Reviewer's report

Title: The effect of Bosentan on exercise capacity in Fontan patients; rationale and design for the TEMPO study

Version: 4  Date: 6 March 2013

Reviewer: Paul Clift

Reviewer's report:

Major Compulsory Revisions: none necessary

Minor Essential revisions: none necessary

Discretionary revisions:

In the 'Background' I am not sure that you can say 'Many TCPC patients are expected to have some degree of increased PVR due to overshunting prior to TCPC completion'. In the modern management of univentricular hearts, great care is made to regulate the pulmonary blood flow in early life in order to reduce any chance of pulmonary vascular remodelling. Similarly a high ET-1 level does not necessarily lead to pulmonary vascular remodelling, endothelin being demonstrated to be a co-mitogen of vascular smooth muscle cells.

Regarding study endpoints; there is limited discussion as to what limits a Fontan and therefore contributes to any reduction in the peak VO2 achieved. Marc Gewillig published two articles (ref 13) and Gewillig et al Interact CardioVasc Thorac Surg 2010;10:428-433, in which this is discussed in detail and I think it sensible to discuss this further. Furthermore, given that the pulmonary blood flow is a stated secondary end point, could the authors discuss whether the method of Stringer-Wassermann is validated in the Fontan patient and what it's limitations may be.

The statistical analysis appears sensible although possibly ambitious in the change in VO2 predicted. I expect the peak VO2 will change little in the study population but that their reported effort tolerance may improve.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I have no financial competing interests. In the past I have done consultancy work for Actelion Pharmaceuticals and held a non-restrictive educational grant which was used to conduct the study cited in reference 27.