Five Respiratory Articles that you should know!

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- This program has no commercial support

Mitigating Potential Bias

- Advisory board for multiple companies making medications for Asthma.

The paradoxes of asthma management: time for a new approach?

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O'Byrne PM et al. Eur Respir J. 2017; 50(3)

The paradoxes of asthma management: time for a new approach?

TABLE 1 Paradoxes in current asthma management

Paradox	Description
1	In step 1 treatment, a SABA bronchodilator alone is recommended despite the fact that asthma is a disease of chronic airway inflammation with increased inflammation at the times of exacerbations.
2	In step 1 treatment, the patient has autonomy and their perception of treatment as needed to control symptoms is accepted, whereas at higher asthma treatment steps it is assumed that patients will adopt a fixed-dose approach.
3	There is a switch in recommendation from using a SABA alone as-needed at step 1 to advising an ICS fixed-dose regimen at step 2 and minimising SABA use. The medication that treats the underlying disease, which patients are encouraged to take (the ICS) is not the one that the patient perceives is benefitting them (the SABA), which they are now discouraged from taking.
4	There is a different safety message in the advice given for the use of SABA and LABA within the guidelines; SABA alone being safe and LABA alone being unsafe.
5	There is a dislocation between patients' understanding of "asthma control" and the frequency, impact and severity of their symptoms.

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist.

O'Byrne PM et al. *Eur Respir J.* 2017; 50(3)

How to Adjust Asthma medication?

The NEW ENGLAND JOURNAL of MEDICINE
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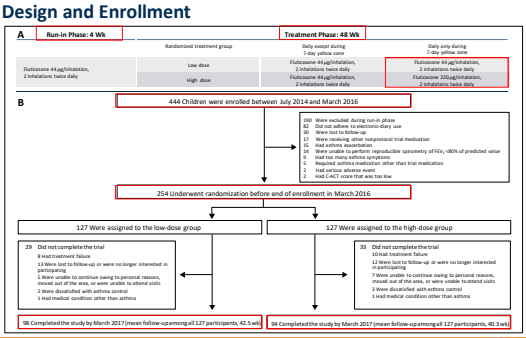
Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

D.J. Jackson, L.B. Bacharier, D.T. Mauger, S. Boehmer, A. Beigelman, J.F. Chmiel, A.M. Fitzpatrick, J.M. Gaffin, W.J. Morgan, S.P. Peters, W. Phipatanakul, W.J. Sheehan, M.D. Cabana, F. Holguin, F.D. Martinez, J.A. Pongracic, S.N. Boo, M. Benson, K. Blake, R. Covar, D.A. Gentile, E. Israel, J.A. Krishnan, H.V. Kumar, J.E. Lang, S.C. Lazarus, J.J. Lima, O. Long, N. Ly, J. Marbin, J.N. Moy, R.E. Myers, J.T. Okin, H.H. Ransay, R.G. Robison, K. Ross, C.A. Sorkness, and R.F. Lemanske, Jr., for the National Heart, Lung, and Blood Institute AsthmaNet*

Hypothesis

- For children with asthma, on low dose inhaled corticosteroids, does quintupling the inhaled corticosteroid when there are early signs of loss of asthma control (yellow zone) decrease severe exacerbations?

Trial Design and Enrollment



DJ Jackson et al. N Engl J Med 2018;378:891-901.

Characteristics of the Participants*

Table 1. Characteristics of the Participants.*

Characteristic	Total (N = 254)	Low-Dose Group (N = 127)	High-dose group (N = 127)
Age at enrollment — yr	8.0 ± 1.9	7.9±1.9	8.1±1.8
BMI percentile — %†	66.8 ± 28.0	67.9±27.3	65.8±28.8
Male sex — no. (%)	163 (64.2)	80 (63.0)	83 (65.4)
Race — no. (%)‡			
White	140 (55.1)	64 (50.4)	76 (59.8)
Black	56 (22.0)	29 (22.8)	27 (21.3)
Other	58 (22.8)	34 (26.8)	24 (18.9)
Hispanic ethnic group — no. (%)‡	75 (29.5)	36 (28.3)	39 (30.7)
Tobacco smoke exposure — no. (%)§	97 (38.2)	46 (36.2)	51 (40.2)
Controller therapy at enrollment — no. (%)¶			
Step 2	181 (71.3)	96 (75.6)	85 (66.9)
Step 3	43 (16.9)	18 (14.2)	25 (19.7)
No previous controller therapy	30 (11.8)	13 (10.2)	17 (13.4)
No. of positive allergen-specific IgE tests, of 16 tests	5.0 ± 4.4	4.8±4.2	5.2±4.5
≥ 1 Positive test for aeroallergen — no./total no. (%)	187/243 (77.0)	88/118 (74.6)	99/125 (79.2)
Blood eosinophil count — cells/mm³	346.4±268.2	367.4±299.8	326.6±234.3
IgE — kU/liter	401.3±585.4	418.3±655.9	385.4±515.1
No. of systemic glucocorticoid courses in previous year	1.7±0.9	1.8±0.9	1.7±0.9
No. of urgent care or emergency department visits in previous year	2.0±1.7	2.0±1.7	2.0±1.7
Hospitalization in previous year — no. (%)	31 (12.2)	16 (12.6)	15 (11.8)

* Plus-minus values are means ±SD. All the children were treated for 48 weeks with maintenance low-dose inhaled glucocorticoids (fluticasone propionate at a dose of 44 μg per inhalation, two inhalations twice daily) and were randomly assigned either to continue the same dose (low-dose group) or to use the quintupled dose (high-dose group; fluticasone at a dose of 220 μg per inhalation, with two inhalations twice daily) for 7 days at the early signs of loss of asthma control. There were no significant between-group differences at baseline. Percentages may not total 100 because of rounding.

† The body-mass index (BMI) is the weight of kilograms divided by the square of the height in meters. The BMI percentile was assessed as the value expected for age.

‡ Race and ethnic group were reported by the participants or their parents or guardians.

§ Tobacco smoke exposure refers to the current or past use of tobacco by a parent or family member in the home.

¶ Controller therapy was categorized according to the National Asthma Education and Prevention Program Expert Panel Report 3. Steps range from 1 to 6, with step 6 therapy being used in patients with the most severe disease. Step 2 indicates therapy for mild persistent asthma, and step 3 therapy for moderate persistent asthma.

DJ Jackson et al. N Engl J Med 2018;378:891-901.

Outcomes*

Table 2. Outcomes.*

Outcomes	Low-Dose Group (N = 127)	High-Dose Group (N = 127)	Treatment Effect (95% CI)†	P Value
Primary outcome				
No. of exacerbations per year (95 % CI)	0.37 (0.25 to 0.55)	0.48 (0.33 to 0.70)	1.3 (0.8 to 2.1)	0.30
Secondary outcomes				
No. of emergency department or urgent care visits per year (95% CI)	0.47 (0.31 to 0.72)	0.64 (0.42 to 0.96)	1.3 (0.8 to 2.4)	0.30
No. of hospitalizations	0	4	—	0.12
Equivalent of hydrocortisone exposure— g/yr (95 % CI)				
Fluticasone only	10.6 (10.4 to 10.9)	12.2 (11.9 to 12.4)	1.14 (1.10 to 1.19)	
Fluticasone and prednisone	11.1 (10.6 to 11.4)	12.8 (12.4 to 13.2)	1.16 (1.10 to 1.22)	
Growth — cm/yr (95 % CI)				
Mean	5.65 (5.48 to 5.81)	5.43 (5.26 to 5.60)	-0.23(-0.47 to 0.01)	0.06
Effect per 7-day exposure to high-dose regimen				
Overall	—	-0.07 (-0.17 to 0.03)	-0.07 (-0.17 to 0.03)	0.20
According to age group‡				
5–7 yr	—	-0.12 (-0.22 to -0.02)	-0.12 (-0.22 to 0.02)	0.02
8–11 yr	—	0.02 (-0.21 to 0.26)	0.02 (-0.21 to 0.26)	0.80

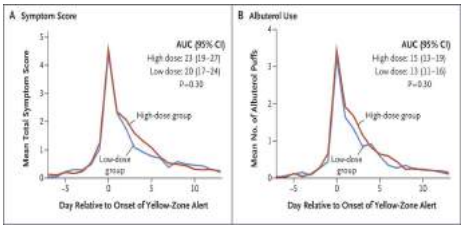
* The primary outcome was the rate of severe asthma exacerbations (number of events per year) treated with systemic glucocorticoids during the blinded treatment period.

† The treatment effect is a relative rate for the primary outcome of the number of exacerbations per year and for the secondary outcomes of the number of emergency department or urgent care visits per year. The treatment effect is a relative difference for the secondary outcomes related to hydrocortisone exposure equivalents. The treatment effect is an absolute difference (measured in centimeters per year) for the secondary outcomes regarding growth.

‡ A total of 126 participants were 5 to 7 years of age, and 128 were 8 to 11 years of age.

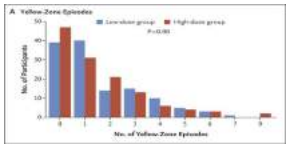
DJ Jackson et al. N Engl J Med 2018;378:891-901.

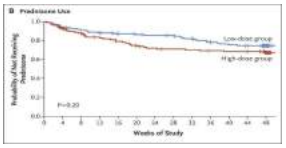
Outcomes During Yellow-Zone Episodes



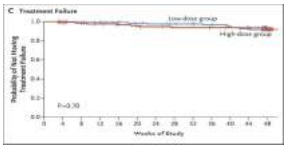
Yellow-zone defined as: two doses (4 puffs) of rescue albuterol in 6 hours, three doses (6 puffs) of rescue albuterol in 24 hours or one night time awakening that was due to asthma and treated with albuterol

Yellow Zones, Exacerbations and Treatment Failure





Yellow Zones, Exacerbations and Treatment Failure (continued)



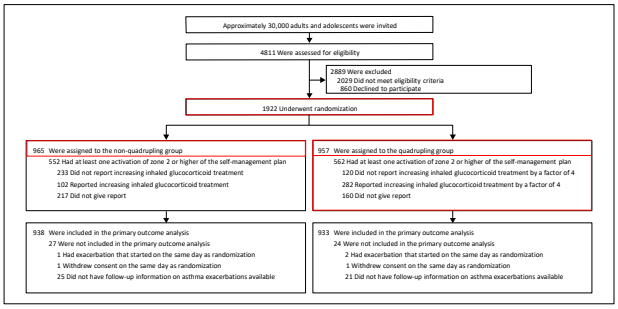
Conclusions

- In children with mild to moderate persistent asthma on low dose inhaled corticosteroids
- Quintupling the dose at early signs of asthma control does not:
  - Reduce the rate of severe exacerbations
  - Decrease symptoms
  - Decrease albuterol use
  - Decrease treatment failures
- But is associated with diminished linear growth

Quadrupling Inhaled Glucocorticosteroid Dose to Abort Asthma Exacerbations

T McKeever et al. N Engl J Med 2018;378:902-910.

Screening, Randomization and Follow-up



Baseline Characteristics of the Participants*

Table 2. Baseline Characteristics of the Participants.*

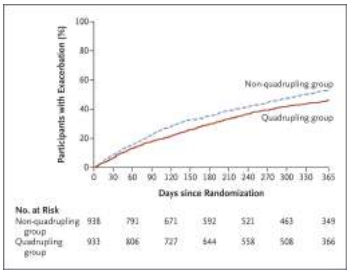
Characteristic	Non-Quadrupling Group (N = 965)	Quadrupling Group (N = 957)
Age — yr		
Mean	56.7±15.2	56.2±15.5
Range	19–98	16–93
Sex — no. (%)		
Male	316 (33)	301 (31)
Female	649 (67)	656 (69)
Source of recruitment— no. (%)		
Primary care	774 (80)	785 (82)
Secondary care	191 (20)	172 (18)
Mean peak expiratory flow at screening— liter/min	381.1±112.2	386.9±110.8
Type of inhaler— no. (%)		
Glucocorticoid	303 (31)	275 (29)
Combination	662 (69)	682 (71)
Type of inhaled glucocorticoid— no. (%)		
Beclomethasone	388 (60)	325 (54)
Budesonide	220 (23)	225 (24)
Fluticasone	350 (36)	401 (42)
Ciclesonide	7 (1)	6 (1)
Maintenance dose of inhaled glucocorticoids		
Median (IQR)— µg/day of beclomethasone or equivalent	800 (400 – 1000)	800 (400–1000)
Range — µg/day of beclomethasone or equivalent	100 – 4000	80–4000
Low : ≤ 1000 µg/day of beclomethasone or equivalent — no. (%)	752 (78)	743 (78)
High : > 1000 µg/day of beclomethasone or equivalent —no. (%)	213 (22)	214 (22)
Smoking status—no. (%)		
Never smoked	552 (57)	564 (59)
Current smoker	66 (7)	59 (6)
Former smoker	347 (36)	334 (35)
Pack-years among current or former smokers		
No. of participants	413	393
Mean pack-yr	13.9±16.1	12.3±14.5
Mini-AQLQ overall score†		
No. of participants	959	944
Mean score	5.0±1.2	5.1±1.2
Mini-AQLQ symptom score†		
No. of participants	954	938
Mean score	4.8±1.3	4.9±1.3

* Plus-minus values are means ± SD. Percentages may not add up to 100 because of rounding. IQR denotes interquartile range.

† Scores on the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) range from 1 to 7, with higher scores indicating a better quality of life. For the Mini-AQLQ overall score, a within-patient change of 0.5 represents the minimal important difference.

T McKeever et al. N Engl J Med 2018;378:902-910.

Kaplan–Meier Curves for the Time to the First Severe Asthma Exacerbation, According to Assigned Group



T McKeever et al. N Engl J Med 2018;378:902-910.

Conclusions

- In adults and adolescents with asthma on at least inhaled corticosteroids
- Quadrupling the dose at early signs that asthma control started to deteriorate resulted in fewer severe asthma exacerbations in the year after randomization than a plan in which the dose was not increased (45% vs 52%, p=0.002).

T McKeever et al. N Engl J Med 2018;378:902-910.

Children are not just Small Adults!!

Thanks to Dr. Paolo Renzi

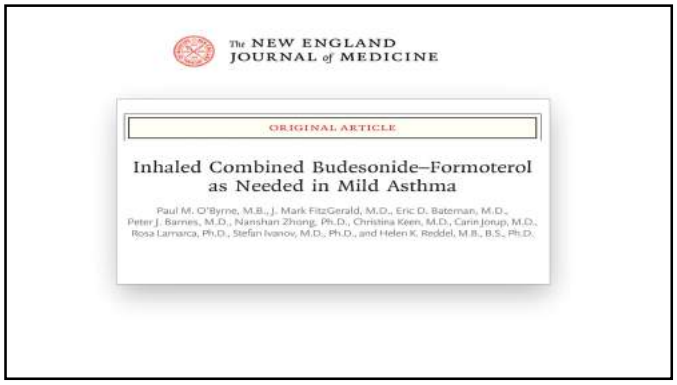
SYGMA Studies: Background

- Guidelines recommend that most patients with asthma should use an inhaled corticosteroid (ICS)-containing medication as maintenance therapy to reduce airway inflammation, symptoms, and risk of exacerbations
- However, poor adherence to asthma medications, particularly maintenance ICS, is a major problem across all severities of asthma
  - Patients continue to rely on short-acting β_2-agonists (SABAs) for symptom relief
  - SABAs neither treat underlying airway inflammation nor protect against exacerbations
  - SABAs remain the most widely used medication for asthma worldwide
- A combination of a fast-acting β_2-agonist and ICS taken only 'as-needed' for rapid symptom relief may address underuse of ICS and reduce exacerbations

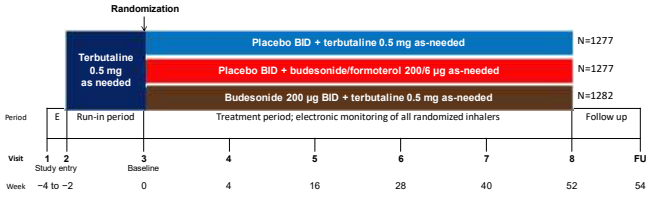
SYGMA 1 & 2: Study Objectives

- To investigate the benefits of as-needed budesonide/formoterol (BUD/FORM) on:
  - asthma control
  - preventing moderate and severe asthma exacerbations
- Compared to standard of care in mild asthma patients either uncontrolled on SABA as needed (Subgroup 1), or controlled on low-dose ICS (Subgroup 2)

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



SYGMA 1: Study Design



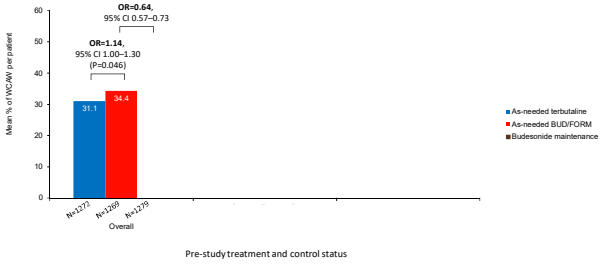
ClinicalTrials.gov identifier: NCT02149199
PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

Baseline Demographics and Clinical Characteristics

	Total (N=3836)	As-needed terbutaline 0.5 mg (N=1277)	As-needed BUD/FORM 200/6 µg (N=1277)	Budesonide maintenance 200 µg BID (N=1282)
Age, mean (SD) years	39.6 (16.6)	40.0 (16.3)	39.8 (16.9)	39.0 (16.7)
Female sex	61.1%	60.4%	60.8%	62.2%
Time since diagnosis, median (range) years	6.4 (0.4–65.7)	6.3 (0.5–62.4)	6.5 (0.4–65.7)	6.3 (0.5–57.1)
ACQ-5 score, mean (SD)	1.57 (0.96)	1.54 (0.95)	1.61 (0.97)	1.55 (0.96)
Pre-BD FEV_1 % predicted, mean (SD)	84.2% (14.1)	84.1% (14.1)	84.2% (14.2)	84.2% (13.9)
Morning PEF ≥80% predicted every day	28.1%	28.4%	26.6%	29.3%
Reversibility (%), mean (SD)	14.6% (11.5)	14.4% (11.5)	14.9% (11.3)	14.6% (11.6)
Pre-study treatment				
Uncontrolled on bronchodilator alone	44.5%	44.2%	44.2%	44.9%
Controlled on ICS or LRTA	55.5%	55.8%	55.8%	55.1%
Severe exacerbation in last 12 months	19.7%	20.0%	20.1%	18.8%

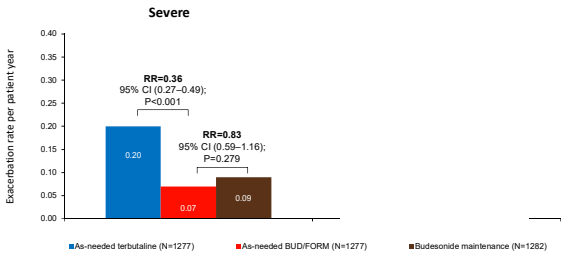
PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

Primary Endpoint: eWCAW



PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

Secondary Endpoint: Asthma Exacerbations



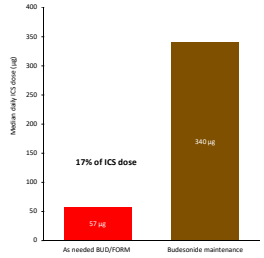
PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

Adherence to Maintenance Treatment

	As-needed terbutaline 0.5 mg (N=1277)	As-needed BUD/FORM 200/6 µg (N=1277)	Budesonide maintenance 200 µg BID (N=1282)
Adherence, %			
Mean (SD)	**79.0 (23.3)**	**79.1 (23.0)**	**78.9 (22.4)**
Median	85.6	85.7	85.1
Range	0–186	0–196	0–176

PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

Measured Mean Daily ICS Load*



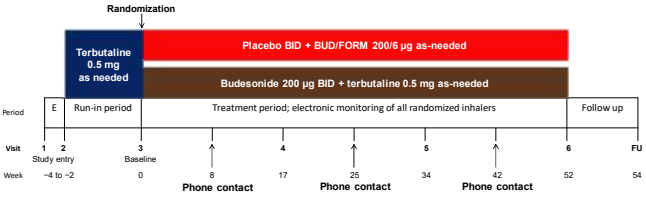
	As-needed terbutaline 0.5 mg (N=1277)	As-needed BUD/FORM 200/6 µg (N=1277)	Budesonide maintenance 200 µg BID (N=1282)
	N=1273	N=1276	N=1281
Days with ICS use	5.8%	30.9%	85.8%
	N=1277	N=1277	N=1282
Total number of days with systemic steroid treatment due to asthma	1237	465	500

* Metered dose

PM O'Byrne et al. N Engl J Med 2018;378:1865-1876.

ED Bateman et al. N Engl J Med 2018;378:1877-1887.

SYGMA 2: Trial Design



Comparison with SYGMA 1: More pragmatic

- Only 2 mid-trial visits
- No daily diary
- No monitoring of PEF
- No medication reminders

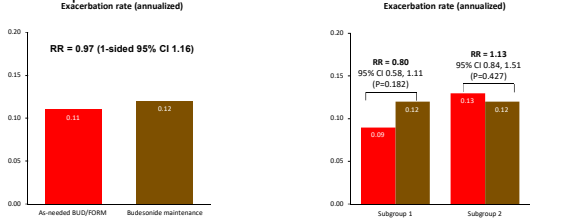
ClinicalTrials.gov identifier: NCT02224157
ED Bateman et al. N Engl J Med 2018;378:1877-1887

Baseline Demographics and Clinical Characteristics

	Total (N=4176)	As-needed BUD/FORM 200/6 µg (N=2089)	Budesonide maintenance 200 µg BID (N=2087)
Age, mean (SD) years	41.0 (17.0)	41.3 (16.8)	40.7 (17.1)
Female sex	62.2%	62.6%	61.8%
Time since diagnosis, median (range) years	7.6 (0.4–71.2)	7.9 (0.5–62.4)	7.3 (0.4–71.2)
ACQ-5 score, mean (SD)	1.51 (0.90)	1.49 (0.89)	1.53 (0.90)
Pre-BD FEV_1, % predicted, mean (SD)	84.3% (13.9)	84.4 (13.9)	84.1 (13.9)
Reversibility (%), mean % (SD)	15.2% (12.7)	15.1% (12.4)	15.2% (13.0)
Pre-study treatment			
Uncontrolled on bronchodilator	46.3%	45.9%	46.7%
Controlled on ICS or LRTA	53.7%	54.1%	53.3%
Severe exacerbation in previous 12 months	22.0%	22.0%	22.0%

ED Bateman et al. N Engl J Med 2018;378:1877-1887.

Primary Endpoint: Annualized Severe Asthma Exacerbation Rate As-needed BUD/FORM compared to budesonide maintenance



Subgroup 1 = uncontrolled on as-needed SABAs
Subgroup 2 = well-controlled on maintenance low-dose ICS or LTRA plus as-needed SABAs

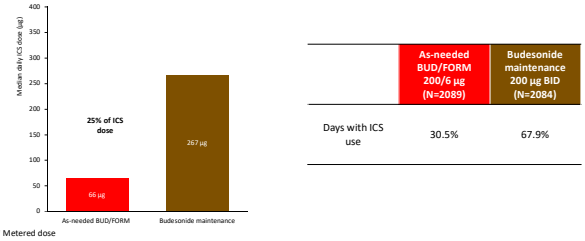
ED Bateman et al. N Engl J Med 2018;378:1877-1887.

Electronically-recorded Adherence Rates with Blinded Maintenance Treatment

	As-needed BUD/FORM 200/6 µg (N=2089)	Budesonide maintenance 200 µg BID (N=2087)
Adherence, %		
Mean (SD)	**64.0 (30.0)**	**62.8 (29.4)**
Median	67.7	66.9
Range	0–230	0–186

ED Bateman et al. N Engl J Med 2018;378:1877-1887.

Median Daily ICS Dose*
As-needed BUD/FORM compared to budesonide maintenance

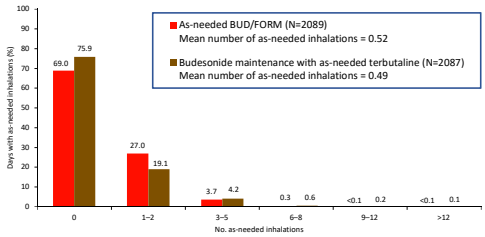


	As-needed BUD/FORM 200/6 µg (N=2089)	Budesonide maintenance 200 µg BID (N=2084)
Days with ICS use	30.5%	67.9%

* Metered dose

ED Bateman et al. N Engl J Med 2018;378:1877-1887.

As-needed Inhalations Expressed as Proportion of Days by Frequency of Use



ED Bateman et al. N Engl J Med 2018;378:1877-1887.

Combined Conclusions from SYGMA 1 and SYGMA 2

- For patients with mild asthma requiring regular maintenance treatment, as-needed BUD/FORM is:
  - more effective than as-needed terbutaline in controlling symptoms and reducing exacerbation risk
  - non-inferior to budesonide maintenance at reducing exacerbation risk at a substantially lower daily ICS dose, without need of twice-daily maintenance
  - Statistically inferior to budesonide maintenance in improving symptoms and lung function
- Budesonide maintenance is an effective treatment for mild asthma in patients adherent to maintenance treatment
- As-needed BUD/FORM is an option in mild asthma

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

Not all SABAS are bad!

Porto Portugal, Thanks Dr. James Kim!!

So, how do we solve this?

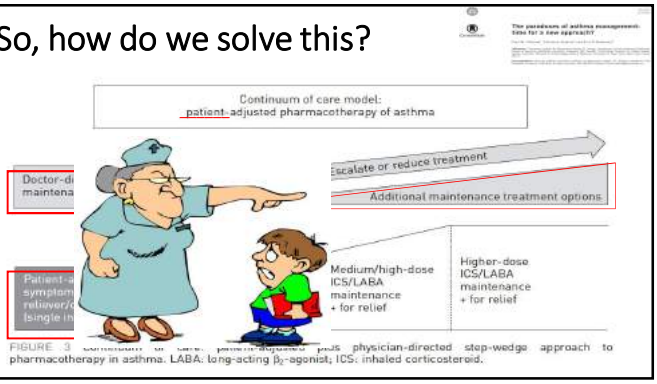
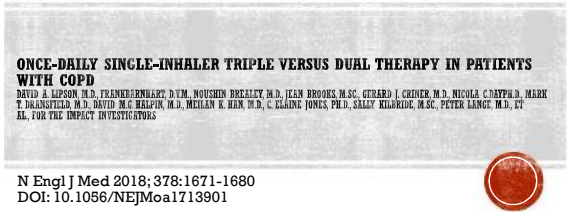


FIGURE 3 ... pharmacotherapy in asthma. LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid.



ONCE-DAILY SINGLE-INHALER TRIPLE VERSUS DUAL THERAPY IN PATIENTS WITH COPD

DAVID A. LIPSON, M.D., FRANKBERNHART, D.V.M., NOUSHIN BREALEY, M.D., JEAN BROOKS, M.SC., GERARD J. CRINER, M.D., NICOLA C DAYPH.D., MARK T. DRANSFIELD, M.D., DAVID M.G. HALPIN, M.D., MEILAN K. HAN, M.D., C. ELAINE JONES, PH.D., SALLY KILGRIDE, M.SC., PETER LANGE, M.D., ET AL., FOR THE IMPACT INVESTIGATORS

N Engl J Med 2018; 378:1671-1680
DOI: 10.1056/NEJMoa1713901

CFPC CoI Templates: Slide 1 – used in Faculty presentation only.

FACULTY/PRESENTER DISCLOSURE

- **Faculty:** Dr Suzanne Levitz
  - Chief of Medicine Mount Sinai Hospital, Montreal, QC
  - McGill University
  - Chair respiratory Communities of practice group, CFPC

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** astra zeneca, Boehringher Ingelheim, Novartis
  - **Consulting Fees:** ICEBM
  - **Patents**: none
  - **Other:** nothing to declare

CFPC CoI Templates: Slide 2

DISCLOSURE OF FINANCIAL SUPPORT

- **This program has received no financial support**.
- **This program has received no in-kind support**

- **Potential for conflict(s) of interest:**
  - Dr Suzanne Levitz has received payment from organization whose product(s) are being discussed in this program, although no company or organization has been involved in the creation of this program.

CFPC CoI Templates: Slide 3

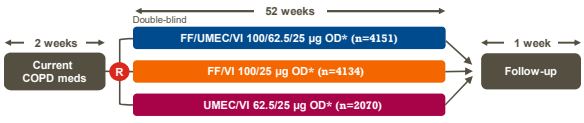
MITIGATING POTENTIAL BIAS

- potential sources of bias identified have been addressed by reviewing and discussing all products made for the coditions discussed in this presentation. Brand names have been avoided and medications discussed by class rather than particular molecules

AIM; COMPARE BENEFITS OF ONCE DAILY LAMA/LABA/ICS TO LAMA/LABA AND ICS/LABA IN COPD

- Randomized trial
- 10,355 patients
- 52 weeks of once daily ICS/LABA vz. LAMA/LABA vz. LAMA/LABA/ICS
- Ellipta device
- Primary outcome; annual rate of moderate or severe exacerbations of COPD (during treatment)

IMPACT: INFORMING THE PATHWAY OF COPD TREATMENT STUDY DESIGN[1]



Co-primary treatment comparisons (ITT population)
- Annual rate of moderate/severe exacerbations comparing:
  - FF/UMEC/VI with FF/VI
  - FF/UMEC/VI with UMEC/VI

For all combinations, delivered doses were as follows: FF (92 µg), UMEC (55 µg) and VI (22 µg); all treatments were administered via the ELLIPTA inhaler. ITT, intent-to-treat; OD, once daily.

1. Lipson DA, et al. *N Engl J Med*. 2018 (ePub ahead of print) 2. Lipson DA, et al. *N Engl J Med*. 2018; (supplementary).

POPULATION

- Matched for age, sex, smoking history, exacerbation rates
- Majority male (66-67%)
- 18% had reversibility of airway disease (Inc FEV1 >12% and 200 ml post bd)
- 43% had blood eosinophil level < 150 cells/microlitre
- Three study groups;
  - Triple therapy 4151
  - ICS/LABA 4134
  - LAMA/LABA 2070

IMPACT: BASELINE DEMOGRAPHICS[1]

	FF/UMEC/VI (n=4151)	FF/VI (n=4134)	UMEC/VI (n=2070)	Overall (N=10355)
Age (y), Mean (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
Sex (% male)	67%	66%	66%	66%
Former smoker n, (%)	2715 (65%)	2711 (66%)	1342 (65%)	6768 (65%)
Post-bronchodilator FEV_1 % predicted, Mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)
COPD exacerbations in prior year, n (%)				
1 moderate and no severe*	1198 (29%)	1242 (30%)	616 (30%)	3056 (30%)
≥2 moderate or ≥1 severe	2953 (71%)	2892 (70%)	1454 (70%)	7299 (70%)
≥1 severe	1087 (26%)	1069 (26%)	515 (25%)	2671 (26%)
Baseline COPD medications,*‡ n (%)				
ICS + LABA + LAMA	1581 (38%)	1563 (38%)	826 (40%)	3970 (38%)
ICS + LABA	1220 (29%)	1177 (28%)	576 (28%)	2973 (29%)
LABA + LAMA	361 (9%)	331 (8%)	187 (9%)	879 (8%)
LAMA	288 (7%)	346 (8%)	146 (7%)	780 (8%)

* These were the most common baseline combinations; treatment combinations may have included PDE4i and/or Xanthine.

1. Lipson DA, et al. *N Engl J Med*. 2018 (ePub ahead of print)

RESULTS

- Rate of moderate-severe exacerbations
  - ICS/LAMA/LABA 0.91 exacerbations/year
  - ICS/LABA 1.07 exacerbations/year
  - LAMA/LABA 1.21 exacerbations/year
- Rate of severe exacerbations (hospitalization)
  - ICS/LAMA/LABA 0.13 exacerbations/year
  - ICS/LABA exacerbations/year
  - LAMA/LABA 0.19 exacerbations/year

BLOOD EOSINOPHIL COUNTS AND EXACERBATIONS

- Blood eosinophil count<150
  - Triple therapy 0.85 exacerbations/year
  - ICS/LABA 1.06 exacerbations/year
  - LAMA/LABA 0.97 exacerbations/year
- Blood eosinophil count >150
  - Triple therapy 0.95 exacerbations/year
  - ICS/LABA 1.08 exacerbations/year
  - LAMA/LABA 1.39 exacerbations/year
- Rate of moderate OR severe exacerbations

ADVERSE EFFECTS

- Cardiovascular complications (arrthythmia,failure,HTA, ischemic heart disease, cerebrovascular) were low and similar in all group (11%)
- Urinary retention rare in all groups
- Anticholinergic symptoms in 4% (in each group)
- Lower RTI (excluding pneumonia)- 5% in each group
- ***PNEUMONIA; rates slightly higher in triple therapy (317 pts-8%) and ICS/LABA (292 patients-7%) vz LAMA/LABA (97 pts- 5%)***

IMPACT: FF/UMEC/VI MORE EFFECTIVE THAN FF/VI AND UMEC/VI

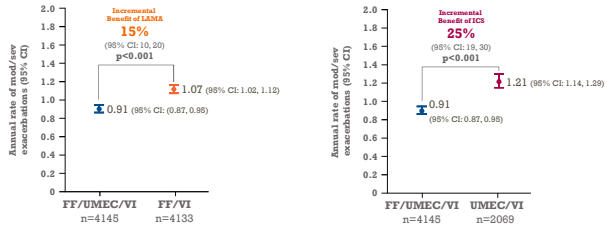
IMPACT has demonstrated the benefit of triple therapy in patients who have experienced at least one exacerbation in the past 12 months

	Moderate/severe	Severe (hospitalised)
Incremental benefit of UMEC FF/UMEC/VI vs FF/VI	↓ 15% 0.91 vs 1.02 p<0.001	↓ 13% 0.13 vs 0.15 p=0.064
Incremental benefit of FF FF/UMEC/VI vs UMEC/VI	↓ 25% 0.91 vs 1.21 p<0.001	↓ 34% 0.13 vs 0.19 p<0.001

1. Lipson DA, et al. *N Engl J Med*. 2018 (ePub ahead of print)

PRIMARY ENDPOINT: MODERATE/SEVERE EXACERBATIONS

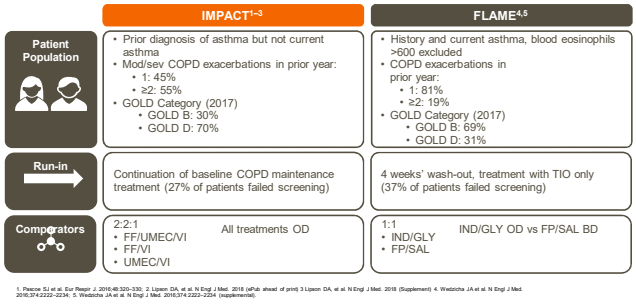
Significant reduction in the annual rate of moderate/severe exacerbations with FF/UMEC/VI vs UMEC/VI



Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.

1. Lipson DA, et al. *N Engl J Med*. 2018 (ePub ahead of print)

IMPACT AND FLAME



1. Pascoe SJ et al. Eur Respir J. 2016;48:320–330. 2. Lipson DA, et al. N Engl J Med. 2018 (ePub ahead of print) 3 Lipson DA, et al. N Engl J Med. 2018 (Supplement) 4. Wedzicha JA et al. N Engl J Med. 2016;374:2222–2234. 5. Wedzicha JA et al. N Engl J Med. 2016;374:2222–2234 (supplemental).

TAKE HOME MESSAGE

- COPD is a spectrum of respiratory disease characterized by irreversible airway changes
- It is often associated with a reversible component (ACOS)
- In this study, 3 treatments for COPD were compared (LAMA/LABA, ICS/LABA, AND ICS/LABA/LAMA) in moderate asthma (average FEV1 47% predicted)
- The outcome measure was annual rate of moderate or severe exacerbations during the study

TAKE HOME MESSAGE

- In this study once daily triple therapy was better than dual in preventing moderate to severe exacerbations
- Pneumonia incidence higher in triple therapy group (as seen in other studies)
- 18% of patients in study had reversible airway disease
- We know ICS have a role in COPD with frequent exacerbations
- Compliance (once daily, one inhaler vz multi dosing and multiple inhalers
- To Watch:
  - What role do ICS have in management of stable COPD? Less stable COPD?
  - How does daily triple therapy compare to other treatment regimens?
  - Howe will the results obtained in this study translate into clinical practice?

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