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PATENT WATCH

Migraine therapies targeting the CGRP pathway: intellectual property landscape

Migraine affects an estimated 850 million people worldwide (*Lancet* 386, 743–800; 2015). There are a wide range of treatment options that benefit many patients, including acute treatments to relieve symptoms during a migraine attack and prophylactic therapies to reduce the severity or frequency of migraines. However, each drug has limitations owing to toxicity, side effects, or refractory or contraindicated populations. New drugs with greater efficacy and improved side-effect profiles are needed.

Among the various potential targets for new migraine therapies, calcitonin gene-related peptide (CGRP) is one of the best validated and most actively studied. Clinical trials of pioneering small-molecule drugs targeting the CGRP receptor showed both efficacy and tolerability, but concerns were raised about liver toxicity. In the past decade, an alternative approach using monoclonal antibodies (mAbs) to target the CGRP pathway has been pursued, and four antibodies are in clinical trials for the

treatment of migraine: three mAbs (developed by Teva, Lilly and Alder Biopharmaceuticals, respectively) target the free CGRP peptide, whereas the fourth mAb (developed by Amgen) targets the CGRP receptor. Although clinical trials have so far reported positive results, it is unknown whether one mAb will be the clear leader with greatest efficacy.

To better understand the intellectual property (IP) surrounding the use of CGRP inhibitors in migraine therapy, we generated a detailed IP landscape by reviewing and indexing English-language US and Patent Cooperation Treaty (PCT) patents and applications published by the end of the first quarter of 2015, and analysing them using GlobalMap, a proprietary visualization tool (see [Supplementary information S1 \(box\)](#) for details). A simplified version is shown in FIG. 1.

It is evident that the majority of the CGRP antagonist space is focused on small molecules, reflecting the focus of earlier work

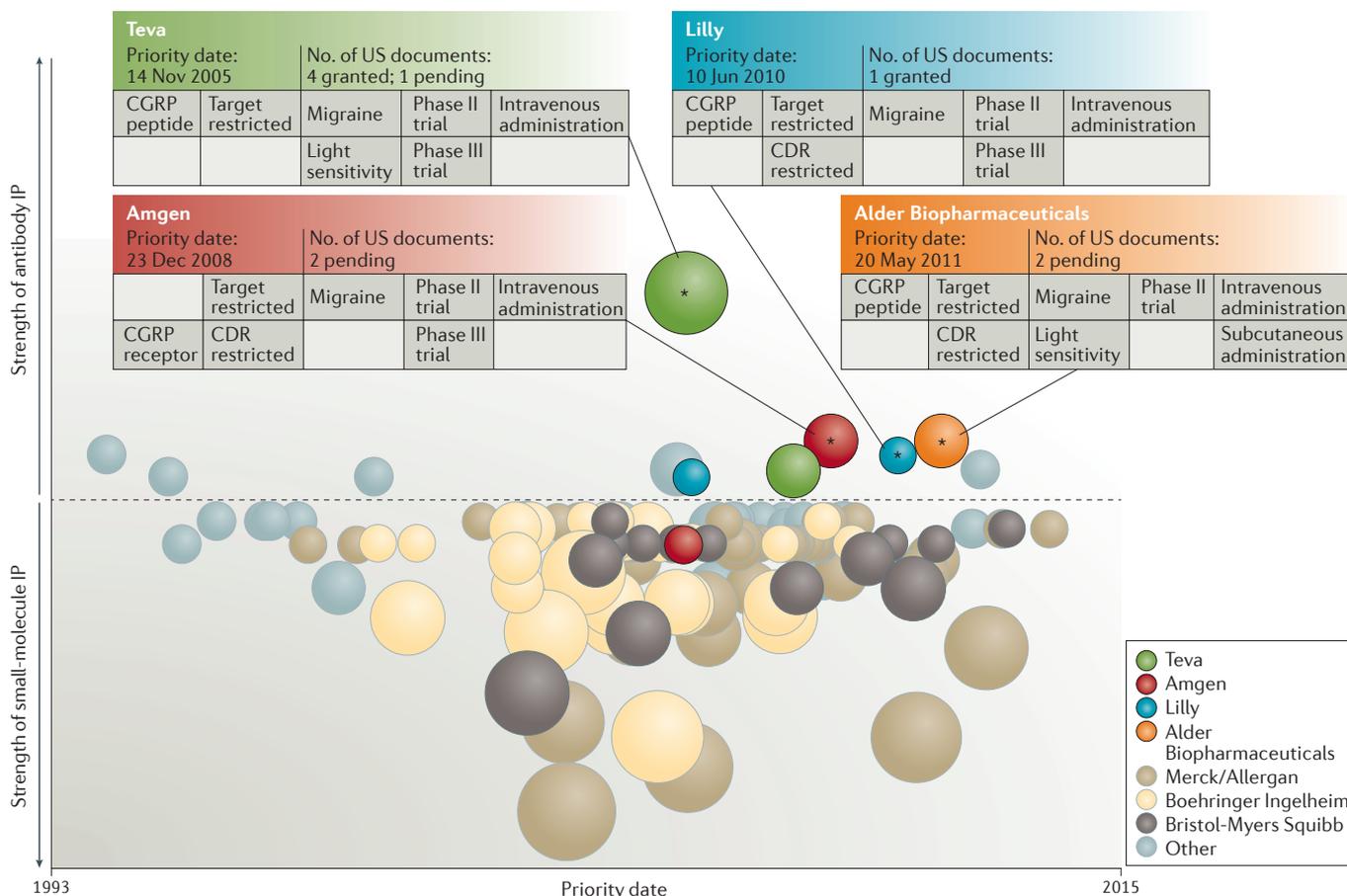


Figure 1 | **Intellectual property landscape for CGRP pathway antagonists.** Patent documents are grouped by assignee and priority date, and then plotted by priority date and technology focus (monoclonal antibody (mAb) or small-molecule antagonist). The number of granted patents, number of pending applications and number of abandoned applications were used to calculate a strength of portfolio score for each technology focus. Bubbles are coloured according to assignee and the size of the bubble represents the number of patent documents held by

a given assignee with that priority date. The patent family bubbles marked with an asterisk protect the four mAbs targeting the calcitonin gene-related peptide (CGRP) pathway that are in clinical trials. The inset boxes summarize each of these four patent families. Each box gives the family priority date, number of US documents and 'attribute flags' detailing the patent claim limitations and technical features of the product. See [Supplementary information S1 \(box\)](#) for details. CDR, complementarity-determining region; IP, intellectual property.

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in the field and also the nature of differences in IP strategy protecting small molecules and biologics. FIG. 1 indicates that Merck & Co. is the leader in the small-molecule space, followed by Boehringer Ingelheim and Bristol-Myers Squibb. Merck has sold its CGRP portfolio to Allergan; Boehringer Ingelheim has cancelled development of its CGRP-targeted small molecules; and it has been reported that Bristol-Myers Squibb is looking to sell its CGRP inhibitor portfolio. FIG. 1 also reveals that 80% of the small-molecule documents were filed 5 or more years ago, whereas >85% of the mAb documents were filed in the past 7 years. So, although the small molecules make up most of the IP space, the filing trends are a reflection of where the technology is headed.

A deeper analysis of the technical features, such as the dosing schedule, of the CGRP mAbs in clinical trials was performed, and selected features are summarized in FIG. 1. Each assignee has documents with claims to protect its specific mAbs (sequence and target disclosures). Teva's documents have the earliest priority dates and include granted claims disclosing the use of a mAb that reduces CGRP receptor activity, which may be broad enough to cover different CGRP pathway targets. Teva also has pending claims on the use of CGRP-targeted mAbs for indications

broader than migraine (vasomotor symptoms), as well as migraine-related conditions (light sensitivity). Amgen stands out from the field as its mAb targets the CGRP receptor, which some believe may yield the best clinical results. Lilly has initiated two Phase III trials to study the use of its CGRP-targeted mAb to treat chronic and episodic cluster headaches. This may reflect a regulatory strategy to get its product approved and on the market, despite Teva's dominance in the IP space for migraine indications. Alder Biopharmaceuticals is developing both infusion and self-administration formulations. Additionally, it is evaluating the efficacy of a less frequent dosing regimen of once per quarter.

Of the four main players in the CGRP mAb space, our analysis shows that Teva has the strongest IP position, with the earliest priority dates and claims disclosing the use of a mAb to reduce CGRP receptor activity. The next set of clinical trial results are highly anticipated.

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