Moving targets in sodium channel blocker development: the case of raxatrigine: from a central NaV1.3 blocker via a peripheral NaV1.7 blocker to a less selective sodium channel blocker

Jan M. Keppel Hesselink*
Professor of molecular pharmacology, consultant drug development, Institute Neuropathic Pain, the Netherlands

Abstract
Raxatrigine (5R)-5-{4-[(2-fluorobenzyl)oxy]phenyl}-L-prolinamide; chemical formula: C18H19FN2O2) is a sodium channel blocker first synthesized by GlaxoSmithKline, explored and developed under de code name GSK1014802 as a central NaV1.3 blocker up to and including phase I in the period 2005-2009. Related to its central mechanism of action, the target indication selected at that time was bipolar disorder, pain and perhaps epilepsy. Subsequently the Glaxo group revamped its R&D focus and stopped working in the field of pain around 2010. The Glaxo research group working on sodium channels left the company and created a spin-out: Convergence Pharmaceuticals, taking with them the rights on the compound, renamed CNV1014802. The characterization of the compound changed into a sodium channel inhibitor reported to have high selectivity for the peripheral Nav1.7 subtype channel, and phase II development started in neuropathic pain, in lumbosacral radiculopathy and trigeminal neuralgia. In 2015 Convergence was taken over by Biogen and the compound was recoded BIB074. Recent published data do not characterize the compound as a selective Nav1.7 inhibitor, but rather as an unspecific sodium channel blocker. We will analyze scientific and press communications referring to this compound in the period 2005-2016 and discuss the moving target for the compound.

Correspondence to:
Jan M. Keppel Hesselink, professor of molecular pharmacology, consultant drug development, Institute Neuropathic Pain, the Netherlands, E-mail: jan@neuropathie.nu

Key words: GSK1014802, raxatrigine, CNV1014802, sodium channels, NaV1.7, NaV1.3, neuropathic pain

Received: January 03, 2017; Accepted: January 16, 2017; Published: January 19, 2017
I program around 2008, consisting of at least 3 phase I studies and referred to the compound as a use-dependent sodium channel blocker and an effective anticonvulsant in animal models. The focus was the treatment of pain, and the third phase I study was indeed designed to evaluate surrogate parameters related to the analgesic effects of the drug. The phase I program consisted of:

1. A study on the safety, tolerability and pharmacokinetics of repeated doses of the compound administered for up to 28 days in healthy male or female subjects, including a food interaction study.

2. A randomized, double-blind, placebo-controlled, repeat dose study, in approximately 60 subjects to receive GSK1014802 400 mg bid and placebo for 36 days with at least 1 week between treatment sessions, including monitoring ambulatory blood pressure.

3. A double blind, placebo controlled, 4-period cross over study in 20 subjects testing one of two doses of the drug or of lidocaine versus placebo with at least 2 weeks between sessions.

In 2009 Glaxo Group presented its pipeline and presented raxatrigine as compound 1014802, a sodium channel blocker for bipolar disorder in phase 1 [6]. In that year the transition of the indication bipolar disorder to pain must have taken place. In 2010 Glaxo Group refocused her strategic fields and wanted to exit the pain field. In that process, Convergence Pharmaceuticals was created in 2010 by 12 scientists from GlaxoSmithKline and they acquired the rights on the compound GSK1014802, renamed as CNV1014802 and a calcium channel ligand. In a press release of 27-10-2010 CNV1014802 was characterized as ‘a potent, state-dependent sodium channel blocker’ [7].

**Selective NaV1.7 blocker?**

The preclinical profile of raxatrigine is hidden in a clinical paper discussing the design of a clinical trial in trigeminal neuralgia. That is unfortunate, because therefore the profile is not easy to find, and more importantly, there are no primary sources mentioned in the paper, it is just a summary of findings, without context.

Raxatrigine is described by the authors (some authors are from Convergence) as a peripherally and centrally acting agent inhibiting sodium channels in a state-dependent fashion. The authors state the compound shows selectivity for the Nav1.7 subtype over the other subtypes tested (Nav1.1, Nav1.2, Nav1.3, Nav1.5, Nav1.6 and TTX-R), for both the resting and depolarized states. The amount of sodium channel block increases with the frequency of stimulation for Nav1.7 and for Nav1.2 and Nav1.6. The block is said to be more activity-driven at Nav1.2 and Nav1.6 than it is at Nav1.7. CNV1014802 is also said to preferentially target and inhibit higher frequencies of firing (from 10 Hz onwards) induced by noxious stimuli or during seizures. We could not find any other sources for this preclinical profile. That is unfortunate, since now we are unable to understand why a more recent paper came to quite different conclusions. Neither can we understand why in one of the first patent the compound was characterized as a Nav1.3 blocker only.

**Raxatrigine: a non selective NaV channel inhibitor**

In a recent paper published by Deuis et al. CNV1014802 is characterized as a Non-Selective NaV Inhibitor. The authors start pointing out that CNV1014802 is reported to be a state-dependent inhibitor of NaV1.7, but information on the potency and selectivity profile has not been reported in literature. The authors tested the compound in a special assay and found the compound to have the
following profile in humanized NaV channels: in rank order of potency (pIC50 ± SEM): NaV1.8 (5.25 ± 0.1) > NaV1.4 (5.09 ± 0.2) > NaV1.2 (4.99 ± 0.2) > NaV1.6 (4.84 ± 0.1) > NaV1.3 (4.82 ± 0.3) > NaV1.1 (4.70 ± 0.2) > NaV1.7 (4.58 ± 0.2) > NaV1.5 (4.18 ± 0.2).

They also documented a state-dependency with a nine-fold shift in the NaV1.7 IC50 between closed/resting state inhibition (54 μM) and open/inactivated state inhibition (6.3 μM), with a clear preference for the open/inactivated state. They could compare this profile with that from the Pfizer sodium channel blocker PF-04856264, which indeed is a selective NaV1.7 inhibitor, and this novel aryl sulfonamide NaV1.7 inhibitor was 50 times more potent at the NaV1.7 channel. Intraplantar administration of CNV1014802 (1 mM) had no significant effect on spontaneous pain behaviors in mice evoked by the scorpion toxin OD1, but intraperitoneal administration of CNV1014802 (3 and 30 mg/kg) did reduced spontaneous pain behaviors. 30 mg/kg of PF-04856264 and 30 mg/kg CNV1014802 had comparable analgesic effects after i.p. injection.

Conclusion and lessons learned

Drug Research and Development is a highly complex endeavor, and companies should understand that it is important to first publish data in peer reviewed journals, before scientific facts are communicated in the lay press, or in press releases or during company presentations for shareholders. Scientific company representatives should not characterize pipeline drugs based on pharmacological and clinical properties, when the primary data have not been published yet. The raxatrigine case analyzed in this article serves as an example to point out why such recommendations are vital for the success and credibility of pharma and biotech industries.

References

7. Former GSK employees form independent biotechnology company.
11. http://adisinsight.springer.com/drugs/800027679

Copyright: ©2017 Hesselink jmk. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.