Treatment Of Migraine And Cluster Headache: Which Options?

‘MONOCLONAL ANTIBODIES TARGETING CGRP: FOR WHOM AND FOR HOW LONG’

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<table>
<thead>
<tr>
<th></th>
<th>Clinical trials</th>
<th>Speaker panels</th>
<th>Advisory board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergan</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Eli-Lilly &amp; Company</td>
<td>X</td>
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<td>IBSA</td>
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<td>Lundbeck</td>
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<td>Novartis</td>
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<td>TEVA</td>
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</table>
Peripheral actions of CGRP:
- Vasodilation
- Neurogenic inflammation
- Peripheral sensitization

Central actions of CGRP:
- Neuromodulator
  a. Modulate glutamatergic activation of second order neurons
  b. Enhance nociceptive-induced activation of second order neurons

**WHY CGRP?**

CGRP is one of the key neuropeptides involved in migraine pathophysiology

TGN activation stimulates release of CGRP from pre-synaptic terminals

CGRP then binds to its post-synaptic receptor to feed-forward CNS sensitisation and pain hypersensitivity

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Systemic Administration of CGRP can Induce Migraine Attacks

WHY CGRP?

Adherence to standard migraine prophylaxis treatment is often low

Low persistence as shown by the “time to discontinuation up to 12 months’ follow-up from the initial prophylactic”

Kaplan-Meier curve – discontinuation up to 12 months

- Persistence of 25% at 6 months
- Persistence of 14% at 12 months

A sizeable decrease in persistence was observed after 1 month

Percentage of persistent patients

Analysis time (days)

Antidepressants
Anticonvulsants
Beta blockers

More than 80% of patients with chronic migraine discontinued prophylaxis treatment within 1 year

Lack of efficacy
Adverse events

MIGRAINE PROPHYLAXYS: A LONG WAY

- Erenumab
- Galcanezumab
- Fremanezumab
- (Eptinezumab)

New treatment in migraine prophylaxis: CGRP Monoclonal Antibodies

Properties of CGRP mAbs

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab humanised</th>
<th>Erenumab human</th>
<th>Fremanezumab humanised</th>
<th>Galcanezumab humanised</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>CGRP peptide or ligand</td>
<td>CGRP receptor (CLR/RAMP1)</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>100%</td>
<td>40-70%</td>
<td>50-66%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>T ½ (days)</strong></td>
<td>28</td>
<td>21-28</td>
<td>45</td>
<td>25-30</td>
</tr>
</tbody>
</table>
FOR WHOM

**Temporal pattern of migraine**

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab humanised</th>
<th>Erenumab human</th>
<th>Fremanezumab humanised</th>
<th>Galcanezumab humanised</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doses and administration</strong></td>
<td>300 mg I.V / 3 monthly</td>
<td>70 or 140 mg S.C / 28 days</td>
<td>225 mg S.C/monthly or 675 mg S.C / quarterly</td>
<td>240 mg S.C loading dose Followed by 120 mg S.C monthly</td>
</tr>
<tr>
<td><strong>Studies</strong></td>
<td>Episodic and chronic migraine</td>
<td>Episodic and chronic migraine</td>
<td>Episodic and chronic migraine</td>
<td>Episodic and chronic migraine Cluster headache</td>
</tr>
</tbody>
</table>

- Efficacy evaluated and confirmed across the entire spectrum of migraine
- Adoption of consistent and validated primary and secondary endpoints
- Evaluation of other aspects that are relevant for the everyday practice
- Evaluation of safety and tolerability profile
Erenumab: early onset of action

Erenumab had an early onset of action, reducing migraine frequency after 1 week of treatment (episodic migraine).

Erenumab had an early onset of efficacy, reducing migraine frequency after 1 week of treatment (chronic migraine).

Rate of ≥50% reduction in weekly migraine days from baseline to Weeks 1–4

- Placebo (N=218)
- Erenumab 70 mg (N=217)
- Erenumab 140 mg (N=218)

* p<0.001 vs. placebo

At Week 1, the odds of achieving a ≥50% reduction in weekly migraine days were greater for both doses of erenumab compared with placebo.

Rate of ≥60% reduction in weekly migraine days from baseline to Weeks 1–4

- Placebo (N=218)
- Erenumab 70 mg (N=217)
- Erenumab 140 mg (N=218)

From Weeks 1–4 after erenumab treatment, the odds of achieving a ≥60% reduction in weekly migraine days were significantly increased compared with placebo.

* p<0.001 vs. placebo

Erenumab had an early onset of action and efficacy, reducing migraine frequency after 1 week of treatment (episodic and chronic migraine).
Erenumab has similar efficacy in:

- Previous treatment failures
- Menstrual-related migraine
- Medication overuse

Compared with placebo, erenumab treatment resulted in greater reductions in MMD in women with and without a history of MRM.
Erenumab: effectiveness maintained over time
Erenumab: effectiveness maintained over time

Erenumab demonstrated sustained efficacy in the open-label treatment phase of the chronic migraine study

FOR WHOM and HOW LONG?

Change from parent study baseline in MMD

Dashed lines indicate transition from end of parent study to Week 4 of OLTP.

CI, confidence interval; DBTP, double-blind treatment phase; MMD, monthly migraine days; OLTP, open-label treatment phase.

Erenumab: effectiveness maintained over time

Change in monthly migraine days

Change in monthly acute migraine-specific medication days

FOR WHOM and HOW LONG?

Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial

Response at year 5 of open-label treatment phase

Baseline monthly migraine days: 8.7 (0.2) days

Mean change from baseline: −5.3 (0.3) days

71.0% ≥ 50% response

47.1% ≥ 75% response

35.5% 100% response

Baseline monthly AMISM days: 6.2 (0.2) days

Mean change from baseline: −4.4 (0.3) days
Erenumab: from chronic to episodic migraine

Reversion from chronic migraine to episodic migraine following treatment with erenumab: Results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension

Richard B Lipton1, Stewart J Tofler2, Stephen D Silberstein3, David Kadrow3, Moustouk Acharia3, Uwe Rother4, David W Dodick5, Feng Zhang6, Gregory A Rippon7, Suetsi Cheng8 and Daniel D Milsa9,10

Figure 3. Classification of attaining reversion from chronic migraine to episodic migraine (i.e. < 45 headache days per 12 weeks) during the OLTP in patients treated with erenumab who had reversion to episodic migraine at week 12 of the DBP and who had complete monthly headache day data for the entire study period.

DBP: double-blind treatment phase; OLTP: open-label treatment phase.

*After 24 weeks of erenumab treatment.

Clinical implications

- Categorical reversion from chronic migraine (CM) to episodic migraine (EM) is an important treatment goal in patients with chronic migraine.
- Treatment with erenumab 70 mg and 140 mg monthly is associated with greater rates of reversion than placebo after 12 weeks; reversion rates up to 64 weeks are higher in those receiving erenumab 140 mg versus those receiving the 70 mg dose.
- Of patients who attained reversion to EM after 12 weeks and who completed the study, 94% remained as EM with ongoing treatment for up to 64 weeks.
- More than 40% of patients who were classified as having CM in the first 12 weeks may attain delayed reversion to EM after a total of 24 weeks ongoing treatment.
- Overall, approximately two-thirds of patients with CM receiving erenumab are likely to attain reversion to EM and persist in this state after 64 weeks of treatment.

Figure 4. Monthly reversion to episodic migraine assessed in the 4-week periods before weeks 40 and 52 of the OLTP by last erenumab dose (overall population).
**FOR WHOM and HOW LONG?**

**Galcanezumab: early efficacy**

**EVOLVE-1 and EVOLVE-2 studies (Episodic Migraine)**

estimated daily percentage of patients with migraine during 1° week of treatment

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### EVOLVE-1

- **PBO (N=433)**
- **Pooled GMB (N=425)**

<table>
<thead>
<tr>
<th>Injection Day</th>
<th>Post-Injection Day</th>
<th>Percentage (%) of Patients with Migraine Headache Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: GMB = galcanezumab; PBO = placebo.

* p<0,05 versus PBO.

Note: poiché tutti i pazienti trattati con GMB hanno ricevuto 240 mg nel primo mese, i gruppi di trattamento di 120 mg e 240 mg di GMB sono stati aggregati per l’analisi post-hoc giornaliera di questi studi.

240 mg dose approved also for laading dose

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### EVOLVE-2

- **PBO (N=461)**
- **Pooled GMB (N=454)**

<table>
<thead>
<tr>
<th>Injection Day</th>
<th>Post-Injection Day</th>
<th>Percentage (%) of Patients with Migraine Headache Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>24</td>
</tr>
</tbody>
</table>

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**FOR WHOM and HOW LONG?**

**Galcanezumab: early efficacy**

**REGAIN Study (CHRONIC MIGRAINE)**
estimated daily percentage of patients with migraine during 1° week of treatment

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**Abbreviations:** GMB = galcanezumab; PBO = placebo.  
* p<0.05 versus PBO.  
Note: poiché tutti i pazienti trattati con GMB hanno ricevuto 240 mg nel primo mese, i gruppi di trattamento di 120 mg e 240 mg di GMB sono stati aggregati per l’analisi post-hoc giornaliera di questi studi.

240 mg dose approved also for loading dose

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Galcanezumab: early onset of efficacy

CONQUER Study (Patients with preventive failures)
estimated daily percentage of patients with migraine during 1° week of treatment


62nd Annual Scientific Meeting American Headache Society. [https://doi.org/10.1111/head.13854](https://doi.org/10.1111/head.13854)
FOR WHOM and HOW LONG?

**Galcanezumab: effectiveness maintained over time**

Episodic Migraine (6 months)

A

**EVOLVE-1**

- ▲ Placebo (N=433)
- ○ GMB 120 mg with 240 mg loading dose (N=213)
- ■ GMB 240 mg (N=212)

B

**EVOLVE-2**

- ▲ Placebo (N=461)
- ○ GMB 120 mg with 240 mg loading dose (N=231)
- ■ GMB 240 mg (N=223)

240 mg dose approved also for loading dose

V. Stauffer et al, JAMA Neurol, 2018
V. Skjarevski et al, Cephalalgia, 2018
**FOR WHOM and HOW LONG?**

**Galcanezumab: effectiveness maintained over time**

Mean Change in Monthly Migraine Headache Days (MHD)

CGAJ Open-Label Extension Study, ITT Population (CM-open label) – 1 year

240 mg dose approved also for loading dose
Galcanezumab: effectiveness maintained over time

One-Year Treatment With Galcanezumab in Patients With Chronic Migraine: Results From the Open-Label Phase of the REGAIN Study

FOR WHOM and HOW LONG?

**Abbreviations:** GMB=galcanezumab; LS=least square; MHD=migraine headache days; SE=standard error.

240 mg dose approved also for loading dose
FOR WHOM and HOW LONG?

Galcanezumab: effectiveness maintained after cessation

240 mg dose approved also for loading dose

Stauffer et al., Headache 2019
**FOR WHOM and HOW LONG?**

**Fremazemub: early effectiveness**

Episodic Migraine

- **Fremazemub quarterly:**
- **Fremazemub monthly:**
- **Placebo:**

**Average reduction in Monthly Migraine Days respect to baseline**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarterly</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
<td>0.0013</td>
</tr>
<tr>
<td>Monthly</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOR WHOM and HOW LONG?

**Fremanezumab: early effectiveness**

**Chronic Migraine**

- **Fremanezumab quarterly:**
- **Fremanezumab monthly:**
- **Placebo:**

**Average reduction in Monthly Headache Days of at least moderate intensity**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarterly</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Monthly</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

FOR WHOM and HOW LONG?

FREMANEZUMAB: effectiveness maintained over time (12 weeks responder):
≥50% reduction in Monthly Migraine Days respect to baseline

* p <0.001 vs placebo

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Responder 50% (%)

Quarterly (N=288) Monthly (N=287) Placebo (N=290)

<table>
<thead>
<tr>
<th></th>
<th>Quarterly</th>
<th>Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder 50% (%)</td>
<td>44.4%</td>
<td>47.7%</td>
<td>27.9%</td>
</tr>
</tbody>
</table>

* p <0.001 vs placebo

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Pazienti rispondente al 50% (%)

Quarterly (N=375) Monthly (N=375) Placebo (N=371)

<table>
<thead>
<tr>
<th></th>
<th>Quarterly</th>
<th>Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder al 50% (%)</td>
<td>38.0%</td>
<td>41.0%</td>
<td>18.0%</td>
</tr>
</tbody>
</table>

* p <0.001 vs placebo
FOR WHOM and HOW LONG?

‘Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study’ - Ashina et al. J Head and Pain, 2021, 22:68

Mean change from baseline (BL) in the monthly average number of migraine days over 6 months, modified intent-to-treat (mITT). DB, double blind; OLE, open-label extension. All patients in the OLE received fremanezumab 225 mg monthly.

Conclusion: Fremanezumab demonstrated sustained efficacy up to 6 months and well tolerated in patients with episodic or chronic migraine and documented inadequate response to multiple migraine preventive medication classes.
‘Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study’ - Ashina et al. J Head and Pain, 2021, 22:68

Proportion of patients achieving **A >50% reduction** and **B >75% reduction** in the monthly average number of migraine days in the DB period and the OLE (open-label extension - mITT). All patients in the OLE received fremanezumab 225 mg monthly.
FOR WHOM and HOW LONG?

Fremenezumab: Efficacy in CM with and without Medication Overuse

A. Headache Days of at Least Moderate Severity

<table>
<thead>
<tr>
<th></th>
<th>With MO at Baseline</th>
<th>Without MO at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fremanezumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Quarterly</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>(n = 201)</td>
<td>(n = 198)</td>
</tr>
<tr>
<td>LSM (SE) Change From Baseline (Days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-4.7</td>
<td>-5.2</td>
</tr>
<tr>
<td></td>
<td>-2.7±0.5</td>
<td>-2.2±0.5</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Migraine days

Silberstein et al., 2020

Moderate-to-severe headache days
FOR WHOM and HOW LONG?

Fremenezumab: No Wearing-off in long term treatment in CM and EM patients

The analysis of migraine days over the course of the 3-month HALO studies and 12-month, long-term study of fremenezumab showed no evidence of a wearing-off effect toward the end of the dosing interval with either monthly or quarterly dosing regimens in patients with CM or EM. These analyses showed no evidence of a wearing-off effect at the end of the monthly or quarterly dosing intervals.

Blumenfeld et al, Headache 2020
FOR WHOM and HOW LONG?

Adverse Events and Safety in clinical studies

<table>
<thead>
<tr>
<th>Erenumab</th>
<th>Frequency* (70 mg / 140 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Common (1.3% / 3.2%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Common (1.0% / 1.8%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>Common (0.7% / 2.0%)</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>Common (5.6% / 4.5%)</td>
</tr>
</tbody>
</table>

The reported adverse drug reactions for erenumab 70 mg and 140 mg were mostly mild or moderate in severity.

Erenumab is expected to have no or negligible influence on the ability to drive or use machinery.

Galcanezumab

Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies

- 3 RCT during 6 months (1435 pts)
- 5 clinical studies during 12 months (2276 pts)

- Adverse Events correlated to treatment:
  - Injection-site pain
  - Injection-site reactions
  - Constipation
  - Vertigo
  - Pruritus

- Discontinuation due to AE: 1.8-3.0% similar to placebo (for 120 mg)

- Serious AE
  - Galcanezumab <2% - PL 1% (not significant)

FREMANEZUMAB

<table>
<thead>
<tr>
<th>AE %</th>
<th>EM 225 mg/mo</th>
<th>CM 225 mg/mo</th>
<th>EM 625 mg/3 mo</th>
<th>CM 625 mg/mo</th>
<th>PI EM / CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site pain</td>
<td>30,0%</td>
<td>26%</td>
<td>29,6%</td>
<td>30%</td>
<td>25,9 / 28%</td>
</tr>
<tr>
<td>Injection-site hardening</td>
<td>24,5%</td>
<td>24%</td>
<td>19,6%</td>
<td>20%</td>
<td>15,4 / 18%</td>
</tr>
<tr>
<td>Injection-site erythema</td>
<td>19,9%</td>
<td>20%</td>
<td>18,9%</td>
<td>21%</td>
<td>14,0 / 16%</td>
</tr>
</tbody>
</table>

Less than 2% of patients discontinued fremanezumab due to AE
FOR WHOM and HOW LONG?

Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial

Table 2: Exposure-adjusted patient incidence rates of adverse events (per 100 patient-years)

<table>
<thead>
<tr>
<th></th>
<th>Placebo, N = 1,043</th>
<th>70 mg, N = 893</th>
<th>140 mg, N = 507</th>
<th>Total, N = 1,400</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>551 [280.2]</td>
<td>460 [261.2]</td>
<td>267 [230.5]</td>
<td>727 [249.0]</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
<td>0 [0.0]</td>
</tr>
</tbody>
</table>

Conclusions: Treatment with erenumab was associated with reductions in migraine frequency and improvements in health-related quality of life that were maintained for at least 5 years. No new safety signals were observed.
Erenumab and Galcanezumab – Italian Real Life

FOR WHOM and HOW LONG?

All studies have shown good tolerability
FOR WHOM and HOW LONG?

Conclusions

For Whom
- Episodic migraine
- Chronic Migraine – MOH
- Previous treatments failures

How Long
- 1 year
- Also long term treatment

Why
- Specificity for target
- Early onset of efficacy
- Effectiveness maintained over time in episodic and chronic migraine
- Good tolerability and few side effects
- Good adherence to treatment over time (lack of titration, infrequent administration)
Centro Cefalee Pavia - Gruppo di lavoro

Staff Medico
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Marta Allena
Alfredo Costa
Giuseppe Cosentino
Silvano Cristina
Roberto De Icco
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Elena Guaschino
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Rosaria Greco (biologa)
Valentina Grillo (tecnica di neurofisiologia)

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Veronica Tosca, (Research Nurse)