Global Medical Affairs Cover Sheet

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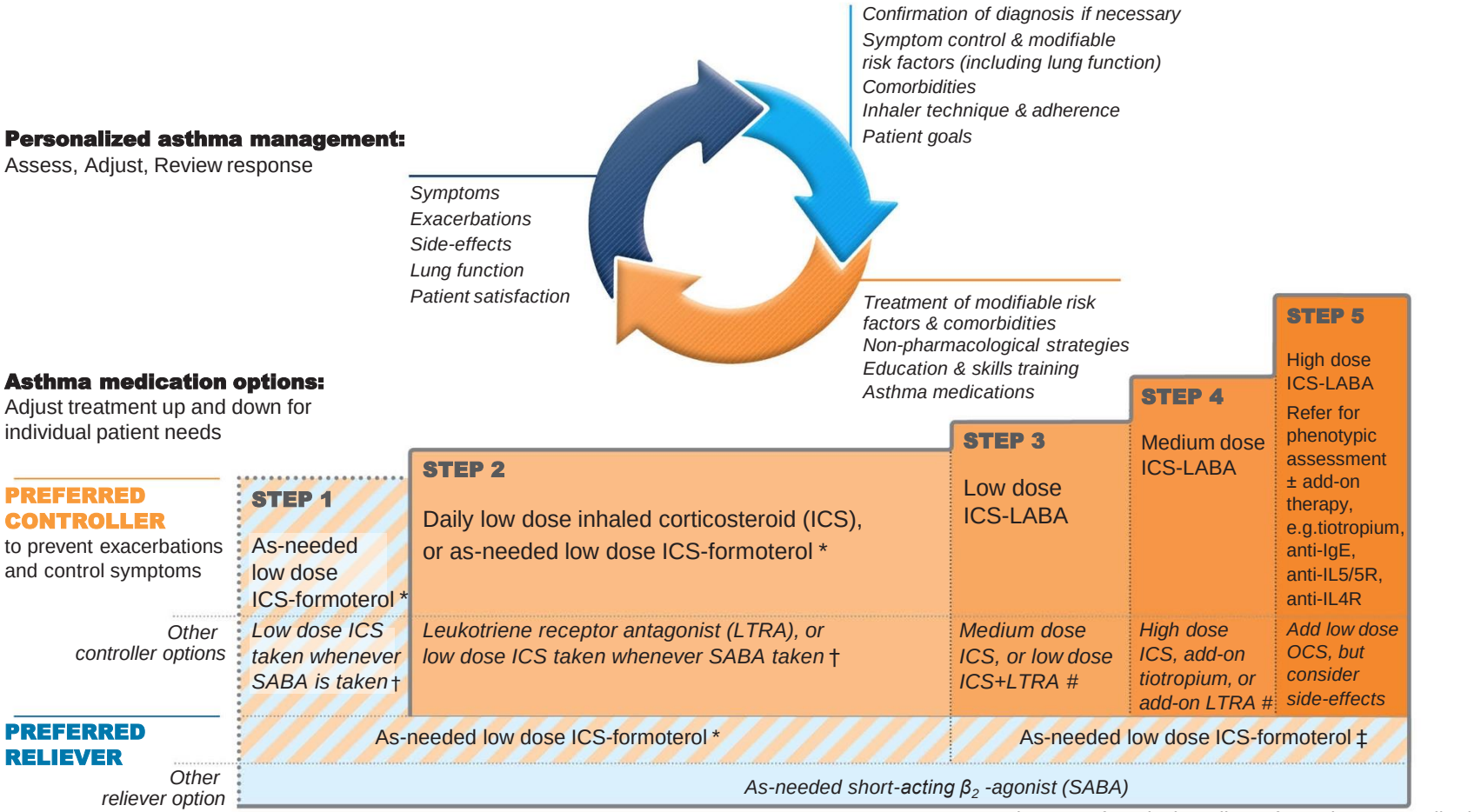
Global Medical Affairs

Symbicort Given as needed in Mild Asthma (SYGMA) Overview

Veeva Vault MedComms Document Number: ML-3010-ALL-0036
Approval Date: 04/19
Expiration Date: 04/20

2019 GINA Asthma Treatment Strategy for Adults and Adolescents + 12 years[1]



* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

1. www.ginasthma.org. Accessed April 2019

AstraZeneca Clinical Programme 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]

SYGMA[2]

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

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

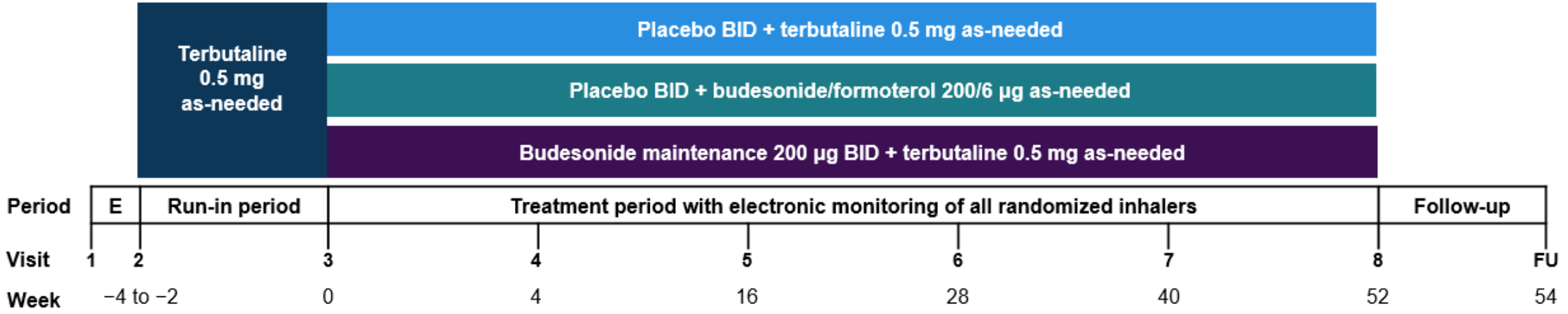
[a]PRACTICAL is not an AstraZeneca study.

ICS = inhaled corticosteroid; Novel START = Symbicort Turbuhaler Asthma Reliever Therapy; PRACTICAL = PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta 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. 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.

SYGMA 1: Study Design[a]

12-month, randomized, double-blind, parallel-group, multicenter study (N=3849)
to assess the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever
in comparison to SABA as-needed or ICS maintenance + SABA as-needed
in patients with mild asthma[1,2]



Primary efficacy endpoint:	WCAW (superiority vs. terbutaline as-needed)
Secondary endpoints:	WCAW (non-inferiority vs. budesonide maintenance + terbutaline as-needed), severe asthma exacerbation rate, FEV_1, ACQ-5, AQLQ, ICS use, use of as-needed inhalations
Safety:	Adverse events

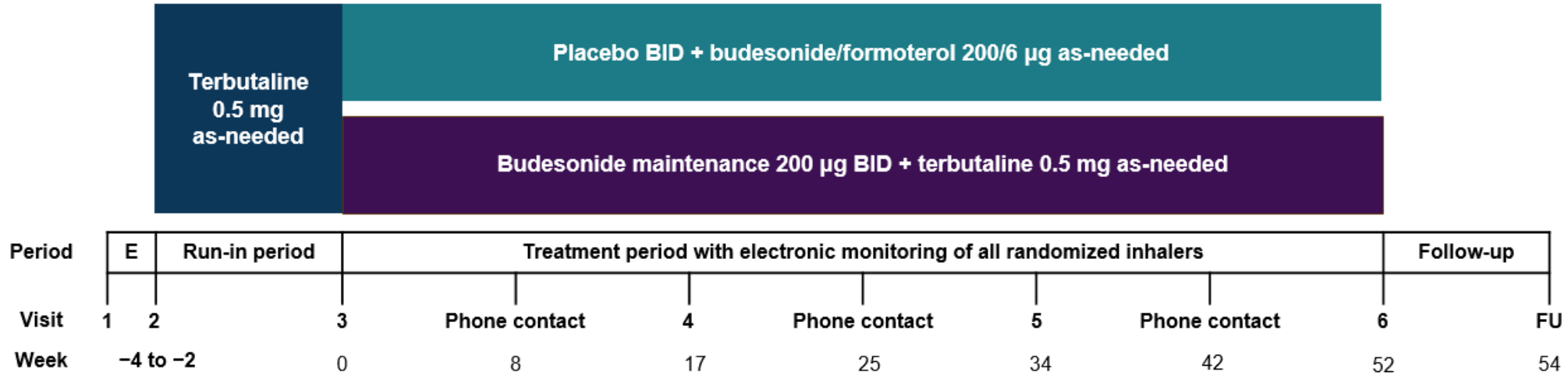
[a]Analysis was based on the full analysis set according to the intention-to-treat principle set forth by the International Conference on Harmonization E9 Working group.[3]

ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; E = enrolment; FEV_1 = forced expiratory volume in 1 second; FU = follow-up phone contact; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SYGMA = SYmbicort Given as needed in Mild Asthma; WCAW = well-controlled asthma week.

1. O'Byrne PM et al. *Trials.* 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed March 4, 2019; 2. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 3. International Conference on Harmonization Steering Committee. Statistical principles for clinical trials. ICH harmonized tripartite guideline. February 5, 1998.

SYGMA 2: Study Design[a]

12-month, randomized, double-blind, parallel-group, multicenter study (N=4215)
to assess the long-term efficacy and safety of budesonide/formoterol anti-inflammatory reliever
in comparison to ICS maintenance + SABA as-needed
in a pragmatic trial of patients with mild asthma[1,2]

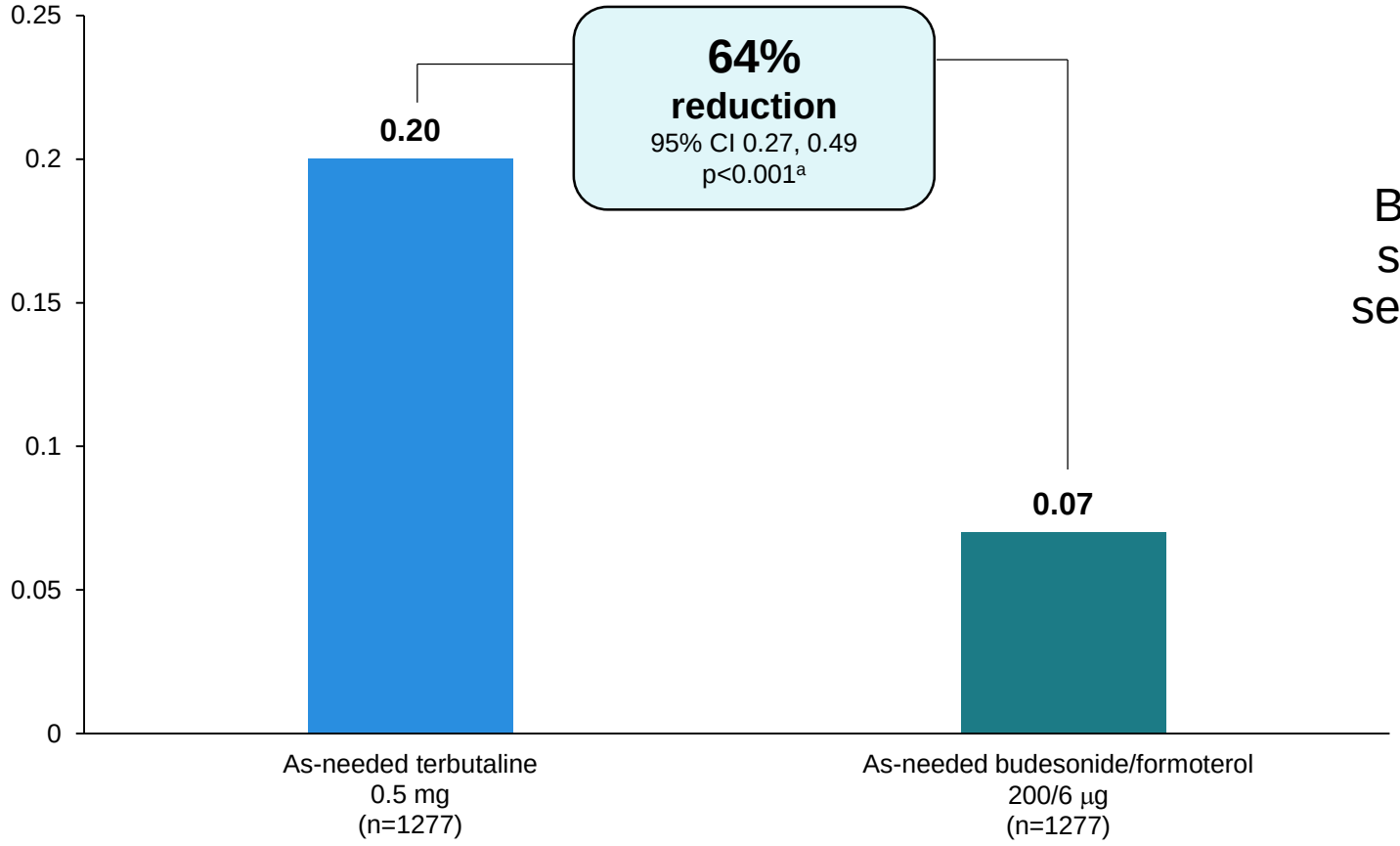


Primary efficacy endpoint:	Annualized severe asthma exacerbation rate (non-inferiority) defined as systemic corticosteroids for ≥3 days or hospitalization or ED visit due to asthma requiring systemic corticosteroids
Secondary endpoints:	FEV_1, ACQ-5, AQLQ, ICS use, use of as-needed inhalations
Safety:	Adverse events

[a]Analysis was based on the full analysis set according to the intention-to-treat principle set forth by the International Conference on Harmonization E9 Working group.[3]
ACQ-5 = Asthma Control Questionnaire-5; AQLQ = Asthma Quality of Life Questionnaire; E = enrolment; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FU = follow-up phone contact; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne PM et al. *Trials.* 2017;18:12. https://doi.org/10.1186/s13063-016-1731-4. Accessed March 4, 2019. 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:1877-1887;
3. International Conference on Harmonization Steering Committee. Statistical principles for clinical trials. ICH harmonized tripartite guideline. February 5, 1998.

SYGMA 1: Lower Severe Exacerbation Rate



Budesonide/formoterol as-needed significantly decreased the rate of severe exacerbations in comparison to terbutaline as-needed.

Severe exacerbation rate reduction is in addition to meeting the primary endpoint of increased odds of a WCAW (OR: 1.14; 95% CI: 1.00, 1.30; p=0.046)

Note: Severe asthma exacerbation rates were analysed by a negative binomial regression model with randomized treatment, pre-study treatment, region, and number of severe exacerbations in the 12 months prior to screening (0 or ≥1) as factors.

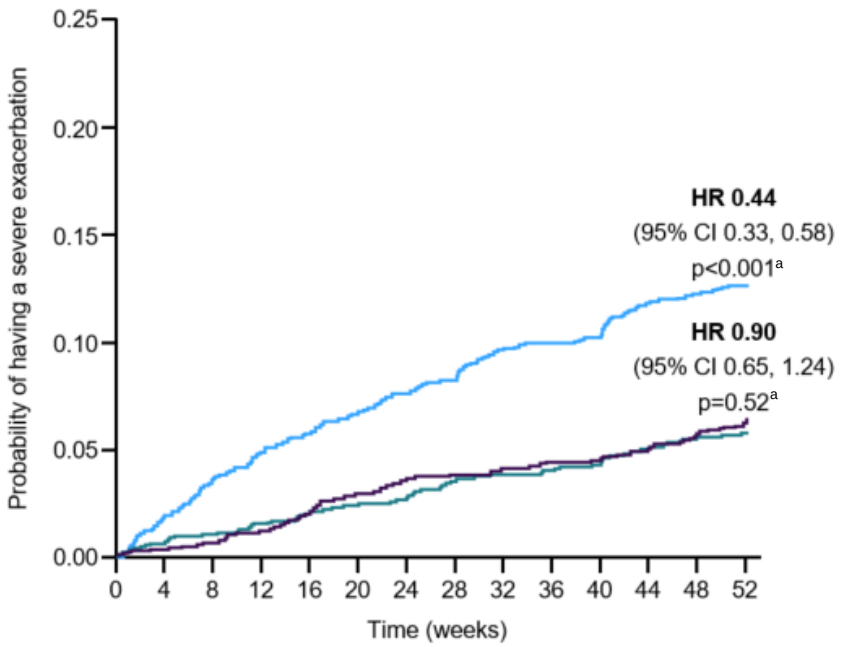
[a]p-values not controlled for multiplicity.

CI = confidence interval; OR = odds ratio; SYGMA = SYmbicort Given as needed in Mild Asthma; WCAW = well-controlled asthma week.

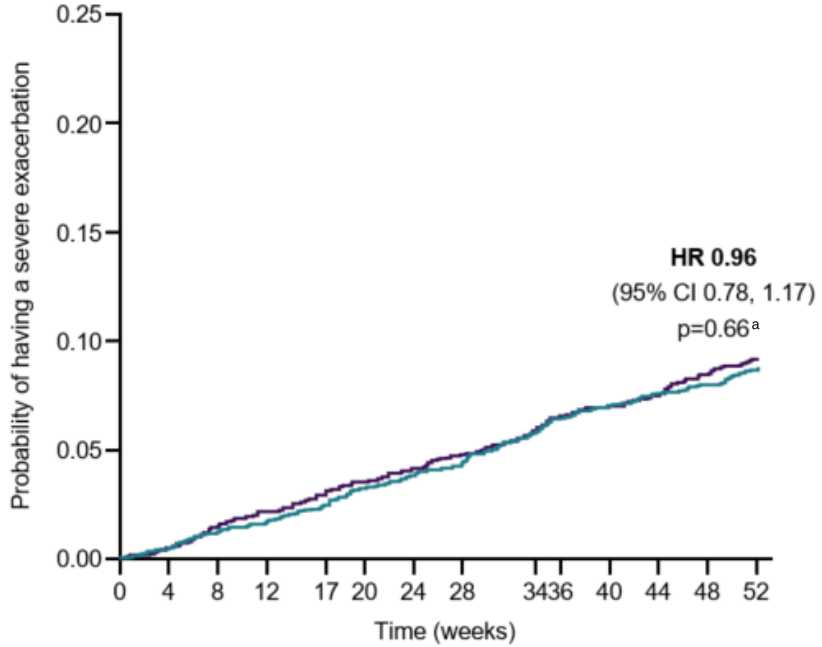
O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876.

SYGMA 1 & 2: Time to First Severe Exacerbation

SYGMA 1[1]



SYGMA 2[2]



Terbutaline as-needed

Budesonide/formoterol as-needed

Budesonide maintenance + terbutaline as-needed

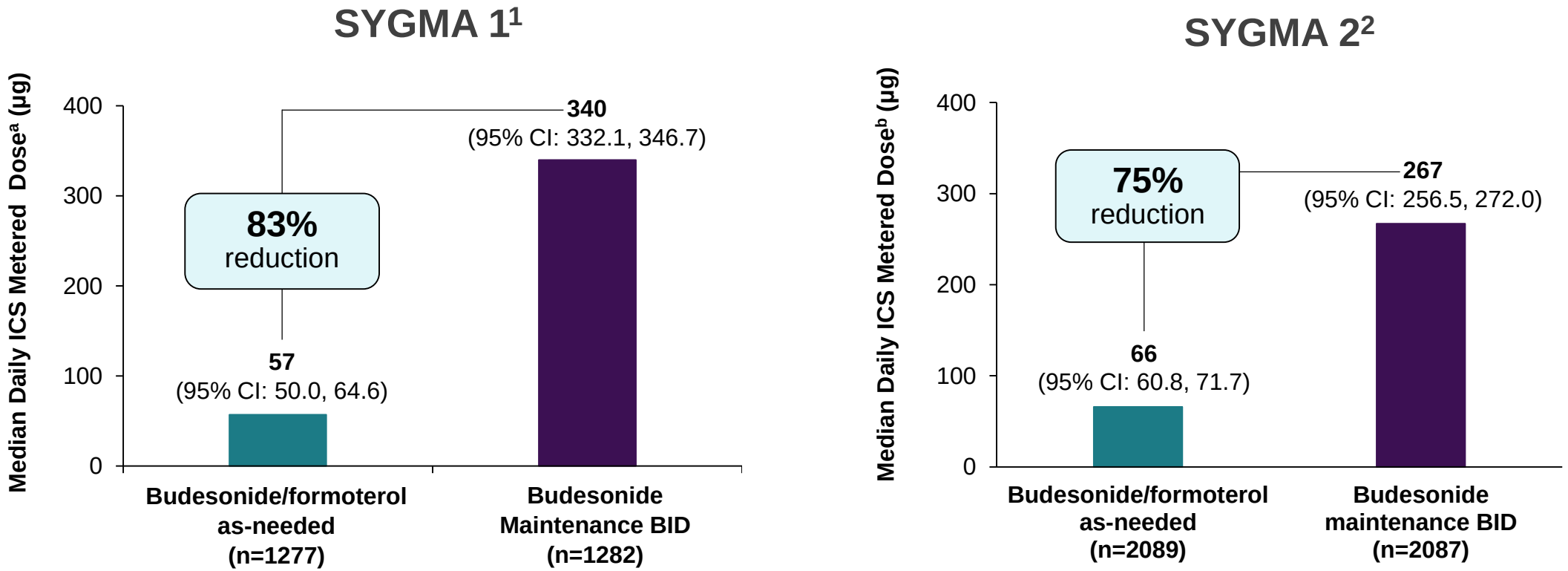
Budesonide/formoterol as-needed was not significantly different from maintenance budesonide and was superior to terbutaline as-needed in prolonging time to first severe exacerbation[1,2]

[a]p-values not controlled for multiplicity.

CI = confidence interval; HR = hazard ratio; SYGMA = SYmbicort Given as needed in Mild Asthma

1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887.

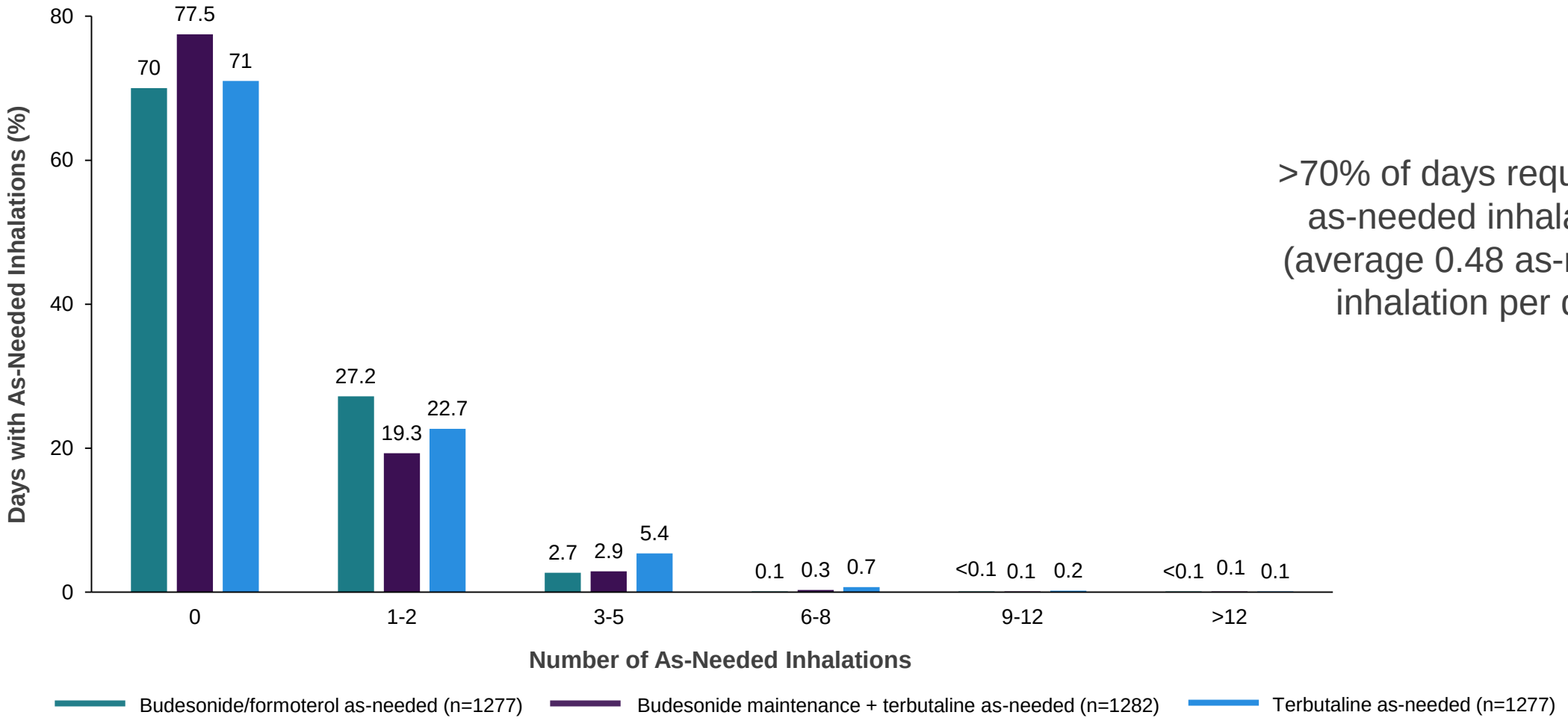
SYGMA 1 & 2: Comparable Risk of Severe Exacerbations With ≥75% Lower Corticosteroid Load



[a]Including open-label glucocorticoid prescribed for moderate or severe exacerbations or for long-term poor asthma control; [b]Including non-blinded ICS use prescribed during severe exacerbations.
BID = twice daily; CI = confidence interval; ICS = inhaled corticosteroid; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1: Percentage of Days With As-Needed Inhalations

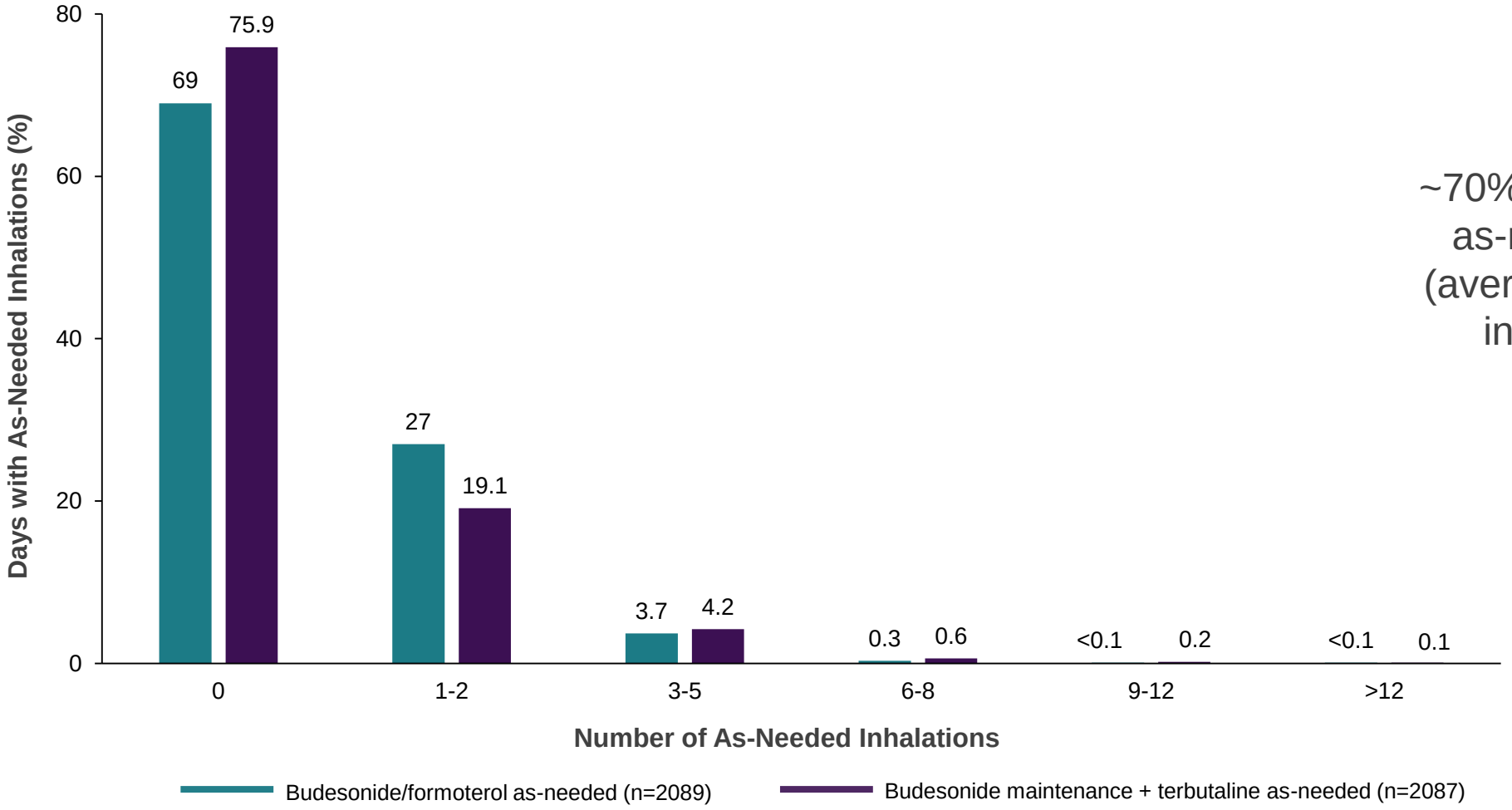


>70% of days required no as-needed inhalations (average 0.48 as-needed inhalation per day)

SYGMA = SYmbicort Given as needed in Mild Asthma.

In House Data, AstraZeneca Pharmaceuticals LP. DoF SD-3010-ALL-0016.

SYGMA 2: Percentage of Days With As-Needed Inhalations

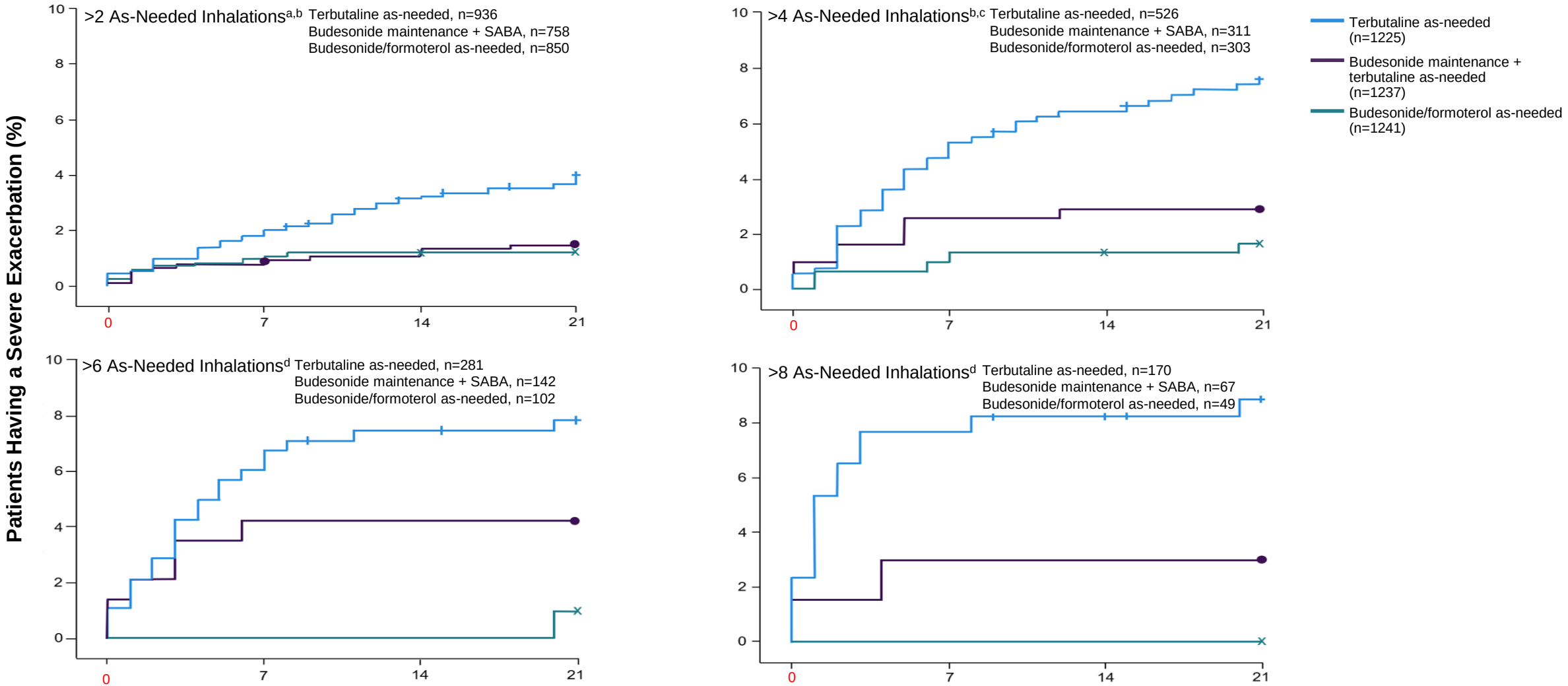


~70% of days required no as-needed inhalations (average ~0.5 as-needed inhalation per day)

SYGMA = SYmbicort Given as needed in Mild Asthma.

Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1 Post Hoc Analysis: Severe Exacerbations Within 21 Days of First Day of High Reliever Use (Day 0)



[a]Budesonide/formoterol as-needed vs. terbutaline as-needed, p=0.001; [b]Budesonide/formoterol as-needed vs. budesonide maintenance plus terbutaline as-needed, not significant; [c]Budesonide/formoterol as-needed vs. terbutaline as-needed, p=0.002; [d]Hazard ratios not calculated owing to low event rates. SABA = short-acting β_2-agonist; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne P et al. *Eur Respir J.* 2018;52(suppl 62). Abs 1680.

SYGMA 1 & 2 Safety and Tolerability

	SYGMA 1[1]			SYGMA 2[2]	
Patients, n (%)	**Terbutaline 0.5 mg As-Needed (n=1277)**	**Budesonide/Formoterol 200/6 µg As-Needed (n=1277)**	**Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-Needed (n=1282)**	**Budesonide/Formoterol 200/6 µg As-Needed (n=2089)**	**Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-Needed (n=2087)**
Patients with ≥1 AE	545 (42.7)	485 (38.0)	512 (39.9)	887 (42.5)	919 (44.0)
Most common AEs (occurring in >5% of patients)					
Upper respiratory tract infection	76 (6.0)	71 (5.6)	93 (7.3)	81 (3.9)	89 (4.3)
Viral upper respiratory tract infection	79 (6.2)	75 (5.9)	84 (6.6)	155 (7.4)	168 (8.0)
Asthma	109 (8.5)	37 (2.9)	57 (4.4)	96 (4.6)	97 (4.6)
Patients with ≥1 SAE (including death)	50 (3.9)	38 (3.0)	37 (2.9)[a]	66 (3.2)[b]	73 (3.5)[c]

[a]Deaths were due to upper gastrointestinal hemorrhage (n=1) and brain neoplasm (n=1); [b]Death was due to cardiorespiratory arrest (n=1); [c]Death was due to asthma (n=1).

AE = adverse event; BID = twice daily; SAE = serious adverse event; SYGMA = SYmbicort Given as needed for Mild Asthma.

1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:1877-1887.

SYGMA 1 & 2 Conclusions

In patients with mild asthma, budesonide/formoterol as-needed:

- Increased the odds of a well-controlled asthma week compared to terbutaline as-needed (OR 1.14) but not compared to budesonide maintenance[1]
- Reduced the rate of severe exacerbations by 64% compared to terbutaline as-needed[1]
- Resulted in a comparable rate of severe exacerbations as maintenance budesonide + terbutaline as-needed[1,2]
- Demonstrated efficacy with a ≥75% lower steroid load than the budesonide maintenance arm[1,2]
- Resulted in fewer days with high reliever use
- Reduced the short-term (21-day) risk of exacerbation versus as-needed terbutaline following a day of high reliever use[3]

OR = odds ratio; SYGMA = SYmbicort Given as needed in Mild Asthma.

1. O'Byrne PM et al. *N Engl J Med*. 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med*. 2018;378:1877-1887; 3. O'Byrne P et al. *Eur Respir J.* 2018;52(suppl 62). Abs 1680.

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SYGMA 1 Post Hoc Analysis: Severe Exacerbation Within 21 Days of First Day of High Reliever Use (Day 0)

	SYGMA 1 [1,2]		
Reliever inhalations and Severe Exacerbations, n (%)	Terbutaline 0.5mg As-needed (n=1225)	Budesonide/Formoterol 200/6 µg As-needed (n=1241)	Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=1237)
Patients with >2 reliever inhalations on ≥ 1 day	936 (73.3)	850 (66.6)	758 (59.1)
Patients with severe exacerbations within 21 days	37 (4.0)	10 (1.2)[a,b]	11 (1.5)
Patients with >4 reliever inhalations on ≥ 1 day	526 (41.2)	303 (23.7)	311 (24.3)
Patients with severe exacerbations within 21 days	40 (7.6)	5 (1.7)[c,d]	9 (2.9)
Patients with >6 reliever inhalations on ≥ 1 day	281 (22.0)	102 (8.0)	142 (11.1)
Patients with severe exacerbations within 21 days	22 (7.8)	1 (1.0)[e]	6 (4.2)
Patients with >8 reliever inhalations on ≥ 1 day	170 (13.3)	49 (3.8)	67 (5.2)
Patients with severe exacerbations within 21 days	15 (8.8)	0 (0.0)[e]	2 (3.0)

[a]BUD/FORM as-needed vs. BUD + terbutaline as-needed: HR 1.24 (95% CI 0.53, 2.91), p=0.63; [b]BUD/FORM as-needed vs. terbutaline as-needed: HR 3.33 (95% CI 1.65, 6.69); p=0.001; [c]BUD/FORM as-needed vs. BUD + terbutaline as-needed: 1.73 (95% CI 0.58, 5.20), p=0.328; [d]BUD/FORM as-needed vs. terbutaline as-needed: HR 4.24 (95% CI 1.67, 10.75), p=0.002; [e]Hazard ratios not calculated due to low event rates in the BUD/FORM as-needed group.
BUD = budesonide; FORM = formoterol; HR = hazard ratio; SYGMA = SYmbicort Given as-needed in Mild Asthma.

1. O'Byrne P et al. *Eur Respir J.* 2018;52(suppl 62). Abs 1680.