What matters most? - a scientific advice role play

Sponsor Presentation
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Background

IL99 new biological treatment for COPD

Prior agreements with agency (not to be discussed today)
– Dose of 1mg by injection every 4 weeks
– Primary endpoint of exacerbations
  – defined as worsening of COPD symptoms requiring oral steroids or antibiotics
– Secondary endpoint of SGRQ (standard QoL measure for COPD)

Topic for today’s discussion
• Estimand for pivotal trials 5062018 and 5062019 (identical trials)
• Specifically strategy for intercurrent events
Trial 5062018: IL99 in severe COPD

Identical design for trial 5062019

- **Objective:** compare efficacy of new IL-99 biologic treatment vs. placebo (superiority study)
- Phase III study, 52 weeks, double blind, parallel group
- Subjects to maintain background standard of care therapy
- Planned follow-up off treatment for subjects prematurely discontinuing randomised treatment, but withdrawals from study expected.

- **Inclusion criteria:**
  - Background treatment: maximal standard of care therapy, triple therapy with LABA+ICS+LAMA
    - (LABA: long acting bronchodilator, ICS: inhaled corticosteroid, LAMA: long acting muscarinic)
  - Use of triple therapy for at least the last year
  - Not completely controlled on triple therapy: ≥1 exacerbation during previous year
Trial 5062018: IL99 in severe COPD

- **Population:** defined by inclusion/exclusion criteria (all patients randomised)
- **Primary Variable:** number of exacerbations
- **Summary:** ratio of rate of exacerbations on IL-99 compared to placebo
- **Secondary variable:** QoL as measured by SGRQ instrument at weeks 12, 24, 36, 52
- **Summary:** average SGRQ score over timepoints
- **Key intercurrent event:** Treatment discontinuation
## Treatment Discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>Expected on placebo</th>
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<tbody>
<tr>
<td>Total</td>
<td>20%</td>
</tr>
<tr>
<td>Death</td>
<td>2%</td>
</tr>
<tr>
<td>Other AE</td>
<td>9%</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>2%</td>
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<tr>
<td>Withdrawal by subject</td>
<td>7%</td>
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<tr>
<td>e.g. burden of study procedures</td>
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- Company expects fewer treatment discontinuations on IL-99 compared to placebo.
Company proposed strategy

“While on-treatment” strategy for discontinuation of randomised treatment.

- Supplementary analysis of frequency and time of treatment discontinuation

**Rationale**

- Most informative to the prescriber and patient
  - Treatment policy: averages periods using treatment with not using treatment and average patients who take medication with patients who discontinue trials
  - Hypothetical: requires extrapolation beyond data observed
- Post-treatment data may include alternative medication
  - Doesn’t reflect efficacy of randomised treatment
- Fair assessment of benefit : risk
  - Safety typically assessed “while on-treatment”