IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

SAFETY AND EFFICACY OF GALCANEZUMAB IN CHRONIC MIGRAINE

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ABSTRACT

AIM AND OBJECTIVE: To evaluate the safety and efficacy of galcanezumab in chronic migraine.

METHODS: An observational study of galcanezumab (LY2951742) in patients with chronic migraine. Eligible patients 18-65 years of age (n=60) with chronic migraine were given monthly injection of placebo, galcanezumab 120 mg or 240 mg. The mean change in monthly migraine headache days was the primary outcome. As safety outcomes, the percentages of patients who reported at least one adverse event, at least one significant adverse event, or who dropped out of the study where considered.

RESULT: Both galcanezumab dose group demonstrated greater overall mean reduction in the number of monthly MHDs compared to placebo. There was a significant reduction in the proportion of remaining MHDs with nausea and vomiting for episodic and chronic migraine studies and with photophobia and phonophobia for episodic migraine studies.Galcanezumab was also found to be more effective in all important secondary outcomes. In terms of safety, the majority of adverse events were mild to moderate, with low dropout rates and significant adverse events.

CONCLUSION: We conclude that both doses of galcanezumab is an efficacious and well tolerated preventive treatment for migraine and were superior to control group in reducing number of monthly MHDs.

KEYWORDS: Galcanezumab, CGRP, Migraine, Monoclonal Antibodies, Preventive Measures.

INTRODUCTION

According to the Global Burden of Disease Study 2016, migraine is the second greatest cause of years lived with disability worldwide, after low back pain, accounting for 45.1 million years lived with disability [(1)]. The global age standardized prevalence of migraine is 17.8% for women and 8.8 %(9.4-10.2) for men, representing a global prevalence of migraine of 17.8 % for women and 8.8 %(9.4- 10.2) for men [(2, 3).]

Migraine is defined as by its most prominent symptom which is a unilateral,moderate to severe,pulsating headache lasting from 4 to72 hours and aggravated by routine physical activity accompanied by nausea, vomiting ,photophobia or phonophobia.[(4).]

Chronic migraine (CM) is a neurological condition marked by at least 15 headache days per month, at least 8 of which are migraine [5]. 1 CM is associated with significantly greater headache –related impairment, concomitant medical and psychiatric illnesses, health-care resource consumption, and poorer quality of life than episodic migraine. 2 individuals with CM are at a higher risk of developing the disease [6].

Calcitonin gene-related peptide (CGRP) monoclonal antibodies are efficacious in the treatment of migraine [7, 8, 9].Studies have shown that the CGRP monoclonal antibodies galcanezumab [10,11,12] now approved in the United States and other countries, are efficacious in decreasing monthly migraine headache day frequency [13]. A study also showed reductions in migraine-associated symptoms of nausea or vomiting, photophobia, and phonophobia in patients with episodic migraine [14].

The development of monoclonal antibodies ,such as galcanezumab ,that bind to CGRP or its receptor inhibiting its activation ,has been shown in subsequent clinical trials to be safe and well tolerated ,as well as beneficial in reducing the frequency of migraine attacks in people with episodic or chronic migraine[15].

MATERIALS AND METHOD

This investigation is done to examine the effects of galcanezumab on the severity and symptoms of migraine in patients with episodic and chronic migraine.

PATIENT SELECTION

Patients were men and women of 18-65 years of age at screening with a diagnosis of chronic migraine. Exclude patients who had persistent daily headache, cluster headache, head or neck trauma within the past 6 months, possible post traumatic headache or primary headache other than CM.

A novel target for migraine treatment is the calcitonin gene related peptide CGRP receptor on the smooth muscle of blood vessels in the head.CGRP is released from trigeminal ganglion efferents to the blood vessels to cause potent vasodialation as part of the trigeminovascular response. Blocking this may there for block this response. Monoclonal antibodies raised against the receptor, or against CGRP itself, have been explored as migraine treatment.

Here we examine the efficacy of galcanezumab on the severity and symptoms of migraine in patients with episodic and chronic migraine, and assess if galcanezumab leads to reductions in non-pain symptoms such as nausea and vomiting, phonophobia and photophobia.

STUDY DESIGN AND PARTICIPANTS

Eligible patients received monthly subcutaneous injections of placebo, galcanezumab 120 mg (with a 240 mg loading dose), or galcanezumab 240 mg for a 3 month period.

Patients recorded headache characteristics, duration and severity, as well as nausea and vomiting, photophobia and phonophobia in a daily electronic patient-reported outcome-Epro diary .A migraine head ache day (MHDs) was defined as a day in which a migraine occurred during the study treatment period. Rating for migraine severity was 1=mild, 2=moderate, and 3=severe.

STATISTICAL ANALYSIS

All patients who received at least one dose of study medication were analysed. We conduced efficacy analysis on an intent – to – treat basis, with patients grouped into treatment groups and analysed accordingly. Rather than using the given dose, we conducted safety studies using the patient's modal dose.

Number of monthly migraine headache days with nausea and or vomiting, photophobia and phonophobia, number of moderate – to-severe migraine headache days, number of severe migraine headache days, and mean severity of remaining migraine headache days were the outcomes examined.

EFFICACY

Symptoms-migraine headache days with nausea and or vomiting, photophobia and phonophobia.

Migraine headache days with nausea and vomiting:

The monthly mean change in MHDs with nausea and or vomiting is represented Figure 1. In the episodic migraine studies, mean reduction from baseline in the number of monthly MHDs with nausea or vomiting across all 6 month was 2.0 days for galcanezumab 120mg, 1.9 days for galcanezumab 240 mg, and 1.1 days for control drug. The mean differences versus control drug were statistically significant for both treatment group (for 120 mg, MD=-0.95 days, 95%CI,-1.19 to – 0.70, p<0.001). In the chronic migraine study mean reduction from baseline in the number of MHDs with nausea or vomiting across all three months was 3.1 days for 120 mg, 3.2 days for 240 mg, and 1.9 days for placebo. The mean differences versus control drug were statistically significant for both treatment groups (for 120 mg, MD=-1.21days, 95%CI, 1.8 to – 0.59, p<0.001; for 240 mg, MD=-1.28 days, 95%CI,-1.90—0.66, p<0.001).

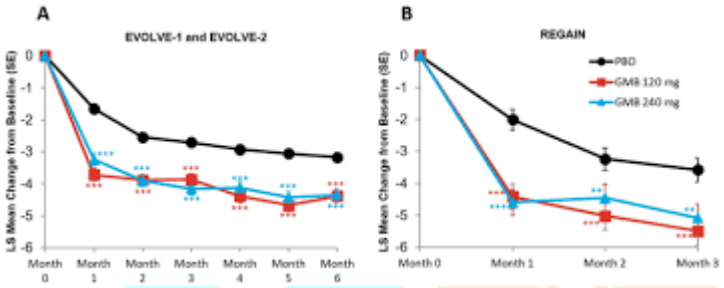


Figure1: Monthly mean change in monthly migraine headache days with nausea and vomiting.

Migraine headache days with photophobia and phonophobia:

Figure 2, shows the monthly mean change in monthly MHDs with photophobia and phonophobia. The average reduction from baseline in the number of monthly MHDs with photophobia and phonophobia was 2.4 days for galcanezumab 120mg , 3.3 days for galcanezumab 240 mg, and 1.8 days for control drug in the episodic migraine investigation. For both treatment groups , the mean differences versus control drug were statistically significant (MD=-1.58 days, CI = 95%, -1.93- -1.23, P 0.001; MD=-1.48 days, 95 % CI, -1.83 to – 1.13, p 0.001) .The number of monthly migraine headache days with photophobia and phonophobia decreased from baseline in chronic migraine trial. The mean differences versus placebo were statistically significant for both treatment groups (for 120 mg, MD=-1.56 days, 95% CI, -2.37 to -0.75, p < 0.001; for 240 mg, MD =- 1.33 days, 95% CI, -2.14 to – 0.52, p= 0.001).

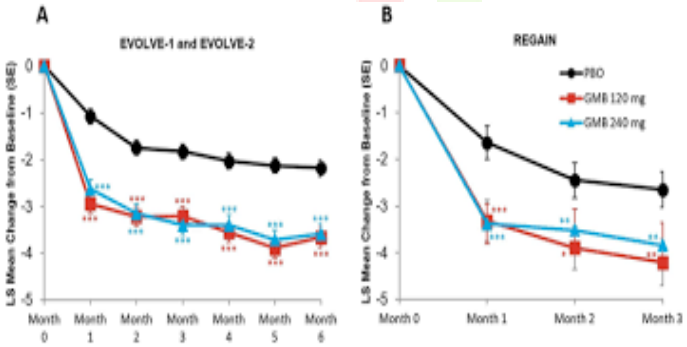
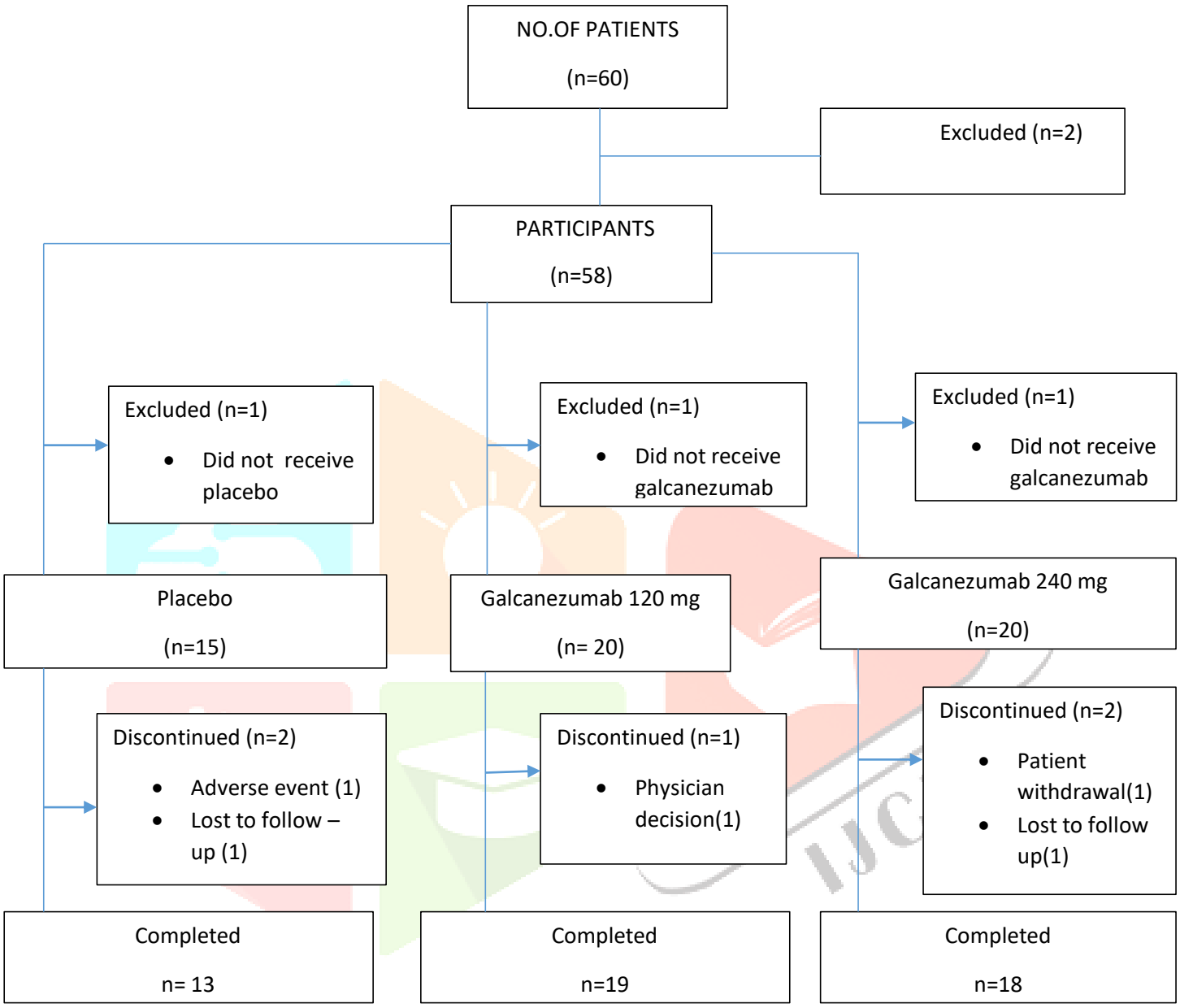


Figure2: Monthly mean change in monthly migraine headache days with photophobia and phonophobia.

RESULTS

PATIENT DISPOSITION

We observed 58 of the 60 patients that were screened. The research medicine was not given to 3 people in the intent –to-treat group. The treatment period was completed by more than 90% of patients in each therapy group.

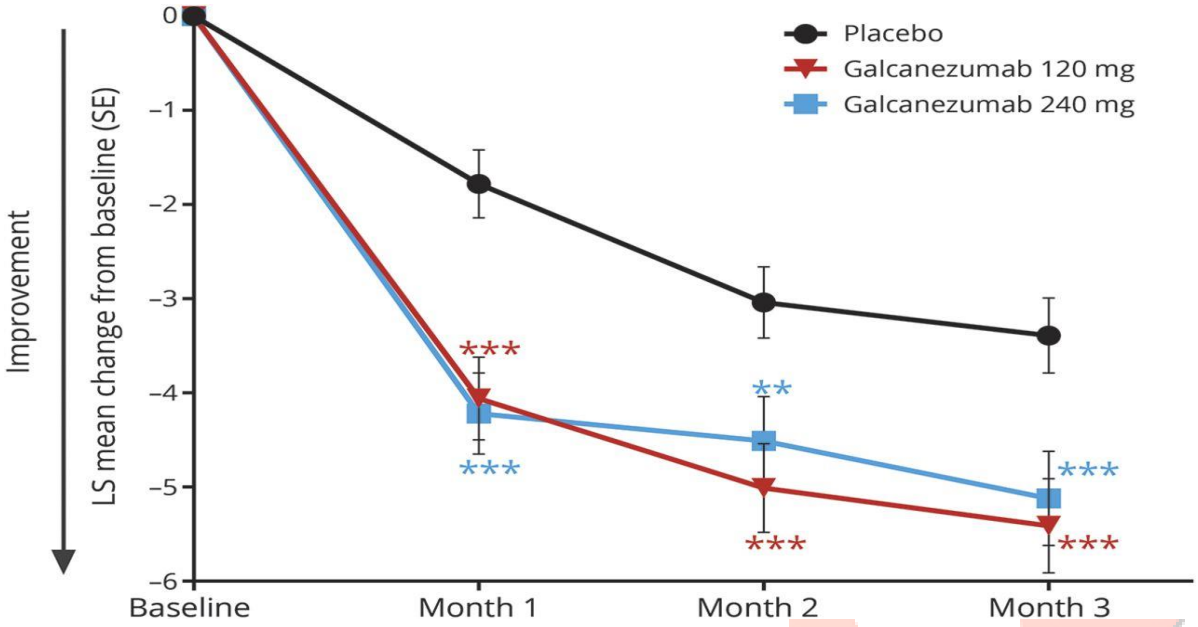


PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographic and baseline features of the therapy group were generally similar. When compared to the galcanezumab 120 mg group, the galcanezumab 240 mg group had a greater percentage of patients who had previously failed two migraine preventives in the previous 5 years. In the galcanezumab 240 mg group, there were a few statistical changes from placebo but were minor.

EFFICACY OUTCOME

On the primary outcome, both dosages of galcanezumab outperformed placebo in terms of overall mean monthly MHDs decrease from baseline. Beginning with month 1, monthly reductions in MHDs significantly different from placebo for both galcanezumab dosages. The mean percentages of patients with a 50% and 75% reduction from baseline throughout the course of three month of therapy. After adjusting for multiplicity, galcanezumab 240 mg showed statistically significant improvement over placebo on the primary and all key secondary end points except the 100 % response rate, whereas galcanezumab 120 mg showed statistically significant improvement over placebo on the primary end point and 50% response rate.



SAFETY

In the study, there were no deaths. In the placebo, galcanezumab 120mg, and galcanezumab 240 mg groups, 50%, 58% and 57% of patient respectively, had treatment – emergent adverse effects .The majority of treatment-related AEs were mild to moderate in severity. Injection – site pain was the most prevalent treatment – emergent AE, but it did not differ substantially between groups. Injection –site reaction, injection-site erythema, injection-site pruritus , and sinusitis were all more common in galcanezumab 240 mg group than in control group , the injection- site pruritus and injection- site erythema also being more common with 240 mg galcanezumab dose than with the 120 mg galcanezumab dose .

DISCUSSION

The primary goal of this 3- month research was achieved when both doses of galcanezumab were found to be superior to placebo in terms of overall mean monthly MHDs reduction in chronic migraine [16].

Efficacy results appeared generally consistent with those from other preventive treatment in a chronic migraine population such as those for CGRP pathway blockers [17].

The high rates of study completion and low rates of discontinuation due to AEs suggest that galcanezumab was well tolerated [18]. Both dosages of galcanezumab were found to be superior to placebo in reducing the number of monthly moderate – to – severe migraine headache days with associated symptoms such as nausea and or vomiting, photophobia and phonophobia in this trial.

In addition to the absolute reduction in number of MHDs with symptoms patients would also benefit from fewer symptoms on days with headache [19]. Both dosages of galcanezumab were superior to placebo in reducing the overall and number of monthly severe MHDs in episodic and chronic migraine studies.

CONCLUSION

Overall, this research shows that, while galcanezumab treatment reduces the number of migraine days compared to placebo, it significantly reduces the number of potentially disabling non –pain symptoms, even on days when migraine is present.

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