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ADISINSIGHT REPORT

Erenumab: First Global Approval

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Abstract
Amgen and Novartis are developing erenumab (AIMOVIG™, erenumab-aooe)—a fully human monoclonal antibody calcitonin gene-related peptide (CGRP) receptor antagonist—for the prevention of migraine. CGRP is a vasodilatory neuropeptide implicated in the pathophysiology of migraine and treatment with erenumab was associated with significant reductions in migraine frequency in phase II and III clinical trials. Based on these positive results erenumab was recently approved in the US for the preventive treatment of migraine in adults and has received a positive opinion in the EU for the prophylaxis of migraines in adults who have at least 4 migraine days per month. This article summarizes the milestones in the development of erenumab leading to this first approval.

1 Introduction

Erenumab (AIMOVIG™, erenumab-aooe) is a fully human monoclonal antibody calcitonin gene-related peptide (CGRP) receptor antagonist being developed by Amgen and Novartis for the prevention of migraine. CGRP is a vasodilator involved in the transmission of nociceptive information and appears to play a key role in migraine pathophysiology. A subcutaneous injection (SC) formulation of erenumab was recently approved in the US for the prevention of migraine in adults [1], and has also received a positive opinion in the EU for the prophylaxis of migraines in adults who have at least 4 migraine days per month [2]. The recommended dosage of erenumab is 70 mg SC once monthly. Some patients may benefit from a higher dosage of 140 mg SC once monthly [1].

1.1 Company Agreements

In September 2015 Amgen entered into a neuroscience collaboration with Novartis granting the latter global co-development and commercial rights to erenumab in territories outside of the US, Canada and Japan in exchange for funding disproportional amounts of global R&D expenses for an agreed period and payment of double-digit royalties on sales [3]. This collaboration was expanded in April 2017 giving the two companies co-commercialisation rights to erenumab in the US, and Novartis exclusive commercialisation rights in Canada, with Amgen retaining exclusive commercialisation rights in Japan. Amgen will receive milestone payments from Novartis and will share US commercialisation costs. Amgen will book sales of erenumab in the US, and will pay a royalty to Novartis on net sales in the US. Novartis will book sales in the rest of the world, excluding Japan, and will pay Amgen royalties on the net sales in those countries. Novartis will assume agreed upon remaining global development costs up to a cap and share global development costs thereafter [4].

1.2 Patent Information

Amgen holds patents for erenumab in the US (expires 2031) and EU (expires 2029). These expiry dates do not include any patent term extension or supplemental protection certificates that may be obtained in the future to extend the patent terms.

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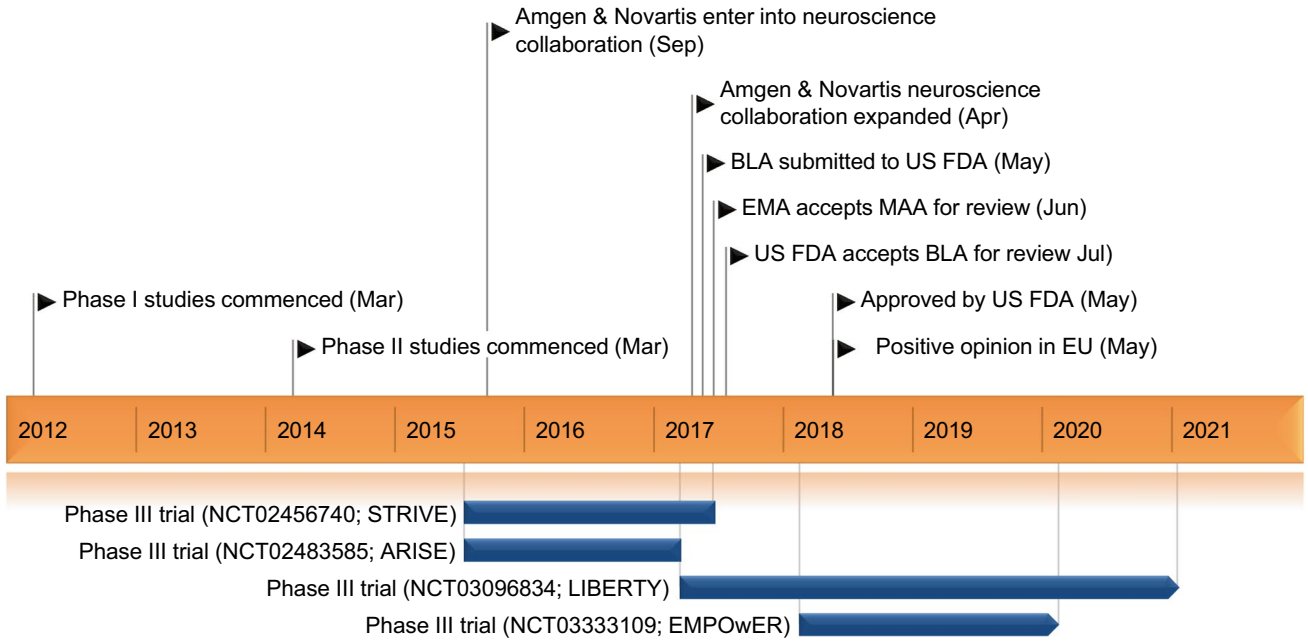

Key milestones in the development of erenumab for the prevention of migraine. *BLA* Biologics License Application, *MAA* Marketing Authorisation Application

2 Scientific Summary

2.1 Pharmacodynamics

In in vitro studies erenumab potently and competitively inhibited [^{125}I]-CGRP binding to the canonical CGRP receptor (*K*i 0.02 nM) and fully antagonised CGRP-stimulated cAMP accumulation (IC_{50} 2.3 nM) in human SK-N-MC neuroblastoma cells. Erenumab was selective for CGRP with no antagonist activity at other human calcitonin family receptors including adrenomedullin, calcitonin, and amylin receptors up to the highest concentration tested (10 µM). In vivo in cynomolgus monkeys erenumab dose-dependently prevented capsaicin-induced increases in dermal blood flow (an indicator of CGRP receptor antagonism) on days 2 and 4 after administration [5].

Erenumab 21–140 mg SC inhibited capsaicin-induced increases in dermal blood flow by 74.6–94.6% compared with placebo measured four days after administration of a single dose to healthy volunteers or patients with migraine. In patients with migraine or healthy volunteers given multiple (three) doses of erenumab, capsaicin-induced increases in dermal blood flow were significantly inhibited at day 8 (the first time point assessed, coinciding approximately with t_{max}) compared with placebo. No apparent erenumab dose-dependency was observed in this pharmacodynamic assay [6].

2.2 Pharmacokinetics

Erenumab exposure increased more than dose proportionally after SC administration of single 1 to 70 mg doses and approximately dose proportionally at higher doses (70 to 210 mg) in a phase I study in healthy volunteers (n = 49) and patients with migraine (n = 12). In healthy volunteers (n = 4 to 6) a single 70 mg dose produced a peak serum concentration (C_{max}) of 6.25 µg/ml after 6 days (t_{max}) and an area under the concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of 171 day · µg/ml. In patients with migraine (n = 6) a single 140 mg dose produced a C_{max} of 9.93 µg/ml after 11 days (t_{max}) and AUC_{last} of 367 day · µg/ml. Erenumab was detectable in serum levels 30 to 160 days post-dose, with doses of ≥ 70 mg resulting in detectable levels at ≥ 100 days post-dose [6]. Erenumab has an effective half-life of 28 days [1].

In a multiple (three)-dose study, mean accumulation ratios of 1.42 to 1.69 were observed after administration of erenumab 21 to 280/210 mg to healthy volunteers. Accumulation ratios were 1.50 and 1.78 after administration of multiple doses of erenumab 21 and 140 mg, respectively in patients with migraine. Mean C_{max} ranged between 2.15 and 24.9 µg/ml and t_{max} ranged from 4 to 11 days following the first dose, and ≈ 7 days following the third dose, across all dosage and subject cohorts [6].

Features and properties of erenumab	
Alternative names	AIMOVIG™, AMG-334, erenumab-aooe
Class	Antimigraine, monoclonal antibodies
Mechanism of Action	Calcitonin gene-related peptide receptor antagonists
Route of Administration	Subcutaneously
Pharmacodynamics	*Ki* 0.02 nM for [^{125}I]-CGRP binding to human CGRP receptors
Pharmacokinetics	C_{max} 0.008 μg/ml, t_{max} 6 hours, AUC_{last} 171 day · μg/ml
Adverse events	
Most frequent	Injection site reactions
Occasional	Constipation, cramps/muscle spasms
ATC codes	
WHO ATC code	C (Cardiovascular System), C01E-B (Other cardiac preparations), N02C (Antimigraine Preparations)
EphMRA ATC code	C1X (All Other Cardiac Preparations), C6 (Other Cardiovascular Products) N2C (Anti-Migraine Preparations)
Chemical Name	Immunoglobulin G2-lambda, anti-[Homo sapiens CALCRL (calcitonin receptor like receptor, calcitonin gene-related peptide receptor, CGRPR, CGRP-R, CRLR)], Homo sapiens monoclonal antibody; gamma2 heavy chain (1-456) [Homo sapiens VH (IGHV3- 30*03 (93.90%) -(IGHD) -IGHJ6*01) [8.8.23] (1–130) -IGHG2*01, G2 m.. (CH1 (131–228), hinge (229–240), CH2 (241–349), CH3 (350–454), CHS (455-456)) (131–456)], (144–215)-disulfide with lambda light chain (1'–216′) [Homo sapiens V-LAMBDA (IGLV1-51*01 (98.00%) -IGLJ2*01) [8.3.11] (1′–110′) -IGLC1*01 (111′–216′)]; dimer (232–232″:233–233″:236–236″:239–239″)-tetrakisdisulfide

2.3 Therapeutic Trials

2.3.1 Migraine

2.3.1.1 Phase III Treatment with erenumab was associated with significant reductions in migraine frequency and requirement for acute migraine specific medication use in the double-blind placebo-controlled phase III ARISE (NCT02483585) [7], STRIVE (NCT02456740) [8] and LIBERTY (NCT03096834) [9] clinical trials in patients with episodic migraine.

In ARISE (A Phase 3, RandomIsed, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention), patients treated with erenumab 70 mg SC once monthly (n = 282) experienced a least-squares mean reduction from baseline of 2.9 days in monthly migraine days after 3 months compared with a 1.8 day reduction in the placebo group (n = 288; $p < 0.001$); monthly migraine days at baseline were 8.1 and 8.4 days for erenumab and placebo recipients respectively. 39.7 and 29.5% of erenumab and placebo recipients, respectively, experienced a ≥ 50% reduction in monthly migraine days (odds ratio: 1.59; $p = 0.010$). Migraine-specific medication treatment days were reduced by 1.2 and 0.6 days in erenumab and placebo recipients, respectively ($p = 0.002$). 33.0 and 27.1%, respectively, experienced a ≥ 5-point reduction in Migraine Physical Function Impact Diary (MPFID)—physical impairment score (odds ratio: 1.33; $p = 0.13$) and 40.4 and 35.8%, respectively, had a ≥ 5-point reduction in MPFID—everyday activities score (odds ratio: 1.22; $p = 0.26$) [7].

In STRIVE (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention), erenumab 70 (n = 312) or 140 mg (n = 318) SC monthly reduced the number of migraine days per month by 3.2 and 3.7 days from baseline, respectively, over the final 3 months of double blind treatment (months 4, 5 and 6) compared with a 1.8 day reduction in the placebo group (n = 316; $p < 0.001$ for both erenumab doses). Monthly migraine days at baseline were 8.3, 8.3 and 8.2 days for erenumab 70 and 140 mg and placebo recipients, respectively. 43.3 and 50% of erenumab 70 and 140 mg recipients, respectively, experienced a ≥ 50% reduction in the mean number of migraine days per month compared with 26.6% of placebo recipients (respective odds ratios were 2.13 and 2.81; $p < 0.001$ for both erenumab doses). The number of days of use of acute migraine–specific medication was reduced by 1.1 days in the 70 mg erenumab group and 1.6 days in the 140 mg erenumab group, compared with a 0.2 day reduction in the placebo group ($p < 0.001$ for both erenumab doses). MPFID—physical-impairment scores improved by 4.2 and 4.8 points in the 70 and 140 mg erenumab groups, respectively, compared with a 2.4 point improvement in the placebo group ($p < 0.001$ for both erenumab doses). MPFID—everyday-activities scores improved by 5.5 and 5.9 points in the 70 and 140 mg erenumab groups, respectively, compared with a 3.3 point improvement in the placebo group ($p < 0.001$ for both erenumab doses) [8].

The LIBERTY trial evaluated the efficacy of erenumab in patients who had failed 2–4 other prophylactic migraine treatments; at baseline, 38.6, 37.8, and 22.8% of patients had failed 2, 3, and 4 prior prophylactic migraine treatments, respectively. At week 12, 30.3% of patients treated with erenumab 140 mg SC achieved a ≥ 50% reduction in monthly migraine days (primary endpoint) compared with 13.7% for placebo (odds ratio: 2.73; $p = 0.002$). Significant improvements were also seen with erenumab 140 mg in terms of monthly migraine days (mean improvement of 1.61 days vs. placebo; $p = 0.004$) and migraine-specific medication treatment days (mean improvement of 1.73 days vs. placebo; $p < 0.001$) [9].

2.3.1.2 Phase II Erenumab was associated with significant reductions in the number of monthly migraine days compared with placebo in two double-blind phase II studies [10, 11]. The first of these (NCT01952574) randomised patients with episodic migraine to 12 weeks' treatment with erenumab 7 (n = 107), 21 (n = 102) or 70 mg (n = 104) or placebo (n = 153) once monthly. Monthly migraine days were significantly reduced from baseline in the erenumab 70 mg group, but not the 7 and 21 mg groups, compared with placebo (least squares mean 3.4 day reduction in erenumab 70 mg recipients [baseline 8.6 days] vs. 2.3 days in the placebo group [baseline 8.8 days]; $p = 0.021$) [11]. Erenumab was associated with promising retention rates, efficacy and patient-reported outcomes after 1 year in an interim analysis of a long term open-label extension of this trial (NCT01952574). All patients enrolled in this extension trial received erenumab 70 mg once monthly [12].

A separate study (NCT02066415) randomised patients with chronic migraine to 12 weeks' treatment with placebo (n = 281), or erenumab 70 (n = 188), or 140 mg (n = 187) once every 4 weeks. Erenumab 70 and 140 mg were each associated with a 6.6 day reduction from baseline in monthly migraine days compared with a 4.2 day reduction with placebo ($p < 0.0001$ for both erenumab doses vs. placebo); monthly migraine days at baseline were 8.3, 8.3 and 8.2 days for erenumab 70 and 140 mg and placebo recipients, respectively. 40 and 41% of erenumab 70 and 140 mg recipients, respectively, achieved a ≥ 50% reduction in the mean number of migraine days per month compared with 23% of placebo recipients (respective odds ratios were 2.2 and 2.3 vs. placebo; $p \leq 0.0001$ for both erenumab doses) [10].

Key clinical trials of erenumab (Amgen, Novartis)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Erenumab	Pharmacokinetics and safety	I	Completed	Belgium	NCT01688739
Erenumab	Pharmacokinetics and safety	I	Completed	Belgium	NCT01723514
Erenumab, oestrogen/progestin	Drug interaction study	I	Completed	US	NCT02792517
Erenumab, placebo	PACAP-38 Induced migraine-like attacks	I	Completed	US, Belgium, Netherlands	NCT02542605
Erenumab, placebo	Menopausal hot flashes	I	Completed	US	NCT01890109
Erenumab, placebo	Pharmacokinetics and safety in paediatric migraine	I	Recruiting	US	NCT03499119
Erenumab, placebo, sumatriptan	Effect on blood pressure in volunteers	I	Completed	Belgium	NCT02741310
Erenumab, placebo	Migraine prevention	II	Ongoing	Multinational	NCT01952574
Erenumab, placebo	Cardiovascular safety in patients with stable angina	II	Completed	Multinational	NCT02575833
Erenumab, placebo	Migraine prevention	II	Completed	Multinational	NCT02066415
Erenumab	Migraine prevention (long-term extension)	II	Completed	Multinational	NCT02174861
Erenumab, placebo	Migraine prevention	II	Ongoing	Japan	NCT02630459
Erenumab, placebo	Migraine prevention	III	Completed	Multinational	NCT02456740 (STRIVE)
Erenumab, placebo	Migraine prevention	III	Completed	Multinational	NCT02483585 (ARISE)
Erenumab, placebo	Migraine prevention in patients who have failed other prophylactic migraine treatments	III	Ongoing	Multinational	NCT03096834 (LIBERTY)
Erenumab, placebo	Migraine prevention	III	Recruiting	Multinational	NCT03333109 (EMPOwER)

2.4 Adverse Events

Adverse reactions occurring with an incidence of ≥ 2%, and at least a 2% greater incidence than with placebo, in patients treated with erenumab during the first 3 months of the phase III STRIVE and ARISE trials and one phase II trial (NCT02066415) included injection site reactions (6 and 5% of erenumab 70 [n = 787] and 140 mg [n = 507] once monthly recipients, respectively, compared with 3% of placebo recipients [n = 890]), constipation (1 and 3%, respectively, vs. 1%) and cramps/muscle spasms (< 1 and 2%, respectively, vs. < 1%). Few (1.3%) patients treated with erenumab in these three studies discontinued double-blind treatment because of adverse events [1].

Anti-erenumab-aooe binding antibodies developed in 6.2% (48 of 778) and 2.6% (13 of 504) of patients receiving erenumab 70 and 140 mg once monthly, respectively, in controlled studies. Two patients receiving erenumab 70 mg and none receiving 140 mg developed anti-erenumab antibodies with *in vitro* neutralising activity [1].

2.5 Ongoing Clinical Trials

A phase I study to evaluate the pharmacokinetic properties and safety of erenumab in paediatric patients with migraine is currently recruiting participants in the US (NCT03499119). Other studies in patients with episodic migraine currently underway include the phase II extension trial described above (NCT01952574) [12], a phase II study in Japanese patients (NCT02630459), the phase III LIBERTY (NCT03096834) study in patients who have failed other prophylactic migraine treatments and the phase III EMPOwER (NCT03333109) trial which is recruiting patients in territories outside the US and Europe.

3 Current Status

Erenumab received its first global approval on 17th May 2018 in the US for the preventive treatment of migraine in adults and a positive opinion on 31 May 2018 in the EU for the prophylaxis of migraines in adults who have at least 4 migraine days per month.

Compliance with Ethical Standards

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