Oral Phospholipase A_2 Inhibition Improved Survival Across Representative US Snake Venoms in an Animal Model Representative of Human Envenoming

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INTRODUCTION

Snakebite envenoming is a time-sensitive toxic injury and a persistent military and global health threat, particularly in austere, deployed, and rural, environments. Globally, snakebite causes >130,000 deaths and 400,000 permanent disabilities yearly. ~75% of deaths occur before definitive care.

Varespladib methyl is a shelf stable oral inhibitor of secretory phospholipase A2, a conserved venom toxin family that is present across approximately 95% of snake venoms globally. A shelf-stable oral therapy that can be administered soon after bite could help bridge the gap between field exposure and definitive care.

Because it would not be ethical to conduct a human efficacy study with varespladib in which antivenom is withheld from snakebite patients, efficacy development is proceeding under the FDA Animal Rule. The pilot study presented was designed to closely reflect the planned pivotal Animal Rule efficacy study.

METHODS

Animal Model: Male and female CD-1 mice

Challenge Agents: 9 medically relevant North American snake venoms

- Broad range of toxin profiles supports extrapolation across North American venomous snakes and informs potential military and global use in snake-inhabited environments.
- Venom doses were selected to produce high lethality in placebo groups, exceeding historic human mortality rates without antivenom.

Treatment: 7.5 mg/kg varespladib or placebo beginning 5 minutes after challenge, then dosing at 6, 12, and 20 hours, then twice daily through 48 hours.

Endpoints: Survival through 48 hours. Clinical severity (disability) scores.

HYPOTHESIS

Early inhibition of sPLA2 with varespladib improves survival and short-term disability across a broad range of venoms.

RESULTS

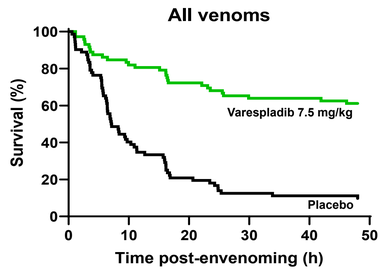
SURVIVAL BENEFIT

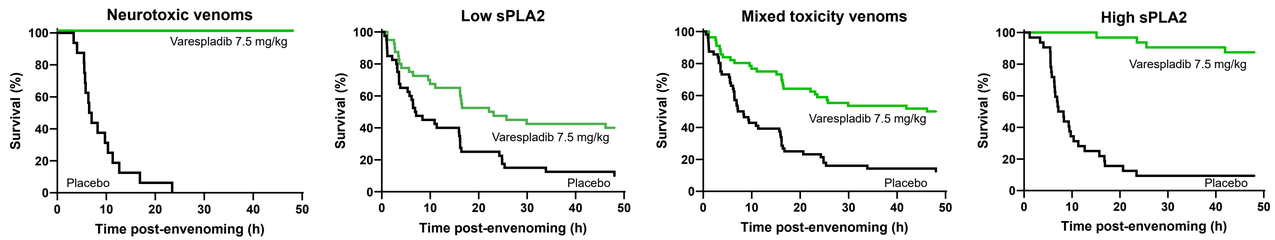
48-HOUR SURVIVAL

9.7% Placebo → **61.1%** Varespladib

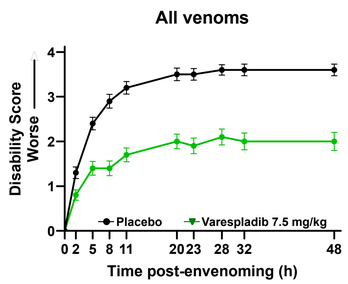
MEDIAN SURVIVAL TIME

7.1h Placebo → **>48h*** Varespladib



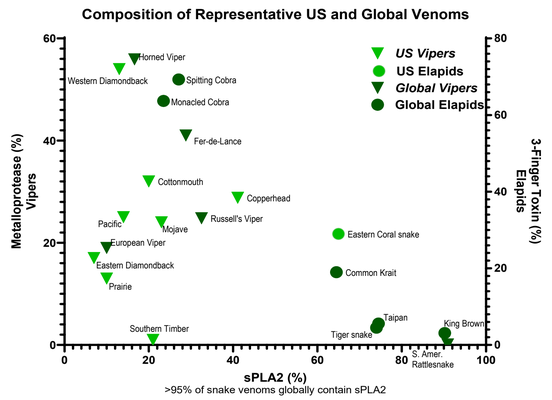


DISABILITY BENEFIT



Varespladib treated animals exhibited lower illness severity scores during the acute post envenoming period, consistent with reduced systemic toxicity and disability.

Global Venom Composition



CHALLENGE AGENTS

Elapids 	➢ *Micrurus fulvius* (Eastern coral snake)	➢ Neurotoxic ➢ High sPLA2, 3-finger toxin
Pit Vipers (Rattlesnakes) 	➢ *Crotalus scutulatus* (Mojave) ➢ *C. atrox* (Eastern diamondback) ➢ *C. adamanteus* (Western diamondback) ➢ *C. viridis* (Prairie) ➢ *C. oreganus* (Pacific)	➢ Mixed neurotoxic, hemotoxic, and cytotoxic phenotypes ➢ Wide range of sPLA2, metalloproteases, and other venom components
Pit Vipers (Cantils) 	➢ *Agkistrodon laticinctus* (Broad-banded copperhead) ➢ *A. piscivorus* (Cottonmouth)	➢ Hemotoxic / cytotoxic with tissue injury ➢ Moderate sPLA2 and metalloproteases

Panel spans major US snakes with a broad range of venom profiles. Represents low to high sPLA2 abundance and major toxin families for extrapolation and potential relevance to military/global use.

DISCUSSION AND CONCLUSIONS

- Stable, field-deployable therapies are needed to bridge the gap between snakebite and definitive hospital care. Varespladib methyl is a shelf-stable oral inhibitor of sPLA2, a conserved venom toxin family.
- This study, designed to reflect the planned pivotal efficacy study under the Animal Rule, demonstrated improved survival and reduced acute disability scores across a diverse panel of North American venoms with varying toxin composition and clinical phenotypes.
- The observed survival and disability benefits support advancement to pivotal efficacy evaluation under the Animal Rule and inform development of a field-to-hospital treatment strategy for snakebite.
- Varespladib methyl is intended for early administration after a bite, either in the field or in more advanced care when field use is not possible. It is not intended to replace antivenom or definitive medical care; patients should seek medical evaluation after any suspected venomous snakebite.
- By targeting a conserved venom mechanism, varespladib methyl has potential relevance to improve survival, reduce systemic toxicity, and support deployed forces, partner-force medical readiness, and global health settings.

LEARNING OBJECTIVES

1. Explain why snakebite remains a military and global health readiness problem.
2. Describe how representative venom selection supports extrapolation across U.S. venomous snakes.
3. Interpret the pilot efficacy data for varespladib as a time of bite treatment for snakebite.

References

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Acknowledgements

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