Impact of Definitions of Vaso-occlusion in Clinical Studies of Sickle Cell Disease (SCD) on Efficacy Outcome Assessment

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INTRODUCTION

- Frequent episodes of vaso-occlusion are a clinical hallmark of sickle cell disease (SCD). Vaso-occlusion results from blood flow blockages that deprive tissues and organs of adequate oxygen and nutrients, resulting in severe pain and contributing to progressive organ dysfunction and failure.[1]
- A variety of therapeutic options are aimed at reducing or eliminating these episodes; however, the definition of vaso-occlusion is not consistent across different clinical trials.
- As the SCD treatment landscape evolves and includes the promise of potentially curative therapies, it is important to understand the impact of differing definitions for vaso-occlusion episodes on efficacy outcome data.
  - This information may be of particular interest to payers and health technology assessment (HTA) agencies as they evaluate potentially curative therapies to ensure a balanced assessment across available products.

OBJECTIVE

- To compare vaso-occlusion endpoint definitions from clinical trials for various therapies, including genetic therapies, and use clinical trial data to demonstrate the potential for outcomes differences based on differing definitions of vaso-occlusive episodes.

METHODS

- We reviewed completed and ongoing clinical trials and published articles using endpoints assessing the reduction or elimination of vaso-occlusive crisis/events, including trials of
  - exagamglogene autotemcel (exa-cel, CRISPR/Cas-9 based genome editing treatment)[2]
  - lovotibeglogene autotemcel (lovo-cel, gene addition therapy)[3]
  - hydroxyurea (HU)[4]
  - crizanlizumab[5]
  - l-glutamine[6]
  - voxelotor[7]
- Outcomes related to vaso-occlusion were compared across variables including care setting, care duration, treatments, and complications.
- Data from the CLIMB SCD-121 trial of exa-cel in patients aged 12 to 35 years with severe SCD (data cut as of 14 Jun 2023) were evaluated using different published definitions of vaso-occlusion.

RESULTS

Comparison of vaso-occlusion endpoint definitions

- All vaso-occlusion endpoints evaluated involved a health care facility visit. The most substantial differences in vaso-occlusion endpoint definitions were associated with frequency and duration of visits to health care facilities for acute pain and inclusion of specific SCD specific complications.
- Definitions of vaso-occlusions for acute pain related events differed across studies (**Table 1**)
  - The definitions of severe vaso-occlusive crises for exa-cel (severe VOC; exa-cel), sickle cell pain-related crises (SCPC; crizanlizumab and L-glutamine), and VOC (VOC; voxelotor) include events with medical facility visits of any duration (severe VOC and SCPC) or medical records of a patient being seen or contacting a physician within 1 business day of an event (VOC).
  - Definition of severe vaso-occlusive events (severe VOE; lovo-cel) requires a ≥ 24-hour hospital or emergency room (ER) observation unit visit or ≥2 visits to a day unit or ER over 72 hours.
  - Vaso-occlusion definition for HU (painful crisis) required a facility visit of ≥4 hours duration.
- All endpoints include acute chest syndrome (**Table 1**).
- All but one vaso-occlusion endpoint (VOC; voxelotor) include priapism, for these endpoints that include priapism, the frequency of visits to health care facility varies (**Table 1**).
  - The definition of severe VOE (lovo-cel) requires ≥4 visits to a medical facility for priapism to meet criterion.
  - The definition of several VOC (exa-cel), painful crisis (HU), and SCPC (crizanlizumab and L-glutamine) require only a single visit.
- The exa-cel phase 3 trial in SCD employs a broad and inclusive definition for severe VOC which counts each individual medical facility visit, regardless of frequency or duration of hospitalization (**Table 2**).

Table 1. Detailed Comparison of Definition of Vaso Occlusive Endpoints Used in SCD Clinical Studies

	Exa-cel	Lovo-cel		Hydroxyurea	Crizanlizumab	L-glutamine	Voxelotor
Endpoint	Severe Vaso-occlusive Crisis "severe VOC"	Severe Vaso-occlusive Event "severe VOE"	Vaso-occlusive Event "VOE"	Painful Crisis	Sickle Cell Related Pain Crisis "SCPC"	Sickle Cell Related Pain Crisis "SCPC"	Vaso-occlusive Crisis "VOC"
Medical facility visit required?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Any duration of healthcare facility visit included?	Yes	No; if admission <24 hours, at least 2 visits to a day unit or ER over 72-hour period required	Yes	No; requires at least 4-hour duration	Yes	Yes	No; requires a patient being seen or contacting a physician within 1 business day of an event
Oral or IV narcotics or IV NSAIDs included?	Yes	No; requires IV treatment	Yes	No; requires IV treatment	Yes	Yes	Yes
Acute chest syndrome included?[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Single priapism event included?	Yes	No; requires 4 episodes to a medical facility	Yes	Yes	Yes	Yes	No
Splenic sequestration included?[b]	Yes	Yes	Yes	No	Yes	Yes	No
Hepatic sequestration included?[c]	No	Yes	Yes	Yes	Yes	Yes	No

[a]Acute chest syndrome definition is generally similar across the endpoints, however severe VOE (lovo-cel) further requires oxygen treatment and/or blood transfusion.
[b]Splenic sequestration definition is generally similar across the endpoints.
[c]Hepatic sequestration definition is generally similar across the endpoints.
Abbreviations: ER: emergency room; IV: intravenous; NSAIDs: non-steroidal anti-inflammatory drugs; SCPC: sickle cell pain-related crises; VOC: vaso-occlusive crises; VOE: vaso-occlusive events.

Table 2. Severe VOC Endpoint Definition Per Exa-cel CLIMB-121 Trial Protocol

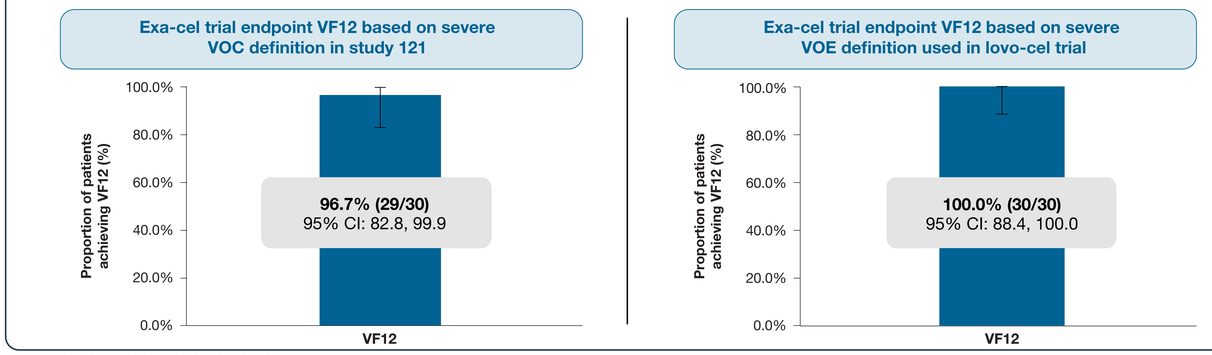
	Severe VOC Requirements per Protocol Definition
The Definition of Severe VOC is Objectively Defined	• Acute pain event requiring a visit to a medical facility and administration of pain medications (oral or IV opioids or IV NSAIDs) or RBC transfusions • Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate on imaging associated with pneumonia-like symptoms, pain or fever • Priapism lasting >2 hours and requiring a visit to a medical facility • Splenic sequestration and an acute decrease in hemoglobin concentrations of ≥2 g/dL
The Definition of Severe VOC is Broad	Includes events that involve: • A short hospital stay (i.e., less than 24 hours) • Administration of oral narcotics • Single emergency room or outpatient clinic visits of any duration • Individual events of priapism (>2 hours)
The Definition of Severe VOC is Inclusive	• Events require either a medical facility visit or an evaluation by a healthcare professional • Events are not restricted to hospital admission

IV: intravenous; NSAIDs: non-steroidal anti-inflammatory drugs; RBC: red blood cell; VOC: vaso-occlusive crises.

Analysis of CLIMB-121 study based on different vaso-occlusion definitions

- Based on the protocol definition for severe VOC in the CLIMB-121, 29 out of 30 patients (96.7%) met the primary endpoint of freedom from severe VOCs for at least 12 consecutive months (VF12; 95% CI: 82.8%, 99.9%) (**Figure 1**).
  - When the primary endpoint was analyzed using the severe VOE definition (see lovo-cel severe VOE definition in Table 1), all patients (30/30; 100.0%) were free from severe VOEs for at least 12 consecutive months (95% CI: 88.4%, 100.0%).

Figure 1. Exa-cel Trial Endpoint Based on Different Vaso-occlusion Definitions



VF12 was calculated based on study 121 primary efficacy set based on data cut as of 14 Jun 2023.
Abbreviations: VF12: freedom from severe VOCs for at least 12 consecutive months; VOC: vaso-occlusive crises; VOE: vaso-occlusive events.

CONCLUSIONS

- Requirements for health care facility visits in the definitions of severe VOC (exa-cel), VOC (voxelotor), and SCPC (crizanlizumab and L-glutamine) were more broadly inclusive and include events that would not be counted in the definitions of severe VOE (lovo-cel) or painful crisis (HU).
- Clinically, support for this observation comes from our analysis of exa-cel SCD pivotal clinical trial data using these different definitions, which showed the number of patients free from vaso-occlusive episodes changed depending on the definition of vaso-occlusion employed.
- The definition of severe VOC in the exa-cel program is one of the most inclusive compared to other approved gene therapies and disease modifying therapies.
- These results show differences in vaso-occlusion definitions have the potential to impact assessments of treatment efficacy, which should be considered by broad stakeholders including payers and HTA agencies in their evaluation of different SCD therapies.

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AUTHOR DISCLOSURES

HF is a consultant to Editas Medicine, Rocket Pharmaceuticals, and Vertex Pharmaceuticals (steering committee); FL is consultant to Amgen, bellicum Pharmaceuticals, Novartis, Novimmune, Sobi, Inc; speaker bureau for Bluebird Bio and Gilead Sciences; steering committee Vertex Pharmaceuticals. SI, FX, NL, JRC, and BH are employees of Vertex Pharmaceuticals.

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