

Asthma in children – What are the unmet needs?

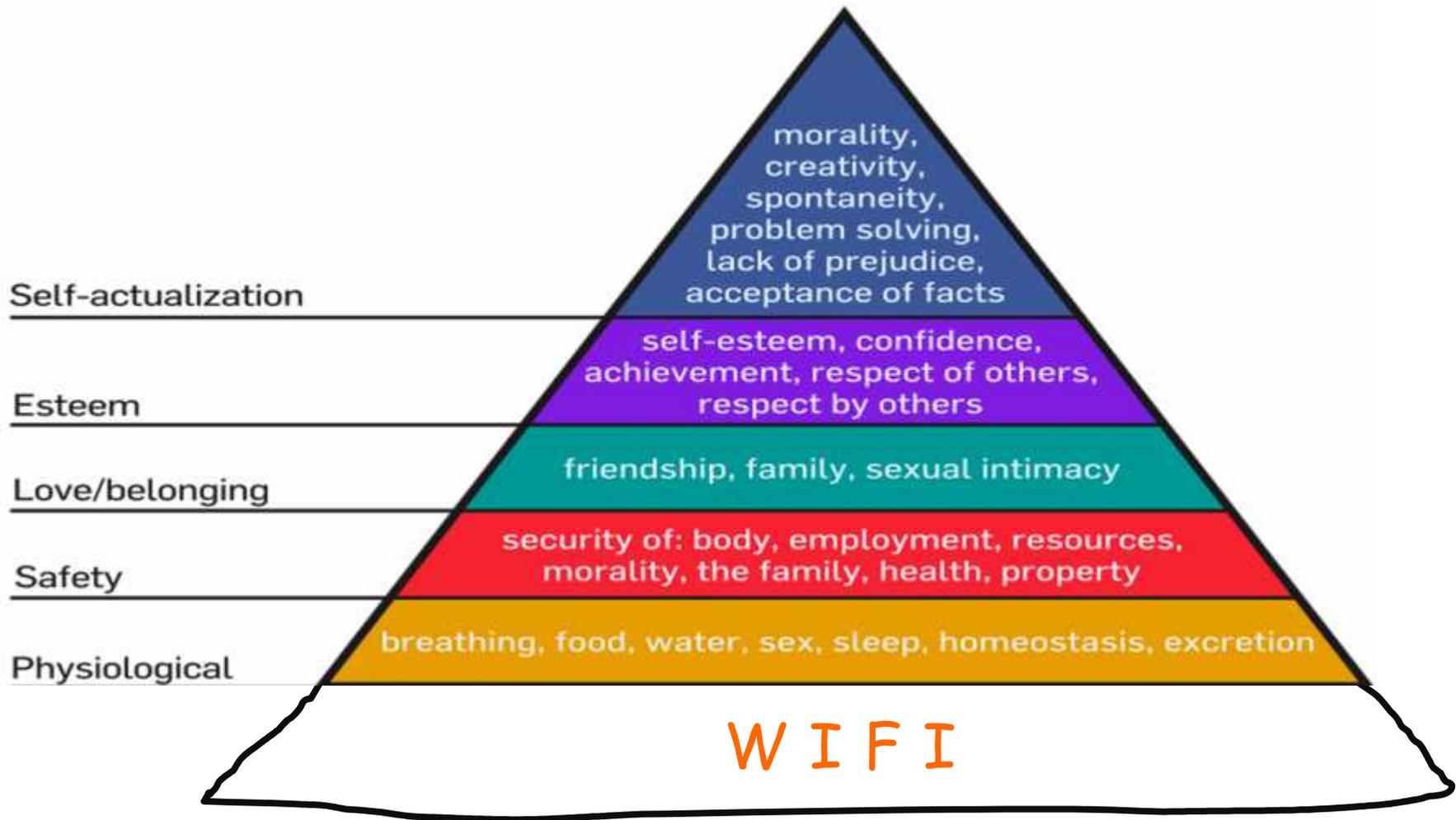
Dr. Eric Mugambi
MBChB, MMed, MSc

Disclosure



- This session is organised and funded by GSK
- I am employed full time by GSK as Therapy Area Lead for East Africa Cluster

What are needs?



*Merriam-Webster Dictionary. <http://www.merriam-webster.com/dictionary/need>



How do these needs arise?

- Research in new medicines and devices for children is complicated by:
 - Small numbers
 - Paediatric physiology
 - Trial design
 - Ethical and legal issues
- Transition of care
- Education of caregivers
- Dependence on parents and carers



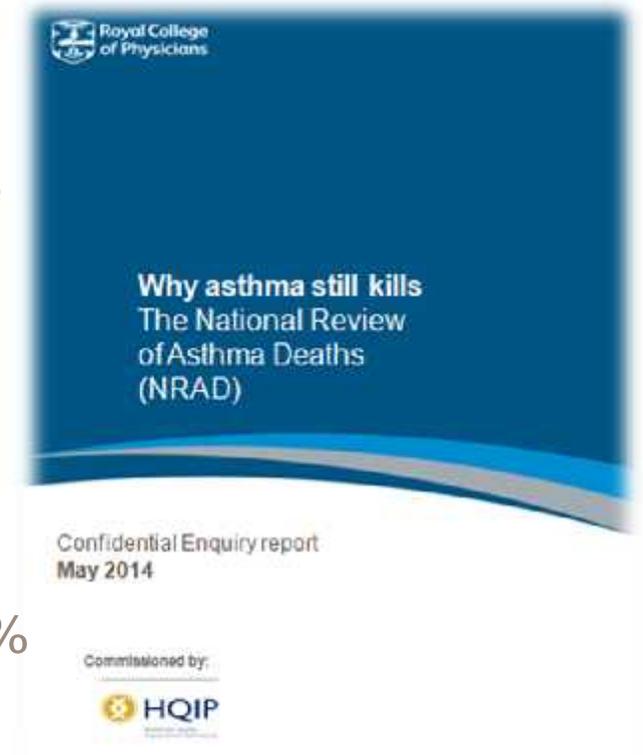
- About 334 million people have asthma globally (GBD study)¹
- Most of these live in low and middle income countries¹
- About 14% of the world's children have had asthma symptoms in the last 12 months (ISAAC studies)¹
- The burden of asthma is greatest in children aged 10-14 and the elderly aged 75-79.¹
- Asthma contributes to <1% of global deaths¹

1. Global asthma report 2014

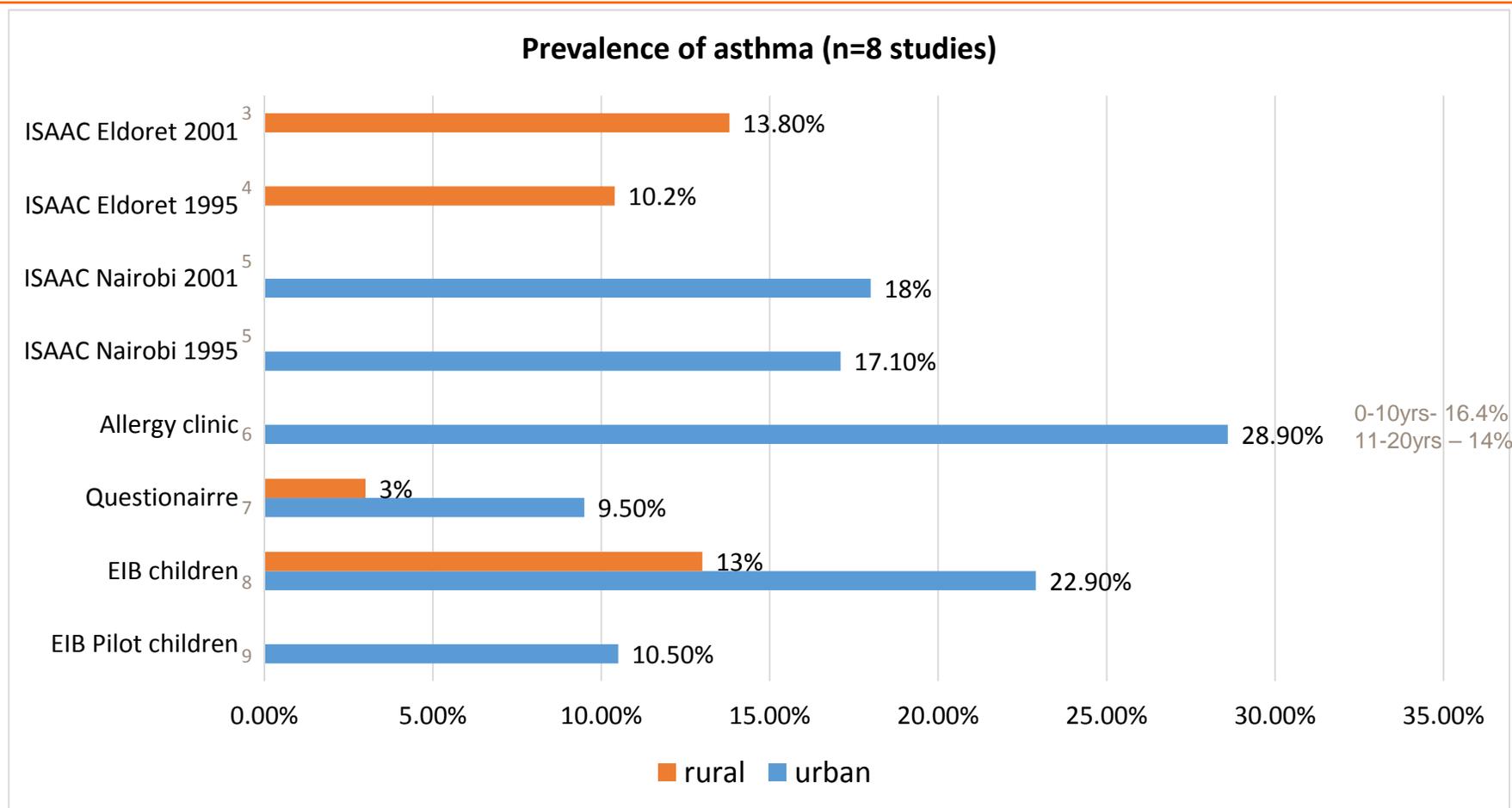
Why asthma still kills?



- In the UK, out of 195 who died from asthma:²
 - 45% died without seeking medical assistance
 - Only 23% of 195 who died had action plans
 - No GP review in the year prior to death in 43%
 - 16% of 195 had satisfactory care vs. 4% of children and young adults!



Local perspective



(3) East African Medical Journal. 2002;79(10):514-8. (4) East Afr Med J. 1996;73(7):474-8. (5) ISAAC study results Phase I & III Nairobi
 (6) East African Medical Journal. 1992;69(12):700-2. (7) The European respiratory journal. 1998;12(5):1105-12. (8)Thorax. 1998;53(11):919-26.
 (9) EIB pilot in children – East African Medical Journal. 1997;74(11):694-8.

What are the goals of management?



- Symptom control (DARN)
 - Maintain normal activity levels

- Risk reduction
 - Prevent exacerbations
 - Relationship between symptom control and future risk of adverse outcomes
not well studied
 - Prevent abnormal lung development
 - Reduce medical side effects

- Goals of the parent/carer?

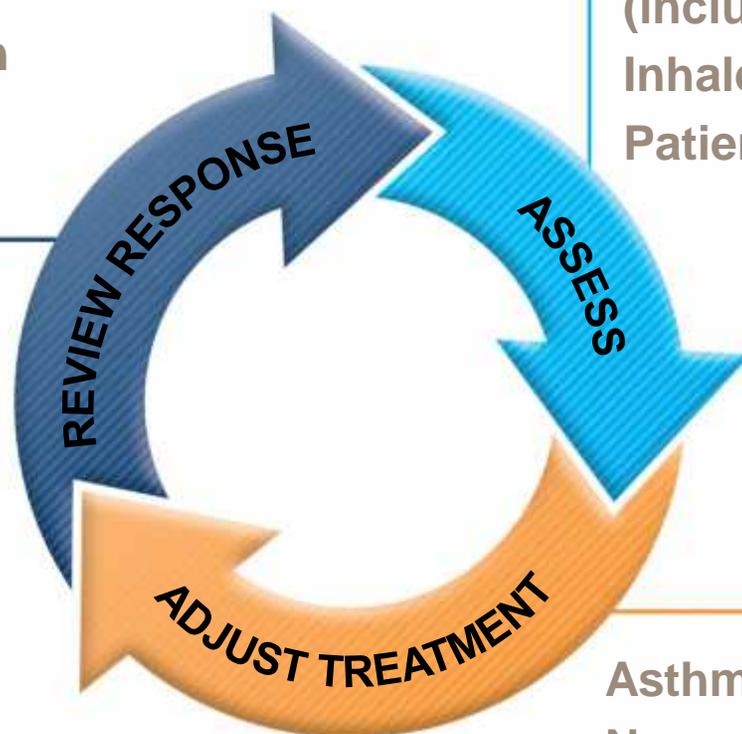
Education
Skills training
Monitoring
Asthma Action plan

Diagnosis

Symptom control & risk factors
(including lung function)
Inhaler technique & adherence
Patient preference

Symptoms

Exacerbations
Side-effects
Patient satisfaction
Lung function



Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors



Key issues

- How do we diagnose Asthma in children aged 5 and below?
- Is it possible to predict which child with wheeze will develop asthma?
- What is asthma control in children < 4 yrs old?
- Add on controller options beyond step 2?
 - LABA?
- Inhaler device?
- Adherence?

Diagnosis of asthma in children 5 years and below

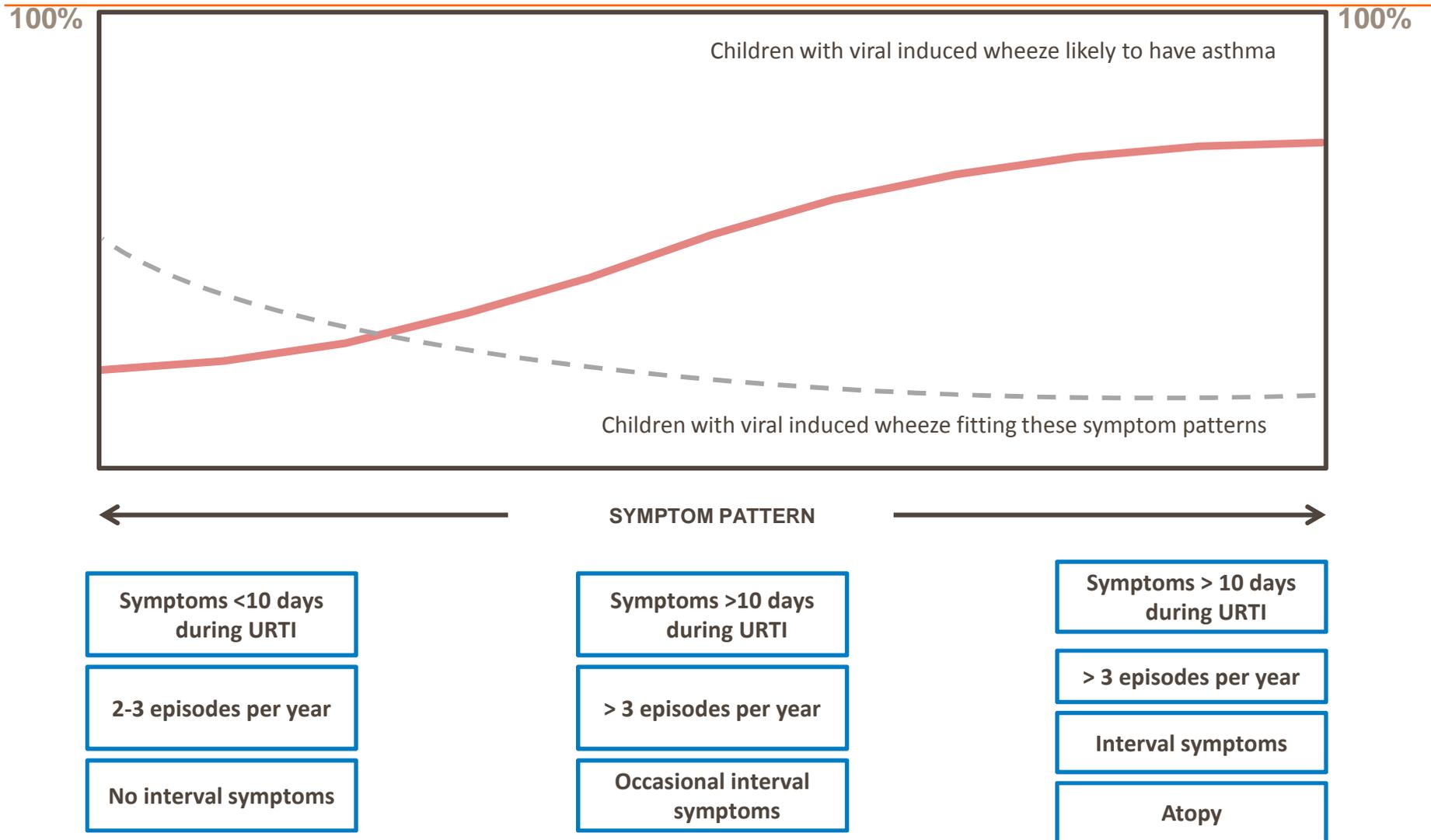


- Diagnosis is extremely difficult
- Although one third of children under 3 years have wheeze with LRTI¹¹
 - 60% stop wheezing by age 6
- Wheeze during the first two years of life has a benign prognosis¹¹
- Airflow limitation is difficult to assess especially between ages 0-2¹⁰

10. Global Initiative for Asthma: Global strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org

11. New England Journal of Medicine. 1995;332(3):133-8.

Probability of asthma diagnosis or response to treatment in children 5 years and younger



10. GINA 2015 at www.ginasthma.org



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Asthma prediction



- In up to half of people with asthma, symptoms commence during childhood¹⁰
- Elevated FENO in preschool children predicts later asthma diagnosis (increase in 5 units triples the risk)¹²
- Phenotypes¹⁰
 - Symptom based (Episodic and Multi-trigger)
 - Time trend based (Transient , Persistent, Late Onset)

10. Global Initiative for Asthma: Global strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org

12. Allergy. 2013;68(4):531-8.

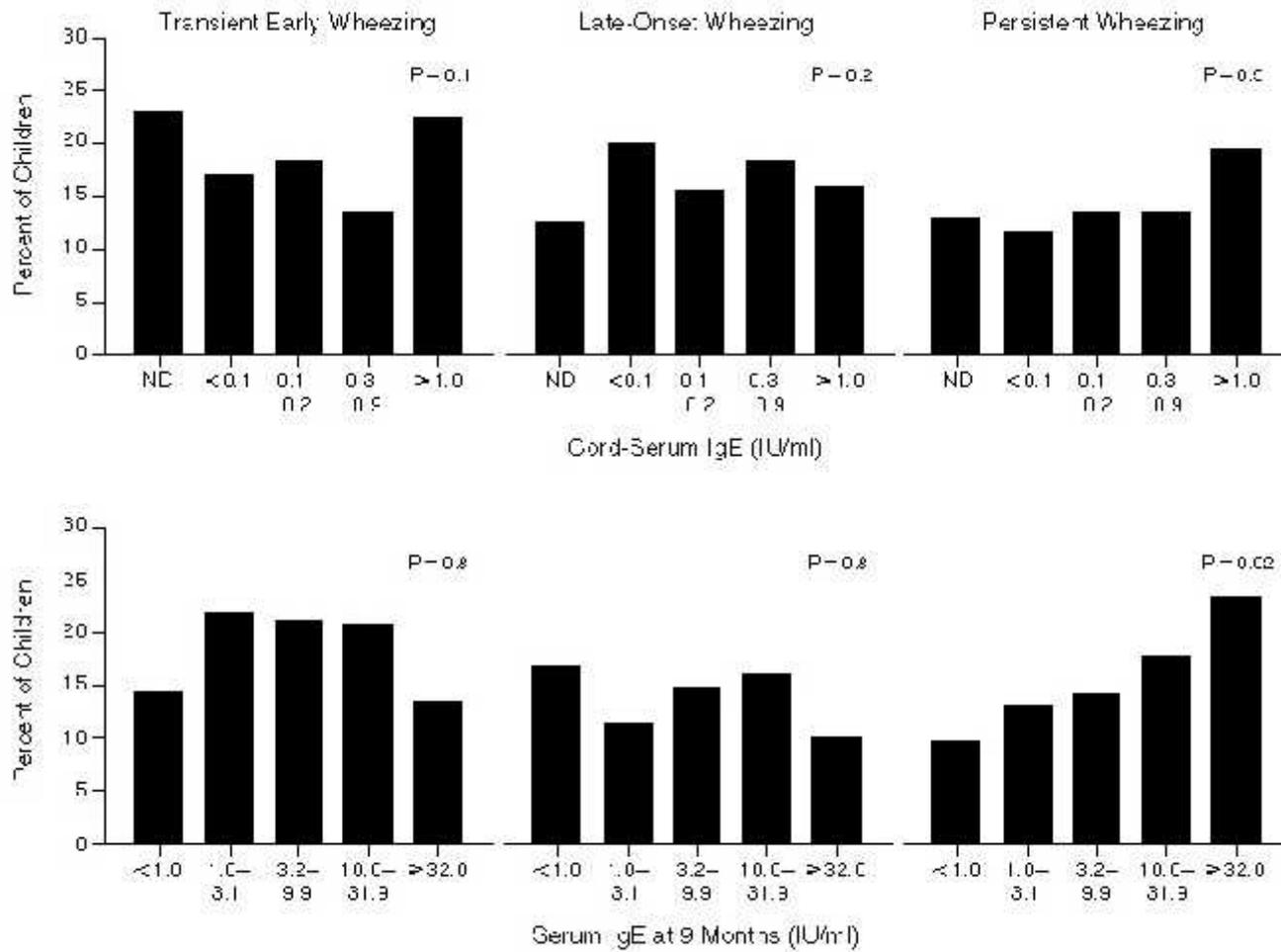
ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE

FERNANDO D. MARTINEZ, M.D., ANNE L. WRIGHT, PH.D., LYNN M. TAUSSIG, M.D.,
CATHARINE J. HOLBERG, M.Sc., MARILYN HALONEN, PH.D., WAYNE J. MORGAN, M.D.,
AND THE GROUP HEALTH MEDICAL ASSOCIATES*

Table 1. Adjusted Odds Ratios for Transient Early Wheezing, Late-Onset Wheezing, and Persistent Wheezing, According to Risk Factors Present at One Year of Age, and Prevalence of Risk Factors.*

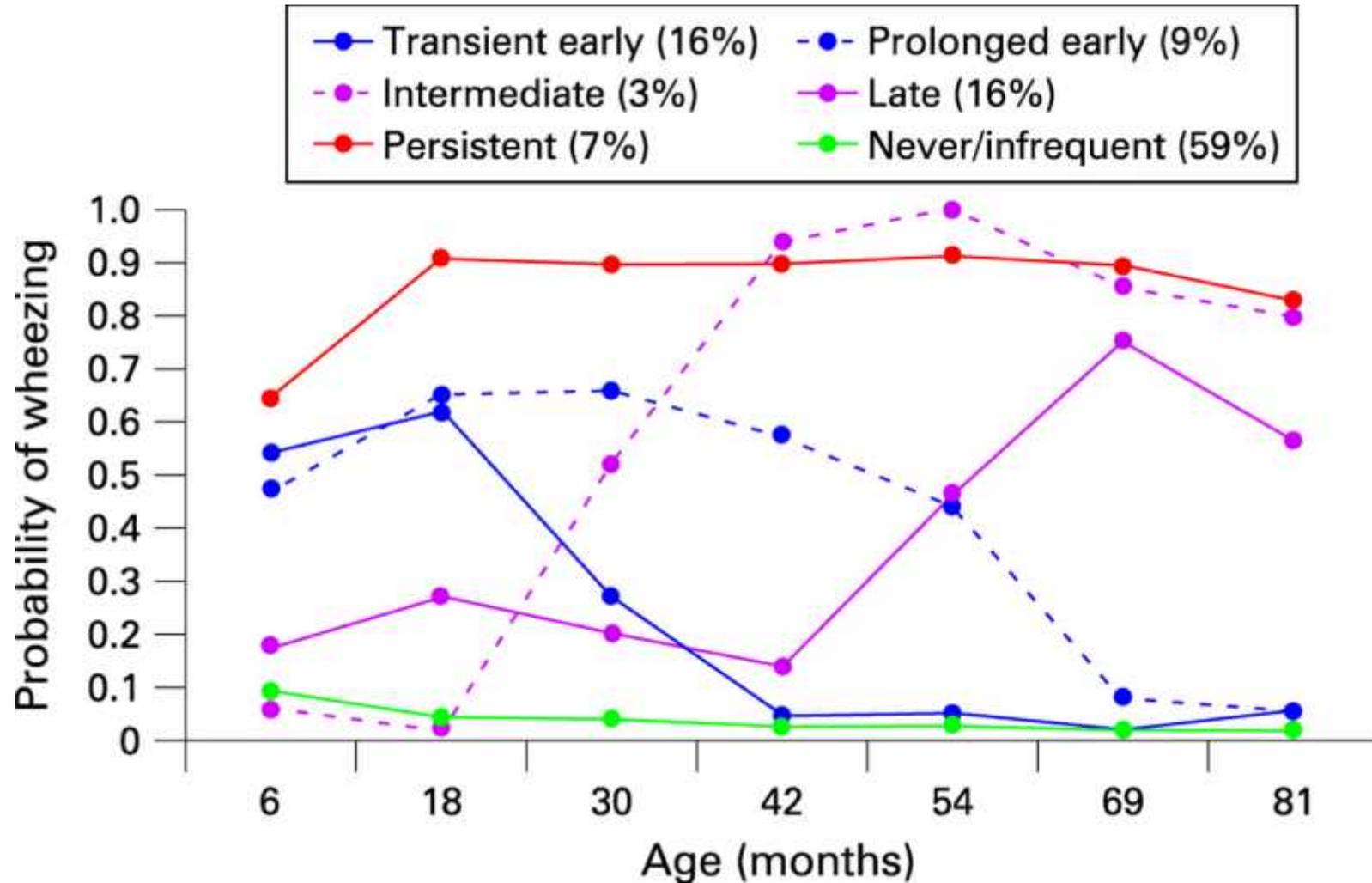
RISK FACTOR	NO WHEEZING (N= 403)	TRANSIENT EARLY WHEEZING (N= 147)	LATE-ONSET WHEEZING (N= 112)	PERSISTENT WHEEZING (N= 100)
Eczema				
Odds ratio (95% CI)	1.0	1.3 (0.7-2.5)	0.7 (0.3-1.6)	2.4 (1.3-4.6)
Prevalence (%)	7.7	10.2	6.3	18.0
Rhinitis apart from colds				
Odds ratio (95% CI)	1.0	1.1 (0.7-1.7)	1.7 (1.1-2.7)	2.0 (1.2-3.2)
Prevalence (%)	24.8	27.2	35.7	42.0
Maternal asthma				
Odds ratio (95% CI)	1.0	1.6 (0.8-3.2)	2.8 (1.4-5.5)	4.1 (2.1-7.9)
Prevalence (%)	6.7	10.2	16.1	22.0
Hispanic ethnic background				
Odds ratio (95% CI)	1.0	1.5 (0.9-2.7)	1.7 (0.9-3.1)	3.0 (1.6-5.5)
Prevalence (%)	10.7	13.6	14.3	22.0
Male sex				
Odds ratio (95% CI)	1.0	1.0 (0.7-1.5)	2.1 (1.3-3.4)	1.9 (1.2-3.0)
Prevalence (%)	42.7	44.2	61.6	61.0
Maternal smoking				
Odds ratio (95% CI)	1.0	2.2 (1.3-3.7)	1.6 (0.9-2.9)	2.3 (1.2-4.4)
Prevalence (%)	11.4	21.2	17.0	21.0

Risk of belonging to any of the three groups with wheezing by serum IgE at 9 months



11. Martinez FD et al. N Engl J Med 1995;332:133-138.

Estimated prevalence of wheezing at each time point for each of the six wheezing phenotypes identified by latent class analysis in 6265 children with complete data



Wheezing phenotypes vs. Physician diagnosed asthma

Phenotype	Physician diagnosed asthma
	OR(95% CI)
Transient early	2.46(1.48-4.09)
Prolonged early	14.87(10.6-20.71)
Intermediate	325.75(137.78-770.14)
Late	84.6(56-127.8)
Persistent	307.93(185.86-510.18)
Never/Infrequent	1



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Asthma control

- No validated tools in children under 4 years¹⁰
 - Childhood ACT is for ages 4-11
- Current recommended tool (GINA) is based on expert opinion (Evidence D)¹⁰
- Two main domains
 - SYMPTOM CONTROL (DARN) IN PAST 4 WEEKS
 - Well controlled (0)
 - Partly controlled (1-2)
 - Uncontrolled (3-4)
 - FUTURE RISK OF POOR ASTHMA OUTCOMES
 - EXACERBATIONS: Symptoms, Exacerbations, Season, Exposures, Socioeconomic, Psychological, Adherence
 - FIXED AIRFLOW LIMITATION: Severe asthma with several hospitalizations, history of Bronchilolitis
 - MEDICATION S/E: Systemic, Local

10. Global Initiative for Asthma: Global strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org



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Controller therapy in young children (age 5 and below)



Region	Step 1	Step 2	Step 3	Step 4
Kenya 2011¹⁴	Controlled As needed SABA	Partly controlled Low dose ICS	Uncontrolled Double Low dose ICS	
other options		LTRA	Low dose ICS+LTRA	
GINA 2015¹⁰	SABA	Low dose ICS	Double Low dose ICS	Continue controller & refer to specialist
other options		LTRA Intermittent ICS	Low dose ICS+LTRA	Add LTRA Increase ICS Frequency Add intermittent ICS
NHLBI¹⁵	SABA	Low dose ICS	Medium dose ICS	Medium dose ICS+LABA/LTRA 
Other options		Cromolyn or LTRA		
BTS/SIGN¹⁶	SABA	ICS (200-400mcg BDP equivalent)	ICS+LTRA	Continue controller & refer to specialist

10. Global Initiative for Asthma: Global strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org

14. National Asthma guidelines Kenya

15. NHLBI guidelines for management of asthma

16. BTS/SIGN guidelines for asthma management

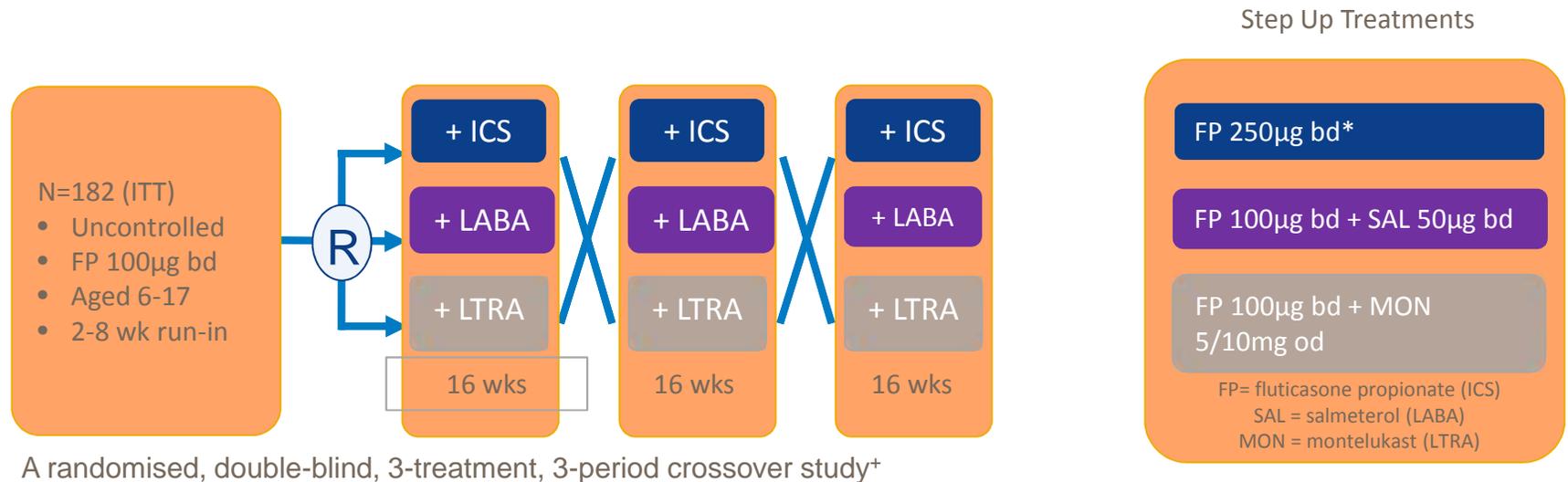


What is best add on therapy to low dose ICS?

BADGER Study (Best ADd-on Therapy Giving Effective Responses)

Aim: To assess if the percentage of patients with a differential response to each of the three step-up treatments was >25%, in asthmatic children uncontrolled on low dose ICS

To answer key question: what is the best step-up treatment for asthmatic children uncontrolled on low dose ICS?



A randomised, double-blind, 3-treatment, 3-period crossover study*

Primary outcome: The differential response to each of the three step-up regimens based on a composite of 3 outcomes (oral corticosteroids for acute exacerbations, no. of asthma control days, and FEV₁)

+Each patient received each step-up option

*The maximum licensed dose of FP in children 4-16 years old is 200µg bd

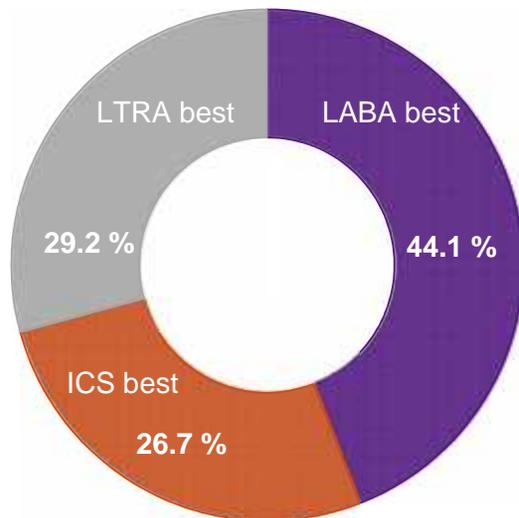
The BADGER study included patients over 16 years old for whom the maximum licensed dose is 1000µg bd

17. Lemanske et al. New Engl. J. Med. 2010; 362(11):975-985

Differential Response

Three-way comparison of step up

- % patients that responded best to each treatment



* Alternative presentation of data from Lemanske et al. 2010¹; actual values for this graph are given in Rabinovitch et al. 2013².

Primary Outcome

- 98% of children had a differential response to treatment (i.e., one step-up treatment was ranked better than the other two step-up treatments)

Additional analysis (graph left)

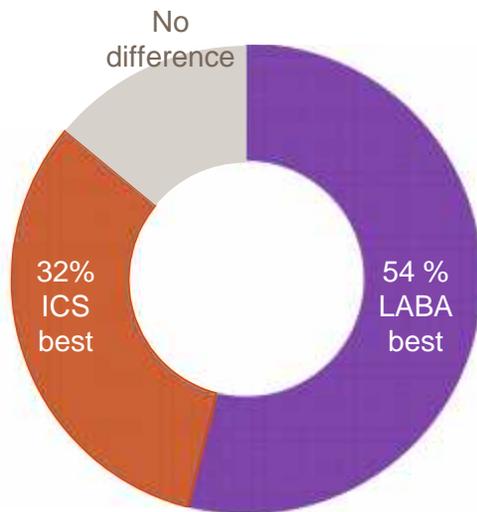
- In the three-way comparison, LABA step-up was significantly more likely to give the best response than either ICS or LTRA step-up:

	vs LTRA	vs ICS
Relative probability	1.6 (1.1, 2.3) p=0.004	1.7 (1.2, 2.4) p=0.002

Differential Response (2)

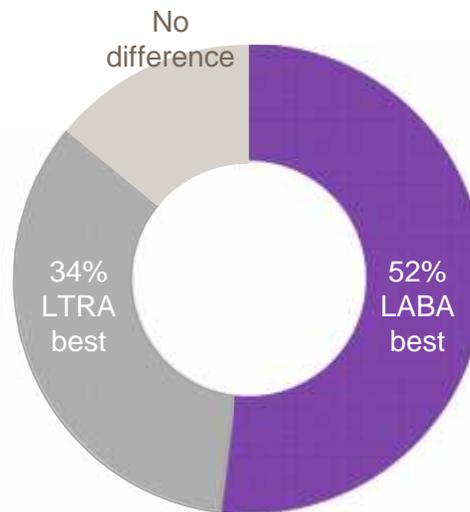
- In the pairwise comparison of three step-up therapies, more patients had a better response to LABA vs. LTRA step-up and LABA vs. ICS step-up (figures show % patients that responded best to each treatment)

a) LABA vs. ICS



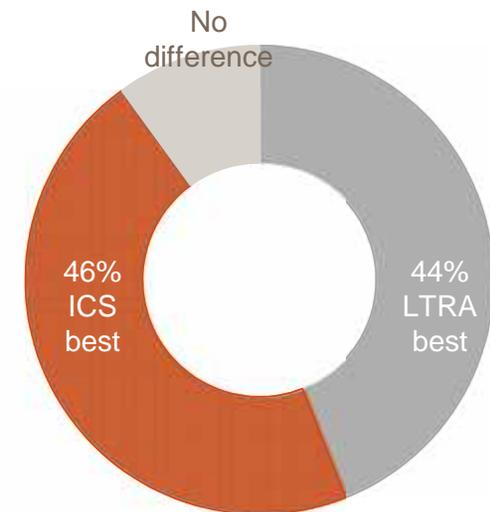
LABA 54% vs. ICS 32%
(p=0.004)

b) LABA vs. LTRA



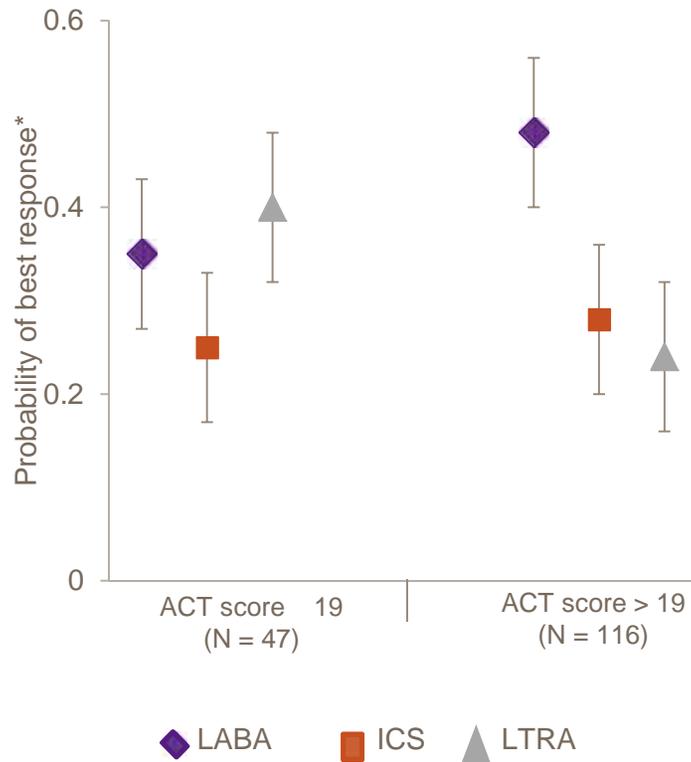
LABA 52% vs. LTRA 34%
(p=0.02)

c) ICS vs. LTRA*



Responses to LTRA and ICS step-up were similar

Predictors of Response

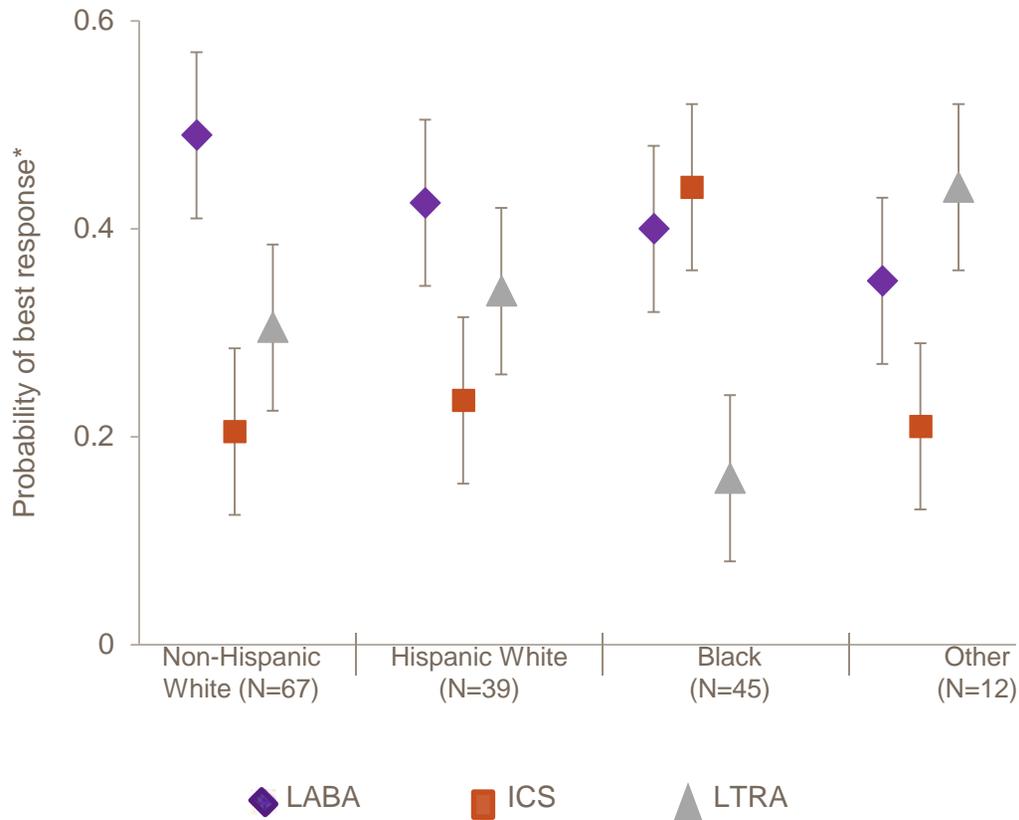


Primary Predictors of Differential Response

- Higher scores on the Asthma Control Test (>19 on ACT) and the Childhood Asthma Control Test predicted a greater probability that the best response would be to LABA step-up.
- Patterns of differential response were not predicted by methacholine PC₂₀ values, fraction of exhaled nitric oxide or genotype at position 16 of the β -adrenergic receptor (data not shown)

* Figure is a schematic using data estimated from Lemanske et al. 2010 [RF/SFC/0064/15]

Predictors of Response



Secondary Predictors of Differential Response (post hoc analysis)

- White patients were most likely to have a best response to LABA step-up
- Black patients were equally likely to have a best response to LABA or ICS step up and less likely to have a best response to LTRA step-up
- Patients who did not have eczema were most likely to have a best response to LABA step-up (data not shown)

* Figure is a schematic using data estimated from Lemanske et al. 2010 [RF/SFC/0065/15]

Which controller medication beyond step 3?

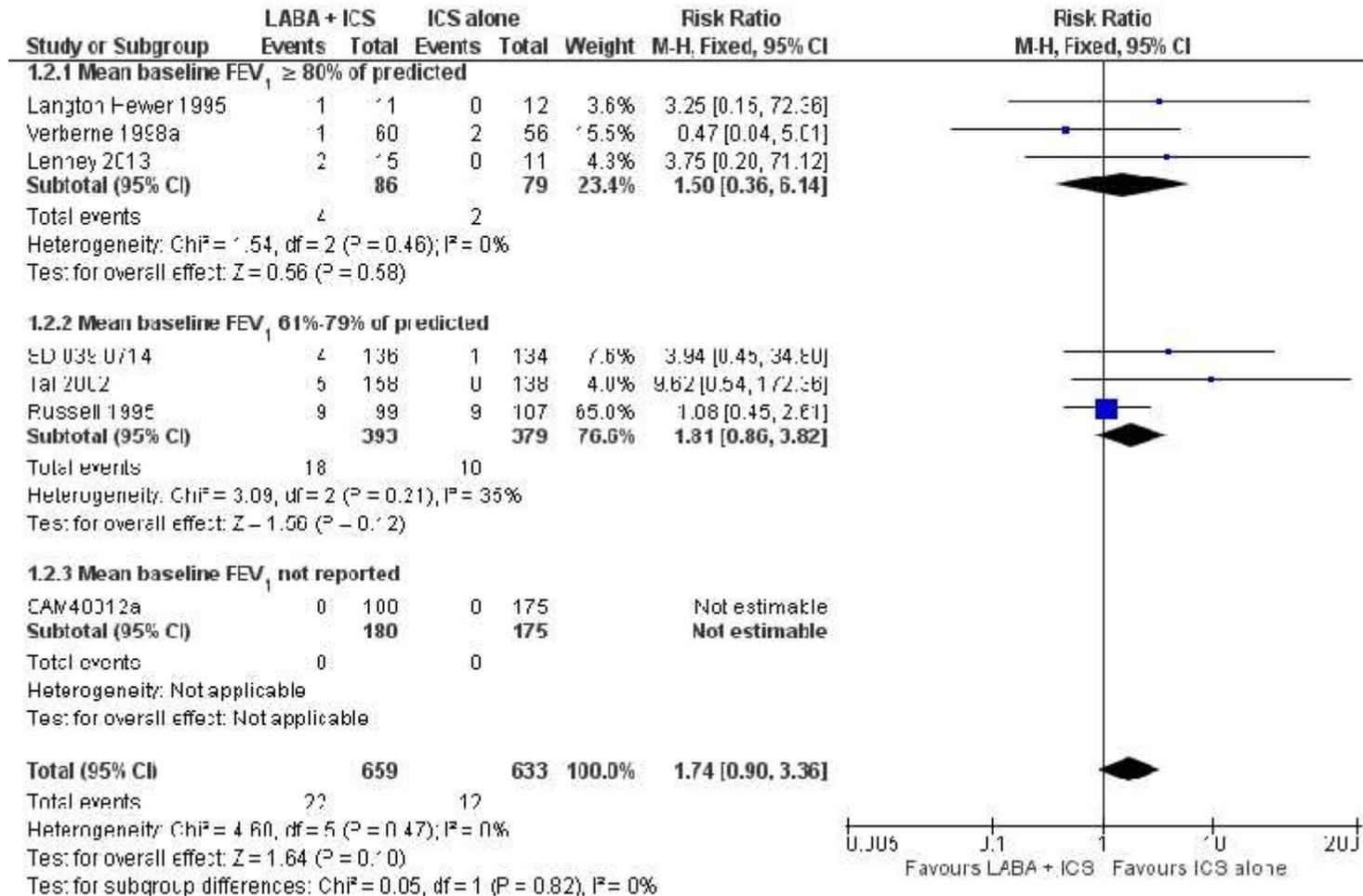
In the BADGER trial, despite step up in daily therapy, 120 exacerbations requiring oral corticosteroids still occurred

Cochrane Review: LABA in paediatric asthma

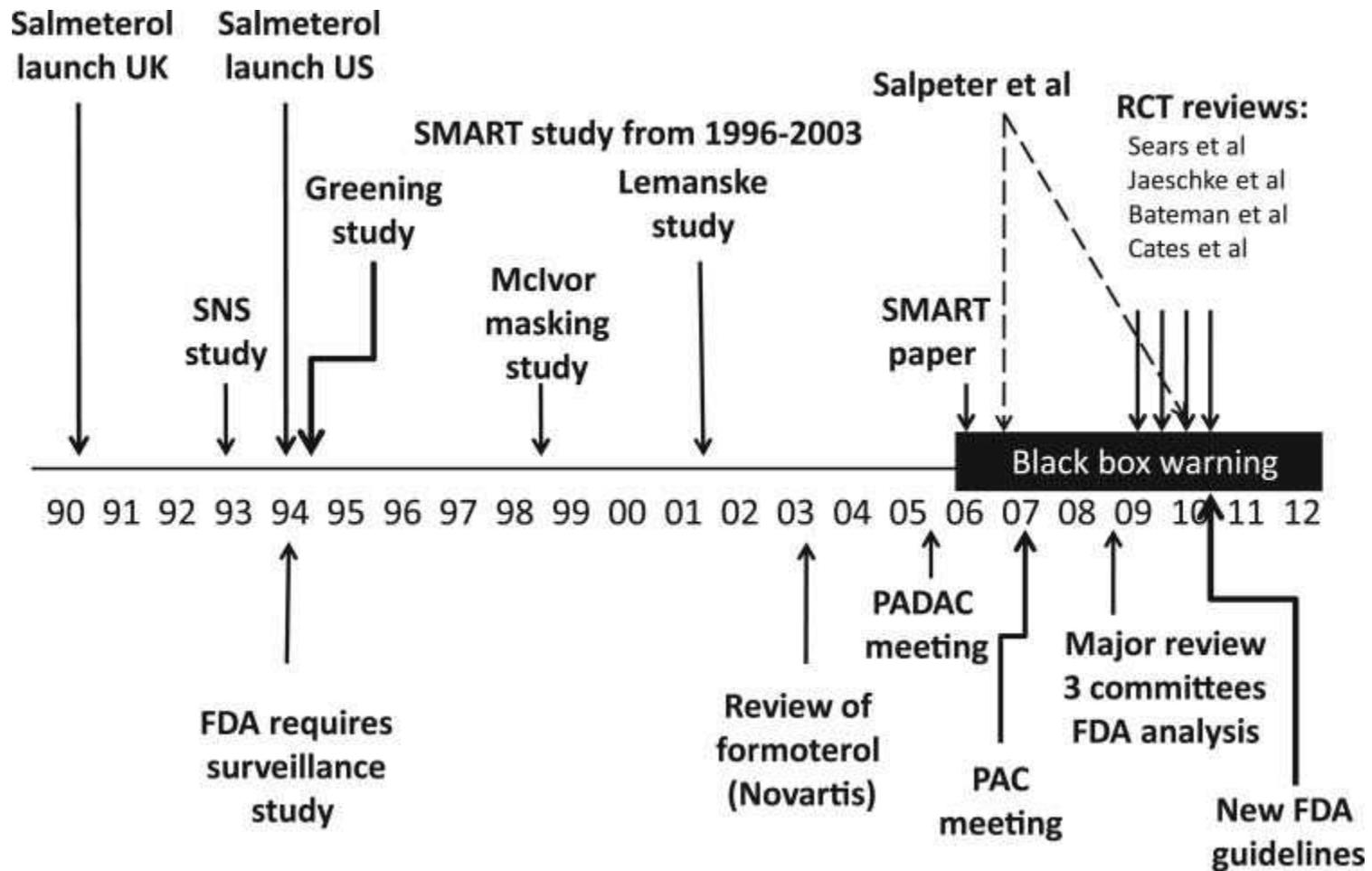
- Included 33 trials with 39 control-intervention comparisons and total of 6381 children.
- Most participants were inadequately controlled on their current ICS dose.
- Review questions:
 - LABA + ICS vs. Same dose of ICS
 - LABA + ICS vs. Increased dose of ICS
- Conclusion:
 - Addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids
 - LABA+ICS superior for improving lung function compared with the same or higher doses of ICS.
 - No differences in adverse effects were apparent, with the exception of greater growth with the use of ICS and LABA compared with a higher ICS dose.



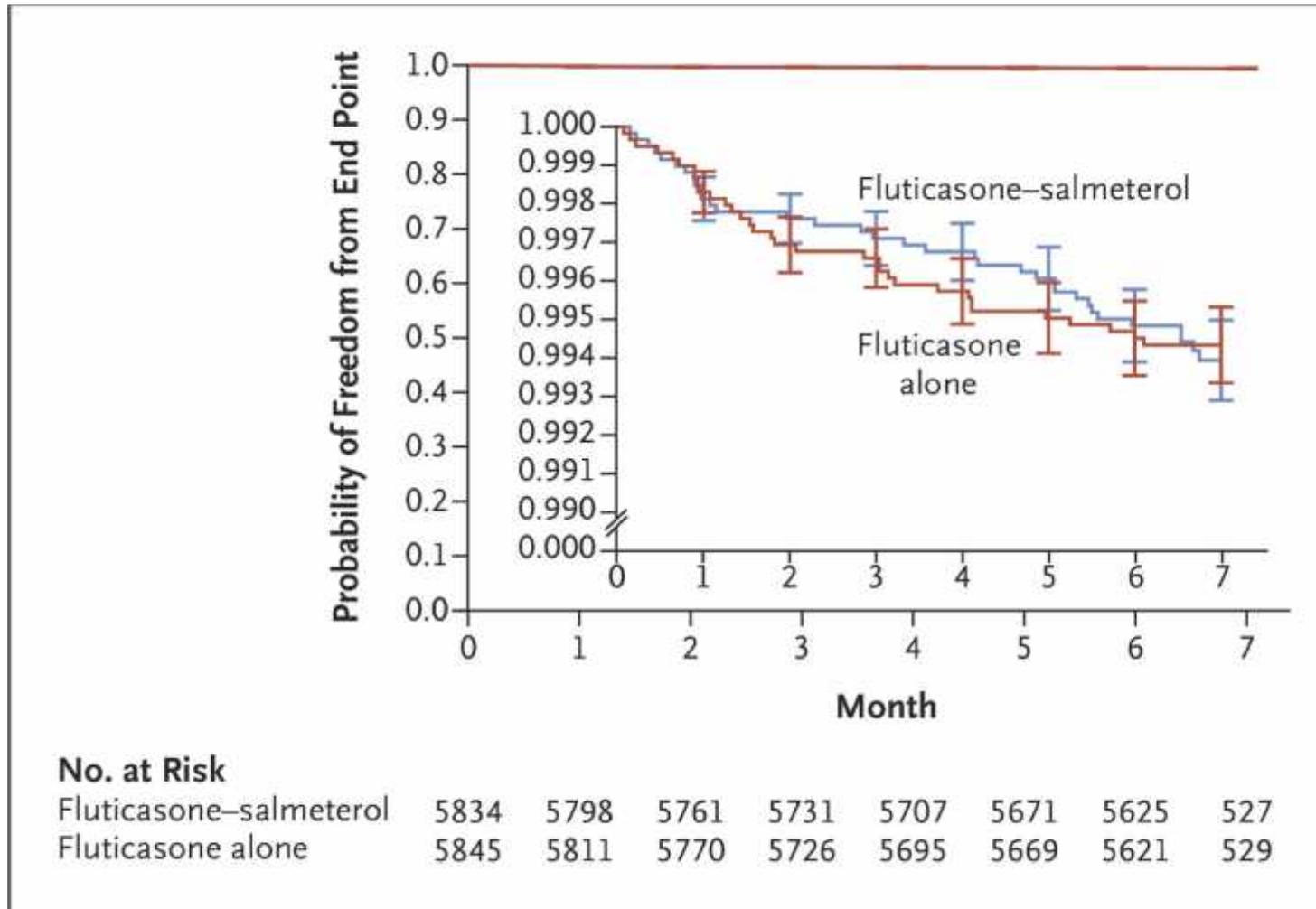
Trend towards more hospitalizations with ICS+LABA



FDA safety review



19. Thorax. 2013;68(2):195-8.





PRESS RELEASE



Issued: Thursday 17th March 2016, London UK - LSE Announcement

GSK's Advair[®] Diskus[®] achieves primary endpoint in LABA safety study of children aged 4-11 years with asthma



Key issues

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- Adherence?

Inhaler device

- A pMDI with a valved spacer is the preferred delivery system
- 5-10 breaths will empty a spacer (<350ml in very young children)
- Child should inhale as soon as possible after actuation
- Face mask should be tight fitting
- Plastic spacers should be regularly washed with detergent and air-dried

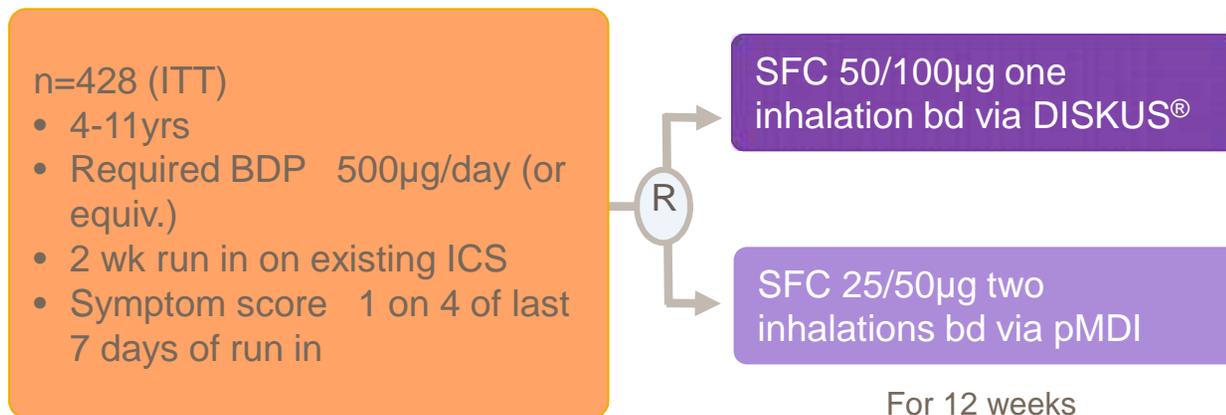
Age	Preferred	Alternate
0-3 years	pMDI plus dedicated spacer + face mask	Nebuliser with face mask
4-5 years	pMDI plus dedicated spacer + mouth piece	pMDI plus dedicated spacer + face mask or Nebuliser with mouthpiece of face mask

10. Global Initiative for Asthma: Global strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org

Bracamonte: Study Design

Aim: to compare the efficacy of SFC delivered via the DISKUS[®] vs pressurised Metered Dose Inhaler (pMDI) in children with persistent asthma

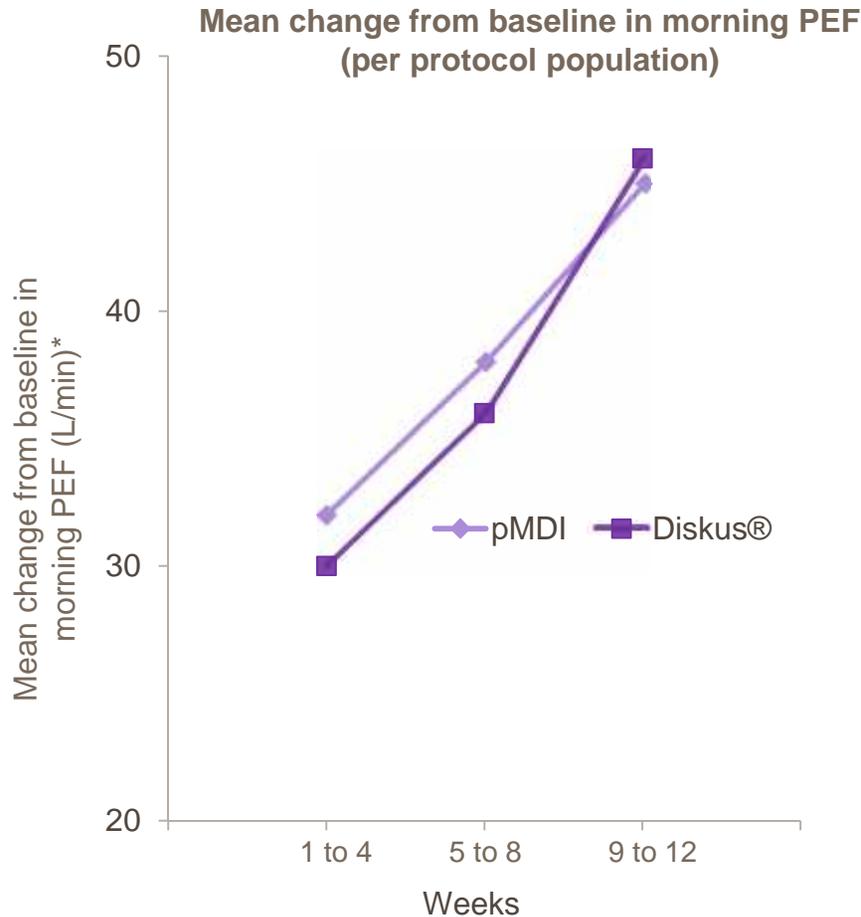
Multicentre, randomised, double-blind, double-dummy, parallel group, equivalence study



Primary endpoint: Mean morning PEF over weeks 1 to 12

Secondaries included: Lung function, day and night time symptoms, rescue medication use, % symptom-free days, % salbutamol-free days

Primary endpoint



Mean morning PEF over weeks 1-12

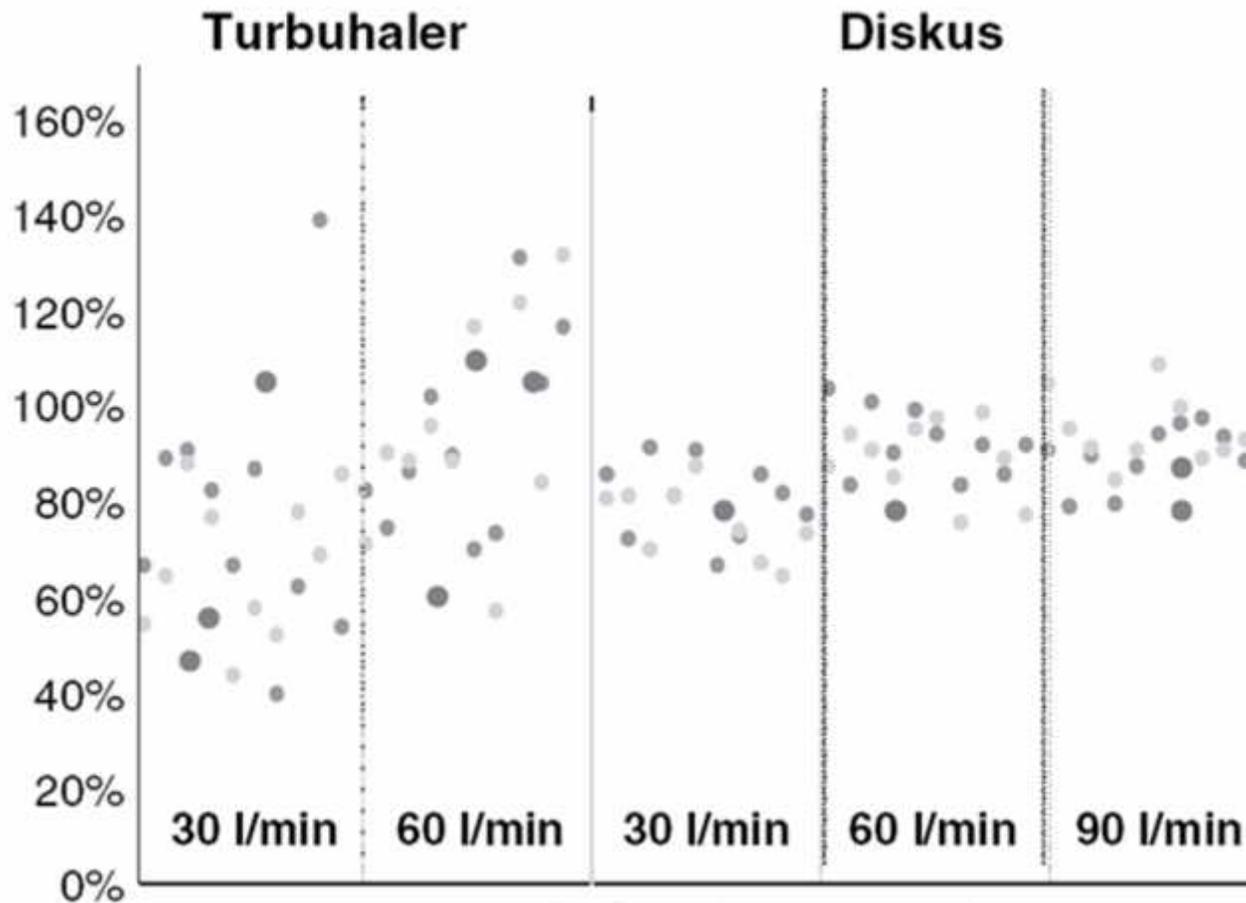
- No significant difference between groups
 - Mean change DISKUS® = 37.7 L/min
 - Mean change pMDI = 38.6 L/min

DISKUS® vs pMDI	
Treatment difference	-0.9 L/min
95% CI	-7.1, 5.4

- -0.9 L/min difference was within pre-defined criterion for equivalence (± 15 L/min)
- Improvement observed in mean morning PEF was evident across all age groups (not shown).

* Figure is a schematic using data estimated from Bracamonte et al. 2005 [RF/SFC/0060/15]

Uniformity of dose delivery from the Diskus and Turbuhaler

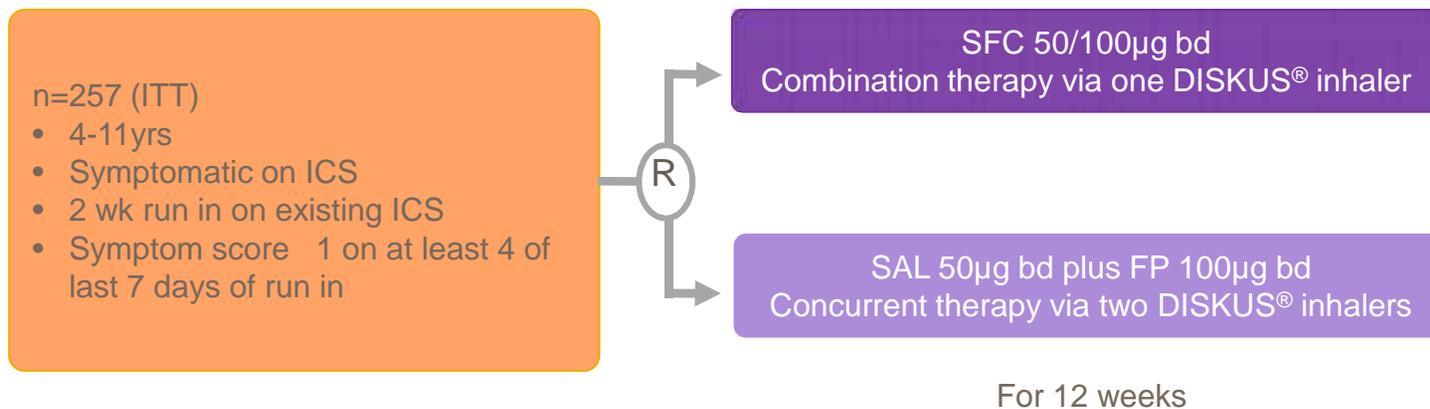


H. Chrystyn Adapted from Chrystyn H., *The Diskus: a review of its position among dry powder inhaler devices*, *International Journal of Clinical Practice*, 61(6), 2007. Pg. 1022-36

Van den Berg: Study Design

Aim: to compare the efficacy and safety of Salmeterol (50µg bd) plus fluticasone propionate (100µg bd) in asthmatic children when delivered together via a single DISKUS[®] inhaler or concurrently using two separate DISKUS inhalers

Multicentre, randomised, double-blind, double-dummy, parallel group equivalence study at 35 centres in 9 countries

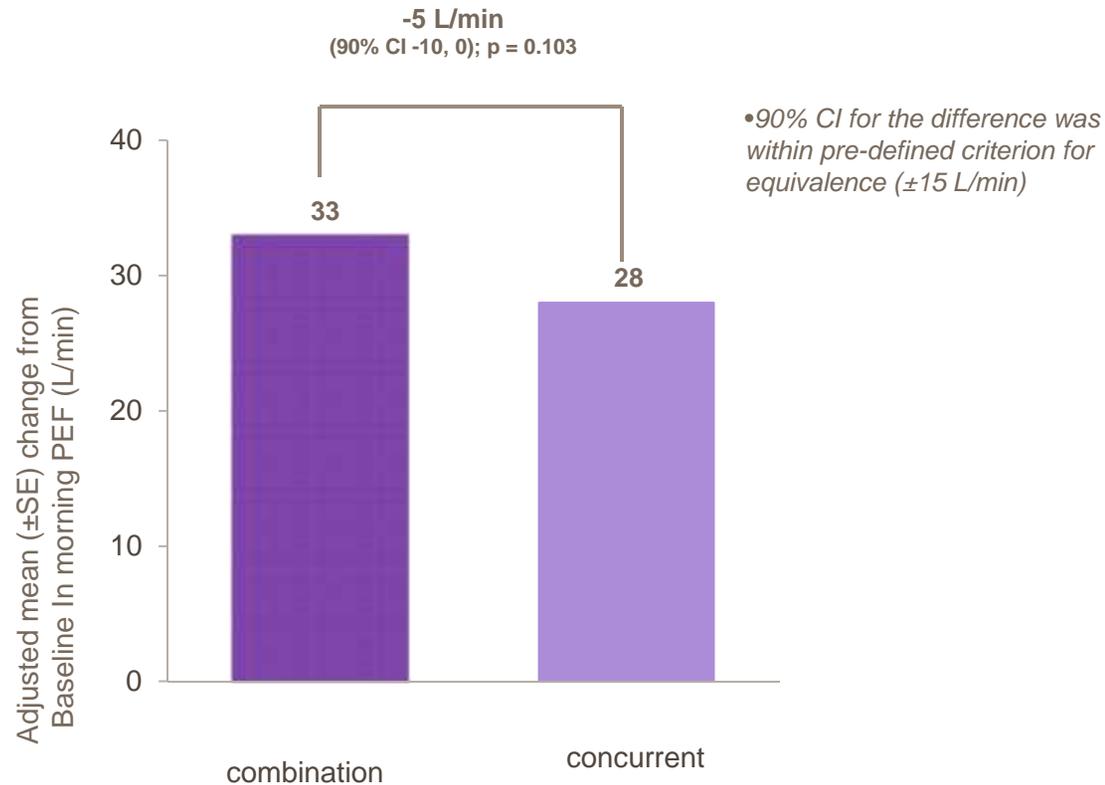


Primary endpoint: Mean morning PEF over weeks 1 to 12

Secondaries included: Lung function, day and night time symptoms, rescue medication use

Van den Berg: Primary endpoint

Change from baseline in adjusted mean morning PEF over weeks 1 to 12



•In asthmatic children symptomatic on ICS, combination therapy with SFC in a single DISKUS[®] inhaler is as effective as the two drugs administered concurrently via two separate DISKUS[®] inhalers.

•Both treatment regimens are generally well tolerated

21. Van den Berg et al. Pediatric Pulmonology 2000; 30:97-105



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Adherence



-
- Children depend on carers for management
 - Transition to adolescence
 - Non-adherence may lead to overuse of PRN medications (Rescue SABA)
 - Adherence to ICS typically between 30-70% in various studies, but <50% on average



- No gold standard currently exists for quantifying adherence to asthma medications.²²
- In one study, a 30-minute tailored asthma education session and an individualized asthma action plan that was reinforced at 2-week intervals were helpful in improving ICS adherence.²³

22. Current Allergy and Asthma Reports. 2011;11(6):454-64.

23. J Allergy Clin Immunol. 2009;123(4):840-6.

Summary



- Asthma burden
- Why children have unique needs
- What some of these needs are
- How some needs are being mitigated
- Importance of adherence



Safety statement



GSK is committed to the effective collection and management of human safety information relating to our products and we encourage healthcare professionals to report adverse events to us on +254 20 693 3200 or ke.safety@gsk.com

Seretide, Flixotide and Ventolin are a trademark of GlaxoSmithKline group of Companies

Full Prescribing Information is available on request from GlaxoSmithKline Pharmaceutical Kenya Limited, P.O. Box 78392-00507, Likoni Road, Nairobi Kenya.

A photograph of four children standing in a field of green plants. The children are of African descent and are smiling. They are wearing simple, everyday clothing. The background shows a clear blue sky with some clouds and more greenery. A large, semi-transparent orange and yellow graphic is overlaid on the left side of the image.

Thank You!

Fluticasone propionate

Contraindications

- Hypersensitivity to any ingredient of the preparation.

Warnings and Precautions

- Increasing use of short-acting inhaled beta₂-agonists to control asthma symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.
- Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. In patients considered at risk, daily peak flow monitoring may be instituted.
- Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see *Overdosage*). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see *Adverse Reactions*).
- It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.
- Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Fluticasone propionate API

- Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.
- The possibility of impaired adrenal response should always be considered in emergency situations (including surgery), and also in elective situations likely to produce stress, especially in patients taking high doses for an extended duration of time. Additional corticosteroid treatment appropriate to a given clinical situation must be considered (see *Overdosage*).
- Similarly replacement of systemic steroid treatment with inhaled therapy may unmask allergies such as allergic rhinitis or eczema previously controlled by the systemic drug.
- Treatment with fluticasone propionate should not be stopped abruptly.
- There have been very rare reports of increases in blood glucose levels (see *Adverse Reactions*) and this should be considered when prescribing to patients with a history of diabetes mellitus.
- As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.
- During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (See *Interactions*).

Fluticasone propionate API



-
- As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast and short-acting inhaled bronchodilator. Fluticasone propionate should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary (*see Adverse Reactions*).
 - # There was an increased reporting of pneumonia in studies of patients with COPD receiving FP 500 micrograms (*see Adverse Reactions*). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.
 - Patients' inhaler technique should be checked to make sure that inhaler actuation is synchronised with inspiration to ensure optimum delivery of the drug to the lungs.

Flixotide is a trademark of GlaxoSmithKline group of Companies. Abbreviated Prescribing Information prepared in March 2014 based on GDS version 31 dated 14th November 2013

Fluticasone propionate API

EA/AST/0019/16

Seretide



Contraindications

- Salmeterol-FP is contraindicated in patients with a history of hypersensitivity to any of the ingredients (*see Excipients*).

Warnings and Precautions

- Salmeterol-FP Accuhaler/Diskus or Evohaler is not for relief of acute symptoms for which a fast and short-acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have their relief medication available at all times.
- Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.
- Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should be reviewed by a physician. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of salmeterol-FP has failed to give adequate control of asthma, the patient should be reviewed by a physician.
- Treatment with salmeterol-FP should not be stopped abruptly in patients with asthma due to risk of exacerbation, therapy should be titrated-down under physician supervision. For patients with COPD cessation of therapy may be associated with symptomatic decompensation and should be supervised by a physician.
- The possibility of impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment considered (*see Overdosage*).



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- There was an increased reporting of pneumonia in studies of patients with COPD receiving salmeterol-FP (see *Adverse Reactions*). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.
 - As with all inhaled medication containing corticosteroids, salmeterol-FP should be administered with caution in patients with active or quiescent pulmonary tuberculosis.
 - Salmeterol-FP should be administered with caution in patients with thyrotoxicosis.
 - Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, salmeterol-FP should be used with caution in patients with pre-existing cardiovascular disease.
 - A transient decrease in serum potassium may occur with all sympathomimetic drugs at higher therapeutic doses. Therefore, salmeterol-FP should be used with caution in patients predisposed to low levels of serum potassium.



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- Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see *Overdosage*). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore for asthma patients, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.
 - It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.
 - Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.
 - Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.
 - There have been very rare reports of increases in blood glucose levels (see *Adverse Reactions*) and this should be considered when prescribing to patients with a history of diabetes mellitus.



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- During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (*see Interactions*).
 - Data from a large US study (SMART) comparing the safety of salmeterol (a component of salmeterol-FP) or placebo added to usual therapy showed a significant increase in asthma-related deaths in patients receiving salmeterol. Data from this study suggested that African-American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors. The SMART study was not designed to determine whether concurrent use of inhaled corticosteroids modifies the risk of asthma-related death. (*see Clinical Studies*)
 - It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with salmeterol. (*see Interactions, and Pharmacokinetics*).

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Full Prescribing Information prepared in April 2015 based on GDS version 33 dated 30 March 2015.

Seretide™ API

EA/AST/0019/16



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- As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast and short-acting inhaled bronchodilator. Salmeterol-FP Accuhaler/Diskus or Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.(*see Adverse Reactions*)
 - The pharmacological side-effects of beta-₂ agonist treatment, such as tremor, subjective palpitations and headache have been reported, but tend to be transient and to reduce with regular therapy. (*see Adverse Reactions*)



Ventolin

Contraindications:

- Salbutamol inhaled formulations are contraindicated in patients with a history of hypersensitivity to any of its components. Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion. Salbutamol dry powder inhaler formulations are contraindicated in patients with severe milk-protein allergy.

Warnings and Precautions

- The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.
- Increasing use of short-acting bronchodilators, in particular beta-₂ agonists to relieve symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.
- Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.
- Salbutamol should be administered cautiously to patients with thyrotoxicosis.
- Potentially serious hypokalaemia may result from beta-₂ agonist therapy mainly from parenteral and nebulised administration.
- Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.



Ventolin

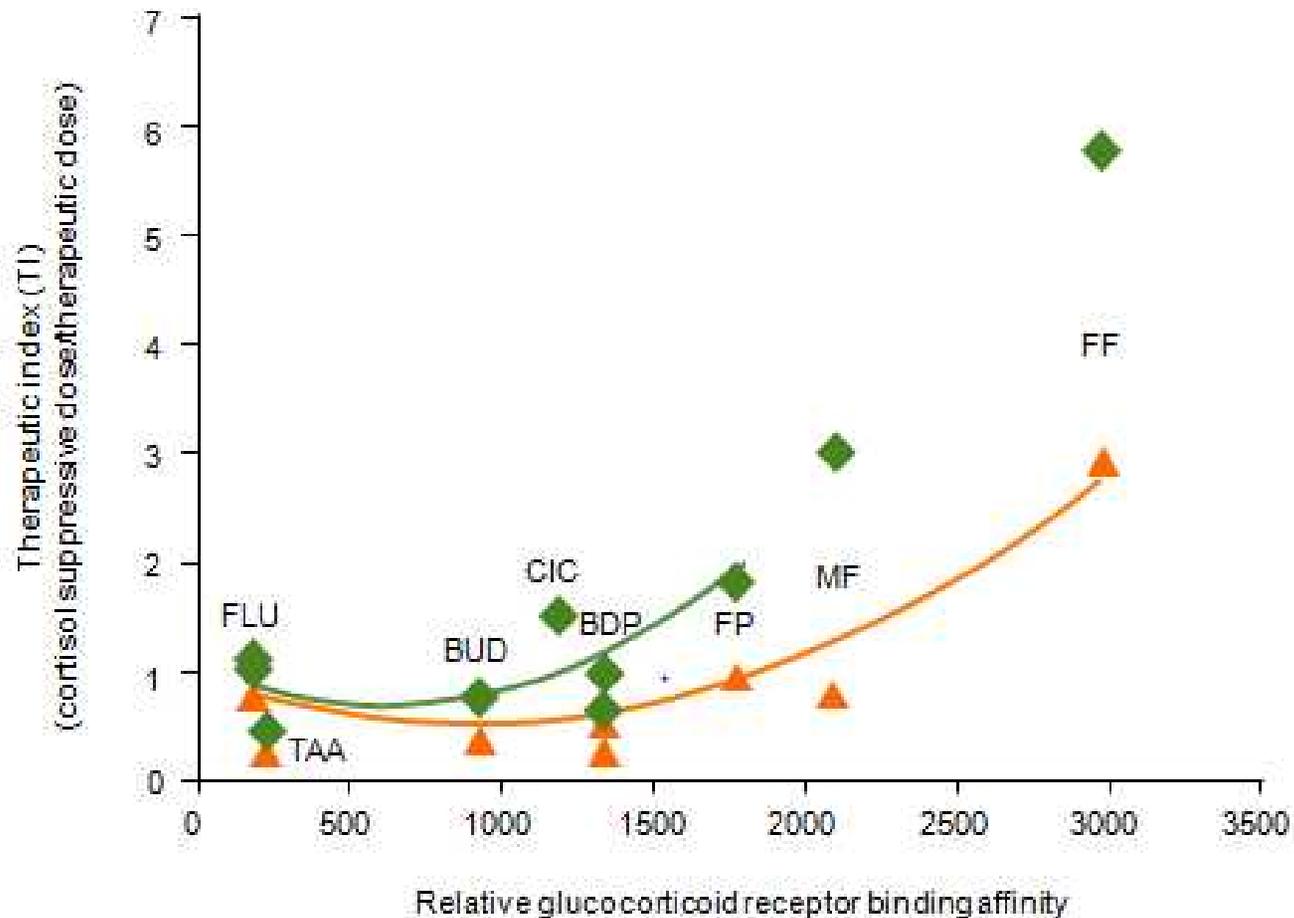
- As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. The specific salbutamol presentation should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.
- *Inhaler, Evohaler, Rotacaps:*
- In the event of a previously effective dose of inhaled salbutamol failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.
- *Inhaler, Evohaler:*
- The patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

GSK is committed to the effective collection and management of human safety information relating to our products and we encourage healthcare professionals to report adverse events to us on +254 20 693 3200 or email us on ke.safety@gsk.com

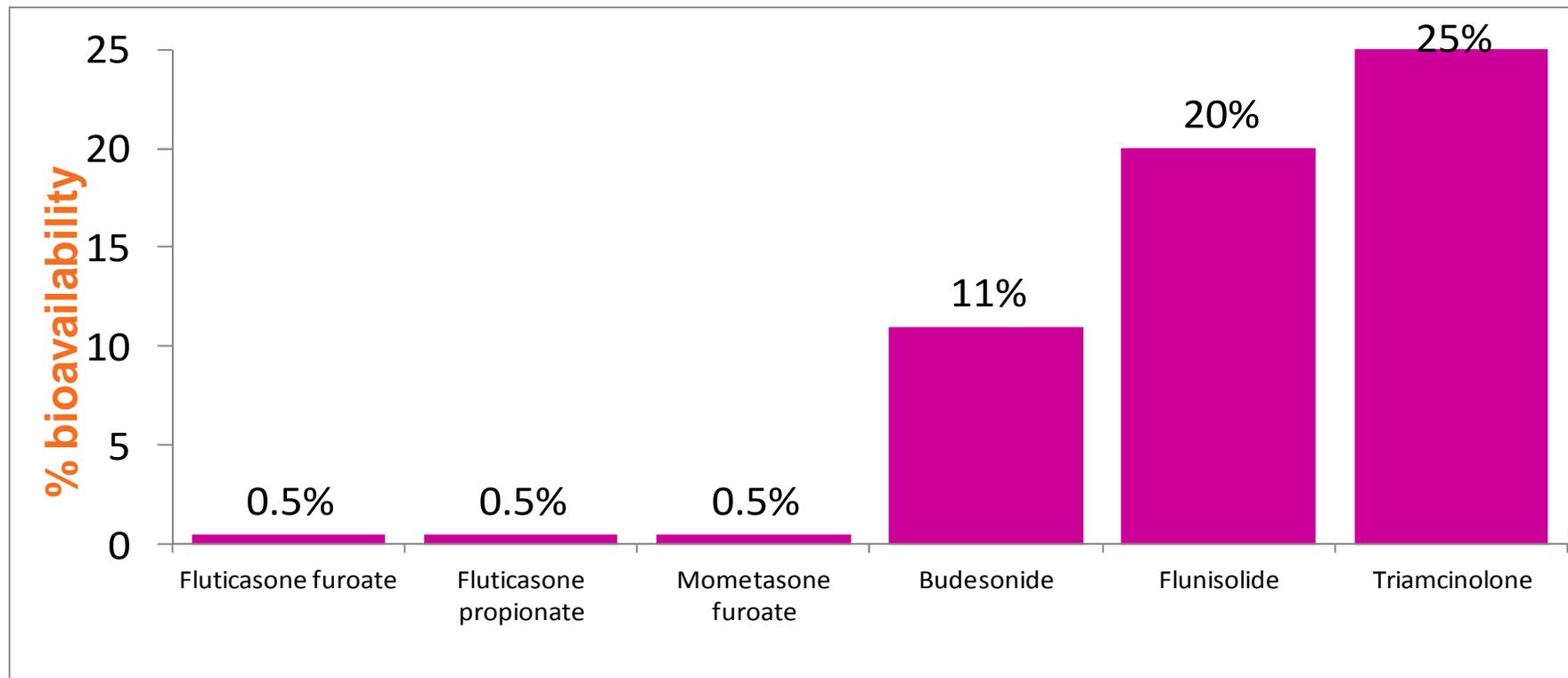
Full Prescribing Information is available on request from GlaxoSmithKline Pharmaceutical Kenya Ltd P.O. Box 78392-00507, Likoni Road, Nairobi Kenya.

VENTOLIN, EVOHALER, ROTACAPS are trademarks of the GlaxoSmithKline group of companies. Full Prescribing Information prepared in April 2014 based on GDS version 24 dated 14th April 2014

Relationship between glucocorticoid receptor binding affinity and the therapeutic index for low/mid () or mid/high () therapeutic daily doses



Oral bioavailability of currently used corticosteroids



Bryson HM, Faulds D. *Drugs* 1992;43:760–75. Daley-Yates PT, Baker RC. *Br J Clin Pharmacol* 2001;51:103–5; Daley-Yates PT et al. *Eur J Clin Pharmacol* 2004;60:265–8; Allen A et al. *Clin Ther* 2007;29:1415–20.

b1

Gonzalez and Derendorf

Add another bar for ciclesonide after mometasone

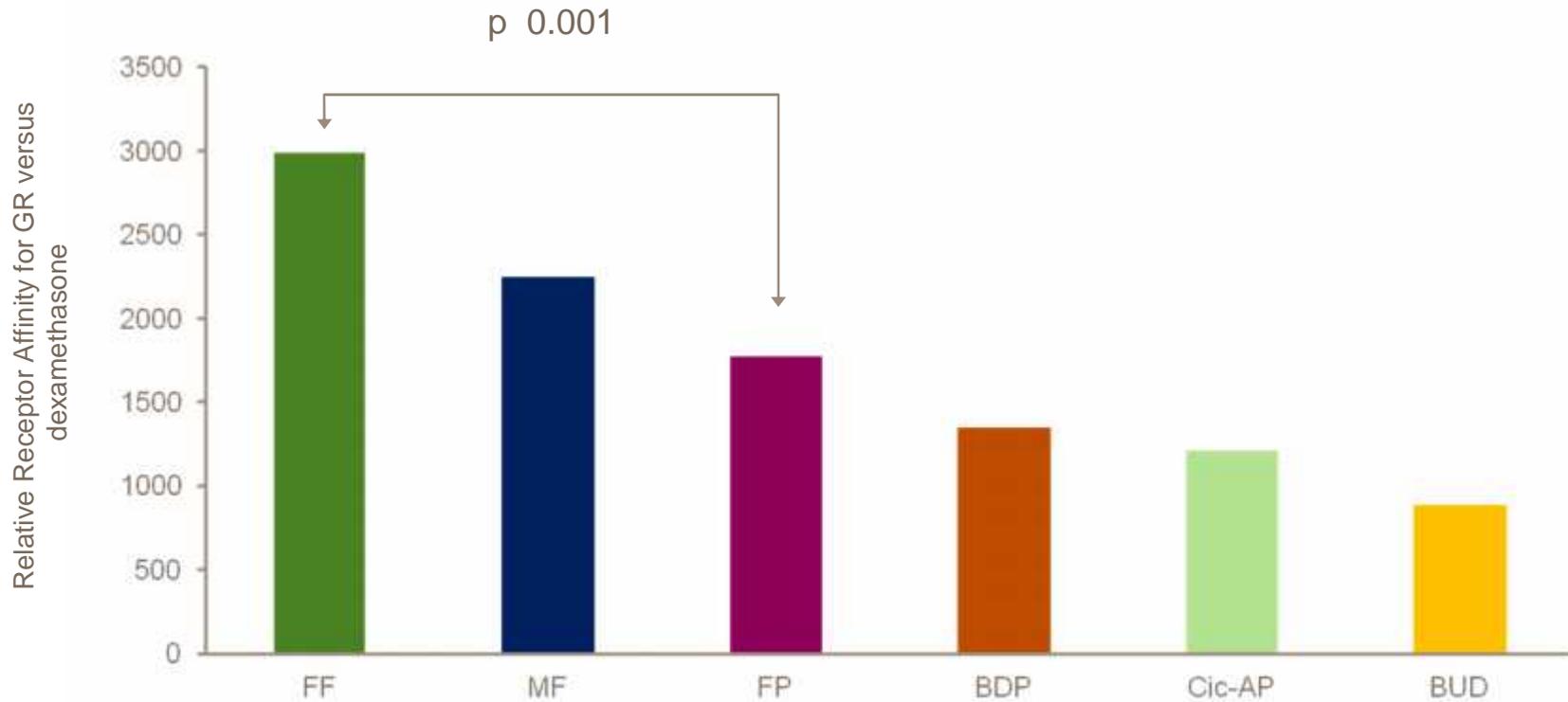
ba748958, 2/12/2016

b2

Affinity for GR



In vitro Glucocorticoid Receptor binding assay



Adapted from Valotis A, Högger P. *Resp Res.* 2007;8:54–62; Salter M et al. *Am J Physiol Lung Cell Mol Physiol.* 2007;293:L660–7.

b2

if we focussing on Flixotide then can remove the FF, MF bars

ba748958, 2/12/2016