Gene Therapy for Diabetic Peripheral Neuropathy: A Phase 3 study of VM202, a plasmid DNA encoding human hepatocyte growth factor

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BACKGROUND

Painful diabetic peripheral neuropathy (DPN) is a common and debilitating complication of diabetes mellitus that has a profound negative impact on quality of life, sleep, and mood. Current therapies, all based on small molecules, are palliative and do not target the mechanisms underlying painful DPN. Moreover, symptomatic relief is often limited with existing neuropathic pain drugs, and many patients with painful DPN use opioids. To overcome the limitations of currently used medicines, gene therapy technology has been explored for some time, but most of the investigations have been at the non-clinical level.

VM202 (Engensis®) is a plasmid DNA encoding two isoforms of hepatocyte growth factor (HGF) and is the first gene medicine to enter advanced clinical trials for the treatment of painful DPN. After an initial dose-ranging Phase 1/2 study in 12 subjects showed the potential for safety and efficacy out to 12 months, a Phase 2 dose-ranging study was conducted in 103 subjects with painful DPN that showed significant reductions in pain and improvements in pain interference scores for 9 months following a single cycle treatment consisting of intramuscular injections on Days 0 and 14 into the calf muscles of both legs. The current study was designed to confirm the potential long-term safety and efficacy of VM202.

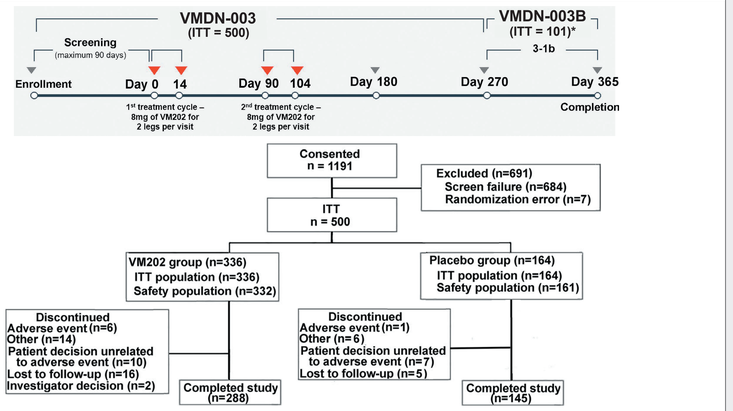
OBJECTIVE

A Phase 3 study was conducted to evaluate the safety and efficacy of VM202 in DPN subjects with two cycles of treatments at 14-day intervals (Days 0 and 14, followed by Days 90 and 104). The primary endpoint in VMDN-003 was change from baseline in the average 24-hour numerical rating scale (NRS) pain score at 3 months. In VMDN-003b, the primary endpoint was safety, while the secondary efficacy endpoint was change in mean pain score at 12 months.

METHODS AND STUDY DESIGN

The trial was conducted in two parts, one for 9 months (VMDN-003; 500 subjects) and a subset of the first study with extension to 12 months (VMDN-003b; 101 subjects). VM202 or placebo was administered to calf muscles of both legs on Days 0 and 14, and again on Day 90 and 104.

Fig. 1: Study Design and Randomization (VM202 vs. Placebo)



*The 101 subjects who participated in VMDN-003b are part of the 500 patients from VMDN-003

PATIENT CHARACTERISTICS AND CLINICAL RESPONSE

VM202 was well-tolerated in both parts of the study (at 9 and 12 months) and the incidence of adverse events was similar for VM202 and placebo. VM202 did not meet the planned 3-month primary efficacy endpoint in VMDN-003. In VMDN-003b, however, VM202 showed significant and clinically meaningful pain reduction vs. placebo at 6, 9, and 12 months. The pain reduction was greater in subjects not receiving gabapentin or pregabalin, confirming an observation noted in the Phase 2 study.

In VMDN-003b, VM202 provided pain reduction for more than 8 months after the last cycle of treatment.

Serum levels of HGF did not change after treatment with VM202, indicating that the effects of treatment must reflect local intracellular effects of HGF in the muscles and nerves surrounding each injection site. Thus, the prolonged effects long after disappearance of the plasmid suggests that VM202 treatment may change the course of disease progression.

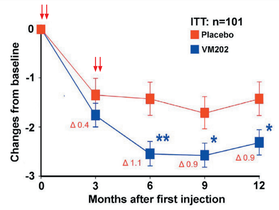
CONCLUSIONS

Current therapies are palliative and do not target the mechanisms underlying painful DPN. In animal models, HGF produced from intramuscularly injected VM202 interacts with the c-Met receptor present on Schwann cells or sensory neurons via ERK or AP-1 signaling pathways, respectively, to promote axon outgrowth and remyelination. Thus, the availability of a potential therapy that changes pain-generating circuits and/or regenerates damaged nerves would fundamentally change approaches to the management of painful DPN.

To our knowledge, this is the first Phase 3 gene therapy study for pain that has ever been conducted. VM202 treatment did not meet efficacy endpoints in the full VMDN-003 population, but VM202 demonstrated long-term, clinically significant reductions in pain in the subset of subjects who were prospectively continued with no further treatment intervention into the 12-month extension study, VMDN-003b. The effects were particularly notable and significant in subjects not receiving gabapentinoids. Similar findings were observed in the Phase 2 study. Given the apparent favorable safety profile of VM202, the potential for disease modifying effects, and the high unmet medical needs of the DPN patient population not on gabapentinoids, further study is warranted, especially in patients not on gabapentinoids. Another confirmatory Phase 3 has started.

GRAPHICS FROM KESSLER ET AL., 2021

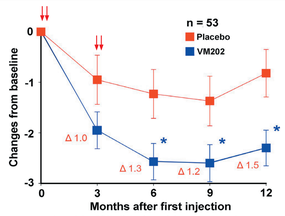
Fig. 2: Reductions in Average Daily Pain Scores, VMDN-003b (ITT population)



(a) Mean pain scores on the daily pain diary in VMDN-003b expressed as change from baseline ± SE for VM202 and placebo groups. Red arrows indicate times of treatment. The Δ values are differences at each timepoint between the groups.

*p < 0.05 **p < 0.01. DPN, diabetic peripheral neuropathy; ITT, intent-to-treat

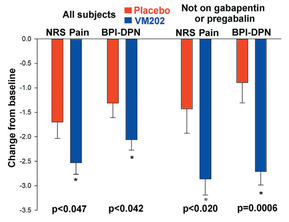
Fig. 3: Reductions in Average Daily Pain Scores, VMDN-003b (no gabapentinoids)



Mean pain scores on the daily pain diary for subjects not on gabapentin or pregabalin in VMDN-003b expressed as change from baseline ± SE for VM202 and placebo groups. Red arrows indicate times of treatment. The Δ values are differences at each timepoint between the groups.

*p < 0.05. DPN, diabetic peripheral neuropathy

Fig. 4: Average Daily Pain Diary (NRS Pain) vs. Brief Pain Inventory (BPI) at 6 months



(a) Mean pain scores at 6 months on both the daily pain diary (NRS-Pain) and the Brief Pain Inventory for diabetic peripheral neuropathy (BPI-DPN) expressed as change from baseline ± SE for VM202 and placebo groups for the 142 subjects enrolled by the second CRO. The first two set of scores are for all subjects, and the second two sets of scores are for subjects not on gabapentin or pregabalin. CRO, contract research organization

References: Kessler JA, et al. Gene therapy for diabetic peripheral neuropathy: A randomized, placebo-controlled phase III study of VM202, a plasmid DNA encoding human hepatocyte growth factor. *Clin Transl Sci.* 2021 Jan 19. doi: 10.1111/cts.12977. Online ahead of print.

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