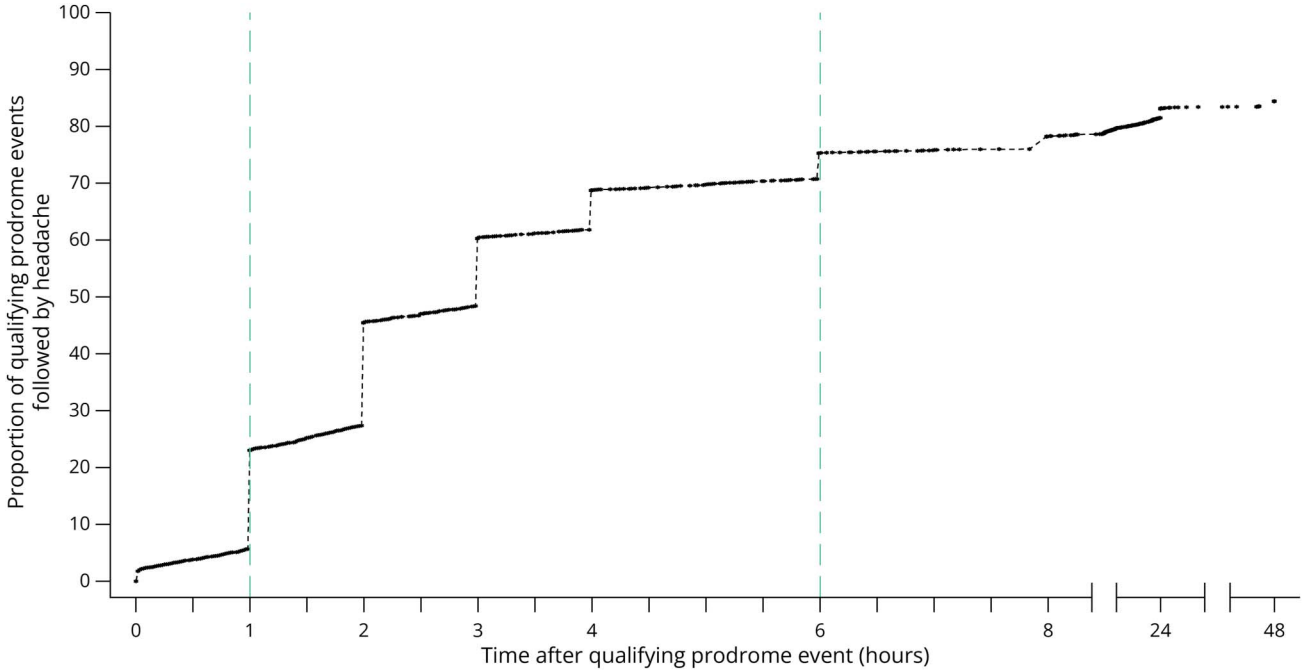


Figure 2 Kaplan-Meier Plot of Time to Onset of a Headache of Moderate to Severe Intensity for All Prodrome Events in the Screening Period



thinking or concentrating (39.6%), feeling irritable or moody (36.4%), and feeling tired or weary (32.5%). The most common categories of symptoms in the PRODROME trial are generally consistent with these previous publications, including fatigue, neck pain, dizziness, sensory hypersensitivities, and mood and cognitive symptoms. This constellation of symptoms supports the notion that widespread areas of the brain are involved in the migraine attack, even during its earliest phase.[20] Furthermore, it is important for clinicians to be knowledgeable about common prodromal symptoms so that they can provide appropriate patient education regarding the recognition of the prodrome phase.

Table 5 Predictive Value of Qualifying Prodrome Events for Headache of Any Intensity Within 1 to 6 Hours

	Participants included in analysis (n = 911)
Positive prodrome event rate	
Mean (SD)	84.4 (24.7)
Median	100.0
Positive prodrome event rate categories, n (%)	
<25%	33 (3.6)
≥25% to <50%	38 (4.2)
≥50% to <75%	139 (15.3)
75% to <100%	164 (18.0)
100%	537 (58.9)

One participant had missing positive/negative status for all screening events and is not included in this analysis. Eight participants had the last screening event recorded after double-blind medication taken and are not included in this analysis.

Few studies have investigated the severity of prodromal symptoms. Data from the PRODROME trial demonstrate that most prodromal symptoms are often rated as mild in intensity. However, for the majority of prodromal symptoms, the symptom was reported as moderate or severe intensity in over one-third of prodrome events. Neck pain and fatigue, 2 of the most common prodromal symptoms, were more often rated as moderate or severe intensity, as opposed to mild. Given these findings, it is reasonable to hypothesize that the prodrome phase has a negative effect on functioning and should be considered when determining total migraine burden. Future studies should investigate the effect of prodromal symptoms on functioning and quality of life, independent from the headache phase of the migraine attack. Furthermore, a greater effect of prodromal symptoms on patient functioning might positively correlate with the likelihood of progressing to the headache phase.[6]

The likelihood of headache after self-identification of prodromal symptoms and timing of onset of headache following prodromal symptom recognition are dependent on the

population of individuals recruited for a study and the instructions on when to report prodromal symptoms (e.g., at their onset; when confident that a headache will follow). In a prospective study that used electronic diaries, 72% of prodrome events were followed by a headache phase and 82% of patients had prodromal symptoms followed by headache at least 50% of the time.[6] The predictive validity of prodromal symptoms was highest when patients were most confident that a headache would ensue. When patients felt it was "very likely" that a headache would ensue, they were correct 85% of the time, and when they felt it was "almost certain" that a headache would follow, they were correct 93% of the time. In the PRODROME trial, individuals were recruited if they routinely experienced prodromal symptom(s) that were reliably followed (≥75% of the time) by a headache within 1–6 hours. They were then asked to record prospectively their prodromal symptoms when they were confident that a headache would begin within 1–6 hours. In this cohort and with these instructions, over three-quarters of participants were able to identify prodromal symptoms that were reliably followed by headache within 1–6 hours at least 75% of the time. The PRODROME trial results demonstrate that a subgroup of people with migraine who believe that they can consistently self-identify prodromal symptoms that are followed by migraine headache are usually correct about this expectation.

Primary results from the PRODROME trial demonstrate that treatment with ubrogepant 100 mg, compared with placebo, administered during a qualifying prodrome event significantly reduced the development of moderate or severe headache for 24 and 48 hours postdose, and headache of any intensity and functional disability for 24 hours postdose.[5] The results presented here complement the data in the primary article by providing details from a large number of prodrome events (n = 4,802) regarding prodromal symptoms and timing until headache onset. These data provide greater insight on the ability of those with migraine to reliably predict the onset of headache from their prodromal symptoms.

Limitations of the PRODROME trial have been previously discussed.[5] This analysis of the screening period data has several limitations that should be noted. Only patients who reported, by history, that they were able to predict reliably the onset of headache based on their prodromal symptoms were selected for participation in the 60-day screening period and subsequent double-blind period. Therefore, these results may not be generalizable to the entire migraine population. In addition, we did not endeavor to improve the ability to predict headache onset based on prodromal features. Individuals differ greatly in their interoceptive awareness. In addition to exploring generalizability of these findings, there may be opportunities to educate patients, as well as treating clinicians, to better predict impending attacks and then treat to prevent those attacks.[21] Additional research is needed to determine the proportion of all people with migraine who experience prodromal symptoms, and the subset of those individuals who feel these symptoms reliably predict the onset of headache. Another potential limitation is that qualifying prodrome events were self-reported and not confirmed by a health care provider. It is possible that some participants could have misattributed aura symptoms as prodrome. The likelihood of this misattribution was limited by requiring that headache occur between 1 and 6 hours after a qualifying prodrome event because headache often begins in less than 60 minutes after aura onset. The use of a structured set of questions to assess prodromal symptoms and timing of headache onset provides reliable results. Furthermore, participants in the PRODROME trial had a history of 2–8 migraine attacks per month. Future studies are needed to determine whether the results reported in this article are shared by those with higher frequency migraine (e.g., chronic migraine).

In conclusion, data from the screening period of the PRODROME trial demonstrate that the most common symptoms during the prodrome phase of a migraine attack are sensitivity to light, fatigue, neck pain, sensitivity to sound, dizziness, and mood and cognitive symptoms. Furthermore, although prodromal symptoms are most often considered to be mild in intensity, moderate to severe intensity prodromal symptoms are common. Most participants in the PRODROME trial were reliably and consistently able to self-identify prodromal symptoms that were followed by a headache in 1–6 hours, highlighting the importance of recognizing prodromal symptoms.

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Disclosure

T.J. Schwedt reports that he serves on the Board of Directors for the American Headache Society. Within the prior 12 months, he has received research support from American Heart Association, Henry Jackson Foundation, Mayo Clinic, National Headache Foundation, NIH, Patient-Centered Outcomes Research Institute, Pfizer, SPARK Neuro, and US Department of Defense. Within the past 12 months, he has received personal compensation for serving as a consultant or advisory board member for AbbVie, Allergan, Eli Lilly,

TAKE-HOME POINTS

- A total of 1,087 participants with migraine recorded 4,802 qualifying prodrome events across the 60-day screening period of the PRODROME trial.
- Sensitivity to light (57.2%), fatigue (50.1%), neck pain (41.9%), sensitivity to sound (33.9%), dizziness (27.8%), irritability (26.4%), nausea (23.1%), difficulty concentrating (20.8%), muscle pain (19.4%), and blurred vision (14.7%) were the most common prodromal symptoms reported.
- Of 4,802 qualifying prodrome events reported, 81.5% were followed by headache within 1–6 hours.

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Todd J. Schwedt, MD	Mayo Clinic, Phoenix, AZ	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Richard B. Lipton, MD	Albert Einstein College of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Peter J. Goadsby, MD, PhD, DSc	NIHR-King's Clinical Research Facility, King's College, London, United Kingdom; University of California, Los Angeles	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Chia-Chun Chiang, MD	Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Brad C. Klein, MD	Thomas Jefferson University, Philadelphia, PA	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Cory Hussar, PhD	OPEN Health, Parsippany, NJ	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Chengcheng Liu, PhD	AbbVie, Madison, NJ	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sung Yun Yu, BA	AbbVie, Madison, NJ	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Michelle Finnegan, MPH	AbbVie, Madison, NJ	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
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References

1. Karsan N, Goadsby PJ. Biological insights from the premonitory symptoms of migraine. *Nat Rev Neurol*. 2018;14(12):699-710. doi:10.1038/s41582-018-0098-4
2. Headache Classification Committee of the International Headache Society (IHS) the International Classification of headache Disorders, 3rd edition. *Cephalalgia*. 2018; 38(1):1-211. doi:10.1177/0333102417738202
3. Schulte LH, Jürgens TP, May A. Photo-osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *J Headache Pain*. 2015;16:14. doi:10.1186/s10194-015-0495-7
4. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. *Cephalalgia*. 2016;36(10):951-959. doi:10.1177/0333102415620251
5. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. *Lancet*. 2023;402(10419):2307-2316. doi:10.1016/S0140-6736(23)01683-5
6. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology*. 2003;60(6):935-940. doi:10.1212/01.wnl.0000052998.58526.a9
7. Eigenbrodt AK, Christensen RH, Ashina H, et al. Premonitory symptoms in migraine: a systematic review and meta-analysis of observational studies reporting prevalence or relative frequency. *J Headache Pain*. 2022;23(1):140. doi:10.1186/s10194-022-01510-z
8. Schwedt TJ, Nahas SJ, Fanning KM, et al. Characterizing pre-headache (prodrome) features of migraine attacks: results from the CaMEO study (S4.004). *Neurology*. 2022;98(18_supplment):1208. doi:10.1212/wnl.98.18_supplement.1208
9. Güven B, Güven H, Çomoğlu SS. Migraine and yawning. *Headache*. 2018;58(2): 210-216. doi:10.1111/head.13195
10. Karli N, Zarifoglu M, Calisir N, Akgoz S. Comparison of pre-headache phases and trigger factors of migraine and episodic tension-type headache: do they share similar clinical pathophysiology? *Cephalalgia*. 2005;25(6):444-451. doi:10.1111/j.1468-2982.2005.00880.x
11. Quintela E, Castillo J, Munoz P, Pascual J. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia*. 2006;26(9): 1051-1060. doi:10.1111/j.1468-2982.2006.01157.x
12. Santoro G, Bernasconi F, Sessa F, Venco A. Premonitory symptoms in migraine without aura: a clinical investigation. *Funct Neurol*. 1990;5(4):339-344.
13. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia*. 2006;26(10):1209-1213. doi:10.1111/j.1468-2982.2006.01195.x
14. Schwedt TJ, Peplinski J, Garcia-Filion P, Berisha V. Altered speech with migraine attacks: a prospective, longitudinal study of episodic migraine without aura. *Cephalalgia*. 2019;39(6):722-731. doi:10.1177/0333102418815505
15. Kallela M, Wessman M, Havanka H, Palotie A, Färkkilä M. Familial migraine with and without aura: clinical characteristics and co-occurrence. *Eur J Neurol*. 2001;8(5): 441-449. doi:10.1046/j.1468-1331.2001.00260.x
16. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache*. 2004;44(9):865-872. doi:10.1111/j.1526-4610.2004.04168.x
17. Viana M, Sances G, Ghiotto N, et al. Variability of the characteristics of a migraine attack within patients. *Cephalalgia*. 2016;36(9):825-830. doi: 10.1177/0333102415613612
18. Wang X, Yin Z, Lian Y, et al. Premonitory symptoms in migraine from China: a multi-clinic study of 4821 patients. *Cephalalgia*. 2021;41:991-1003. doi:10.1177/0333102421997850
19. Gago-Veiga AB, Pagán J, Henares K, et al. To what extent are patients with migraine able to predict attacks? *J Pain Res*. 2018;11:2083-2094. doi:10.2147/JPR.S175602
20. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci*. 2015;35(17):6619-6629. doi:10.1523/JNEUROSCI.0373-15.2015
21. Lipton RB, Pavlovic JM, Haut SR, Grosberg BM, Buse DC. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache*. 2014; 54(10):1661-1669. doi:10.1111/head.12464

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