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

	Expected on placebo
Total	20%
Death	2%
Other AE	9%
Lack of efficacy	2%
Withdrawal by subject e.g. burden of study procedures	7%

– 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”