



**pan-Canadian Oncology Drug Review
Submitter or Manufacturer Feedback on a
pCODR Expert Review Committee Initial
Recommendation**

**Siltuximab (Sylvant) for Multicentric
Castleman's Disease**

June 22, 2015

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): SYLVANT™ (siltuximab) for the treatment of patients with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8) -negative.

Role in Review (Submitter and/or Manufacturer): Submitter and Manufacturer
Organization Providing Feedback Janssen Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

- a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

agrees agrees in part disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees, agrees in part or disagrees with the initial recommendation.

Janssen Inc. agrees with the committee’s decision that there is a significant clinical benefit of SYLVANT™ based upon the statistically significant and clinically meaningful improvement in fatigue and quality of life (QoL). SYLVANT™ is also aligned with patients’ values for treatments, in that it allows symptom control, reduced fatigue and has a manageable side effect profile.

In support, there is a need for an effective therapy for patients with HIV and HHV-8 negative MCD where there are virtually no treatment options. Therefore SYLVANT™ fills a high unmet need in the clinical disease management of this patient population , by not only demonstrating improvements in fatigue and QoL, but also demonstrating statistically significant improvements in durable tumour and symptomatic responses in the first and only phase II, randomized controlled double-blind trial.

Janssen Inc. agrees with the pERC’s assessment of MCD being a rare disease with a prevalence estimated to be less than 90 cases in Canada with the HIV and HHV-8 negative subtype making up an even smaller proportion of this number. From the onset, it was known that due to the fact that MCD is defined by dramatic symptoms and notable physical findings, as well as the extreme rarity of the disease itself, there would be challenges in conducting a randomized double-blinded controlled trial, validating outcomes and obtaining data to inform an economic model.

A relevant rigorous and prospectively defined composite endpoint was established given the lack of existing response criteria for MCD. The submitted health economic model was populated with the best available data found for this particular patient population; namely, data originating from the MCD2001, the first and only randomized, double-blind controlled trial (RCT) in MCD.

However, Janssen Inc. does not agree with the pCODR Economic Guidance Panel (EGP)'s assumption of no survival benefit associated with SYLVANT™ (pg. 2, Section 1.3 in Summary of Results in Initial Economic Guidance Report, 3rd bullet). As acknowledged by pERC and expressed in the pCODR Clinical Guidance Panel (CGP)'s report, MCD is a rare disease where significant effort was demonstrated by investigators to collect relevant data within the MCD2001 trial. As such, the MCD2001 trial is the only RCT in a patient population in which no treatment options exists. The low level of evidence (i.e., case studies) and the underpowered sample size of the MCD2001 and MCD2002 trials used as data to develop the model are indicative of the low prevalence of the disease.

The base case analysis in the submission only assumed survival benefit for the first five years if the patients did not experience treatment failure. No survival benefit was assumed beyond 5 years before treatment failure or after treatment failure. Although the MCD2001 and 2002 trials at the current data cut were not powered to identify statistically significant benefit on survival, there is a clear trend towards better survival outcome among SYLVANT™ patients. The 1-year survival rate was 100% for SYLVANT™ and 92% for placebo. This trend continued at the end of the follow up, where there were 4% (2 out of 53) deaths in the SYLVANT™ arm and 15% (4 out of 26) deaths in the placebo arm. The four deaths within the placebo arm were patients who did not cross over to SYLVANT™.

Furthermore, clinical expert opinion treating MCD patients recommended the base case assumption of survival as it was deemed reasonable that patients achieving response or disease control would be subject to lower mortality risk. Based on recommendation by clinical experts who has treated HIV-negative and HHV8-negative MCD patients, the current base case survival projection of patients achieving response or disease control would be subject to lower mortality risk than patients who had failure treatment was deemed reasonable. Given the rarity of the disease, the experts recommended this was the best evidence to use in the model and agreed this had clinical face validity.

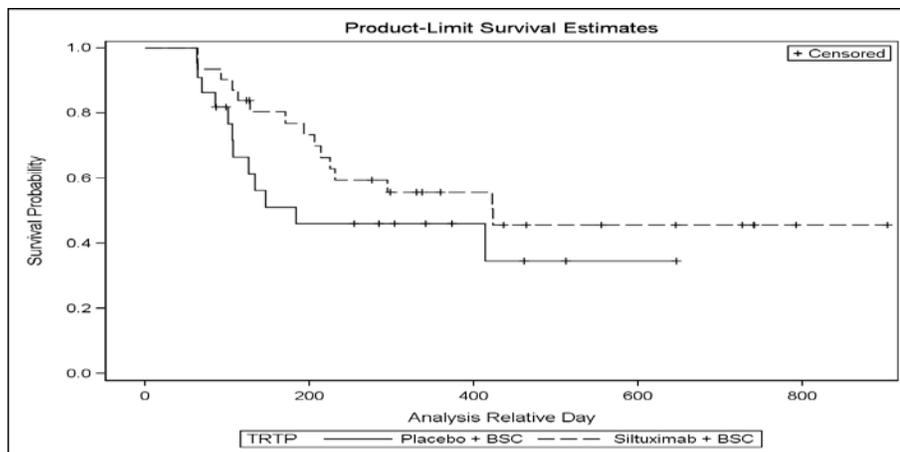
The first analysis conducted by the reviewer assumed no survival difference regardless of response status, treatment or whether the patients experienced treatment-failure. It was believed that it represented the most conservative assumption for survival. As the MCD2001 trial was the only placebo-controlled study in the very rare condition of HIV-negative and HHV-8-negative MCD, using trial data to the largest extent as done in the base case analysis is a better alternative than relying completely on pooled case studies over a time span of 50 years. Scenarios based on the trial data would provide more reasonable estimates of the ICER, around \$200,000/QALY or at the maximum around \$300,000/QALY.

Janssen Inc. does not agree with the assumption of no utility benefit additional to that of tumour response and delay of treatment failure by being on SYLVANT™ used by the

EGP to re-analyze the base case analysis (pg. 2-3, Section 1.3 in Summary of Results in Initial Economic Guidance Report, 4th bullet.

Treatment was demonstrated to be an independent predictor of outcome, supported by the QoL and clinical data from the MCD2001 trial. As presented in Health Economic model report (Section 6.10 - Utility Inputs, p.24) submitted by Janssen, the MCD2001 trial's QoL data analysis showed that there was a treatment-related utility increment for SYLVANT™ regardless of response status. As shown by MCD2001 clinical data, when comparing stable disease (SD) patients on the SYLVANT™ arm vs. placebo arm, there was a delay in time-to-treatment failure (Figure 1), which supported that SYLVANT™ patients had better clinical performance than placebo patients with the same SD status. The CGP deems the net clinical benefit of SYLVANT™ is based on the fatigue and QoL improvements demonstrated by patients on treatment. Furthermore, clinical experts experienced with treating HIV-negative and HHV-8-negative MCD patients consider the QoL data from MCD2001 trial to be the best data available for this patient population and purported clinical face validity.

Figure 1. MCD2001: Time-to-treatment-failure Kaplan-Meier Analysis: SD Patients from the SYLVANT™ + BSC Arm vs. Placebo + BSC Arm (Appendix B, Table B-1 of Economic Submission, p.49)



The scenario conducted by the reviewer where patients lost all treatment-related utility benefit after the trial period required a bigger assumption than the model base case. The trial duration is a time point determined by trial design for data analysis, but it is not related to the disease status. As the patients stay in the same health states (complete response [CR], partial response [PR] or SD) and continue to receive the same treatment (SYLVANT™), there is little justification on why they would experience a decrease in utility at the end of the trial follow-up.

- b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			NO COMMENTS

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			NO COMMENTS

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			NO COMMENTS

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an “early conversion” of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

- a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.
- b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.
- c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)
- d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

- e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.
- f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.
- g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.
- h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.
- i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.