BIOBUSINESS BRIEFS

TRIAL WATCH

CGRP receptor antagonist meets Phase III migraine end points

Merck has announced that the antagonist of the calcitonin gene-related peptide (CGRP) receptor telcagepant has met the primary end points in two Phase III trials to treat migraine, which is characterized by attacks of intense throbbing head pain that can last from 4 to 72 hours. One study showed that the compound led to significant pain relief compared with placebo 2 hours after treatment and sustained freedom from pain up to 24 hours after treatment. A second study comparing telcagepant with rizatriptan (Maxalt; Merck) — a drug from the triptan class of serotonin receptor agonists, which are currently the standard of care for migraine — showed that fewer patients reported pre-specified adverse events (5% versus 11.2%) when given telcagepant.

The rationale for targeting CGRP receptors is based on two key clinical observations, explains Professor Andrew Russo, Director of the Biosciences Program, University of Iowa, USA. "It was almost 20 years ago that Lars Edvinsson and Peter Goadsby showed that CGRP was elevated in the jugular outflow during severe migraine attacks and that treatment with sumatriptan restored the levels to normal, co-incident with the alleviation of the symptoms. Further work from Jes Olesen's group then showed that injection of CGRP led to the development of headaches in a small group of migraine patients. These observations point to CGRP being a key neuromodulator that may act by sensitizing glutamatergic synapses in the central nervous system, and that too much sensitization leads to migraine."

Unlike serotonin receptor agonists, CGRP receptor antagonists do not constrict blood vessels and therefore do not seem to have deleterious cardiovascular side effects. These side effects limit the use of triptans in patients who also suffer from cardiovascular disease or uncontrolled hypertension. "In addition, since these drugs act by different mechanisms, it is likely that telcagepant and other CGRP receptor antagonists will help some patients who are not helped by triptans," says Russo.

However, Merck is delaying its submission of a new drug application for telcagepant owing to the increased levels of liver transaminases that were observed in patients receiving the drug twice daily for 3 months in a Phase IIa study to prevent migraine. Whether this potential hepatotoxicity signal is a class effect or is specific to this compound, and its relation to the dose and frequency of administration of telcagepant, still need to be elucidated. However, if telcagepant shows comparable efficacy to triptans, with no vasoconstriction and a more tolerable side-effect profile, analysts have predicted that sales could reach more than US$1 billion per year. Recent evidence has also implicated CGRP in tumour angiogenesis (*Proc. Natl Acad. Sci. USA* **105**, 13550–13555; 2008), therefore CGRP antagonists might also have potential in other indications.

FURTHER READING Goadsby, P. J. Can we develop neurally acting drugs for the treatment of migraine? *Nature Rev. Drug Discov.* **4**, 741–750 (2005)