APPENDIX II INTERVENTION SPECIFIC APPENDICES

A: USUAL CARE ARM

1. INTRODUCTION, RATIONALE AND PROTOCOL STRUCTURE

The master protocol describes the overall structure and processes of the study, while this Intervention Specific Appendix (ISA) outlines details specific to the study arm. This Usual Care arm will follow current standard care in the specific country and provides a control against which the effect of new interventions that are added to usual care can be assessed. Usual Care in the trial will not be specified or mandated, and it may vary over time according to emerging evidence, evolving national recommendations, and can be tailored by responsible healthcare practitioners according to patient characteristics, the respiratory infection, clinical picture, and individual needs. In addition, individual patients are able use over-the-counter remedies. Usual Care can therefore involve prescribed and/or over-the-counter medication and/or advice on self-care. Use of key treatments will be captured in CRFs and may be considered in analyses.

2. OBJECTIVES

As per master protocol.

3. STUDY DESIGN

Participants randomised to the Usual Care arm will receive usual clinical care according to standard care in the specific country, at the discretion of responsible treating clinicians and according to participant's own decisions about self-care for their respiratory tract infection.

4. STUDY POPULATION

Patients will be only eligible for the Usual Care arm if they meet the in- and exclusion criteria for eligibility to at least one other investigational product intervention.

4.1 Sample size calculation

The maximum sample size of 333 per arm has a one-sided error rate less than 2.5% and power around 90% for median time to recovery ranging from 12 to 6 days in the control group and a hazard ratio of 1.33. This assumes analysis using a Bayesian piecewise exponential model with weakly informative priors and interim analyses with early stopping rules for futility and superiority when 150 and 225 patients have been recruited to the control group and have been followed for 28 days. Early stopping rules for both superiority and futility are based on thresholds of the posterior distribution that have been justified using simulation (see M-SAP). Success is declared at maximum sample size if the posterior probability of superiority is greater than a final superiority threshold, which again is specified in the M-SAP.

5. STUDY TREATMENTS

This Usual Care arm will follow current standard care in the specific country at the discretion of responsible treating clinicians and according to participant's own decisions about self-care and provides a control against which the effect of new interventions that are added to usual care can be assessed.

6. OTHER TREATMENTS AND RESTRICTIONS

Not applicable.

7 TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

Not applicable.

8 METHODS

8.1 Study parameters/ endpoints

No blood samples will be collected.

8.2 Randomisation, blinding and treatment allocation

As per master protocol.

8.3 Study procedures

As per master protocol.
In addition, pregnancy should be ruled out by a negative urine pregnancy test for all women of child-bearing potential prior to randomisation if this is required per the in- and exclusion criteria of at least one other investigational product intervention.

8.4 Withdrawal of individual participant

As per master protocol.

8.5 Replacement of individual participants after withdrawal

As per master protocol.

8.6 Discontinuation of treatment of individual participants

As per master protocol.

8.7 Premature termination of the study or arm

As per master protocol.

9 SAFETY REPORTING

9.1 Adverse events (AEs)
As per master protocol

9.2 Serious adverse events (SAEs)

As per master protocol

10 STATISTICAL ANALYSIS

As per master protocol.

11 ETHICAL CONSIDERATIONS

As per master protocol.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

As per master protocol.

13 STRUCTURED RISK ANALYSIS

Not applicable.

14 Appendices

14.1 German Specific Appendix

In Germany usual care should adhere to the national S3 guideline on respiratory tract infections by DEGAM (S3-Leitlinie Akuter und chronischer Husten), available on the AWMF Leitlinien-Register (https://register.awmf.org/de/start).