WORKSHOP ON REGULATORY ASPECTS OF ACUTE HEART FAILURE
30 June 2010 - London

Conclusions

A. The overarching question asked was: "do we need to change/update the current guidance on acute heart failure" and the group overwhelmingly agreed that there was a need for updated guidance that would be meaningful.

B. Possible updates were considered under 5 headings

1. target population
2. end-points
3. biomarkers
4. treatment comparisons – placebo versus active controlled
5. safety measures

During the discussion it became clear that there was considerable overlap between these areas.

C. Summary of discussion

1. **TARGET POPULATION:** The main conclusion from extensive discussion of this point was that sponsors should be asked to justify the specific population selected for study based upon the mode of action of the treatment under investigation and the pathophysiological mechanism targeted. Two cases examples were discussed – use of a new vasodilator (avoid in patients with a low blood pressure etc) and use of a new inotrope (inappropriate in patients with preserved ejection fraction etc). Sponsors should recognise that, irrespective of population selected, patients must be well characterised and that, at a minimum, aetiology, ejection fraction, blood pressure, renal function and plasma B-type (or NT pro B-type) natriuretic peptide should be described. To ensure that patients enrolled early after presentation do indeed have heart failure causing their breathlessness, it was strongly recommended that B-type (or NT pro B-type) natriuretic peptide should be an entry criterion i.e. patients should be required to have a minimum plasma concentration to be eligible for study. The value of BNP/NT pro BNP was further recognised as a risk-marker (for future clinical events) and as a potentially supportive measure of drug efficacy i.e. that effective treatments might reduce BNP/NT proBNP.

2. **END-POINTS:** Two types of efficacy end-points were discussed – a) end-points for short-term, in-hospital evaluation and b) end-points for longer-term in-hospital and post-discharge evaluation.

a) **Short-term, in-hospital, end-points** – the following were advocated:

Primary efficacy – persistent improvement in dyspnoea; it was agreed that it would be desirable that this was coupled with persistent improvement in clinical signs of congestion.

Supportive efficacy – examples included reduction in pulmonary capillary wedge pressure; reduction in BNP/NT pro BNP.

Safety – i) general measures – standard physiological measures including blood pressure, heart rate and relevant clinical events including death.

ii) measures of organ damage – to exclude important organ damage, specifically cardiac (e.g. by measurement of troponin) and renal (e.g. by measurement of glomerular filtration rate, urinary albumin excretion markers of renal tubular damage)

iii) other specific measures – if relevant to particular treatment under study

b) **Longer-term end-points**. The discussants suggested that these should largely mirror those used in chronic heart failure trials (e.g. the primary efficacy end-point might be the composite of death or hospital re-admission for worsening heart failure). Other complex composites incorporating symptoms/quality of life, biochemical or functional measures, changes in concomitant therapy were not favoured. It was accepted that morbidity-mortality might be measured over a fixed period of time (e.g. 6 months, 1 year) as opposed to the trial being end-point driven without a fixed period of follow-up; however, such a design would not preclude the need to demonstrate that the treatment under investigation does not increase mortality. Supportive efficacy outcomes might include measures such as days of hospital-free survival (days alive and out of hospital).

3. **BIOMARKERS:** It was agreed that there had been many important advances in this area since the last guidance document was produced. The value of biomarkers has largely been addressed under the earlier two topics but can be summarised as follows:

i) **Patient selection** – Elevated BNP/NT pro BNP is recommended as an entry criterion. Troponin (as a marker of ischaemic myocardial damage) or markers of renal dysfunction might be used to exclude certain patients in studies with particular treatments.

ii) **Supportive efficacy measures** – reduction in BNP/NT pro BNP, improvement in renal function, reduction in cardiac injury (as judged by troponin release) etc. are examples of biomarker changes that might be considered as supportive measures of efficacy.

iii) **Safety measures** – this is largely the converse of ii). With many treatments for acute heart failure there is concern that they may directly or indirectly (e.g. by lowering blood pressure) cause damage to vital organs and, in particular, the kidney and heart. Measurement of biomarkers may help address such concerns.

iv) **Other uses** – biomarkers may be used for risk-stratification (and, therefore, patient selection, subgroup analyses) and to identify pathophysiological targets for treatment or the pathophysiological response to treatment.

4. **TREATMENT COMPARISONS** – both placebo-controlled and active controlled trial are appropriate. Sponsors should ensure that patients receive appropriate background therapy e.g. patients with a diagnosis of chronic low ejection fraction heart failure before the acute event leading to trial entry should usually be treated with guideline-recommended treatment for chronic low ejection fraction heart failure.

5. **SAFETY MEASURES:** These have been discussed in the earlier sections. Monitoring for atrial and ventricular arrhythmias may also be appropriate in certain circumstances, depending on the particular treatment under investigation.