Development of a Cathepsin S Inhibitor for Neuropathic Pain: Efficacy in a Preclinical Model of Taxol-Induced Neuropathy and Phase 1 Clinical Profile

Poster 714.10/BB27

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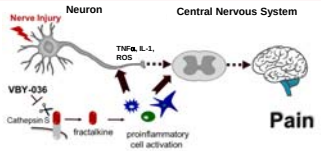
Abstract

Cathepsin S is a cysteine protease known to be critical in the development of neuropathic pain. Following neuronal injury, membrane bound fractalkine (FKN) is expressed at the surface of injured neurons. Also following injury cathepsin S is released from resident immune cells, including microglia and macrophages, where it cleaves membrane bound FKN allowing the release of the pro-nociceptive chemokine soluble FKN. FKN-mediated recruitment and activation of microglia and other cells involved in immune defense triggers release of pro-inflammatory cytokines and other inflammatory mediators, which then propagate an exaggerated pain response. Cathepsin S lies at the intersection of neuronal-immune communication now recognized as critical in the development of chronic pain.

We have demonstrated efficacy of two selective cathepsin S inhibitors, VBY-036 and VBY-285, in rodent models of taxol-induced neuropathic pain. VBY-036 and VBY-285 are potent inhibitors with high selectivity for cathepsin S. Both compounds are efficacious at reversing established tactile allodynia which had been induced by repeated taxol administration. VBY-285 was efficacious in reversing established tactile allodynia in a rat model after a single dose. Maximal efficacy, equal to that observed after gabapentin administration, was achieved with repeated once-a-day dosing. No tolerance to repeated dosing was observed and, unlike gabapentin, cathepsin S inhibition produces no sedative effects. Cessation of VBY-285 dosing resulted in a slow return of allodynia, with analgesic efficacy re-established when daily dosing was resumed. VBY-036 was also efficacious in reversing established tactile allodynia in a mouse model after taxol dosing. VBY-036 administration started prior to taxol administration resulted in a greater level of analgesic efficacy in a shorter time frame than administration following the establishment of allodynia. Virobay is progressing VBY-036 in human clinical studies in neuropathic pain. Results of these studies and a VBY-036 Phase 1 single-ascending dose and multiple-ascending dose studies in healthy volunteers will be presented where the safety and pharmacokinetics of VBY-036 oral administration were evaluated. VBY-036 was well tolerated with plasma pharmacokinetics exhibiting roughly dose-proportional exposures. Target engagement on cathepsin S was detected in PBMCs using a pharmacodynamic biomarker, identifying plasma exposures required for maximal cathepsin S inhibition. VBY-036 is in development as a treatment for neuropathic pain, with a planned proof-of-concept Phase 2a study in chronic chemotherapy-induced peripheral neuropathy.

Introduction



Cathepsin S Biology in Pain

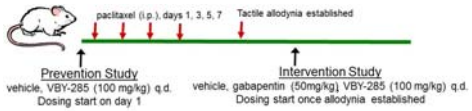
- Cathepsin S is a new target with a novel mechanism of action that regulates neural-immune interaction
- Cathepsin S is a cysteine protease responsible for the cleavage and activation of the pronociceptive chemokine fractalkine (FKN)
- FKN activates and recruits microglia, activates the release of inflammatory cytokines and lymphocyte chemotaxis, and is essential in the maintenance of neuropathic pain
- Inhibition of cathepsin S is reported to reverse thermal hyperalgesia and mechanical allodynia in multiple pain models

Results

Enzyme	VBY-036 K_i (app) (nM)	VBY-285 K_i (app) (nM)
Cathepsin S	0.113	0.01
Cathepsin L	160	2.2
Cathepsin B	250	2.8
Cathepsin F	300	3.4
Cathepsin K	100	2.4
Neither compound has significant activity (IC_{50} >50μM) against other cysteine/serine/aspartic proteases including trypsin, thrombin, chymotrypsin, cathepsin E, BACE, Factor Xa, Factor VIIa, ELA1, ELA2		

Table 1. VBY-036 is a potent, selective, and reversible inhibitor of human cathepsin S with an inhibition constant (K_{app}) of 113pM. VBY-036 is orally bioavailable, and has an attractive profile in 28-day GLP toxicology studies and safety pharmacology. VBY-285 is a second potent and selective reversible inhibitor of human cathepsin S (K_{app}=10 pM) with potency against rat cathepsin S as well as human cathepsin S (Rat CatS K_{app}=230 pM).

Model of paclitaxel-induced neuropathy in rats: testing a Cathepsin S inhibitor in preventional and interventional studies



Method: Jolivalt et al. Pain 121:14-21. 2006

Figure 1: VBY-285 was assessed in a rat model of paclitaxel-induced neuropathy as outlined. VBY-285 was administered after pain was established, and also administered in a separate study prior to the onset of pain. Gabapentin was dosed in the first study as a comparator. Tactile allodynia was established by day 7 after repeated i.p. administration of paclitaxel.

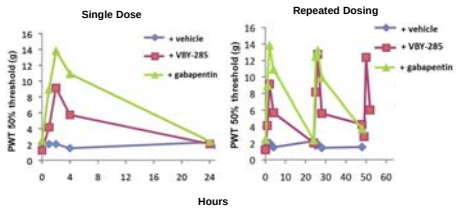


Figure 2: VBY-285 is efficacious in a rat model of chemotherapy-induced neuropathy in an interventional dosing study. VBY-285 was administered after tactile allodynia was established. Pain thresholds were measured at 0, 1, 2, 4, and 24 hours after a single dose in the left panel, and after repeated dosing in the right panel. Maximal efficacy was achieved after the second day of dosing and achieved a level of efficacy similar to that of gabapentin.

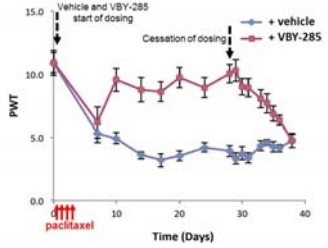


Figure 3. VBY-036 is efficacious in a rat model of chemotherapy-induced neuropathy in prevention dosing model. Pain is not inhibited immediately (at the first time point assessed on day 8) when dosing was started on day 1 with VBY-285, but efficacy is very rapidly developed after repeated dosing. No tolerance to repeated administration was observed. Efficacy is long lasting with some analgesic activity seen beyond the cessation of dosing. When dosed is stopped pain returned slowly to the level observed in vehicle-dosed rats.

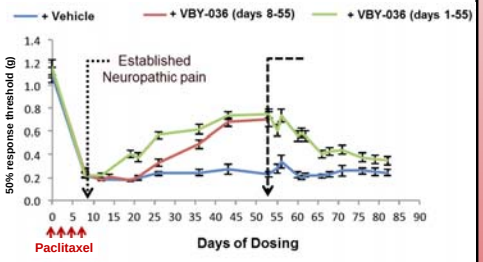


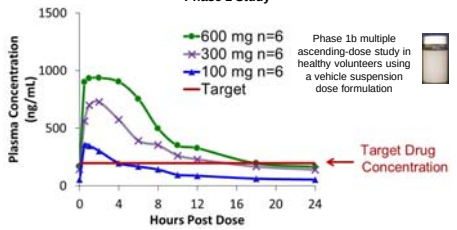
Figure 4: VBY-036 is efficacious in a mouse model of paclitaxel-induced neuropathy. Pain was induced with repeated administration of paclitaxel and tactile allodynia established by day 7. VBY-036 (100 mg/kg, q.d.) was administered prophylactically beginning prior to the onset of pain concurrent with paclitaxel administration, or beginning on day 8 on established pain. Both doses were efficacious with increasing efficacy after repeated dosing. Cessation of dosing resulted in a slow return of tactile allodynia.

Animal Model	Positive Results
Chemotherapy-induced neuropathy (paclitaxel, vincristine)[1, 2]	✓
Spinal nerve ligation[2]	✓
Acute inflammation	✓
Chronic inflammation	✓
Partial sciatic nerve ligation[2]	✓
Diabetic neuropathy[1]	✓
Post-surgical incisional pain[3]	✓

[1] collaborative studies with Nigel Calcutt, UCSD; [2]collaborative studies with Marzia Malcangio, Kings College London; [3]collaborative studies with Ed Bilsky, University of New England

Table 2: Cathepsin S inhibition inhibition has analgesic efficacy in multiple rodent models of neuropathic and inflammatory pain in addition to chemotherapy-induced neuropathy (data not shown but models assessed summarized here). This data is consistent with cathepsin S playing a key role in the maintenance of the chronic pain.

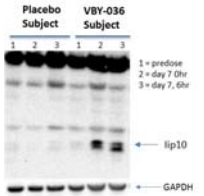
VBY-036 Plasma concentrations after 7 days of dosing in a Phase 1 Study



Phase 1b multiple ascending-dose study in healthy volunteers using a vehicle suspension dose formulation

Figure 5: VBY-036 pharmacokinetics evaluated in a multiple ascending-dose Phase I study in healthy volunteers using a vehicle suspension formulation. The compound was safe and well tolerated at all doses for 7 days of dosing up to 900 mg. Plasma exposures on day 7 with doses of 100, 300, and 600 mg are shown. Plasma concentrations of VBY-036 achieved a target plasma concentration in subjects predicted to sustain inhibition of cathepsin S and achieve analgesic efficacy.

Pharmacodynamic Biomarker detection with 7 days of dosing in a Phase 1 Study in Healthy Volunteers



Detection Method	# Positive / Cohort Size	
	Placebo	VBY-036
Ii10 by Western	1/6	5/6
MS-based Cathepsin S Biomarker	0/6	6/6

Phase 1 PK/PD study in healthy volunteers using a 250 mg tablet dose formulation

Figure 6: A Phase 1 PK/PD study was performed in healthy volunteers with a 250 mg tablet formulation. The target plasma concentration was sustained with 250 mg TID dosing. Accumulation of a biomarker of cathepsin S inhibition, the 10kDa intermediate of invariant chain, was detected in PBMC lysates from subjects using immunoblotting. This biomarker is cell-associated substrate of cathepsin S. A second biomarker of cathepsin S inhibition was detected in PBMC samples from subjects in the study using MRM Mass Spectrometry detection. This 250 mg dose is planned for use in a Phase 2 double-blind, placebo-controlled study to evaluate the effect of VBY-036 on chemotherapy-induced painful peripheral neuropathy.

Conclusions

- ❑ Cathepsin S inhibitors VBY-036 and VBY-285 are efficacious in reversing established tactile allodynia in rat and mouse models of neuropathic pain induced by administration of paclitaxel.
- ❑ Cathepsin S inhibition is efficacious with no tolerance to repeated dosing and no sedation
- ❑ VBY-036 is safe and well tolerated following repeated oral administration in a Phase 1 study in healthy volunteers
- ❑ Use of a pharmacodynamic biomarker measured in PBMC samples in Phase 1 has established a dose in which cathepsin S inhibition is achieved
- ❑ VBY-036 is in clinical development as a therapeutic for neuropathic pain with a Phase 2 study planned in CIPN

Society for Neuroscience Annual Meeting, November 2014, Washington DC

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