Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Erenumab

Trial Indication(s)
Migraine

Protocol Number
CAMG334AFI03

Protocol Title
Real-world impact of erenumab on sick-leaves, health care resource use and comorbidities based on occupational health care registry in Finland: an observational retrospective mirror-image study (REFI)

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 03/07/2020

Study Completion date: 14/05/2021

Reason for Termination

NA

Study Design/Methodology

This was a retrospective registry-based study utilizing data collected in association with clinical care of patients. All data was stored in electronic health records at Terveystalo data base, and no patients were contacted for the study.

Patients initiating erenumab treatment between 20.9.2018 – 15.10. 2019, and data on sick leave days, diagnoses and health care visits as well as medications based on prescriptions were assessed.

Following time frames for analyses of sick leaves and health care utilization in patients on erenumab treatment and in controls were reported:

Follow-up analyses: For cases (erenumab) with occupational healthcare, a minimum of 12 months on erenumab treatment was required for the analysis of sick leaves and visits

Pre erenumab: Follow-up data before index (defined as the first reimbursement decision/prescription for erenumab, or initiation of erenumab injections (before reimbursement approval)) from the Terveystalo database of those with consent

Post erenumab: Follow-up data after index, from the Terveystalo database of those with consent

Time frames for comparison (sick leaves and visits): One year before index vs. >12 months erenumab after index, One year before index vs. 6-12 months of erenumab after index (patient years), sensitivity analysis

Time frames for comparison (medications): 12 months before index vs. 12 months post follow-up

Controls (triptan treated migraine patients): Corresponding time frames as in cases.

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

- In a pre- and post- erenumab treatment setting, assessing the impact of erenumab treatment initiation on sick leave days, in patients that are on erenumab treatment.

Secondary objective(s)

- In a pre- and post- erenumab treatment setting, assessing the impact on sick leaves and healthcare resource utilisation
- Assessing number and proportion of patients continuing erenumab treatment after assessment of treatment benefit
- Assess medication patterns before and after treatment (switch from botox to erenumab, erenumab add on to botox, and erenumab switch to fremanezumab or another CGRP-inhibitor)
- Assessing difference in ICD-10 codes from visits and sick leaves before and after erenumab treatment initiation

Test Product (s), Dose(s), and Mode(s) of Administration

NA

Statistical Methods

Primary objective 1: In a pre- and post- erenumab treatment setting, assessing the impact of erenumab treatment initiation on sick leave days, in patients that are on erenumab treatment

The annualized number of sick leave days in erenumab treated patients pre- and post-erenumab treatment initiation were estimated. The total, per patient and per patient year sick leave days were reported, as well as total sample size, total follow-up length, and median per patient follow-up length. The difference in sick leave days pre vs. post erenumab treatment initiation with each patient as their own control was tested. To calculate significance, a paired Wilcoxon signed ranks test was used. The median per patient year change in sick leave days was calculated, further, the numbers in all-cause sick leave days as well as in sick leave days only related to migraine or headache based on the diagnosis codes recorded (G43*, G44*, and R51*) as the causes for the sick leaves were calculated, reported and tested.

Secondary objective 1: In a pre- and post- erenumab treatment setting, assessing the impact on sick leaves and healthcare resource utilisation
The health care contacts and sick leaves in erenumab treated migraine patients as described in primary objective 1 were analyzed.

Secondary objective 2: Assessing number and proportion of patients continuing erenumab treatment after assessment of treatment benefit
In order to assess treartment persistence, a Kaplan-Meier from time since the first erenumab prescription until the first prescription of another CGRP-inhibitor other than erenumab (e.g. fremanetsumab) was fitted. All erenumab treated patients regardless of occupational health care customership status, length of follow-up or the timepoint of first prescription were included in the analyses. Censoring events were end of follow-up. End of follow-up was defined to be 15.10.2020. Patient proportions under erenumab treatment, with the corresponding 95% Cis were reported, as well as median time under erenumab treatment and the corresponding 95% CIs.

Secondary objective 3: Assess medication patterns before and after treatment (erenumab switch to fremanezumab or another CGRP-inhibitor)
The number and proportion of patients receiving medications of interest (Table 3) in erenumab treated patients pre- and post-erenumab treatment initiation and in migraine patient controls were reported. Changes in medications, on a group level, pre- and post-index were assessed with McNemar's test and the p-values are reported.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria
- Adult patients on erenumab treatment ATC: N02CX07
- Diagnosis of migraine (ICD G43)
- Consented
- Occupational healthcare

Exclusion criteria
None

Participant Flow
A total of 162 patients with an erenumab prescription were entitled to employer-sponsored occupational health care. Of these patients, half met the responder definition (n=82) of two or more erenumab prescriptions with no evidence of switch to other CGRPi and were thus included in the main analyses. A one-to-one age and sex matched control group of migraine patients not receiving CGRP to control for potential changes in patient behavior and health care practices during the COVID-19 pandemic was included. The patients in the control group were selected based on having received at least one triptan prescription for migraine after 2018.

Baseline Characteristics
Of the 82 patients identified as responders, the majority were females (85.4%) and the mean age of the cohort at initiation was 45 years (±SD 10 years)

Primary and Secondary Outcome Result(s)

Distribution of sick leave days and healthcare visits

						P value 1	P value 2	P value 3	Median ch.	Median ch.
SickDays	Before 12	After 12	After 6-12	C before 12	C after 12	12 vs 12	12 vs 6-12	Controls	12 vs 12	12 vs 6-12
Total	1740	1402	807	1233	1023					
Per pat	21.2	17.1	9.8	15.0	12.5					
Per pat year	21.2	17.1	19.7	15.0	12.5	0.442	0.268	0.128	0	0
PPY st. dev.	43.9	45.0	51.7	43.1	16.2					
SickDaysHA	Before 12	After 12	After 6-12	C before 12	C after 12					
Total	398	104	53	60	54					
Per pat	4.9	1.3	0.6	0.7	0.7					
Per pat year	4.9	1.3	1.3	0.7	0.7	**0.035**	**0.003**	0.520	0	0
PPY st. dev.	13.6	3.8	4.6	7.5	2.4					
SickPeriods	Before 12	After 12	After 6-12	C before 12	C after 12					
Total	283	254	148	215	202					
Per pat	3.5	3.1	1.8	2.6	2.5					
Per pat year	3.5	3.1	3.6	2.6	2.5	0.467	0.440	0.354	0	0
PPY st. dev.	5.7	4.5	5.5	4.1	3.4					
SickPeriodsHA	Before 12	After 12	After 6-12	C before 12	C after 12					
Total	69	22	13	23	8					
Per pat	0.8	0.3	0.2	0.3	0.1					
Per pat year	0.8	0.3	0.3	0.3	0.1	**0.019**	**0.004**	0.061	0	0
PPY st. dev.	2.2	0.9	1.1	0.8	0.4					
Visits	Before 12	After 12	After 6-12	C before 12	C after 12					
Total	812	702	332	544	553					
Per pat	9.9	8.6	4.0	6.6	6.7					
Per pat year	9.9	8.6	8.1	6.6	6.7	0.202	**0.006**	0.875	-1	-2
PPY st. dev.	7.5	6.4	8.3	7.5	7.2					
VisitsHA	Before 12	After 12	After 6-12	C before 12	C after 12					
Total	404	224	86	104	96					
Per pat	4.9	2.7	1.0	1.3	1.2					
Per pat year	4.9	2.7	2.1	1.3	1.2	**<0.001**	**<0.001**	0.395	-1	-2
PPY st. dev.	3.8	1.9	2.7	2.8	2.2					

Medication prescriptions of erenumab responder patients and control at the time of erenumab treatment initiation

Variable		Erenumab responder patients N=82	Migraine controls N=82
Triptans*	Selective serotonin 5HT1 agonists (triptans), N02CC	68 %	39 %
Other pain medication*	Propionic acid derivatives, M01AE	43 %	35 %
	Paracetamol, N02BE	21 %	12 %
	Opioids in combination with non-opioid analgesics, N02AJ	18 %	5 %
	Coxibs, M01AH	16 %	10 %
	Acetic acid derivatives, M01AB	15 %	9 %
	Combined, other pain medication	68 %	33 %
Antiemetics*	Propulsives (metoclopramide), A03FA	13 %	1 %
Prophylactic medication*	Non-selective monoamine reuptake inhibitors, N06AA	30 %	9 %
	Angiotensin II receptor blockers, C09CA	30 %	10 %
	Other antidepressants (incl. venlafaxine, mirtazapine), N06AX	21 %	5 %
	Other antiepileptics (incl. topiramat), N03AX	20 %	7 %
	Selective beta blockers, C07AB	15 %	11 %
	Muscle relaxants (botulinum toxin), M03AX	11 %	0 %
	Combined, prophylactic medication	66 %	23 %
Other medication*	Proton pump inhibitors, A02BC	28 %	21 %
	Corticosteroids, R01AD	17 %	11 %
	Sympatomimetics, R01BA	16 %	13 %
	Other centrally acting agents (incl. tizanidine), M03BX	16 %	11 %
	Selective serotonin reuptake inhibitors, N06AB	13 %	6 %
	Natural and semisynthetic estrogens, G03CA	12 %	0 %
	Benzodiazepine derivates, N05BA	11 %	7 %

*assessed from prescriptions at 12 months pre index

Safety Results
In general no safety related aspects were investigated in this study

Other Relevant Findings
No other analyses were performed

Conclusion
This registry study on electronic health records suggests that the effect of erenumab on monthly migraine days documented in both clinical trials and real world studies translates into reduced number of headache related sick leave days and health care visits in employed patients with migraine managed in routine clinical practice.

Date of Clinical Study Report
27 January, 2022