EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Methodological Considerations

EMA /FDA / HC Meeting on PAH

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Powering PK / PD studies

- Power of a study depends on (amongst other things):
  - Sample Size;
  - Alpha, The Type 1 Error Rate.
- So to ensure your study is suitably powered you need to know what the hurdle is you need to cross.
- Methodologists very keen that this is pre-specified.
- Need to be able to have clear rules that the study was successful, or not, and to design accordingly (not a plea for $p<0.05$!).

Controlled efficacy data may still be required

- There may be the need for some controlled efficacy data.
- In the presence of a reasonable (see later) pharmacodynamic marker, this may not need to be demonstrated at $p<0.05$.
  - Especially if the PD variable does demonstrate this.
- Placebo control may not be possible:
  - Non-licensed active comparators also problematic globally;
  - Though sildenafil licensed in >1 in EU;
  - (Very) Low dose of active may be possible;
  - Preferable to show some sort of slope for dose response. Flat curves harder to interpret.

What variables might we be interested in?

- Non-invasive.
- Easily measurable.
- Sensitive:
  - Ability to show an effect if one exists.
- Often patient reported outcomes suffer from this. Measurements are very variable over time.
- One way to reduce this, and thus make a blunt instrument more sensitive, is to average over time – or an analysis that is more “Area under the curve”.

What is or could be recorded regularly

- Oxygen levels – daily data uploaded via an app at the end of each day. 10 seconds effort per day.
- Actigraphy via smart watches / small devices.
- Days spent out of school.
- Others…
- Further work is needed to show if these measures:
  - Can be reliably measured;
  - Are sufficiently sensitive;
  - Correlate with (or actually are) something meaningful for patients;
  - What are the data sources and timings for this?

Conclusions

- We need to know how to judge whether PK/PD studies are a success or not:
  - Means we can power them;
  - May depend on the PD endpoint in question.
- Important that if an endpoint is chosen for a study in terms of practicality and acceptability that it is also sufficiently sensitive.
- Cannot waste patients in studies that are inconclusive because we did not get the design right.
- Would like to have at least one PD / Efficacy variable where $p<0.05$ to give some degree of surety that we are not just seeing noise in the data.