Table 1.0. Standardizing Exacerbation Outcomes in Clinical Studies of COPD

Endpoint[a]	Definition	Measurement Approach	
		Medically-Treated Events (MTEs)	**Symptom-Defined Events:**
Frequency Event rate	– Event rate: per person per year – Event definition: acute sustained symptomatic worsening of COPD; treated with antibiotics, steroids, in hospital, or self-treated at home	Number of health care resource utilization (HCRU) events: – Clinic or urgent care visit for an acute sustained symptomatic worsening of COPD, treated with antibiotics and/or steroids – Hospitalization for an acute sustained symptomatic worsening of COPD EXACT score changes may be used to document change in symptoms associated with HCRU events.	Number of symptom-defined events: – Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score ≥9 points for 3 days or ≥12 points for 2 days, above Baseline Reported: accompanied by clinic or urgent care visit with antibiotic and/or steroid treatment or hospitalization Unreported[b]: no associated visit or hospitalization; self-treated at home
Time to first event **Time to subsequent (next) event**	– Days from initiation of treatment/placebo to first event – Days from recovery to subsequent (next) event	First HCRU Event: – Days to Day 1, clinic or urgent care visit – Days to Day 1, hospitalization Subsequent HCRU event: – Days from end of treatment for first HCRU event to Day 1 of next HCRU event	First symptom-defined event: – Days to Day 1 of sustained increase in EXACT score exceeding event threshold Subsequent symptom-defined event: – Days from Recovery from first symptom-defined event to Day 1 of next symptom-defined event
Proportion of patients with ≥ 1 event	– % patients with ≥1 event	% with ≥1 HCRU event: – % with ≥1 clinic or urgent care visit – % with ≥1 hospitalization	– % with ≥1 symptom-defined event: – % with ≥1 unreported symptom-defined event
Severity	– Degree or magnitude of the event(s)	Type of treatment: – Moderate: antibiotics or steroids – Severe: hospitalization Symptom severity: – Maximum EXACT score during the HCRU event – Change in EXACT score, baseline to HCRU Day 1 – Mean EXACT score during treatment; area under the curve (AUC)	Unreported, symptom-defined events: – Mild: self-treated at home[b] Symptom severity: – Maximum EXACT score during the event – Change in EXACT score, baseline to event Day 1 – Mean EXACT score during the event; AUC
Duration	– Length of the event(s)	Duration of treatment: – Days of treatment with antibiotics or steroids – Days of hospitalization	Duration of symptoms: – Days from symptom onset to symptom recovery – Recovery: improvement in EXACT score ≥9 points from the maximum value, sustained for ≥7 days

[a]Consistent with the FDA Draft COPD Guidance, if 1 of these endpoints is chosen as the primary efficacy endpoint, the others also should be assessed to ensure that another exacerbation outcome has not worsened. [1, pp.8]

[b]Characterized as "mild" in EMA COPD Guideline.[2]

[1] Food and Drug Administration. Draft guidance for industry on chronic obstructive pulmonary disease: developing drugs for treatment. Silver Spring, MD: Center for Drug Evaluation and Research (CDER). 2007; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071575.pdf.

[2] European Medicines Agency, Respiratory Drafting Group. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/483572/2012. London: European Medicines Agency. 2012; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf.