25th September 2007

Dear Mr. Minehan

Re: Clinical and cost effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications

Encysive (UK) Ltd. has reviewed the above report and would like to bring to your attention the following;

Point 1

Within the document there were repeated references that the breakdown of the STRIDE-1 (study FPH-01) NYHA functional class III patients was not available for review, and this was highlighted in 'no data available' in Table 25 (pg 134-135), and similar statements made in the following locations:

- Functional Class (FC) – pg 136: *The results specifically for FC III patients for both outcomes were in the same direction but did not reach statistical significance (see Analysis A, Table 25).*
- Exercise capacity 9 pg 136: *Data specifically for FCIII patients were not available.*
- Page 39, 2nd bullet: *Improvement in FC was observed in FCIII patients but this did not reach statistical significance.*
- Table 33, page 158: The primary analysis is of WHO functional class III patients from STRIDE-2, which was not available for review
- Section 6.3.1.2, page 198: *The odds ratios for sitaxentan were obtained from pooled analysis using data from STRIDE-2[48] and STRIDE-4[37] but excluding data from STRIDE-1[49] (data stratified by FC was not available).*
- Table 41, page 199: data includes STRIDE-2 and 4 only

In order to address this issue, we have enclosed data analyses focusing entirely on the 100mg sitaxentan dose (licensed dose) versus placebo in WHO/NYHA Functional Class III patients (licensed functional class and indication (idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease). The data enclosed includes baseline characteristics and results from STRIDE-1 and the integrated analysis of STRIDE-1, 2, and 4:

Table 1.1	STRIDE-1 Baseline Demographics
Table 1.2	STRIDE-1,2,4 Baseline Demographics
Table 2.1	STRIDE-1 Change from Baseline in 6-Minute Walk Distance
Table 2.2	STRIDE-1,2,4 Change from Baseline in 6-Minute Walk Distance
Table 3.1	STRIDE-1 Change from Baseline in WHO/NYHA Functional Class
Table 3.2	STRIDE-1,2,4 Change from Baseline in WHO/NYHA Functional Class
Table 4.1	STRIDE-1 Baseline Haemodynamic Parameters
Table 4.	STRIDE-1 Change from Baseline in Haemodynamic Parameters
Table 5.1	STRIDE-1 Estimate of Time to Clinical Worsening
Table 5.2.1	STRIDE-1,2,4 Estimate of Time to Clinical Worsening (same definition for time to clinical worsening applied to all trials)

Table 5.2.2 STRIDE-1,2,4 Estimate of Time to Clinical Worsening (STRIDE-1 definition for time to clinical worsening per original protocol, definition for STRIDE-2 and 4 the same)

Point 2

Table 43, page 200: It appears that the FC II to III and the FC III to IV columns are the same. This may be in error.

Point 3

Table 73, page 270 – STRIDE-2 PVR values: The values in the table are in Wood units, but footnote (b) states that the number has been converted from Wood units to dynes*sec*cm^{-5}

Table 1 Extracted data for cardiac index and pulmonary vascular resistance

	Pulmonary Vascular Resistance (dyn*sec*cm^{-5})								
	Baseline n	mean	SD	Post-Rx n	mean	SD	Change n	mean	SD
STRIDE-2 / Barst 2006[48] 18 wks									
Placebo	62	880[b]	640[b]	NR	NR	NR	NR	NR	NR
Bosentan 125 mg bd	60	880[b]	400[b]	NR	NR	NR	NR	NR	NR
Sitaxentan 50 mg od	62	800[b]	560[b]	NR	NR	NR	NR	NR	NR
Sitaxentan 100 mg od	61	800[b]	560[b]	NR	NR	NR	NR	NR	NR

We appreciate the thorough and comprehensive review that has been undertaken to compile this report, and have provided this information for your consideration for inclusion. If there is anything else that I can be of assistance with please do not hesitate to contact me.

Yours sincerely

[redacted]
Encysive (UK) Ltd.

tel. [redacted]
fax. [redacted]
mob. [redacted]