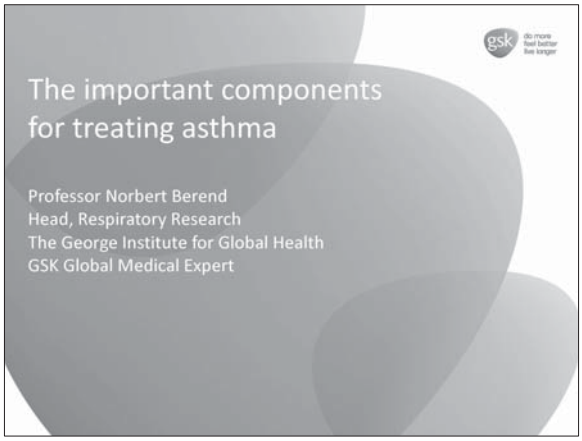
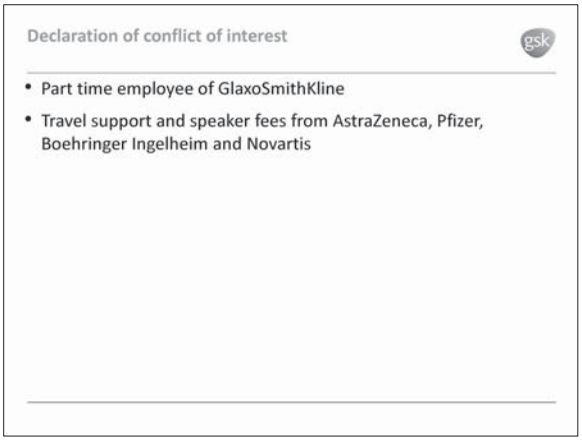
Luncheon Symposium 1

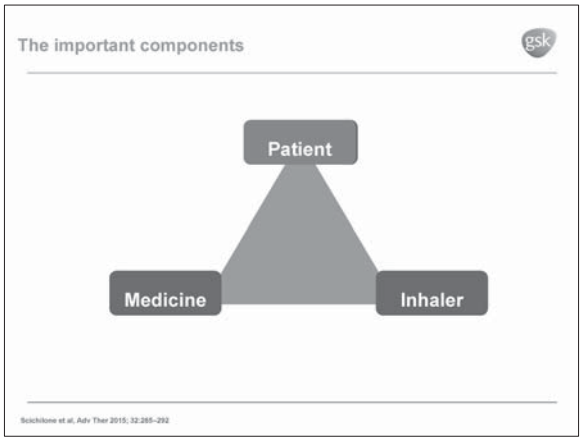
The important components for treating asthma

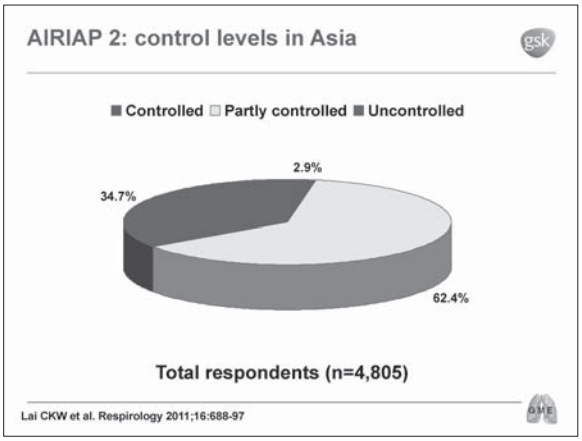
Respiratory Research, The George Institute for Global Health, GSK Global Medical Expert

Norbert Berend









May 12, Friday

Why is it so important to understand the patient experience of asthma?

- Successful asthma management requires a good partnership between patients and HCPs; a shared language and understanding is vital[1]
- The European REALISE survey (n=8000) published in 2014 highlighted a disconnection between patients' perceptions of their asthma and guideline-defined levels of control[1]
  - Of those who considered their asthma controlled, 55.5% had experienced symptoms that interfered with normal activities and 52.5% had awoken at night owing to asthma in the previous week[1]

1. Price D *et al. NPJ Prim Care Respir Med* 2014;24:14009.

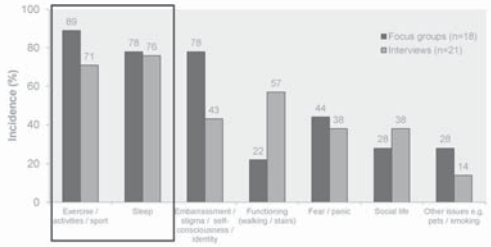
Overview of symptoms experienced by patients[2]

Symptom	Focus groups (n=18) n (%)	Interviews (n=21) n (%)
Shortness of breath	7 (39)	20 (95)
Wheezing	7 (39)	18 (86)
Coughing	4 (22)	14 (67)
Chest tightness	4 (22)	14 (67)
Flare ups	0	12 (57)
Back/chest/lung pain	0	6 (29)
Coughing up mucus	0	3 (14)
Tiredness	0	2 (10)
Lack of energy	0	2 (10)
Chest infections	0	2 (10)

Within the group setting, many patients downplayed their symptoms and were less likely to admit to them. When probed individually, however, they were more likely to admit to having symptoms

Svedsater, H., Hilton, E., Patel, C., Macey, J., Roberts, J., & Bradshaw, L. (2016). Qualitative Interviews And Focus Groups With COPD And Asthma Patients: Understanding Patient Burden, Life Impact And Treatment Preferences. In *A50. ASTHMA: OBSERVATIONAL STUDIES* (pp. A1747-A1747). American Thoracic Society.

Aspects of quality of life most commonly reported as impacted by asthma[2]

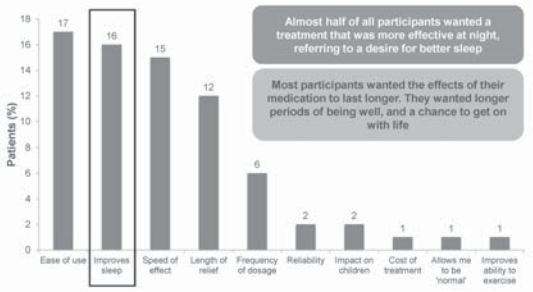


Aspects of quality of life most commonly impacted by asthma were exercise / activities / sports and sleep

Only data for HRQoL aspects reported by >20% of patients in either focus groups or interviews are included.

Svedsater, H., Hilton, E., Patel, C., Macey, J., Roberts, J., & Bradshaw, L. (2016). Qualitative Interviews And Focus Groups With COPD And Asthma Patients: Understanding Patient Burden, Life Impact And Treatment Preferences. In *A50. ASTHMA: OBSERVATIONAL STUDIES* (pp. A1747-A1747). American Thoracic Society.

Attributes of an ideal treatment[2]

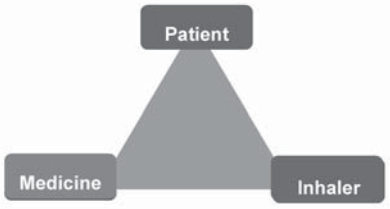


Almost half of all participants wanted a treatment that was more effective at night, referring to a desire for better sleep

Most participants wanted the effects of their medication to last longer. They wanted longer periods of being well, and a chance to get on with life

Svedsater, H., Hilton, E., Patel, C., Macey, J., Roberts, J., & Bradshaw, L. (2016). Qualitative Interviews And Focus Groups With COPD And Asthma Patients: Understanding Patient Burden, Life Impact And Treatment Preferences. In *A50. ASTHMA: OBSERVATIONAL STUDIES* (pp. A1747-A1747). American Thoracic Society.

The important components



Scichilone et al. Adv Ther 2015; 32:285–292

The puzzle of asthma

The pieces are coming together but do not make a single picture
Asthma may not be a single disease/ has a number of phenotypes

New directions in asthma

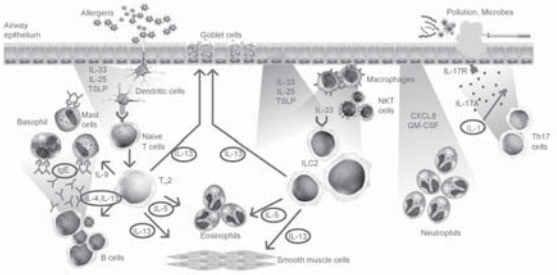
Asthma as a collection of endotypes (biologically related subtypes)

"Endotype.....is a subtype of disease defined functionally and pathologically by a molecular mechanism or by treatment response"

"Asthma is likely to have several specific endotypes associated with distinct clinical features, divergent underlying molecular causes, and distinct treatment responses"

Anderson GP. *Lancet* 2008; 372: 1107-19

Inflammation in asthma



Allergic eosinophilic asthma | Nonallergic eosinophilic asthma | Neutrophilic asthma

Adapted from Brusselle G, et al Ann Am Thorac Soc. 2014;11:S322-S328.

Biomarkers of Type 2 Inflammation

Sputum eosinophils

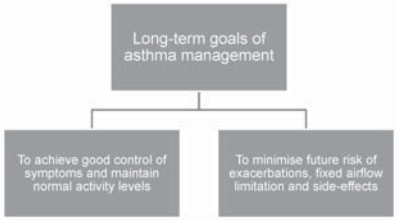
- Early marker for steroid responsiveness (absence = poor response)
- Marker of IL-5 importance

Blood eosinophils

- Surrogate biomarker for eosinophilic inflammation in asthma
- Relatively easy to obtain
- Cut-off used in clinical trials ranged between 150 and 300 cells/μL

Wan XC & Woodruff PG. *Immunol Allergy Clin North Am* 2016; 36(3): 547-57

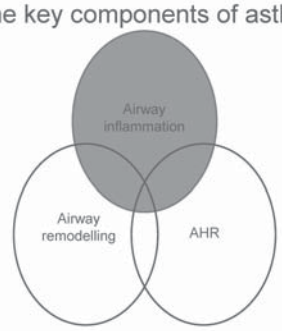
There are two long-term goals of asthma management[1]



It is also important to elicit the patients' own goals regarding their asthma

1. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: http://www.ginasthma.org/ (Accessed 14 July 2015)

Goals of asthma treatment can be achieved by reducing the key components of asthma

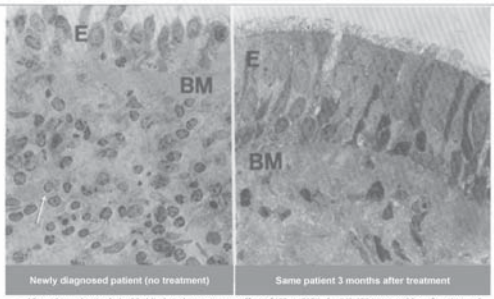


AHR: airway hyperresponsiveness

1. Ozier et al. J Allergy 2011;742710

Epithelial repair following inhaled steroid treatment

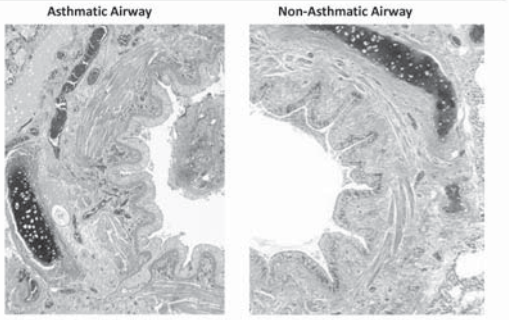
– Electron microscopic section: biopsy specimen from airway



– 12 week, randomised, double blind study to compare effect of ICS vs SABA (n=14). ICS improved lung function and airway inflammation (p<0.05). There was an observed increased number of ciliated airway cells nerves and reduced inflammatory cells, including eosinophils, with ICS.

Adapted from Laitinen et al. J Allergy Clin Immunol 1992; 90: 32-42

Asthma airway remodelling



Courtesy of Prof Judy Black

Airway Remodelling in Asthma

Mechanisms not well understood

- Reflection of severe disease ?[1]
- Cause for progressive decline of lung function?
- Reflection of undertreatment, poor control ?

1. James AL et al. Eur Respir J 2009; 34: 1040-1045

Treatment of airway remodelling in asthma

- Corticosteroids
- Reduce basement membrane thickening after 3-9 months[1]
- Reduce sputum eosinophils, periostin and wall thickness measured by imaging after 4 months[2]
- Reduce long-term loss of FEV_1[3]

1. Ward C et al. Thorax 2002; 57:309-16 2. Hoshino M et al. Respirology 2016; 21: 297-303 3. Haahtela T et al. N Engl J Med 1994; 331: 700-5

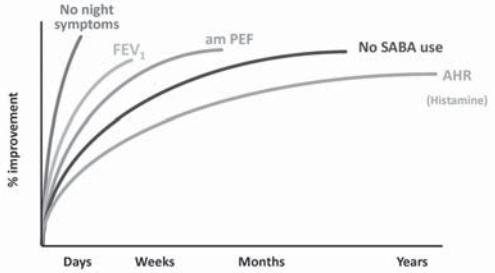
Airway Hyperresponsiveness

Predicts:

- Risk of development of asthma and COPD[1]
- Risk of exacerbations[2]
- Decline of lung function [2]
- Associated with severity of asthma[3]

1. Brutsche MH et al. Thorax 2006. Thorax 61; 671-677, 2. Leuppi JD et al. Am J Respir Crit Care med 2001; 163: 406-412, 3. Woolcock AJ et al. Am Rev Respir Dis 1984; 130: 71-75

Time course of gaining asthma control



Woolcock AJ Clin Exp Allergy Rev 2001; 1: 62-4.

Using biomarkers to gain asthma control

- Symptoms and exacerbations[1]
- AHR[2]
- FeNO[3]
- Sputum cells[4]

] TH_2 Phenotype

1. Bateman et al. Am J Respir Crit care Med 20014; 170: 836-850 2. Sont et al. Am J Respir Crit Care Med 1999; 159: 1043-1051 3. Smith et al. N Engl J Med 2005; 352: 2163-2173 4. Petsky et al. Thorax 2012; 67: 199-208

Summary

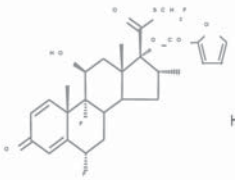
ICS is the mainstay treatment for:

- airway inflammation
- remodelling
- hyperresponsiveness

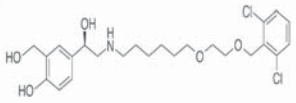
Fluticasone furoate (FF) and Vilanterol trifenatate (VI)

ICS/LABA once daily combination

Fluticasone furoate

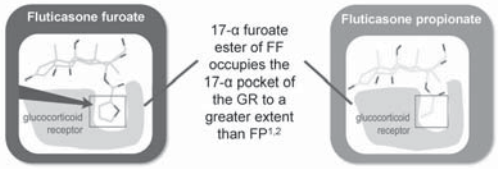


Vilanterol



Fluticasone furoate exhibits greater occupancy of ligand binding domain of the GR than fluticasone propionate

More Effective contact between FF ligand binding domain of GR

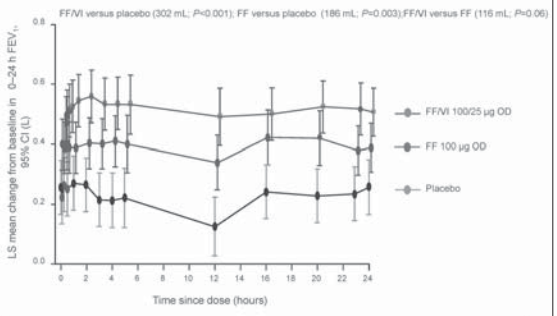


FF, fluticasone furoate; FP, fluticasone propionate; GR, glucocorticoid receptor

1. Biggadike K et al. *Ann Allergy Asthma Immunol.* 2007;98 (Suppl 1):A91–2;
2. Biggadike K et al. *J Med Chem.* 2008;51:3349–52.

Continuous 24-hour improvement in lung function

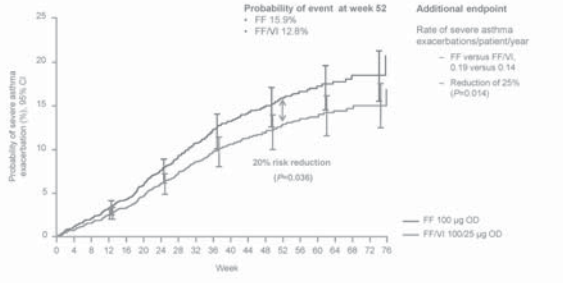
Co-primary endpoint: Mean change from baseline 0–24 hour FEV1 at week 12



Adapted from Bleecker ER *et al. J Allergy Clin Immunol Pract* 2014;2:553–61.

Reduced risk of severe exacerbation with FF/VI versus FF alone

Time to first severe asthma exacerbation

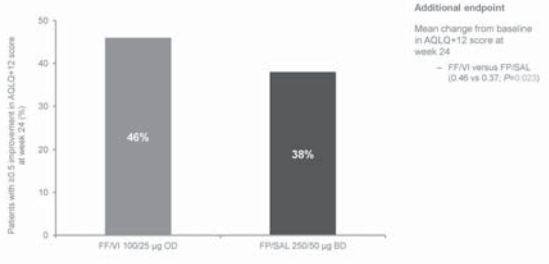


Cox proportional hazards model.

Adapted from Bateman ED et al. *Thorax.* 2014;69:312–9.

Clinically meaningful improvement in QoL more likely with FF/VI*

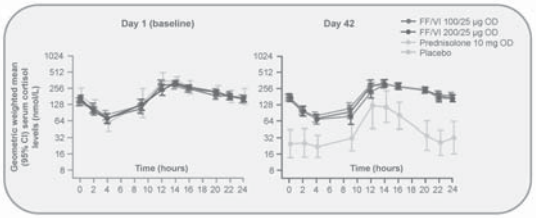
Patients with AQLQ+12 score ≥0.5 at week 24



*Post-hoc analysis of a head-to-head study in which the primary superiority endpoint (0-24 h wmFEV1) was not met

Woodcock A et al. *Chest.* 2013;144:1222–9.

Fluticasone furoate/vilanterol has little or no effect on HPA axis function

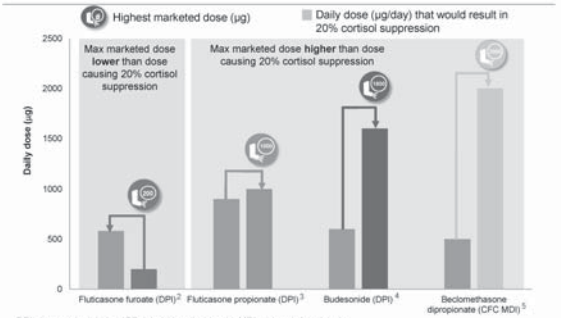


No indication of significant cortisol suppression at Day 42 with FF/VI 100/25, FF/VI 200/25 µg or placebo; however, serum cortisol levels were notably lower in the prednisolone group at Day 42

FF, fluticasone furoate; HPA, hypothalamic-pituitary-adrenal; OD, once daily; VI, vilanterol

Allen A et al. *Clin Respir J*. 2013;7:397–406.

FF is the only ICS with a maximum indicated dose lower than the dose causing 20% cortisol suppression[1]



DPI, dry-powder inhaler; ICS, inhaled corticosteroid; MDI metered-dose inhaler

1. Daley-Yates PT. *Br J Clin Pharmacol*. 2015;80:372–380. 2. Relvar ELLIPTA 200/25mcg inhalation powder, GSK Prescribing Information 2016. 3. Seretide 100, 250, 500 Accuhaler, GSK Prescribing Information 2015. 4. Symbicort Turbohaler 400. SPC AZ; 2015. 5. Pulvinal Beclometasone 400 microgram inhaler SPC. Chiesi; 2015

Adverse event profile of Relvar Ellipta (once daily) compare with an existing ICS/LABA (twice daily)?

On treatment adverse events ≥ 3% in any treatment group

Event	Breo Ellipta 100/25mcg OD pm (n=403)	Seretide Acc 250/50mcg BID (n=403)
Nasopharyngitis	46 (11)	46 (11)
Headache	34 (8)	41 (10)
URTI	26 (6)	16 (4)
Cough	15 (4)	13 (3)
Back pain	11 (3)	11 (3)
Oropharyngeal pain	11 (3)	9 (2)
Sinusitis	12 (3)	7 (2)
Pyrexia	13 (3)	5 (1)
Productive cough	11 (3)	5 (1)
Treatment-related AEs (any)	19 (5)	15 (4)

AE, adverse event; BID, twice-daily; OD, once-daily; URTI, upper respiratory tract infection.

1. Adapted from Woodcock A et al. Chest 2014: 144:1222–1229

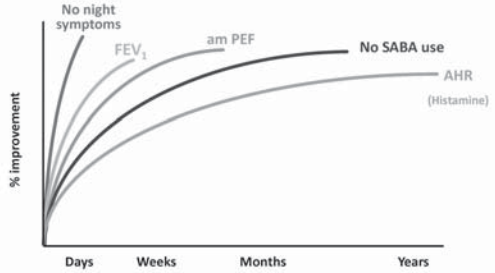
GINA classification of inhaled steroids, 2016

Low, medium and high daily doses of ICS, as defined in GINA 2016

Inhaled corticosteroid	Daily doses (µg) in adults and adolescents (≥12 years)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	N/A	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

Backtitration

Time course of asthma control

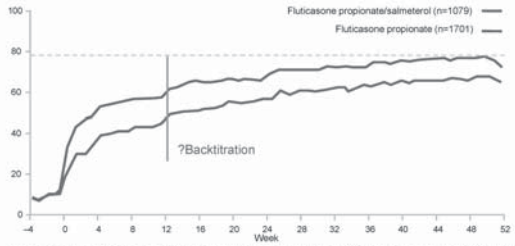


Woolcock AJ Clin Exp Allergy Rev 2001; 1: 62-4.

Well controlled asthma[1]

Continued improvements with sustained treatment

Proportion of patients achieving well-controlled over weeks 4 to 52 for all strata combined

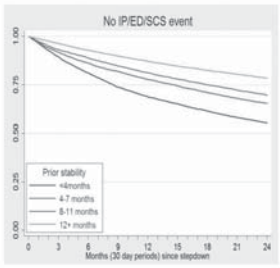


1 year randomised, stratified, double blind, parallel group study comparing SFC (fluticasone propionate/salmeterol) and FP (fluticasone propionate). Proportion of patients well controlled was greater for SFC than FP during phase I (71% vs 59%, p<0.001) (primary endpoint)

1. Adapted from Bateman et al. Am J Respir Crit Care Med 2004; 160: 836-44

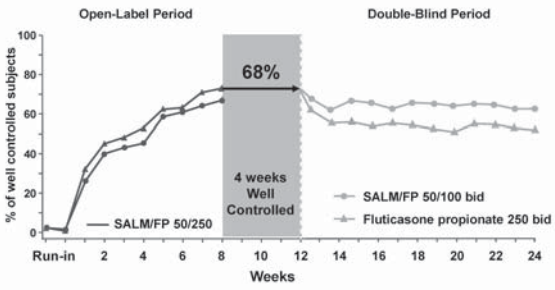
Backtitration

N=26,292
Database study
ICS reduced 50%



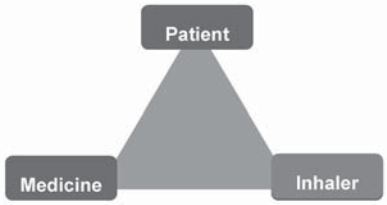
Rank MA et al. Chest 2015; 148: 630-639

Step down at three months



Bateman E et al, JACI 2006; 117: 563

The important components



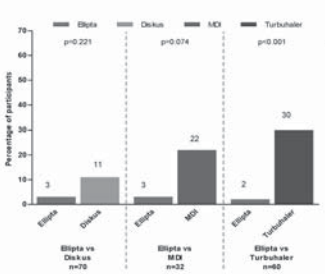
Scichilone et al, Adv Ther 2015; 32:285–292

Relvar Ellipta inhaler device[1]

Two 30 dose foil blister strips for combination products

Breo Ellipta Approved Product Information.

Inhaler errors

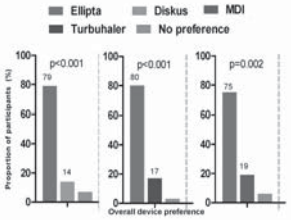


Critical errors: After reading the patient information leaflet, the proportion of participants with at least one critical error was lower with the Ellipta inhaler, compared with the Diskus inhaler, MDI or Turbuhaler. The difference was statistically significant between Ellipta and Turbuhaler (p<0.001)

Van Der Palen, J., Thomas, M., Chrystyn, H., Sharma, R. K., Van Der Valk, P. D., Goossens, M., ... & Zhu, C. Q. (2016). Abbreviations

Patient preference

- **Preference:** The majority of participants preferred Ellipta overall, compared with Diskus (55/70 vs 10/70; p<0.001), MDI (24/32 vs 6/32; p=0.002), and Turbuhaler (48/60 vs 10/60; p<0.001)



Van Der Palen, J., Thomas, M., Chrystyn, H., Sharma, R. K., Van Der Valk, P. D., Gosens, M., ... & Zhu, C. Q. (2016).
Abbreviations

Poor inhalation technique and critical errors associated with worsened clinical outcomes

- Large observational study (n=1664)
- COPD 52%; asthma 42%
- MDI: n=843; DPI: n=1113

Inhaler misuse associated with significantly increased risk of*

Hospitalisation	ER visits	Oral corticosteroid use	Antimicrobial use
(OR: 1.47; *P*=0.001)	(OR: 1.62; *P*<0.001)	(OR: 1.54; *P*<0.001)	(OR: 1.50; *P*<0.001)

*Ps0.001; based on logistic regression analysis for the relationship between risk of at least one critical inhaler error and self-report of unscheduled healthcare resource use in the previous year.

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; ER, emergency room; MDI, metered dose inhaler; OR, odds ratio

Adapted from Melani AS et al. Respir Med. 2011;105:930–938.

The evolution of asthma management and inhalation therapy – a long journey

In 2017 we don't have:

- Major advances in patient adherence
  - Approaches to address adherence should be specifically tailored to patient profiles in order to maximise the benefits – still some time off
- Inhaler sensors to detect timing and effectiveness of the inhaler
  - these are coming soon
- Real-life effectiveness trials (rather than efficacy trials) similar to SLS COPD
  -This is coming in 2017

The evolution of asthma management and inhalation therapy – a long journey

In 2017 we have:

- Efficacious medications with prolonged duration of action allowing OD treatment – Relvar Ellipta
- Easy to use inhalers with few critical patient errors
- Evolving understanding of asthma phenotypes and endotypes which will lead to more personalised medicine eg new biologicals for treatment of severe asthma (Anti-IgE, Anti IL-5, others)

Thank You!

Relvar Safety Information & API