

Background Examples of Issues Facing the Agency in the Regulatory Review of Drugs Intended to Treat Peripheral Neuropathy and Neuropathic Pain

The following are examples of questions that Sponsor have presented to the Agency in the development of clinical plans to study new treatments to slow or reverse the progression of neuropathy or to treat neuropathic pain.

Company A is developing a drug to slow or reverse the progression of diabetic peripheral neuropathy (length-dependent distal symmetric polyneuropathy). The drug is believed to work by affecting a pathogenetic mechanism that is specific to diabetic neuropathy. The company sought FDA's opinion on its primary efficacy endpoint, the motor F-wave minimum latent time and conduction velocity. The FDA asked the company to justify the use of this measure in terms of its clinical relevance and clinical correlates. Specifically, the FDA was concerned that this measure of proximal motor demyelination or demyelination over large segments would not be able to measure effects that may be distal, axonal, and sensory in nature.

Company B is developing a drug for the treatment of chronic neuropathic pain, which is believed to work by affecting neurotransmission, and not by affecting the underlying pathogenesis of any particular type of neuropathy neuropathy. The Sponsor is seeking guidance on its development plan, especially with regard to the number of trials required for each type of neuropathic pain condition and the type of indication that will be granted based on the development plan. Specific questions include:

- Will two adequate and well-controlled studies in diabetic neuropathy support a claim of “treatment of pain due to diabetic neuropathy”?
- Will a single adequate and well-controlled study in diabetic neuropathy plus a single adequate and well-controlled study in post-herpetic neuralgia support a specific claim for each condition? Will these two studies support a broad neuropathic pain claim?
- Will two adequate and well-controlled studies in a specific condition such diabetic neuropathy plus a large placebo-controlled study in a mixed neuropathic pain condition support a broad neuropathic pain claim?
- Will two adequate and well-controlled studies in diabetic neuropathy plus two adequate and well-controlled studies in post-herpetic neuralgia support indications for a broad neuropathic pain indication?

In this example, the Agency is concerned that there is an insufficient body of data to allow extrapolation from success of a specific agent in treating one form of neuropathic pain to multiple other forms of neuropathic pain.

Company B above is also interested in the duration of clinical trials required to demonstrate efficacy of a product to treat chronic neuropathic pain. Company B believes onset of analgesia may occur two weeks after the drug is started, and want to know if it is sufficient simply to demonstrate onset of analgesia, or if a minimum period of study

duration is required. The Agency is concerned that because treatment of neuropathic pain generally requires long-term treatment, the pattern of analgesic activity over time, as well as the durability of the analgesic effect, need to be demonstrated.

Company C is developing a drug that is believed to slow the progression of diabetic peripheral neuropathy by affecting a mechanism that is believed to be specific to the pathogenesis of diabetic peripheral neuropathy. It plans a two-phase development. In the first phase, it plans to show that the is effective in treatment the symptoms of diabetic peripheral neuropathy in patients with positive neuropathic symptoms. It studies for this phase of the development program have as their primary outcome measure a symptoms scale, in this case one provides a composite score that takes into account the intensity and frequency of six symptoms (“pain”, “burning”, “prickling”, “numbness”, “allodynia”, and “lancinating”). In the second phase of development, they plan to demonstrate that the drug slows (or reverses) the progression of diabetic peripheral neuropathy. The proposed primary endpoint for these studies will be the NIS(LL)+4+VDT, which is a composite score comprised of a subset of the Neuropathy Impairment Score for the lower limbs (NIS(LL)), four electrophysiologic measures of peripheral nerve function (peroneal motor amplitude, peroneal motor nerve conduction velocity, peroneal motor nerve distal onset latency, and tibial motor nerve distal onset latency), and vibratory detection threshold (VDT). The company sought FDA’s view on the appropriateness of the primary endpoints for each of the two sets of studies.
