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POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Dual P-Selectin and Complement Inhibition with Subcutaneous IHP-102 Treatment Potently Reduces Lung Vaso-Occlusion in Sickle Cell Disease Mice

John Paderi, PhD[1], *Rikesh K Dubey, PhD*[2], *Gabriel Njikang, PhD*[1], *Prithu Sundd, PhD*[2]

[1] IHP Therapeutics, San Carlos, CA
[2] Pittsburgh Heart, Lung and Blood Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, PA

One of the most debilitating manifestations of sickle cell disease (SCD) are the excruciatingly painful vaso-occlusive episodes (VOEs), commonly referred to as "pain crises." Vaso-occlusion, which underlies the pathomechanism of VOE, also causes downstream tissue and organ damage resulting in complications that plummet life-expectancy by more than 20 years. Current treatment options for VOE are limited and all require chronic administration, often with intolerable side-effects, and none fully prevent VOE. An acute VOE rescue therapy that could be administered in the home-setting would transform care for the more than 100,000 people in the U.S. and over 7 million worldwide who suffer from this inherited condition.

IHP-102 is a novel glycan-based drug with dual anti-P-selectin and anti-complement activity. It is bioavailable by subcutaneous route of administration and could therefore be self-administered at the earliest sign of VOE. Early intervention in VOE is critical, before ischemia and tissue damage becomes irreversible. This treatment paradigm would also circumvent the wholly inadequate treatment experience that the SCD community has widely described, being treated as an opioid "drug-seeker" when engaging the healthcare system during a debilitating VOE.

There are multiple pathomechanisms of VOE. P-selectin is a clinically validated therapeutic target for partially attenuating VOE, while complement has more recently been identified as an important driver of VOE, in part due to hemolysis and ischemia. While several therapeutics targeting P-selectin or complement are currently in clinical development, no therapy targets both pathomechanisms.

We have previously shown that IHP-102 inhibits P-selectin mediated cell adhesion in vitro (IC50 = 0.7 μg/mL) and that intravenous administration of IHP-102 reduces lung vaso-occlusion by 75% in Townes SCD mice challenged with oxy-hemoglobin (oxy-Hb). Here, we extend these studies with subcutaneous delivery of IHP-102, achieving greater than 75% reduction in lung vaso-occlusion. This magnitude of effect is greater than that achieved in P-selectin deficient Townes SCD mice (~50% reduction), thus indicating additional activity of IHP-102 beyond P-selectin inhibition. In studies using human serum, IHP-102 inhibits complement by upstream mechanisms, including through inhibition of Factor B. Factor B is responsible for alternative pathway amplification of complement. Its fragment Bb has been found in elevated concentrations during VOE in patient serum, suggesting it plays an important role in the pathomechanism of VOE. By inhibiting Factor B, IHP-102 reduces downstream complement fragments of C3 and C5, which are widely recognized complement targets given their critical role in the complement system and promoting inflammation.

The dual anti-complement and anti-P-selectin activity of IHP-102, together with its potential for home-based treatment, offers great potential to fill a major treatment gap for acute VOE. Its potent *in vivo* activity suggests that this dual target approach could provide robust therapeutic benefit and warrants further investigation toward clinical trials.

Disclosures Paderi: *IHP Therapeutics:* Consultancy, Current equity holder in private company; *Osanni Bio:* Consultancy, Current equity holder in private company; *Dexcom:* Consultancy. **Njikang:** *IHP Therapeutics:* Consultancy, Current equity holder in private company; *Optics Medical:* Consultancy. **Sundd:** *Novartis AG:* Research Funding; *IHP Therapeutics:* Research Funding; *CSL Behring Inc:* Research Funding.

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