Global Medical Affairs Cover Sheet

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Global Medical Affairs

Novel Symbicort Turbuhaler Asthma Reliever Therapy (START) – Study Overview

Veeva Vault MedComms Document Number: ML-3010-ALL-0123

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Clinical Programs Investigating Budesonide/Formoterol as an Anti-inflammatory Reliever in Mild Asthma

START Study Analysis: Mild patients benefit from early introduction and long-term ICS (budesonide)[1]

Novel START:
As-needed budesonide/formoterol in mild asthma[3]

To investigate if an open-label, clinical trial of as-needed budesonide/formoterol in adults previously treated with as-needed SABA only could extend the results from SYGMA to a real world setting

PRACTICAL:[a]
An independent study
As-needed budesonide/formoterol[4,5]

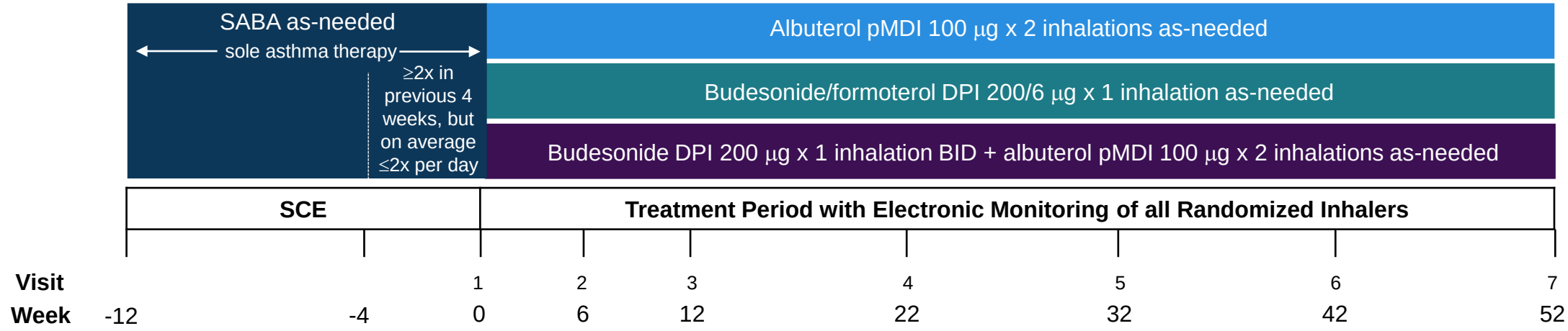
[a]PRACTICAL is not an AstraZeneca study.

ICS = inhaled corticosteroid; Novel START = Novel Symbicort Turbuhaler Asthma Reliever Therapy; PRACTICAL = PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist; SABA = short-acting beta$_2$- agonist; START = Steroid Treatment As Regular Therapy; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. Reddel HK et al. *Lancet.* 2017;389:157-166; 2. O'Byrne PM et al. *Trials.* 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed March 4, 2019; 3. 2. Beasley R et al. *Eur Respir J.* 2016;47:981-984.; 4. Study ACTRN12616000377437. Australian New Zealand Clinical Trials Registry website. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370122. Accessed March 4, 2019; 5. Fingleton J et al. *BMJ Open Resp Res*. 2017;4:e000217. https://bmjopenrespres.bmj.com/content/4/1/e000217. Accessed March 7, 2019.

Study Design[a]

12-month, **pragmatic**, randomized, open-label, parallel-group, multicenter study (N=675) to assess the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever compared to SABA as-needed or ICS maintenance + SABA as-needed in patients with mild asthma **previously treated with SABA alone**[1,2]



Primary efficacy endpoint:	Annualized rate of asthma exacerbations per patient
Secondary endpoints:	Number[b] of exacerbations by exacerbation treatment criteria and time to first exacerbation; number of severe exacerbations;[c] percentage of patients withdrawn due to treatment failure;[d] ACQ-5; FE_{NO}; on-treatment FEV_1; electronically-recorded ICS use and $beta_2$-agonist use; OCS use.
Safety:	Adverse events

[a]Analyses were intention-to-treat; [b]Resulting in medical care consultation and/or systemic glucocorticoids and/or high $beta_2$-agonist use; [c]Prescription of systemic glucocorticoids for ≥3 days for asthma and/or hospitalization or ED visit due to asthma leading to systemic glucocorticoids; [d]A total of three exacerbations, one severe exacerbation, or unstable asthma resulting in change in randomized treatment.

ACQ-5 = Asthma Control Questionnaire-5; DPI = dry powder inhaler; ED = emergency department; FE_{NO} = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; OCS = oral corticosteroid; pMDI = pressurized metered-dose inhaler; SABA = short-acting β_2-agonist; SCE = screening, consent, enrollment.

1. Beasley R et al. *Eur Respir J.* 2016;47;981-984; 2. Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Baseline Characteristics

	Albuterol 100 µg x 2 Inhalations As-Needed (n=223)	Budesonide/Formoterol 200/6 µg x 1 Inhalation As-Needed (n=220)	Budesonide Maintenance 200 µg x 1 Inhalation BID + Albuterol 100 µg x 2 Inhalations As-Needed (n=225)
Age, years, mean (SD)	35.8 (14.0)	36 (14.1)	34.9 (14.3)
Female sex, n (%)	113 (50.7)	122 (55.5)	129 (57.3)
Current smoker,[a] n (%)	24 (10.8)	18 (8.2)	22 (9.8)
Patient-reported SABA use in the 4 weeks prior to enrollment:			
Occasions per week, n, mean (SD)	3.4 (3.3)	3.8 (3.5)	3.2 (3.0)
Patients with ≤2 occasions per week, n (%)	127 (57.0)	105 (47.7)	132 (58.7)
≥1 severe exacerbations in the prior 12 months,[b] n (%)	20 (9.0)	12 (5.5)	17 (7.6)
ACQ-5 score, mean (SD)	1.1 (0.7)	1.1 (0.7)	1.1 (0.7)
On-treatment[c] FEV_1 % predicted, mean (SD)	89.2 (13.7)	89.8 (14.1)	90.3 (13.6)
Median FE_{NO} (range), ppb	40 (5-235)	37 (3-300)	38 (5-200)
Blood eosinophils x 10^{-9}/L, mean (SD)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)

[a]Patient-reported smoking history >20 pack-years or onset of respiratory symptoms after the age of 40 years in current or previous smokers with a smoking history of ≥10 pack-years was a key exclusion criterion; [b]Hospitalization for asthma in the previous 12 months was a key exclusion criterion; [c]There was no specific instruction for patients to withhold their bronchodilator use prior to the baseline measurement.

ACQ-5 = Asthma Control Questionnaire-5; FE_{NO} = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; SABA = short-acting β_2-agonist; SD = standard deviation.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Exacerbation Definitions

Primary Endpoint

Exacerbations:

Worsening asthma resulting in ≥1 of the following:

- **An urgent medical care consultation:**
  - Primary care visit
  - Emergency department visit
  - Hospital admission
- **A prescription for glucocorticoids for any duration**
- **An episode of high β_2-agonist use:**
  - >16 actuations of albuterol within 24 hours
  - >8 actuations of budesonide/formoterol within 24 hours

Secondary Endpoint

Severe Exacerbations:

Based on ATS/ERS Task Force criteria

Worsening asthma leading to:

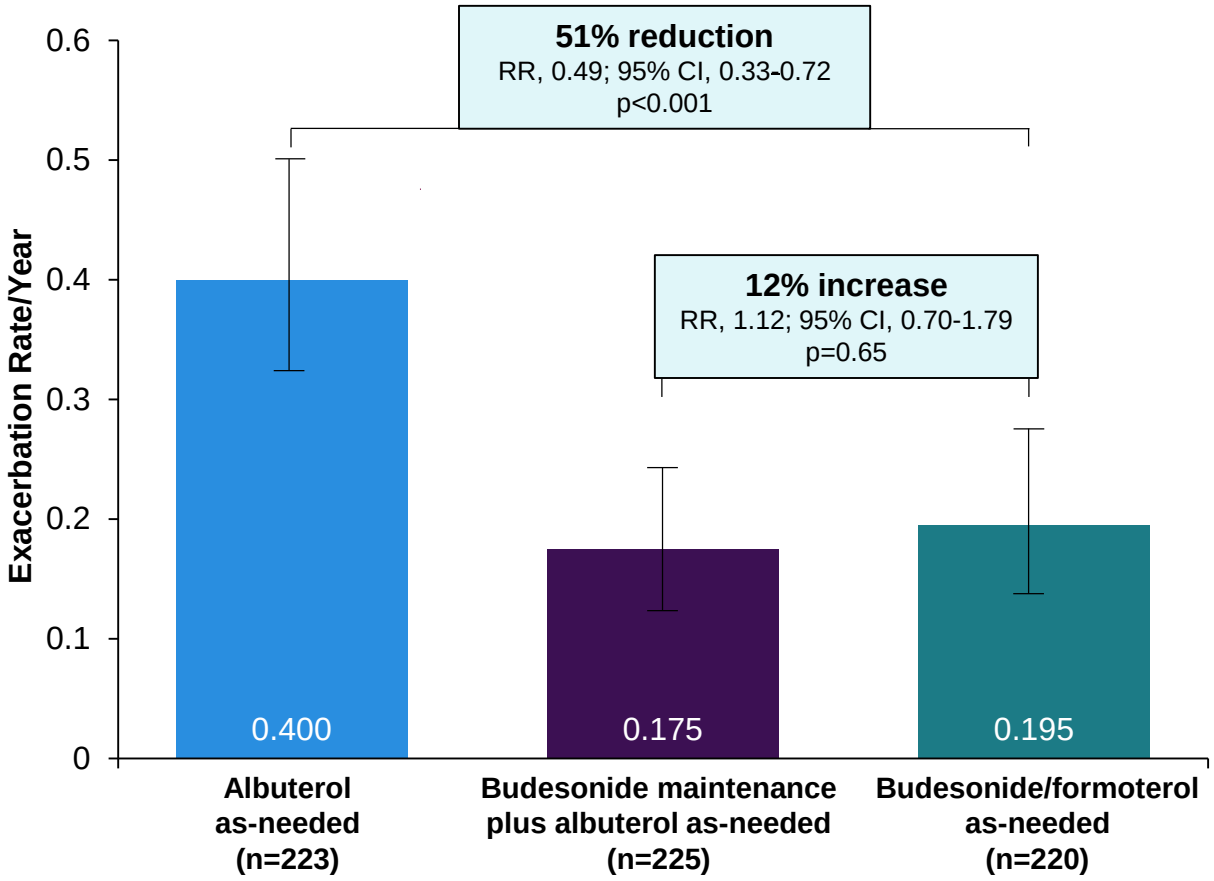
- **A prescription** for systemic glucocorticoid treatment for ≥3 days *or*
- **Hospitalization or emergency department visit** leading to a prescription for systemic glucocorticoid treatment

ATS = American Thoracic Society; ERS = European Respiratory Society.

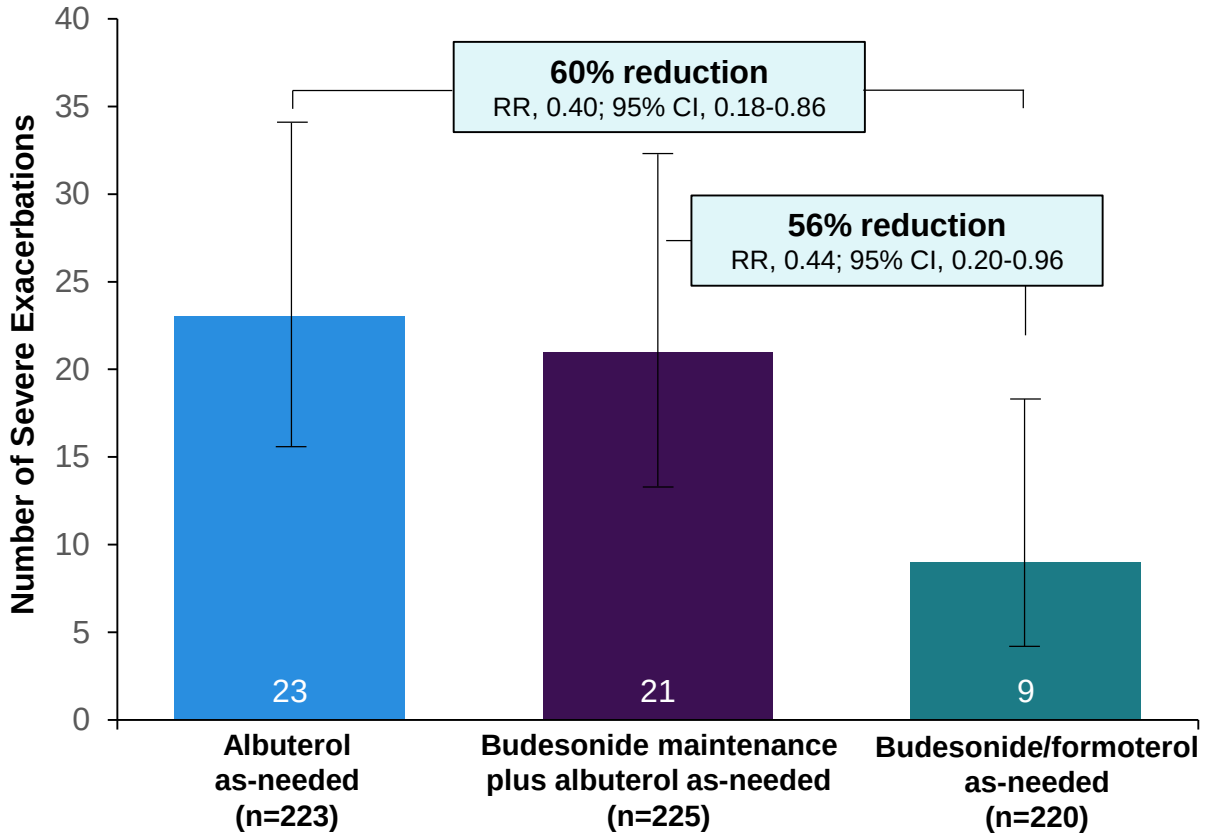
Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Exacerbation Outcomes

Annualized Exacerbation Rate[1] (Primary Outcome)



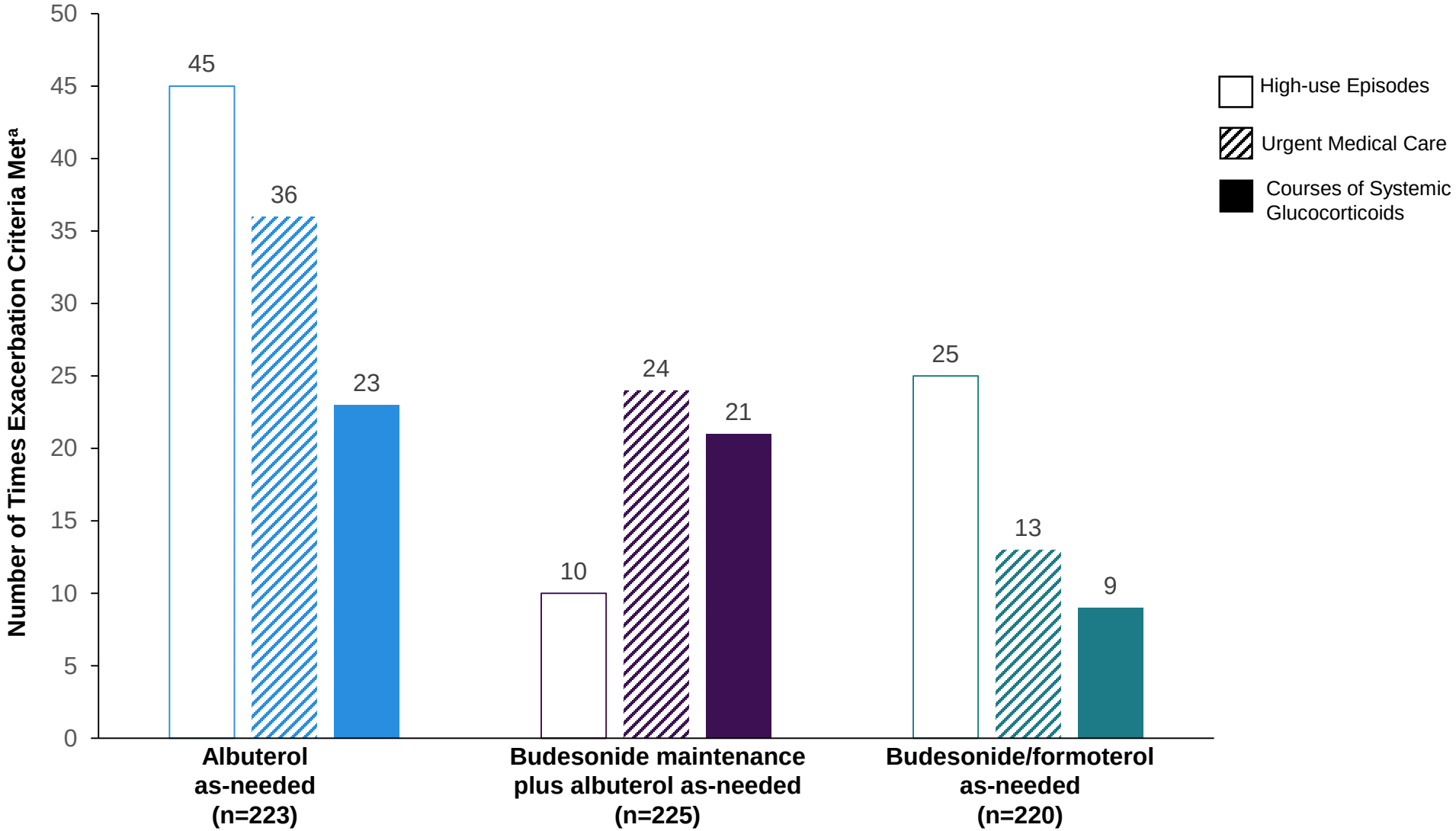
Number of Severe[a] Exacerbations (Secondary Outcome)[1b]



[a]For severe exacerbations, the *relative risk* was estimated as opposed to the *relative rate*, as participants could only have 1 severe exacerbation after which they were withdrawn from the study;[2] [b]Secondary endpoints were not adjusted for multiplicity. RR = relative rate (left graph); RR = relative risk (right graph).

1. Beasley R et al. *N Engl J Med*. 2019;380:2020-2030; 2. Beasley R et al. Supplementary appendix. *N Engl J Med*. 2019. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1901963/suppl_file/nejmoa1901963_appendix.pdf. Accessed 19 May, 2019.

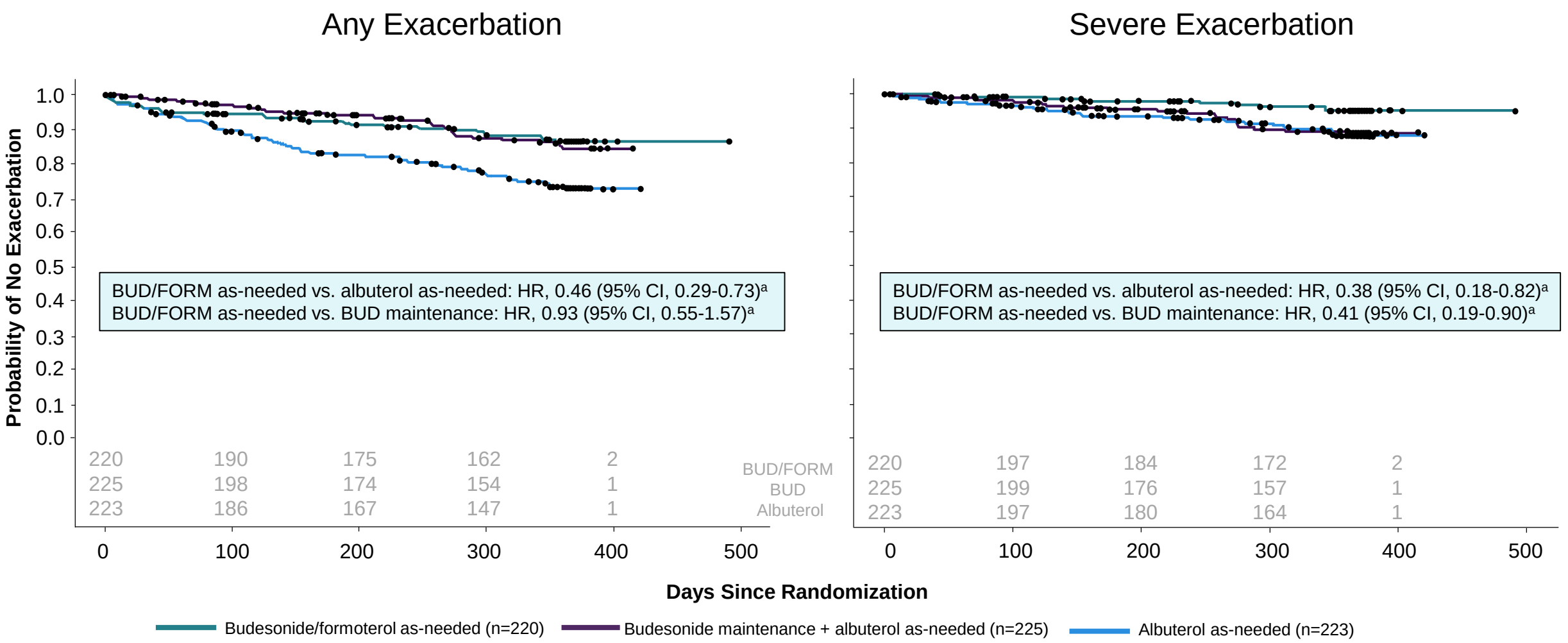
Number of Exacerbations By Exacerbation Treatment Criteria



[a]Secondary endpoints were not adjusted for multiplicity.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

First Exacerbation

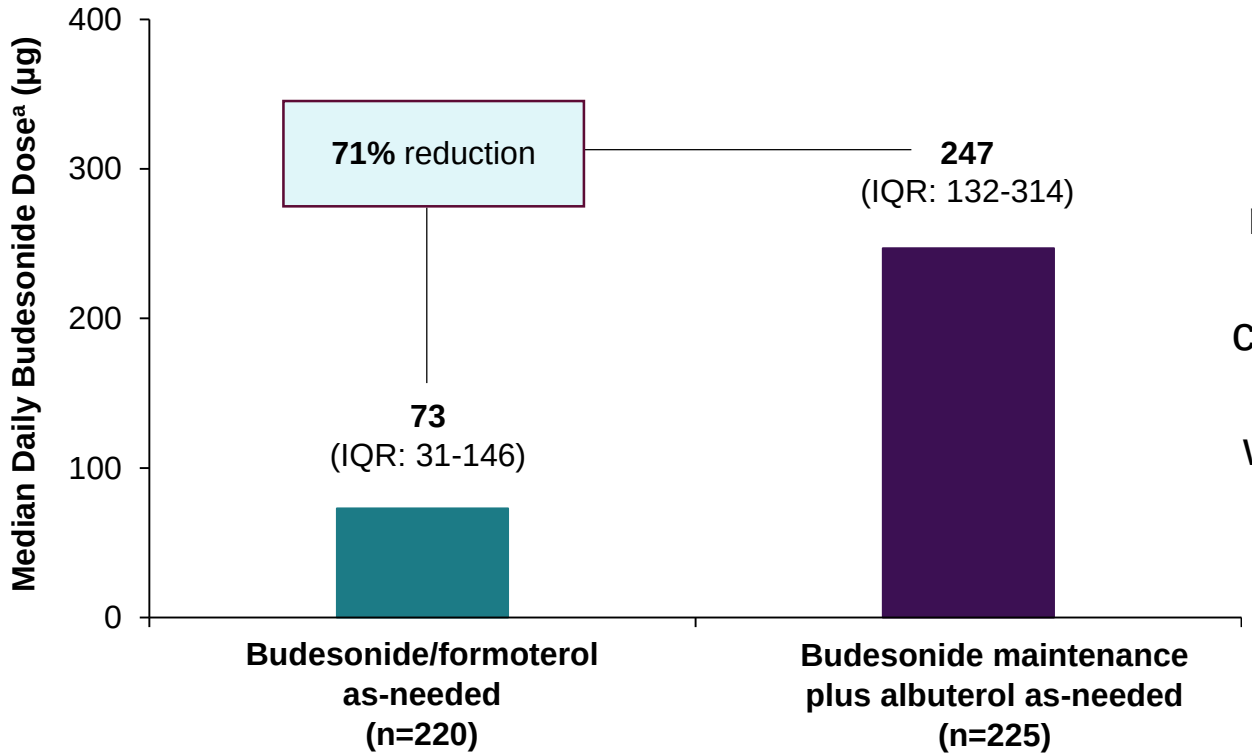


[a]Secondary endpoints were not adjusted for multiplicity.

BUD = budesonide; FORM = formoterol; HR = hazard ratio; Novel START = Symbicort Turbuhaler Asthma Reliever Therapy; SABA = short-acting β_2-agonist.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Fewer Severe Exacerbations With >70% Lower Corticosteroid Load



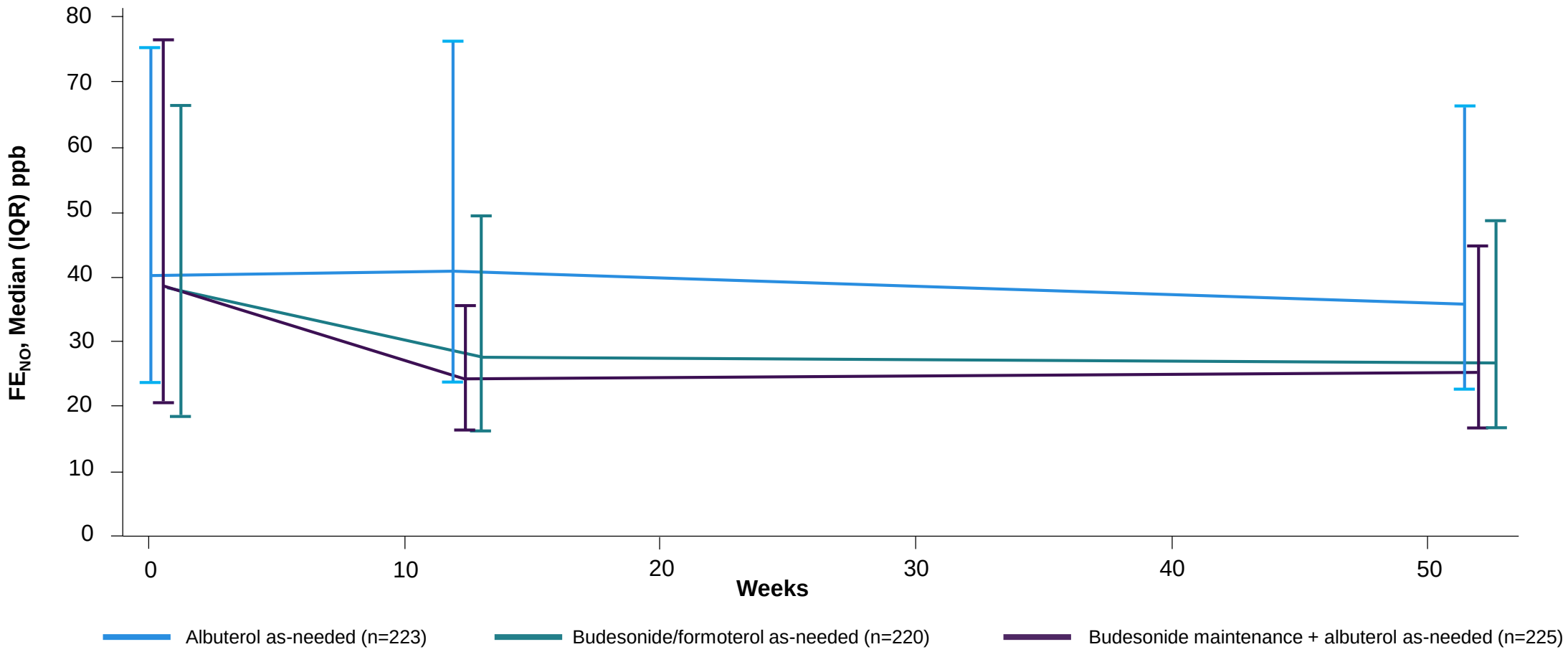
A 56% reduction (p=0.038)[a] in the number of severe exacerbations with budesonide/formoterol as-needed compared to budesonide maintenance plus SABA as-needed was achieved with a >70% lower corticosteroid load

[a]Secondary endpoints were not adjusted for multiplicity.

IQR = interquartile range; Novel START = Novel Symbicort Turbuhaler Asthma Reliever Therapy.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Fraction of Exhaled Nitric Oxide



Ratio of Geometric Mean FE_{NO} at 52 weeks:[a] BUD/FORM as-needed vs. albuterol as-needed, 0.83 (95% CI, 0.75-0.91); BUD/FORM as-needed vs. BUD maintenance, 1.13 (95% CI, 1.02-1.25)

[a]Secondary endpoints were not adjusted for multiplicity. BUD = budesonide; FE_{NO} = fraction of exhaled nitric oxide; FORM = formoterol; IQR = interquartile range; ppb = parts per billion.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Safety and Tolerability

Patients, n (%)	Albuterol 100 μg x 2 Inhalations As-Needed (n=226)	Budesonide/Formoterol 200/6 μg x 1 Inhalation As-Needed (n=222)	Budesonide Maintenance 200 μg x 1 Inhalation BID + Albuterol 100 μg x 2 Inhalations As-Needed (n=227)
Patients with ≥1 AE	185 (81.9)	174 (78.4)	190 (83.7)
Most common AEs (occurring in ≥2% of patients)			
Upper respiratory tract infection	75 (33.2)	71 (32.0)	75 (33.0)
Viral upper respiratory tract infection	5 (2.2)	6 (2.7)	8 (3.5)
Asthma	46 (20.4)	17 (7.7)	26 (11.5)
Patients with ≥1 SAE (including death)	6 (2.7)	13 (5.9)[a]	7 (3.1)[b]

Adverse events were consistent with prior trials and with reports in clinical use

[a]Death was due to motor vehicle accident (n=1); [b]Death was due to suicide (n=1).
AE = adverse event; BID = twice daily; SAE = serious adverse event.
Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.

Conclusions

In an open-label study of patients with mild asthma who were previously treated with SABA as-needed, treatment with budesonide/formoterol as-needed resulted in the following:

- Compared to albuterol as-needed:
  - Reduced rate of any exacerbation by 51%
  - Reduced rate of severe exacerbations by 60%
- Compared to maintenance budesonide:
  - Comparable rate of any exacerbation
  - Reduced rate of severe exacerbations by 56% at a >70% lower steroid load

SABA = short-acting β_2-agonist.

Beasley R et al. *N Engl J Med*. 2019;380:2020-2030.