



A Novel $\alpha 2\delta 1$ Agonist for Neuropathic Pain: NVA1309 of Novassay

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Abstract

NVA1309 is a New Chemical Entity for neuropathic pain in the preclinical phase, and is synthesized and currently explored in animal models by Novassay SA, a privately owned Swiss-based Biotechnology company. NVA1309 is claimed to have nanomolar affinity for the target, the voltage-dependent calcium channels $\alpha 2\delta$ -1 subunit, and its potency in animal models is said to be 10 times higher compared to pregabalin. It is also claimed by the company to have a set of superior properties compared to pregabalin and other gabapentinoids. It is the lead compound of a family of comparable GABA analogues, all covered in a recent patent, and filed in 2014. The fact that it seems not to penetrate in the brain is positioned as a pro for the drug, but this might also be less desirable, given the anxiolytic efficacy of brain-penetrating gabapentinoids. Currently the company is looking for a development partner, to test the compound in phase 1, starting in the second quarter of 2018.

Keywords: NNT: Numbers Needed to Treat; DPNP: Diabetic Painful Neuropathic Pain; PSP: Post-Surgical Pain; PHN: Post-Herpetic Neuralgia; LR: Lumbar Radiculopathy; POC: Proof of Concept; USP: Unique Selling Point

Introduction

Neuropathic pain is the result of a lesion or disease of the peripheral or central somato sensory system and its prevalence in the general population is estimated to be around 7-8% [1]. The treatment of neuropathic pain is still quite difficult, and most analgesics and co-analgesics have relative high Numbers Needed to Treat (NNT), between 3-8, meaning that only 1 in 3 or 1 in 8 patients treated will respond with a pain reduction at the end of the treatment period of at least 50% [2]. Gabapentin and pregabalin are also not overwhelmingly active in neuropathic pain, as recent NNT's recently calculated for both drugs were 7.2 and 7.7 respectively [3]. New lead compounds following new treatment principles or having superior pharmacological properties compared to existing compounds are therefore urgently needed. NVA 1309 might be such a drug and hopefully it might score better on the NNT's compared to the old gold standard gabapentinoids gabapentin and pregabalin. Representatives of this class of drugs target the voltage-dependent calcium channels $\alpha 2\delta$ -1 subunit, and binding results in the inhibition of calcium currents and the decrease of concentrations of excitatory neurotransmitter release and thus the decrease of spinal sensitization [4].

As there is no literature published in Pub Med on NVA1309, a new lead in the class of gabapentinoids currently in the pre-

clinical stage, we tried to pull together and discuss what is presently known about this new compound, based on press releases, the website from the company, and patent WO 2015091463 A1. NVA1309 is claimed to have a set of unique properties: non-brain penetration (but spinal cord penetration), peripheral nerve localization and $\alpha 2\delta 1$ versus $\alpha 2\delta 2$ specificity. These features together with its 10x higher potency over pregabalin support the company's argumentation that NVA 1309 might be a promising drug candidate for a broad range set of chronic pain conditions such as diabetic painful neuropathic pain (DPNP), post-surgical pain (PSP), post-herpetic neuralgia (PHN), lumbar radiculopathy (sciatica, LR) and fibromyalgia.

NVA 1309

NVA1309 is a novel proprietary GABA-analogue and lead of Novassay SA, a privately owned Swiss-based Biotechnology company established in 2013, specializing in Ion channels and channelopathies [5]. It is the lead compound, currently in the preclinical state and scheduled for start phase I by the second quarter of 2018. Back up compounds, NVA 1501 up to and including NVA 1516 are also small molecules, targeted for the neuropathic pain indications. Novassay also explores seven $\alpha 2\delta 1$ antibodies, NVA 1517 up to and including NVA 1523 for the same indication [6]. NVA 1309 has nanomolar binding activity

for the calcium-gated membrane channel, more specifically to the $\alpha 2\delta 1$ ($\alpha 2\delta 1$) calcium membrane subunit, just as classical gabapentinoids and novel drugs such as atagabalin (PD-0200,390), 4-methylpregabalin and PD-217,014. On 30-4-2015 Novassay announced positive Proof of Concept (PoC) data for NVA1309 in a chronic neuropathic pain model, the Chronic Constriction Injury (CCI) animal pain model.

Patent WO 2015091463 A1

In patent 'Gamma-aminobutyric acid analogues for the treatment of pain and other disorders, WO 2015091463 A1' a series of novel GABA analogues are described [7]. In examples 1-4 of the patent many routes of synthesis are described, and only example 5 discloses binding data. No animal pharmacology is presented, neither dose-effect curves nor studies in neuropathic pain models.

Comparison between pregabalin and NVA1309

It is important to note that neither gabapentin nor pregabalin were originally also designed as analogs of GABA, but these compounds did not have any affinity for GABA receptors and subsequently gabapentin was discovered to bind to $\alpha 2\delta 1$ subunits. Molecular pharmacological studies strongly support $\alpha 2\delta 1$ as the only molecular target for the analgesic actions of gabapentinoids. The company states that NVA 1309 has 10x higher potency compared to pregabalin, and thus lower dosages are possible in the clinic compared to pregabalin. Better efficacy should preferably translate into a higher analgesic effect (a smaller numbers needed to treat, NNT). The fact that the lead compound is 10-fold more potent in activity than pregabalin, in binding to the $\alpha 2\delta 1$ target in vitro however, does not necessarily mean better analgesic properties. Indeed, the positive read out of the compound in a neuropathic pain model is important, but it is not yet clear whether the company is developing nothing more than a pregabalin-like me-too until those data have been published in detail.

Discussion and Conclusion

To date there are no scientific papers published on the pharmacology of NVA1309. The information on the net and the information described in the patent and on the website of the company does not yet help to see a clear 'Unique Selling Point' (USP) for this compound. It might very well be that the compound has remarkable properties, such as no penetration in brain, while good penetration in the spinal cord (quite difficult to understand), or good peripheral penetration, and special pharmacological properties, as well as superior analgesic efficacy in the neuropathic pain model. In order to evaluate these statements, we need data. It is recommended to the company to, as soon as possible; publish data on the preclinical profile of this interesting drug. It is relevant to make some remarks on the said absence of penetration of NVA1309 in the brain. It is for pregabalin generally well known that CNS penetration of the compound contributes to its efficacy, and sadly enough also to its

side-effect profile and tolerability. The CNS penetration relates to [8]:

- i. intrathecally and intra cerebroventricularly administered gabapentin are efficacious after peripheral nerve injury,
- ii. Systemic administered pregabalin normalizes elevated spontaneous and evoked neuronal activity in the central nucleus of the amygdala,
- iii. amygdala hyperactivity induces increased anxiety, which can be reduced by pregabalin,
- iv. Pregabalin displays anxiolytic effects in patients and is licensed for anxiety disorders and
- v. Many patients suffering from chronic pain states also suffer from high anxiety levels.

The fact that NVA1309 showed activity in a relevant animal neuropathic pain model is difficult to match with the five above mentioned aspect and might thus not be of pivotal importance. Moreover, other gabapentinoids previously in development, with good affinity to the $\alpha 2\delta 1$ target, failed in animal models, due to absent CNS penetration, probably related to the absence of binding to the L-transporter protein [9,10]. A better pregabalin, with less CNS side effects is very much wished for. Many patients suffering from neuropathic pain have to stop treatment, because the emergence of unacceptable side effects. If the compound indeed has a superior analgesic profile, it will probably be explored in more detail in the near future. The company is currently looking for a development partner.

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