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https://doi.org/10.31925/farmacia.2026.4.23 **ORIGINAL ARTICLE**

POST-MARKETING SAFETY EVALUATION OF ATOGEPANT FOR MIGRAINE PREVENTION: A COMPREHENSIVE REAL-WORLD PHARMACOVIGILANCE AND SIGNAL DETECTION STUDY

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Abstract

This study evaluated atogepant-associated reports in the FDA Adverse Event Reporting System from Q4 2021 to Q1 2026. After deduplication, 4,819 reports listed atogepant as the primary suspect drug, containing 11,287 reaction records across 1,356 distinct MedDRA Preferred Terms (PTs). Disproportionality analyses used ROR, PRR, IC and EBGM, with signal positivity based on conservative lower confidence-bound metrics. Most reports involved females (76.22%) and originated from the United States (90.29%). The most frequent PTs were "migraine", "drug ineffective", "headache, nausea" and "constipation". A total of 137 PTs met all conservative signal criteria. Top EBGM05-ranked signals included migraine, hemiplegic migraine and vestibular migraine. Selected reproductive, menstrual, autonomic and sensory signals were observed, including Raynaud's phenomenon, POTS, menstrual irregularities, hyperacusis and tinnitus. Congenital-keyword PTs were rare. These findings provide atogepant-specific post-marketing safety evidence but remain hypothesis-generating and require confirmation in prospective studies.

Rezumat

Studiul a analizat raportările asociate atogepantului din Sistemul de Raportare a Evenimentelor Adverse al FDA (FAERS), în perioada cuprinsă între trimestrul al patrulea al anului 2021 și primul trimestru al anului 2026. După eliminarea duplicatelor, 4.819 raportări indicau atogepantul drept medicament principal investigat, însumând 11.287 înregistrări de reacții și 1.356 termeni preferați (PT) distincți din dicționarul MedDRA. Analizele de disproporționalitate au utilizat indicatorii ROR, PRR, IC și EBGM, pozitivitatea semnalelor fiind stabilită pe baza limitelor inferioare conservatoare ale intervalelor de încredere. Majoritatea raportărilor vizau femei (76,22%) și proveneau din Statele Unite (90,29%). Cei mai frecvenți PT au fost „migrena", „ineficacitatea medicamentului", „cefaleea", „greața" și „constipația". În total, 137 de PT au îndeplinit toate criteriile conservatoare de semnalizare. Printre semnalele cu cel mai ridicat scor EBGM05 s-au numărat migrena, migrena hemiplegică și migrena vestibulară. Au fost observate și semnale reproductive, menstruale, autonome și senzoriale, precum fenomenul Raynaud, sindromul de tahicardie ortostatică posturală (POTS), tulburările menstruale, hiperacuzia și tinitusul.

Keywords: Atogepant, pharmacovigilance, FAERS, adverse events, disproportionality analysis, migraine, real-world evidence

Introduction

A migraine is a headache that can cause severe throbbing pain or a pulsing sensation, usually on one side of the head, and is often accompanied by nausea, photophobia and phonophobia). Migraine affects over a billion people globally and is a leading cause of years lived with disability). The management strategies encompass acute treatments for immediate relief during attacks, and preventive therapies to reduce the frequency and severity of attacks).

Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist which is indicated for the prevention of episodic migraine headaches). CGRP, a neuropeptide, is involved in migraine pathophysiology, and it contributes by promoting vasodilation, neurogenic inflammation and central pain sensitization during migraine attack). Therefore, targeting CGRP has been a significant advancement in the management of migraine therapy.

Historically, the preventive migraine treatments included

beta-blockers, antiepileptic drugs and tricyclic antidepressants). Although effective for some patients, these medications were originally developed for other conditions and often caused a range of side effects such as cardiovascular risks, cognitive impairment, drowsiness and weight gain). Furthermore, their unpredictable efficacy led to poor adherence and treatment cessation). CGRP-targeting therapies such as monoclonal antibodies and receptor antagonists, are migraine-specific preventive options, that have shown improved safety and efficacy). Atogepant is an oral second-generation, small-molecule CGRP receptor antagonist). Unlike the first-generation CGRP antagonists (gepants), which had hepatotoxicity concerns, atogepant was developed with a favourable safety profile). While CGRP-targeting monoclonal antibodies such as eptinezumab, erenumab, fremanezumab and galcanezumab, which require subcutaneous or intravenous administration, atogepant offers the advantage of once-daily oral dosing, making it a more convenient option for patients).

Clinical trials, including the ADVANCE and the PROGRESS studies, demonstrated that atogepant significantly reduces the mean number of monthly migraine days compared to placebo). The phase 3 clinical trials have reported that atogepant is well tolerated, with the most commonly observed adverse events being constipation, fatigue and nausea). However, as with all newly approved drugs, long-term safety data from real-world populations remain limited. The clinical trials may not fully capture rare or delayed-onset AEs, drug interactions, or differences in tolerability among diverse patient populations.

Clinical trial data support the efficacy and safety of atogepant but real-world pharmacovigilance studies are still needed to assess adverse events across diverse patient populations. Recent FDA Adverse Event Reporting System (FAERS)-based analyses have evaluated gepants as a therapeutic class including the study by Chen and Li which assessed rimegepant, ubrogepant, atogepant and zavegepant together). The present study adds value by providing an updated atogepant-specific FAERS analysis through Q1 2026 and by clearly separating case-level reports from reaction-level and Preferred Term (PT) records. These updated findings provide clearer drug-specific context for real-world atogepant safety surveillance using the most recent FAERS data available through Q1, 2026.

Methodology

Data source

The FAERS served as the primary data source, providing access to patient demographics, drug exposure information and spontaneously reported AEs. The study period ranged from Q4-2021 to Q1-2026 focusing on reports on where atogepant was the primary suspected drug. The database was accessed *via* FDA's FAERS Public Dashboard (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html).

Data extraction and preprocessing

Initial data extraction focused on key fields, including CASEID, PRIMARYID, suspected drugs, AEs coded using MedDRA PT and patient demographics. To ensure data integrity, we implemented deduplication strategies recommended by the FDA, which involved removing duplicates based on hierarchies of CASEID, FDA_DT and PRIMARYID. Data preprocessing steps included sorting the data by CASEID and FDA_DT, retaining only the records with the latest FDA_DT for each CASEID. Additionally, records with identical CASEID and FDA_DT but smaller PRIMARYID values were removed to eliminate redundancies. Further details of this process are illustrated in Figure 1.

Data mapping and standardization

The AE terms were standardized using the MedDRA dictionary to ensure consistency. Atogepant and related terms were identified through text searches using its generic, brand names and known abbreviations. The extracted data were further refined by excluding any reports listing atogepant as interacting or concomitant with other drugs not under study.

Statistical analysis

The current study employed a range of statistical techniques to comprehensively analyse the data. Descriptive statistics were first utilized to summarize the clinical characteristics of the reports. The four complementary disproportionality methods were applied: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network with Information Component (IC) and Empirical Bayes Geometric Mean (EBGM) were utilized to evaluate the strength and significance of associations between atogepant and reported AEs. A PT was considered signal-positive only when all prespecified conservative thresholds were met: at least 3 atogepant reports, ROR05 > 1, PRR05 > 1, IC025 > 0 and EBGM05 > 1. To address false-positive concerns and improve consistency between Methods and Results, signal prioritization in the revised manuscript was based on lower confidence-bound metrics, particularly EBGM05, whereas point estimates are presented only as descriptive measures of signal magnitude. Missing data were reported explicitly to ensure transparency.

Data visualization and reporting

The findings were summarized using tables, a case-selection flowchart, bar charts of frequently reported PTs and graphical displays of signal strength. All figure legends define abbreviations, and PS and PT are not used interchangeably. Data management and updated visualizations were performed using Python/SQLite, Microsoft Excel and SPSS v25.0.

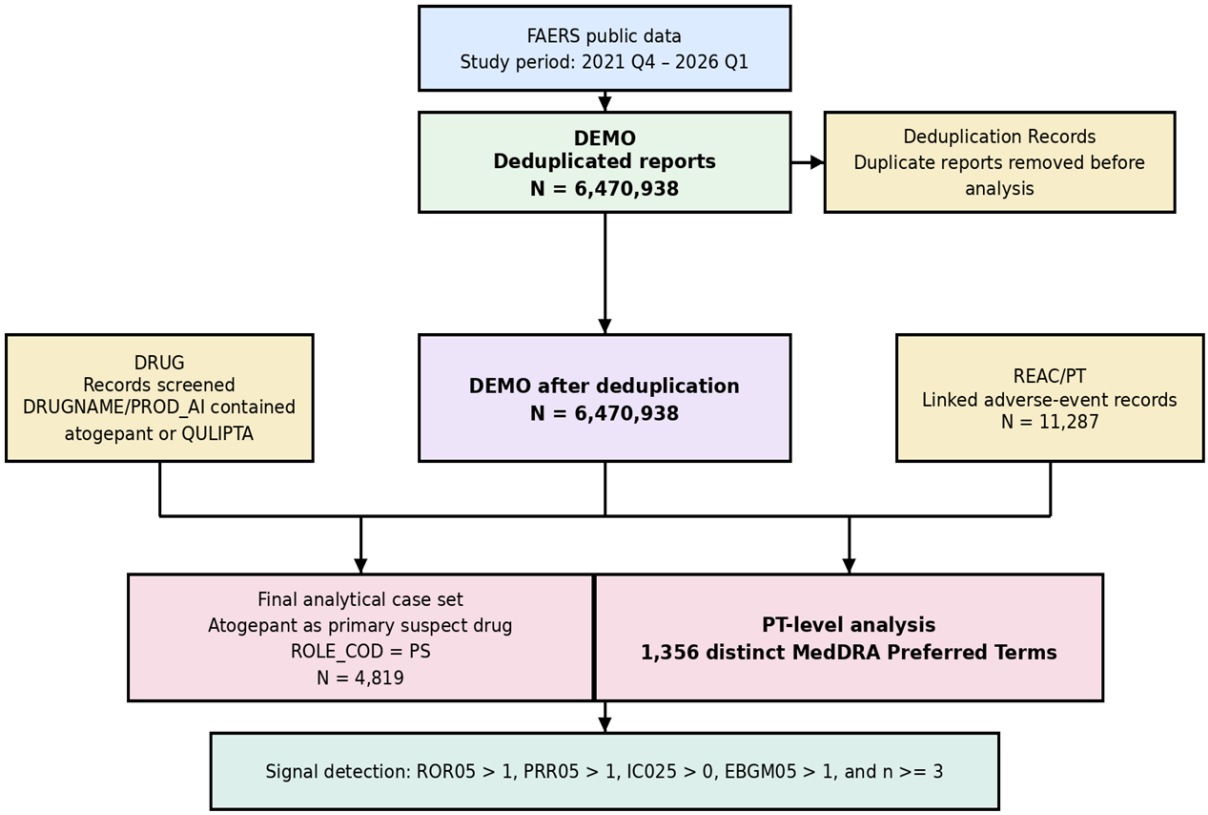

Figure 1.
Flowchart of the Data Extraction and Case Selection Process for Atogepant Adverse Event Analysis from the FAERS Database

FAERS, FDA Adverse Event Reporting System; PS, primary suspect drug; PT, MedDRA Preferred Term. Case-level reports refer to deduplicated individual FAERS reports in which atogepant was listed as the primary suspect drug. Reaction/PT records refer to adverse-event entries linked to these reports and do not represent additional individual cases. Deduplication was performed by CASEID with retention of the most recent FDA_DT and highest PRIMARYID

Data source

The study utilized publicly available data from the FAERS database, ensuring transparency and reproducibility of the research findings.

Results and Discussion

The analysis used FAERS data from Q4 2021 to Q1 2026. After deduplication 6,470,938 FAERS reports were available and 4,819 reports listed atogepant as the primary suspect drug. These reports included 11,287 reaction/PT records which represented 11,169 distinct report-PT pairs and 1,356 distinct MedDRA Preferred Terms. The extraction workflow is shown in Figure 1. The distinction between case-level reports and reaction/PT records was retained throughout the analysis to avoid denominator confusion. Table I presents the full set of signal-positive MedDRA Preferred Terms (PTs) associated with atogepant, along with their report frequencies and disproportionality measures (ROR, PRR, IC, and EBGM), ranked by the lower confidence bound of EBGM (EBGM05).

Table I

Full updated PT-level signal-positive results for atogepant, ranked by EBGM05

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Migraine	931	31,535	50.353 (46.837–54.134)	40.819 (38.489–43.289)	5.279 (5.187)	39.660 (37.549)
Hemiplegic migraine	6	145	57.990 (25.598–131.370)	57.919 (25.592–131.081)	3.418 (2.309)	59.981 (31.018)
Vestibular migraine	5	146	47.630 (19.513–116.263)	47.581 (19.510–116.041)	3.176 (1.970)	50.407 (24.672)
Post concussion syndrome	3	92	45.257 (14.317–143.053)	45.229 (14.319–142.867)	2.622 (1.111)	50.803 (20.743)
Brain operation	19	885	29.552 (18.741–46.599)	29.439 (18.702–46.340)	4.072 (3.432)	29.567 (20.289)
Migraine with aura	13	700	25.457 (14.695–44.099)	25.391 (14.678–43.920)	3.724 (2.955)	25.876 (16.466)
Cluster headache	8	412	26.613 (13.211–53.611)	26.570 (13.205–53.464)	3.397 (2.427)	27.667 (15.646)
Ligament operation	3	130	31.715 (10.090–99.687)	31.696 (10.091–99.558)	2.552 (1.041)	36.010 (14.773)
Nerve block	5	250	27.411 (11.303–66.475)	27.384 (11.302–66.349)	3.003 (1.797)	29.480 (14.507)
Raynaud's phenomenon	20	1,672	16.308 (10.484–25.368)	16.245 (10.462–25.223)	3.554 (2.930)	16.457 (11.418)
Aura	6	488	16.722 (7.472–37.427)	16.703 (7.470–37.346)	2.912 (1.803)	17.865 (9.331)

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Oophorectomy	3	221	18.476 (5.911–57.754)	18.465 (5.911–57.679)	2.397 (0.885)	21.216 (8.745)
Premenstrual syndrome	3	255	15.983 (5.118–49.909)	15.974 (5.119–49.845)	2.343 (0.831)	18.393 (7.589)
Intervertebral disc operation	4	377	14.400 (5.374–38.586)	14.389 (5.374–38.525)	2.527 (1.194)	16.005 (7.336)
Cystitis interstitial	4	392	13.844 (5.167–37.087)	13.833 (5.168–37.028)	2.506 (1.174)	15.394 (7.057)
Breast operation	3	296	13.746 (4.406–42.885)	13.739 (4.407–42.830)	2.280 (0.769)	15.849 (6.545)
Constipation	381	72,082	7.656 (6.894–8.503)	7.130 (6.473–7.853)	2.816 (2.671)	7.106 (6.531)
Ophthalmic migraine	5	575	11.781 (4.883–28.427)	11.770 (4.882–28.374)	2.567 (1.361)	12.832 (6.342)
Medication overuse headache	3	319	12.746 (4.087–39.747)	12.739 (4.088–39.696)	2.247 (0.735)	14.708 (6.076)
Brain neoplasm	18	2,961	8.234 (5.176–13.098)	8.207 (5.168–13.033)	2.774 (2.116)	8.387 (5.715)
White matter lesion	4	491	11.029 (4.121–29.517)	11.021 (4.121–29.471)	2.378 (1.045)	12.293 (5.641)
Abnormal dreams	24	4,518	7.197 (4.814–10.759)	7.166 (4.803–10.692)	2.664 (2.093)	7.280 (5.217)
Spinal operation	31	6,101	6.891 (4.836–9.818)	6.853 (4.820–9.742)	2.643 (2.139)	6.932 (5.167)
Cerebrospinal fluid leakage	4	550	9.837 (3.677–26.316)	9.830 (3.678–26.275)	2.307 (0.974)	10.975 (5.038)
Hyperacusis	6	977	8.300 (3.718–18.531)	8.291 (3.718–18.492)	2.405 (1.296)	8.928 (4.673)
Postural orthostatic tachycardia syndrome	5	790	8.554 (3.549–20.619)	8.546 (3.549–20.581)	2.337 (1.132)	9.342 (4.621)
Limb operation	10	1,975	6.841 (3.672–12.742)	6.828 (3.671–12.703)	2.414 (1.541)	7.136 (4.290)
Tonsillectomy	3	465	8.718 (2.800–27.139)	8.713 (2.801–27.105)	2.048 (0.537)	10.095 (4.176)
Menstruation irregular	15	3,330	6.087 (3.663–10.117)	6.071 (3.659–10.075)	2.379 (1.661)	6.249 (4.111)
Abdominal operation	3	502	8.071 (2.593–25.120)	8.067 (2.594–25.089)	2.002 (0.490)	9.352 (3.870)
Medical device implantation	4	722	7.481 (2.799–19.994)	7.475 (2.799–19.964)	2.117 (0.784)	8.363 (3.842)
Therapy interrupted	172	53,887	4.419 (3.794–5.146)	4.297 (3.709–4.977)	2.086 (1.871)	4.298 (3.791)
Menstruation delayed	8	1,721	6.275 (3.131–12.576)	6.266 (3.131–12.544)	2.254 (1.284)	6.629 (3.766)
Medical procedure	5	973	6.937 (2.879–16.712)	6.931 (2.880–16.682)	2.167 (0.961)	7.586 (3.754)
Amenorrhoea	14	3,451	5.479 (3.239–9.267)	5.466 (3.236–9.231)	2.240 (1.497)	5.641 (3.659)
Hysterectomy	11	2,618	5.672 (3.135–10.262)	5.662 (3.134–10.229)	2.231 (1.397)	5.897 (3.626)
Tension headache	7	1,537	6.146 (2.924–12.922)	6.139 (2.923–12.892)	2.189 (1.157)	6.550 (3.587)
Headache	500	175,303	4.167 (3.798–4.571)	3.838 (3.532–4.171)	1.933 (1.807)	3.833 (3.561)
Motion sickness	3	548	7.390 (2.375–22.993)	7.386 (2.376–22.965)	1.946 (0.435)	8.568 (3.546)
Neck surgery	5	1,041	6.482 (2.691–15.612)	6.476 (2.691–15.585)	2.109 (0.903)	7.090 (3.509)
Therapeutic product effect incomplete	121	40,881	4.060 (3.389–4.864)	3.983 (3.340–4.751)	1.973 (1.717)	3.990 (3.436)
Head discomfort	22	6,230	4.772 (3.137–7.260)	4.755 (3.132–7.220)	2.130 (1.534)	4.849 (3.426)
Menstrual disorder	8	1,971	5.476 (2.733–10.971)	5.468 (2.732–10.944)	2.111 (1.141)	5.789 (3.289)
Tinnitus	39	12,488	4.230 (3.085–5.799)	4.204 (3.074–5.749)	2.011 (1.561)	4.247 (3.267)
Surgery	63	22,107	3.872 (3.019–4.967)	3.835 (2.999–4.903)	1.904 (1.549)	3.857 (3.136)
Spinal cord injury	3	620	6.528 (2.099–20.302)	6.524 (2.099–20.277)	1.864 (0.352)	7.573 (3.136)
Giant cell arteritis	3	625	6.475 (2.082–20.139)	6.472 (2.082–20.114)	1.858 (0.347)	7.513 (3.111)
Vertigo	44	15,223	3.916 (2.909–5.272)	3.890 (2.897–5.222)	1.911 (1.487)	3.925 (3.066)
Intracranial pressure increased	6	1,519	5.326 (2.388–11.881)	5.321 (2.388–11.857)	1.994 (0.885)	5.744 (3.009)
Concussion	9	2,518	4.820 (2.504–9.281)	4.813 (2.503–9.256)	2.000 (1.082)	5.065 (2.967)
Foot operation	7	1,877	5.029 (2.393–10.569)	5.023 (2.392–10.545)	1.983 (0.950)	5.363 (2.938)
Aneurysm	5	1,264	5.333 (2.215–12.842)	5.329 (2.215–12.819)	1.932 (0.726)	5.840 (2.891)
Shoulder operation	7	1,909	4.944 (2.352–10.390)	4.938 (2.352–10.367)	1.965 (0.932)	5.274 (2.889)
Derealisation	3	683	5.923 (1.905–18.417)	5.920 (1.905–18.394)	1.795 (0.283)	6.875 (2.847)
Brain fog	36	13,155	3.702 (2.666–5.141)	3.682 (2.658–5.101)	1.826 (1.358)	3.725 (2.836)
Suicidal ideation	57	21,934	3.526 (2.715–4.580)	3.496 (2.700–4.527)	1.772 (1.399)	3.520 (2.832)
Peripheral coldness	12	3,736	4.332 (2.456–7.640)	4.324 (2.455–7.615)	1.929 (1.129)	4.492 (2.818)
Patella fracture	3	698	5.795 (1.864–18.018)	5.792 (1.864–17.996)	1.779 (0.268)	6.728 (2.786)
Impaired driving ability	8	2,335	4.619 (2.306–9.253)	4.613 (2.305–9.230)	1.925 (0.955)	4.887 (2.777)
Trichorrhexis	3	705	5.737 (1.845–17.838)	5.734 (1.846–17.816)	1.772 (0.260)	6.661 (2.759)
Craniocerebral injury	4	1,008	5.349 (2.003–14.287)	5.346 (2.003–14.266)	1.847 (0.514)	5.991 (2.754)
Photophobia	17	6,186	3.707 (2.301–5.972)	3.698 (2.299–5.947)	1.777 (1.101)	3.798 (2.562)
Nausea	457	223,570	2.932 (2.662–3.228)	2.748 (2.519–2.999)	1.454 (1.322)	2.748 (2.544)
Self-injurious ideation	4	1,098	4.909 (1.838–13.109)	4.906 (1.839–13.090)	1.772 (0.439)	5.500 (2.529)
Disability	17	6,308	3.635 (2.256–5.856)	3.626 (2.255–5.832)	1.751 (1.075)	3.725 (2.512)
Brain injury	9	2,980	4.070 (2.114–7.836)	4.065 (2.114–7.815)	1.805 (0.887)	4.280 (2.508)
Spinal fusion surgery	5	1,465	4.599 (1.910–11.071)	4.595 (1.911–11.052)	1.789 (0.584)	5.039 (2.495)
Tachyphrenia	3	789	5.124 (1.648–15.927)	5.121 (1.649–15.908)	1.686 (0.175)	5.952 (2.466)
Shoulder arthroplasty	4	1,153	4.674 (1.751–12.481)	4.671 (1.751–12.462)	1.728 (0.395)	5.238 (2.408)
Post-acute COVID-19 syndrome	4	1,158	4.654 (1.743–12.426)	4.651 (1.743–12.408)	1.724 (0.391)	5.215 (2.398)
Pregnancy	9	3,131	3.873 (2.012–7.456)	3.868 (2.012–7.437)	1.746 (0.829)	4.073 (2.387)
Cerebral disorder	8	2,754	3.914 (1.954–7.839)	3.909 (1.954–7.820)	1.736 (0.767)	4.143 (2.355)

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Panic attack	22	9,216	3.221 (2.118–4.899)	3.211 (2.115–4.874)	1.612 (1.015)	3.278 (2.316)
Nightmare	19	7,789	3.290 (2.096–5.166)	3.281 (2.094–5.142)	1.630 (0.990)	3.361 (2.315)
Sinus operation	3	843	4.794 (1.543–14.901)	4.792 (1.543–14.883)	1.634 (0.122)	5.571 (2.308)
Product use complaint	22	9,304	3.190 (2.098–4.852)	3.180 (2.095–4.828)	1.599 (1.003)	3.247 (2.294)
Knee arthroplasty	20	8,641	3.122 (2.011–4.846)	3.113 (2.009–4.823)	1.564 (0.939)	3.185 (2.214)
Decreased appetite	142	75,595	2.572 (2.176–3.039)	2.525 (2.147–2.970)	1.327 (1.090)	2.531 (2.205)
Heavy menstrual bleeding	16	6,751	3.195 (1.955–5.222)	3.188 (1.953–5.202)	1.578 (0.882)	3.281 (2.188)
General symptom	4	1,277	4.219 (1.580–11.263)	4.216 (1.581–11.247)	1.633 (0.300)	4.730 (2.175)
Cerebrovascular accident	67	34,691	2.619 (2.057–3.334)	2.596 (2.047–3.294)	1.358 (1.014)	2.612 (2.138)
Deafness	18	7,981	3.041 (1.913–4.833)	3.033 (1.912–4.812)	1.522 (0.864)	3.112 (2.122)
Alopecia	98	52,801	2.526 (2.068–3.086)	2.495 (2.051–3.036)	1.307 (1.022)	2.505 (2.122)
Somnolence	100	54,140	2.514 (2.062–3.066)	2.483 (2.045–3.015)	1.300 (1.018)	2.492 (2.115)
Depression suicidal	3	956	4.226 (1.360–13.131)	4.224 (1.360–13.116)	1.530 (0.019)	4.913 (2.036)
Feeding disorder	18	8,623	2.814 (1.770–4.472)	2.807 (1.769–4.453)	1.418 (0.761)	2.880 (1.964)
Intermenstrual bleeding	10	4,405	3.057 (1.643–5.690)	3.053 (1.643–5.675)	1.474 (0.601)	3.200 (1.925)
Gastric disorder	11	4,964	2.984 (1.651–5.396)	2.980 (1.650–5.381)	1.454 (0.620)	3.110 (1.914)
Seizure	73	43,445	2.278 (1.807–2.871)	2.258 (1.798–2.836)	1.162 (0.832)	2.271 (1.875)
Feeling abnormal	94	58,322	2.189 (1.785–2.686)	2.166 (1.773–2.647)	1.105 (0.814)	2.176 (1.837)
Therapeutic response unexpected	21	11,141	2.541 (1.654–3.902)	2.534 (1.653–3.884)	1.289 (0.679)	2.591 (1.817)
Abnormal loss of weight	4	1,534	3.510 (1.315–9.368)	3.508 (1.315–9.355)	1.454 (0.121)	3.937 (1.811)
Musculoskeletal disorder	10	4,865	2.767 (1.487–5.150)	2.764 (1.487–5.137)	1.349 (0.476)	2.898 (1.743)
Food poisoning	5	2,112	3.186 (1.324–7.667)	3.184 (1.325–7.655)	1.408 (0.202)	3.496 (1.732)
Drug ineffective	553	400,280	1.967 (1.800–2.150)	1.856 (1.716–2.008)	0.890 (0.770)	1.857 (1.731)
Palpitations	50	31,458	2.148 (1.625–2.839)	2.136 (1.621–2.815)	1.078 (0.680)	2.155 (1.710)
Dizziness	195	136,697	1.955 (1.694–2.257)	1.917 (1.670–2.200)	0.934 (0.732)	1.920 (1.707)
Disturbance in attention	23	13,183	2.352 (1.561–3.543)	2.345 (1.559–3.527)	1.188 (0.604)	2.393 (1.704)
Euphoric mood	5	2,175	3.094 (1.286–7.444)	3.092 (1.286–7.432)	1.376 (0.170)	3.394 (1.682)
Chemotherapy	4	1,656	3.251 (1.218–8.675)	3.249 (1.218–8.663)	1.376 (0.043)	3.647 (1.678)
Transient ischaemic attack	13	6,926	2.527 (1.466–4.358)	2.523 (1.465–4.345)	1.255 (0.485)	2.617 (1.672)
Gastrointestinal motility disorder	4	1,689	3.187 (1.194–8.505)	3.185 (1.195–8.493)	1.356 (0.023)	3.576 (1.645)
Impaired gastric emptying	12	6,436	2.510 (1.424–4.426)	2.506 (1.424–4.413)	1.240 (0.440)	2.608 (1.637)
Impaired work ability	9	4,591	2.639 (1.371–5.078)	2.636 (1.371–5.066)	1.277 (0.360)	2.778 (1.628)
Product use issue	95	66,928	1.926 (1.571–2.360)	1.907 (1.563–2.328)	0.924 (0.634)	1.916 (1.619)
Nerve injury	6	2,895	2.789 (1.251–6.216)	2.787 (1.252–6.205)	1.291 (0.182)	3.014 (1.580)
Depression	72	50,962	1.912 (1.515–2.413)	1.898 (1.509–2.388)	0.915 (0.583)	1.910 (1.574)
Anxiety	104	76,109	1.854 (1.527–2.252)	1.836 (1.518–2.221)	0.870 (0.593)	1.843 (1.569)
Knee operation	8	4,199	2.564 (1.281–5.133)	2.561 (1.281–5.122)	1.229 (0.259)	2.718 (1.545)
Adverse drug reaction	51	36,194	1.903 (1.444–2.508)	1.893 (1.441–2.488)	0.908 (0.514)	1.910 (1.519)
Neck pain	25	16,314	2.065 (1.393–3.060)	2.059 (1.393–3.046)	1.011 (0.451)	2.099 (1.515)
Blindness	20	12,668	2.126 (1.370–3.300)	2.122 (1.370–3.287)	1.045 (0.421)	2.173 (1.510)
Insomnia	88	67,081	1.777 (1.439–2.194)	1.763 (1.433–2.168)	0.811 (0.510)	1.771 (1.487)
Rotator cuff syndrome	6	3,158	2.556 (1.147–5.697)	2.554 (1.147–5.687)	1.189 (0.079)	2.763 (1.448)
Post procedural complication	8	4,524	2.379 (1.188–4.763)	2.377 (1.189–4.753)	1.135 (0.166)	2.522 (1.434)
Fatigue	296	253,464	1.606 (1.428–1.807)	1.569 (1.405–1.752)	0.648 (0.483)	1.571 (1.427)
Weight decreased	105	85,270	1.669 (1.375–2.025)	1.654 (1.369–1.999)	0.721 (0.446)	1.661 (1.415)
Back disorder	8	4,658	2.311 (1.154–4.626)	2.308 (1.154–4.616)	1.099 (0.129)	2.450 (1.393)
Unevaluable event	25	17,779	1.894 (1.278–2.807)	1.889 (1.278–2.794)	0.892 (0.332)	1.926 (1.390)
Intervertebral disc protrusion	9	5,404	2.241 (1.165–4.311)	2.238 (1.165–4.302)	1.070 (0.153)	2.360 (1.383)
Swollen tongue	11	6,996	2.116 (1.170–3.825)	2.113 (1.170–3.815)	1.010 (0.176)	2.207 (1.358)
Therapeutic product effect decreased	32	24,444	1.764 (1.246–2.498)	1.759 (1.245–2.485)	0.797 (0.301)	1.785 (1.337)
Irritability	17	12,069	1.896 (1.177–3.053)	1.893 (1.177–3.043)	0.883 (0.207)	1.947 (1.313)
Amnesia	20	14,647	1.838 (1.184–2.853)	1.835 (1.184–2.842)	0.846 (0.221)	1.879 (1.306)
Abdominal pain upper	71	60,622	1.582 (1.251–2.000)	1.573 (1.249–1.982)	0.647 (0.313)	1.584 (1.303)
Adverse event	31	24,702	1.690 (1.187–2.407)	1.686 (1.187–2.395)	0.737 (0.233)	1.712 (1.277)
Hypophagia	11	7,491	1.975 (1.093–3.571)	1.973 (1.093–3.562)	0.920 (0.086)	2.061 (1.268)
Aphasia	11	7,534	1.964 (1.087–3.551)	1.962 (1.087–3.542)	0.912 (0.078)	2.049 (1.261)
Neoplasm malignant	28	22,490	1.677 (1.156–2.431)	1.673 (1.156–2.420)	0.724 (0.195)	1.701 (1.250)
Memory impairment	47	40,229	1.575 (1.182–2.100)	1.569 (1.181–2.086)	0.641 (0.231)	1.585 (1.249)
Loss of consciousness	37	31,467	1.584 (1.146–2.189)	1.580 (1.146–2.178)	0.648 (0.186)	1.600 (1.223)
Dyspepsia	34	28,740	1.593 (1.137–2.233)	1.589 (1.137–2.222)	0.655 (0.174)	1.612 (1.218)

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Therapeutic response decreased	23	18,683	1.657 (1.100–2.497)	1.654 (1.100–2.487)	0.705 (0.122)	1.689 (1.203)
Fibromyalgia	12	8,899	1.814 (1.029–3.197)	1.812 (1.029–3.189)	0.811 (0.011)	1.886 (1.184)
Nephrolithiasis	19	15,481	1.651 (1.052–2.592)	1.649 (1.052–2.583)	0.697 (0.057)	1.691 (1.165)
Abdominal distension	34	30,487	1.502 (1.071–2.104)	1.498 (1.071–2.095)	0.572 (0.091)	1.519 (1.148)
Balance disorder	25	22,245	1.512 (1.021–2.241)	1.510 (1.021–2.232)	0.579 (0.019)	1.539 (1.111)

This appendix contains all 137 Preferred Terms meeting the signal criteria in the final cumulative analysis. Abbreviations: CI, confidence interval; EBGM, Empirical Bayes Geometric Mean; EBGM05, lower 95% confidence bound for EBGM; IC, Information Component; IC025, lower 95% credibility interval for IC; PRR, Proportional Reporting Ratio; PRR05, lower 95% confidence bound for PRR; PT, Preferred Term; ROR, Reporting Odds Ratio; ROR05, lower 95% confidence bound for ROR

Demographic characteristics and reported outcomes

The demographic profile and reported outcomes of the 4,819 atogepant primary-suspect reports are summarized in Table II. Females accounted for most reports (n = 3,673, 76.22%) while males accounted for 584 reports (12.12%) and sex information was missing in 556 reports (11.54%). Age and weight data showed substantial missingness with missing or invalid age in 3,143 reports (65.22%) and missing or invalid weight in 4,217 reports (87.51%). Most reports originated from the United States (n = 4,351, 90.29%). Any serious outcome was recorded in 1,535 reports (31.85%) while 3,284 reports (68.15%) had no outcome code recorded. The most frequent specific outcomes were other serious outcome (n = 1,231, 25.54%) and hospitalization (n = 318, 6.60%). Death was reported in 53 cases (1.10%) and congenital anomaly in 5 cases (0.10%).

System Organ Class – level signal profile

System Organ Class-level disproportionality results are presented in Table III. The highest report frequencies were observed for nervous system disorders (n = 2,112), general disorders and administration site conditions (n = 1,471), gastrointestinal disorders (n = 1,305), psychiatric disorders (n = 546) and injury poisoning and procedural complications (n = 454). Based on lower confidence-bound metrics, several SOCs retained strong disproportionality signals including congenital familial and genetic disorders (EBGM05 = 11.135), neoplasms benign malignant and unspecified (EBGM05 = 11.889), surgical and medical procedures (EBGM05 = 8.603), reproductive system and breast disorders (EBGM05 = 7.603) and psychiatric disorders (EBGM05 = 5.931). Although congenital familial and genetic disorders showed a high SOC-level EBGM05 value, this category included only six reports. The SOC-level findings were interpreted as broad screening results, and the main clinical interpretation was based on PT-level signals.

Table II

Demographic and clinical characteristics of individual case safety reports

Variable	n (%)
Gender	
Female	3673 (76.22%)
Male	584 (12.12%)
Unknown	6 (0.12%)
Missing	556 (11.54%)
Age	
< 18 years	7 (0.15%)
18 - 29 years	162 (3.36%)
30 - 49 years	636 (13.20%)
50 - 64 years	596 (12.37%)
65 - 74 years	189 (3.92%)
≥ 75 years	86 (1.78%)
Missing/invalid	3143 (65.22%)
Weight	
< 40 kg	6 (0.12%)
40 - 59.9 kg	158 (3.28%)
60 - 79.9 kg	238 (4.94%)
80 - 99.9 kg	132 (2.74%)
≥ 100 kg	68 (1.41%)
Missing/invalid	4217 (87.51%)
Reported country	
United States	4351 (90.29%)
Canada	185 (3.84%)
United Kingdom	145 (3.01%)
EU	52 (1.08%)
Puerto Rico	17 (0.35%)
Spain	11 (0.23%)
Others	58 (1.20%)
Outcome	
Death	53 (1.10%)
Life-threatening	30 (0.62%)
Hospitalization	318 (6.60%)
Disability	95 (1.97%)
Congenital anomaly	5 (0.10%)
Required intervention	32 (0.66%)
Other serious	1231 (25.54%)
Any serious outcome	1535 (31.85%)
No outcome code recorded	3284 (68.15%)

The percentages were calculated using 4,819 deduplicated atogepant primary-suspect reports as the denominator. Missing and unknown categories are shown explicitly to avoid denominator ambiguity

Table III

Disproportionality analysis of adverse events by System Organ Class (SOC)

System Organ Class (SOC)	Frequency	IC (IC025)	EBGM (EBGM05)	ROR (95% CI)	PRR (95% CI)
Nervous system disorders	2112	3.156 (3.048)	8.913 (8.539)	8.961 (8.586 - 9.353)	8.927 (8.555 - 9.315)
General disorders and administration site conditions	1471	1.655 (1.525)	3.148 (2.991)	3.164 (3.006 - 3.331)	3.150 (2.993 - 3.314)
Gastrointestinal disorders	1305	2.339 (2.202)	5.059 (4.791)	5.078 (4.809 - 5.362)	5.063 (4.796 - 5.345)
Psychiatric disorders	546	6.092 (3.345)	24.685 (5.931)	24.785 (5.949 - 157.555)	24.775 (5.947 - 157.431)
Injury, poisoning and procedural complications	454	3.346 (0.814)	8.286 (3.062)	8.297 (3.065 - 28.855)	8.294 (3.065 - 28.838)
Surgical and medical procedures	379	3.250 (2.998)	9.516 (8.603)	9.546 (8.630 - 10.559)	9.532 (8.619 - 10.542)
Skin and subcutaneous tissue disorders	259	0.819 (0.515)	1.765 (1.562)	1.766 (1.564 - 1.995)	1.765 (1.563 - 1.993)
Metabolism and nutrition disorders	229	2.148 (1.825)	4.433 (3.893)	4.447 (3.905 - 5.063)	4.436 (3.897 - 5.048)
Musculoskeletal and connective tissue disorders	216	0.413 (0.080)	1.331 (1.165)	1.332 (1.165 - 1.522)	1.331 (1.165 - 1.521)
Infections and infestations	203	0.473 (0.131)	1.388 (1.210)	1.389 (1.210 - 1.594)	1.388 (1.210 - 1.593)
Eye disorders	152	1.360 (0.966)	2.567 (2.189)	2.569 (2.191 - 3.012)	2.568 (2.190 - 3.010)
Cardiac disorders	149	1.368 (0.970)	2.582 (2.199)	2.585 (2.201 - 3.035)	2.583 (2.200 - 3.032)
Investigations	145	0.540 (0.136)	1.454 (1.235)	1.454 (1.236 - 1.711)	1.454 (1.236 - 1.711)
Respiratory, thoracic and mediastinal disorders	142	0.290 (-0.118)	1.223 (1.037)	1.223 (1.037 - 1.442)	1.223 (1.037 - 1.441)
Vascular disorders	100	0.702 (0.219)	1.626 (1.337)	1.627 (1.337 - 1.979)	1.626 (1.337 - 1.978)
Immune system disorders	87	1.098 (0.582)	2.141 (1.735)	2.143 (1.737 - 2.645)	2.142 (1.736 - 2.642)
Reproductive system and breast disorders	77	3.249 (2.702)	9.508 (7.603)	9.530 (7.620 - 11.919)	9.524 (7.617 - 11.910)
Neoplasms benign, malignant and unspecified	71	7.586 (3.454)	23.792 (11.889)	23.887 (11.937 - 50.787)	23.847 (11.931 - 50.653)
Product issues	64	0.822 (0.224)	1.768 (1.383)	1.769 (1.384 - 2.261)	1.768 (1.384 - 2.258)
Ear and labyrinth disorders	57	1.766 (1.135)	3.401 (2.623)	3.407 (2.627 - 4.418)	3.403 (2.625 - 4.411)
Social circumstances	52	2.046 (1.387)	4.130 (3.146)	4.137 (3.152 - 5.431)	4.133 (3.149 - 5.423)
Renal and urinary disorders	50	0.297 (-0.374)	1.228 (0.931)	1.229 (0.931 - 1.621)	1.228 (0.931 - 1.621)
Pregnancy, puerperium and perinatal conditions	29	0.997 (0.134)	1.996 (1.386)	1.997 (1.387 - 2.875)	1.996 (1.387 - 2.872)
Hepatobiliary disorders	21	0.890 (-0.109)	1.853 (1.208)	1.853 (1.208 - 2.843)	1.853 (1.208 - 2.842)
Endocrine disorders	15	0.706 (-0.450)	1.632 (0.983)	1.632 (0.984 - 2.708)	1.632 (0.984 - 2.707)
Blood and lymphatic system disorders	8	-0.633 (-2.129)	0.645 (0.322)	0.644 (0.322 - 1.289)	0.645 (0.322 - 1.289)
Congenital, familial and genetic disorders	6	4.634 (2.969)	24.838 (11.135)	24.966 (11.192 - 55.692)	24.957 (11.191 - 55.653)

SOC, System Organ Class; IC, Information Component; IC025, lower 95% credibility interval for IC; EBGM, Empirical Bayes Geometric Mean; EBGM05, lower 95% credibility bound for EBGM; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; CI, confidence interval

Preferred term frequency and signal detection

At the PT level, the most frequent reported terms were migraine (n = 931, 19.32%), drug ineffective (n = 553, 11.48%), headache (n = 500, 10.38%), nausea (n = 457, 9.48%) and constipation (n = 381, 7.91%). Other common PTs included fatigue (n = 296, 6.14%), dizziness (n = 195, 4.05%), therapy interrupted (n = 172, 3.57%) and decreased appetite (n = 142, 2.95%). The pattern indicates that migraine-related symptoms and effectiveness-related reports were prominent in real-world atogepant reporting. A total of 137 PTs met all conservative signal criteria, and the revised signal ranking was based on EBGM05 rather than EBGM point estimates. The leading signal-positive PTs are presented in Table IV. The strongest EBGM05 signals included migraine (EBGM05 = 37.549), hemiplegic migraine (EBGM05 = 31.018), vestibular migraine (EBGM05 = 24.672), post-concussion syndrome (EBGM05 = 20.743) and brain operation (EBGM05 = 20.289). This PT-level approach helped identify the specific events underlying broader signal categories.

Table IV

Signal detection results for PTs associated with atogepant based on frequencies and disproportionality metrics across detection algorithms

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Migraine	931	31,535	50.353 (46.837 - 54.134)	40.819 (38.489 - 43.289)	5.279 (5.187)	39.660 (37.549)
Hemiplegic migraine	6	145	57.990 (25.598 - 131.370)	57.919 (25.592 - 131.081)	3.418 (2.309)	59.981 (31.018)
Vestibular migraine	5	146	47.630 (19.513 - 116.263)	47.581 (19.510 - 116.041)	3.176 (1.970)	50.407 (24.672)
Post concussion syndrome	3	92	45.257 (14.317 - 143.053)	45.229 (14.319 - 142.867)	2.622 (1.111)	50.803 (20.743)
Brain operation	19	885	29.552 (18.741 - 46.599)	29.439 (18.702 - 46.340)	4.072 (3.432)	29.567 (20.289)
Migraine with aura	13	700	25.457 (14.695 - 44.099)	25.391 (14.678 - 43.920)	3.724 (2.955)	25.876 (16.466)
Cluster headache	8	412	26.613 (13.211 - 53.611)	26.570 (13.205 - 53.464)	3.397 (2.427)	27.667 (15.646)
Ligament operation	3	130	31.715 (10.090 - 99.687)	31.696 (10.091 - 99.558)	2.552 (1.041)	36.010 (14.773)
Nerve block	5	250	27.411 (11.303 - 66.475)	27.384 (11.302 - 66.349)	3.003 (1.797)	29.480 (14.507)
Raynaud's phenomenon	20	1,672	16.308 (10.484 - 25.368)	16.245 (10.462 - 25.223)	3.554 (2.930)	16.457 (11.418)
Aura	6	488	16.722 (7.472 - 37.427)	16.703 (7.470 - 37.346)	2.912 (1.803)	17.865 (9.331)
Oophorectomy	3	221	18.476 (5.911 - 57.754)	18.465 (5.911 - 57.679)	2.397 (0.885)	21.216 (8.745)
Premenstrual syndrome	3	255	15.983 (5.118 - 49.909)	15.974 (5.119 - 49.845)	2.343 (0.831)	18.393 (7.589)
Intervertebral disc operation	4	377	14.400 (5.374 - 38.586)	14.389 (5.374 - 38.525)	2.527 (1.194)	16.005 (7.336)
Cystitis interstitial	4	392	13.844 (5.167 - 37.087)	13.833 (5.168 - 37.028)	2.506 (1.174)	15.394 (7.057)
Breast operation	3	296	13.746 (4.406 - 42.885)	13.739 (4.407 - 42.830)	2.280 (0.769)	15.849 (6.545)
Constipation	381	72,082	7.656 (6.894 - 8.503)	7.130 (6.473 - 7.853)	2.816 (2.671)	7.106 (6.531)
Ophthalmic migraine	5	575	11.781 (4.883 - 28.427)	11.770 (4.882 - 28.374)	2.567 (1.361)	12.832 (6.342)
Medication overuse headache	3	319	12.746 (4.087 - 39.747)	12.739 (4.088 - 39.696)	2.247 (0.735)	14.708 (6.076)
Brain neoplasm	18	2,961	8.234 (5.176 - 13.098)	8.207 (5.168 - 13.033)	2.774 (2.116)	8.387 (5.715)
White matter lesion	4	491	11.029 (4.121 - 29.517)	11.021 (4.121 - 29.471)	2.378 (1.045)	12.293 (5.641)
Abnormal dreams	24	4,518	7.197 (4.814 - 10.759)	7.166 (4.803 - 10.692)	2.664 (2.093)	7.280 (5.217)

PT	n	All FAERS reports with PT	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)
Spinal operation	31	6,101	6.891 (4.836 - 9.818)	6.853 (4.820 - 9.742)	2.643 (2.139)	6.932 (5.167)
Cerebrospinal fluid leakage	4	550	9.837 (3.677 - 26.316)	9.830 (3.678 - 26.275)	2.307 (0.974)	10.975 (5.038)
Hyperacusis	6	977	8.300 (3.718 - 18.531)	8.291 (3.718 - 18.492)	2.405 (1.296)	8.928 (4.673)

SOC, System Organ Class; IC, Information Component; IC025, lower 95% credibility interval for IC; EBGM, Empirical Bayes Geometric Mean; EBGM05, lower 95% credibility bound for EBGM; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; CI, confidence interval. Signal-positive terms met all prespecified thresholds: n >= 3, ROR05 > 1, PRR05 > 1, IC025 > 0 and EBGM05 > 1. This table is ranked by EBGM05 to align signal prioritization with lower confidence-bound metrics

Table V

PT-level signal summary of selected reproductive, menstrual, pregnancy-related, congenital, autonomic and sensory events reported with atogepant in FAERS from Q4-2021 to Q1-2026

PT	n	ROR05	PRR05	IC025	EBGM05	Signal-positive
Raynaud's phenomenon	20	10.484	10.462	2.930	11.418	Yes
Oophorectomy	3	5.911	5.911	0.885	8.745	Yes
Premenstrual syndrome	3	5.118	5.119	0.831	7.589	Yes
Breast operation	3	4.406	4.407	0.769	6.545	Yes
Postural orthostatic tachycardia syndrome	5	3.549	3.549	1.132	4.621	Yes
Menstruation irregular	15	3.663	3.659	1.661	4.111	Yes
Menstruation delayed	8	3.131	3.131	1.284	3.766	Yes
Amenorrhoea	14	3.239	3.236	1.497	3.659	Yes
Hysterectomy	11	3.135	3.134	1.397	3.626	Yes
Menstrual disorder	8	2.733	2.732	1.141	3.289	Yes
Tachyphrenia	3	1.648	1.649	0.175	2.466	Yes
Pregnancy	9	2.012	2.012	0.829	2.387	Yes
Heavy menstrual bleeding	16	1.955	1.953	0.882	2.188	Yes
Intermenstrual bleeding	10	1.643	1.643	0.601	1.925	Yes
Palpitations	50	1.625	1.621	0.680	1.710	Yes
Radical hysterectomy	1	23.583	23.588	-0.741	55.200	No
Ovarian necrosis	1	9.951	9.953	-0.764	25.626	No
Prosthetic cardiac valve regurgitation	1	6.303	6.304	-0.787	16.683	No
Menstruation normal	1	5.909	5.910	-0.791	15.687	No
Autonomic dysreflexia	1	4.297	4.298	-0.815	11.551	No
Salpingo-oophorectomy bilateral	1	3.939	3.940	-0.823	10.618	No
Left-to-right cardiac shunt	1	3.151	3.152	-0.847	8.547	No
Cleft lip	1	1.929	1.929	-0.920	5.283	No
Ovarian cyst ruptured	2	2.265	2.265	0.005	3.969	No
Arnold-Chiari malformation	2	2.156	2.156	-0.017	3.779	No
Uterine cyst	1	1.360	1.360	-0.995	3.741	No
Menstrual clots	1	1.093	1.093	-1.055	3.012	No
Invasive lobular breast carcinoma	1	0.959	0.960	-1.095	2.648	No
Cardiac septal defect	1	0.945	0.945	-1.100	2.609	No
Uterine enlargement	1	0.892	0.892	-1.120	2.462	No
Breast conserving surgery	1	0.771	0.772	-1.173	2.133	No
Uterine prolapse	1	0.765	0.765	-1.176	2.115	No
Breast neoplasm	1	0.705	0.705	-1.208	1.951	No
Cardiac ablation	2	1.066	1.067	-0.421	1.877	No
Cardiac fibrillation	1	0.606	0.606	-1.274	1.677	No

PT, Preferred Term; FAERS, FDA Adverse Event Reporting System; EBGM05, lower 95% confidence bound of the Empirical Bayes Geometric Mean; ROR05, lower 95% confidence bound of the Reporting Odds Ratio; PRR05, lower 95% confidence bound of the Proportional Reporting Ratio; IC025, lower 95% confidence bound of the Information Component. Signal positivity was defined using conservative lower confidence-bound criteria. Selected PTs were included because they were clinically relevant to reproductive menstrual pregnancy-related congenital-keyword autonomic or sensory reporting patterns. Low report counts should be interpreted cautiously. FAERS disproportionality signals do not establish incidence or causality

Reproductive and autonomic PTs were generally low-frequency signals. Raynaud's phenomenon showed the highest signal in this group (n = 20, EBGM05 = 11.418), followed by postural orthostatic tachycardia syndrome (n = 5, EBGM05 = 4.621), menstruation irregular (n = 15, EBGM05 = 4.111), amenorrhoea

(n = 14, EBGM05 = 3.659) and heavy menstrual bleeding (n = 16, EBGM05 = 2.188). These PTs are summarized in Table V. Congenital-keyword PTs were rare and did not support a specific congenital risk signal at the PT level.

Frequency-signal relationship

The frequency-signal analysis showed that common PTs and high-strength low-frequency PTs had different reporting patterns. Migraine was both frequent and strongly disproportionate (n = 931, EBGM05 = 37.549), while drug ineffective was frequent with lower signal strength (n = 553, EBGM05 = 1.731). Constipation showed moderate frequency with stronger disproportionality (n = 381, EBGM05 = 6.531). By contrast, hemiplegic migraine (n = 6, EBGM05 = 31.018), vestibular migraine (n = 5, EBGM05 = 24.672), post-concussion syndrome (n = 3, EBGM05 = 20.743) and brain operation (n = 19, EBGM05 = 20.289) showed high signal strength despite low report counts. The relationship between reporting frequency and EBGM05 is shown in Figure 2. The complete PT-level signal list was retained as an appendix to provide transparent access to all signal-positive terms and their corresponding disproportionality metrics, as shown in Table I.

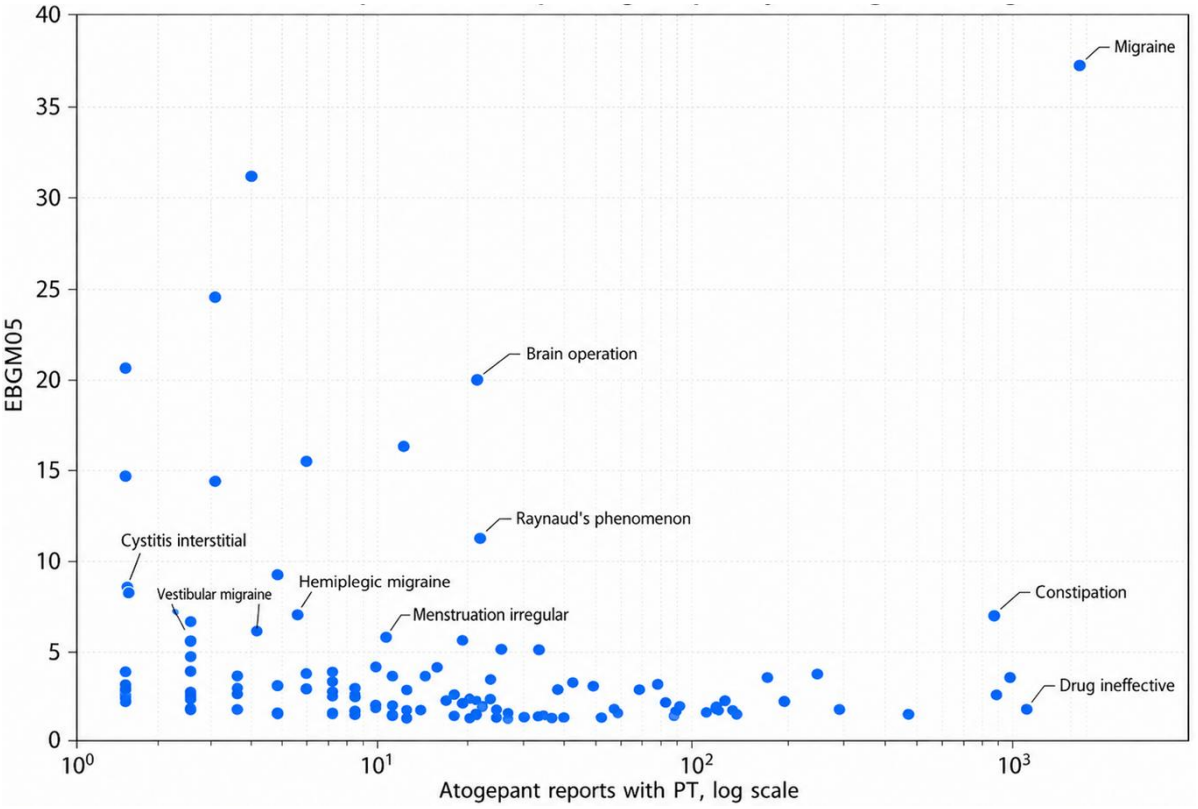

Figure 2.

Frequency *versus* EBGM05 among signal-positive preferred terms

The scatter plot separates high-frequency effectiveness/symptom reports from rare but higher-strength disproportionality signals

Time to onset patterns

Time to onset patterns were evaluated for selected clinically important PTs with valid complete-date onset records. Nausea showed the clearest early onset pattern with 68% of valid records occurring within 0 - 7 days. Fatigue and drug ineffective also clustered early with 69% and 59% of valid records in the 0 - 7-day interval. Headache and constipation showed mixed distributions although early onset remained common. Migraine had a broader temporal pattern with 35% of valid records occurring within 0 - 7 days and 39% after more than 90 days. These times to onset patterns are illustrated in Figure 3.

The present FAERS analysis evaluated atogepant primary-suspect reports from 2021 Q4 to 2026 Q1 using the most recent FAERS data available at the time of analysis. A total of 4,819 deduplicated atogepant primary-suspect reports were included and reaction/PT rows were clearly separated from individual case-level reports. The findings should be read alongside recent class-level gepant pharmacovigilance analyses such as Chen and Li (20). The most frequent reported terms were migraine drug ineffective headache nausea and constipation. Drug ineffective was reported in 553 cases and represented an important effectiveness-related reporting pattern in routine practice. Reproductive and menstrual events such as amenorrhoea heavy menstrual bleeding menstruation irregular menstrual disorder and intermenstrual bleeding were also identified as focused signals. Autonomic and sensory

signals including postural orthostatic tachycardia syndrome hyperacusis tinnitus and Raynaud's phenomenon were observed but were based on low report counts and require cautious interpretation. Congenital-keyword findings were also reviewed as low-frequency hypothesis-generating signals rather than confirmed safety risks.

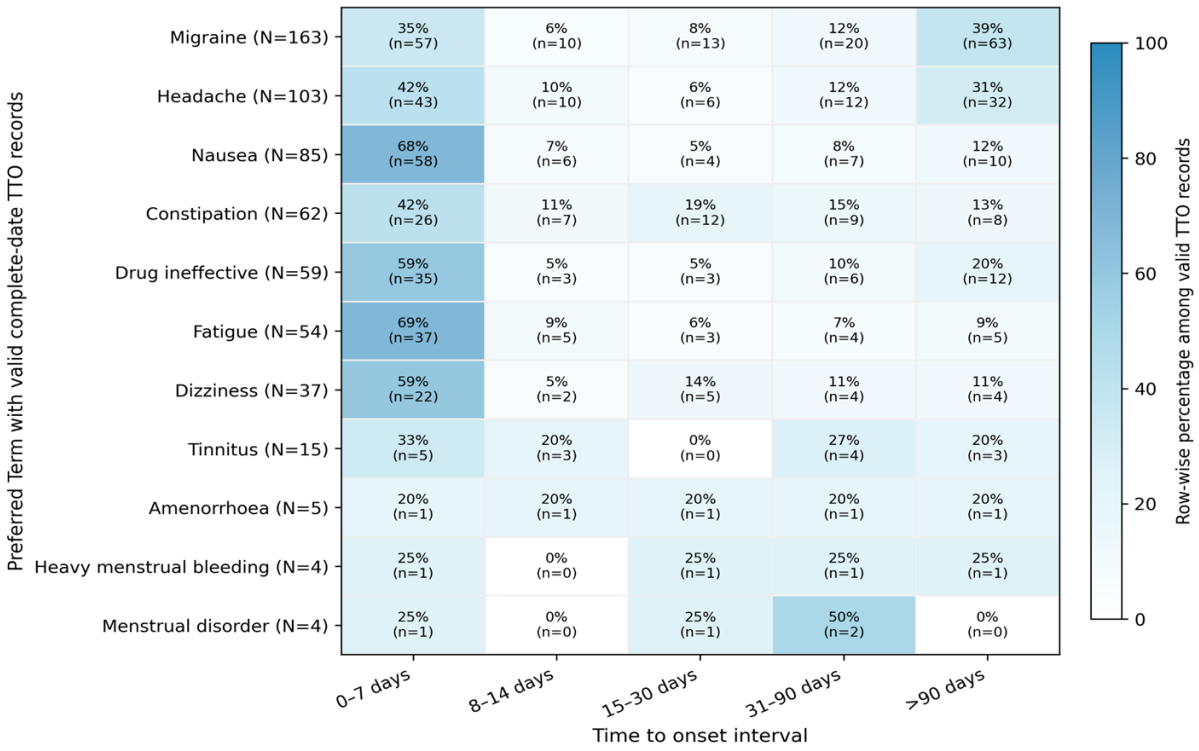

Figure 3.

Time-to-onset heatmap for selected clinically important Preferred Terms reported with atogepant

The heatmap presents row-wise time-to-onset distributions for selected clinically important Preferred Terms among atogepant primary-suspect FAERS reports from Q4 2021 to Q1 2026. TTO was calculated using complete therapy-start and event dates only, and cells show percentages with valid record counts. Reports with missing, incomplete, negative, or invalid onset values were excluded. Abbreviations = FAERS, FDA Adverse Event Reporting System; PT, Preferred Term; TTO, time to onset

Most reports involved females which remains consistent with the higher migraine burden reported among women). Female reports accounted for 76.22% of atogepant primary-suspect cases while sex information was missing in 11.54% of reports. This pattern should therefore be interpreted as a reporting distribution within FAERS rather than a population incidence estimate. Similar caution is required for age and weight because 65.22% of age data and 87.51% of weight data were missing or invalid. The reproductive and congenital-keyword findings also require cautious interpretation because pregnancy exposure information is limited in FAERS and atogepant safety during pregnancy remains insufficiently established in prescribing information and clinical trials). Congenital anomaly was recorded as an outcome in 5 reports or 0.10%. Individual congenital-keyword PTs were rare, and several did not meet conservative PT-level signal criteria. Cleft lip Arnold-Chiari malformation and cardiac septal defect were each reported at very low counts. These findings should therefore be considered hypothesis-generating only and do not establish a causal association between atogepant and congenital abnormalities.

The PT-level analysis provided more clinically interpretable information than sparse SOC-level signals. Migraine remained the most frequent and strongest signal-positive PT with 931 reports and EBGM05 = 37.549. Drug ineffective was also frequent with 553 reports and EBGM05 = 1.731. This finding is important because it may reflect treatment failure patient dissatisfaction adherence problems refractory migraine or a difference between clinical trial efficacy and real-world effectiveness. The high frequency of headache nausea and constipation was consistent with migraine symptom reporting and known tolerability patterns for atogepant). Constipation showed a stronger disproportionality pattern than nausea and headache with EBGM05 = 6.531. These findings suggest that both expected adverse events and effectiveness-related reports contribute substantially to the real-world reporting profile of atogepant.

Several low-frequency but high-strength PT signals were identified. Hemiplegic migraine, vestibular

migraine, post-concussion syndrome and brain operation showed high EBGM05 values despite low report counts. Brain operation was reported in 19 cases with an EBGM05 = 20.289. These findings should not be interpreted as evidence of causality because FAERS reports do not confirm that a drug caused an event and disproportionality analyses may be affected by reporting bias, confounding by indication, comorbid disease and incomplete clinical context). These signals should therefore be considered screening findings that may guide further clinical review.

Autonomic and sensory signals require careful interpretation because migraine itself is associated with autonomic symptoms and related comorbidities). Postural orthostatic tachycardia syndrome was reported in 5 cases with EBGM05 of 4.621 and Raynaud's phenomenon showed a stronger signal with 20 reports and EBGM05 of 11.418. Hyperacusis and tinnitus were also observed among sensory-related PTs. Pooled clinical trial data suggest a low incidence of cardiac disorders with atogepant). Phase 1 data reported mild postural orthostatic tachycardia syndrome and orthostatic hypotension as drug-related adverse events). Because migraine and postural orthostatic tachycardia syndrome may share mechanisms such as sympathetic dysregulation and central sensitization, these signals may reflect comorbidity rather than a direct pharmacological effect).

Psychiatric disorders (n = 546, EBGM 24.685) and Neoplasms (n = 71, EBGM 23.792) also showed strong signals. While migraine itself is associated with psychiatric comorbidities (*e.g.*, depression, anxiety), the high reporting odds suggest a possible drug-related effect that should be explored in longitudinal studies. The signal for neoplasms is particularly intriguing, as CGRP plays a role in tumour biology, though no causal link has been established.

The most frequently reported AEs associated with atogepant include nervous system disorders (*e.g.*, headache/migraine, potentially reflecting treatment-emergent symptoms or paradoxical worsening) and gastrointestinal effects (*e.g.*, nausea, constipation), consistent with its known safety profile). However, the postmarketing data revealed a prominent signal for *drug ineffectiveness* (516 cases) – absent from FDA trial results – raising concerns about real-world efficacy gaps, potential tolerance, or misdiagnosis in refractory cases. This aligns with longitudinal study showing that ineffective acute migraine treatment more than doubles the risk of progression from episodic to chronic migraine (OR 2.55, 6.8% *vs*. 1.9% progression rates), suggesting that suboptimal prophylaxis like atogepant's real-world failure reports could similarly exacerbate disease burden. Several rare but high-strength signals emerged, including brain operation (EBGM = 71.338), cystitis interstitial (EBGM = 48.087) and postural orthostatic tachycardia syndrome (POTS) (EBGM = 27.583). These associations, though based on limited cases, suggest potential off-target effects that require further pharmacovigilance scrutiny.

A principal strength of this study is the atogepant-specific analysis of the most recent FAERS data available through Q1 2026, with clear separation of case-level reports from reaction/PT records and conservative signal prioritization. The analysis further provides clinically relevant context for effectiveness-related reports, reproductive and autonomic signals, congenital-keyword terms and selected time-to-onset patterns. However, the findings should be interpreted in view of the inherent limitations of spontaneous reporting systems, including reporting bias, missing information, incomplete exposure timing, confounding by indication and lack of incidence estimation. Disproportionality signals therefore remain hypothesis-generating and require confirmation through prospective studies, pregnancy registries and real-world database analyses.

Conclusions

This FAERS-based post-marketing analysis suggests that atogepant maintains an acceptable real-world safety profile. Frequent reports mainly reflected migraine symptoms, known tolerability events and effectiveness-related concerns. The analysis included 4,819 deduplicated atogepant primary-suspect reports from Q4 2021 to Q1 2026, with migraine, drug ineffective, headache, nausea and constipation as the most frequent PTs. Signal prioritization based on lower confidence-bound metrics identified selected rare or clinically relevant terms including brain operation, Raynaud's phenomenon, postural orthostatic tachycardia syndrome and reproductive or menstrual PTs. Congenital-keyword findings were sparse and did not indicate a specific congenital risk signal. These findings support continued pharmacovigilance and further hypothesis-driven studies, particularly for effectiveness-related, reproductive, pregnancy-related and autonomic reporting patterns, while clinical use should continue to balance preventive benefit against emerging real-world safety signals.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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