BREO® ELLIPTA® 100/25 and 200/25 (Fluticasone furoate / Vilanterol)

Introduction

Katharine Knobil, MD
SVP, Research and Development
GlaxoSmithKline
Impact of Asthma in the US

- Affects an estimated 25.6 million Americans
  - 18.7 M adults\(^1\), 2.6 M adolescents\(^2\), 4.2 M children\(^2\)

- Significant annual healthcare utilization
  - 14.2 million primary care visits,\(^4\) 1.8 million ED visits\(^5\)
  - 439,000 hospital inpatient stays\(^6\)
  - $18 billion attributable to asthma\(^3\)

- Significant patient burden
  - ~50% of patients have uncontrolled asthma when presenting to primary care clinics for non-respiratory reasons\(^7\)
  - 46.7 million days of school, work, or activities missed in the past year\(^8\)

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\(^4\) CDC/NCHS. NAMCS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
\(^5\) CDC/NCHS. NHAMCS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
\(^6\) CDC/NCHS. NHDS, 2010. Available at http://www.cdc.gov/nchs/fastats/asthma.htm
Adherence Affects Outcomes in Asthma

- Poor adherence may contribute to poor outcomes in asthma
- Once daily dosing is associated with higher ICS adherence\(^1\)
  - Increased adherence by ~20 percentage points
  - Doubled proportion of patients >75% adherence
- Improved adherence lowers rates of exacerbations and improves asthma control
  - Every 25% increase in ICS adherence was associated with a ~10% decrease in asthma exacerbations\(^2\)
  - Nearly 1 in 4 exacerbations attributable to poor adherence\(^2\)
- Innovative study ongoing to assess asthma control and adherence in a real world setting\(^3\)

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BREO ELLIPTA Once Daily for Asthma

- Vilanterol (VI) 25mcg: long-acting selective beta$_2$-adrenergic agonist (LABA)
- Fluticasone furoate (FF) 100 & 200mcg: long-acting inhaled corticosteroid (ICS)
Approved Medicines Containing FF and VI  
All Once Daily Dosing

● ARNUITY ELLIPTA: 20 August 2014  
  – FF 100 and 200mcg QD approved for use in asthma in patients ≥12 years of age

● BREO ELLIPTA: 10 May 2013  
  – FF/VI 100/25mcg QD approved for use in COPD

● ANORO ELLIPTA: 18 December 2013  
  – Umeclidinium (UMEC) 62.5mcg with VI 25mcg QD approved for use in COPD

● VERAMYST (FF): 27 April 2007  
  – approved for QD use in perennial and seasonal allergic rhinitis in adults and children ≥2 years of age
Proposed Indication and Dosing

● Indication:
  – BREO ELLIPTA is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 12 years and older.

● Dosing:
  • The recommended starting dosage of BREO ELLIPTA is 100/25 or BREO ELLIPTA 200/25 administered as 1 inhalation once daily.
  • The starting dose is based on patients’ asthma severity. For patients previously treated with low- to mid-dose corticosteroid-containing treatment, BREO ELLIPTA 100/25 should be considered. For patients previously treated with mid- to high-dose corticosteroid-containing treatment, BREO ELLIPTA 200/25 should be considered.
Safety of LABAs for the Treatment of Asthma: Class Labeling

- Boxed warning requirement in the prescribing information for all LABAs for the treatment of asthma
- Early studies of LABAs in patients in asthma in which ICS was either not required or not supplied showed increase risk of serious asthma events

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including vilanterol, an active ingredient in BREO® ELLIPTA™. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids [see Warnings and Precautions (5.1)].
Timeline of LABA-related Discussions

1990-1992
SEREVENT Nationwide Surveillance (SNS) Conducted N=25,180

1996-2003
Salmeterol Multicenter Asthma Research Trial (SMART) Conducted N=26,355

- Concomitant use of inhaled corticosteroids not mandated or monitored
- Increase in serious asthma-related outcomes with salmeterol, including asthma-related death
- Risk of serious asthma-related outcomes was mitigated when patients reported ICS use at baseline

Mar 2015
FDA BREO Asthma Advisory Committee
Timeline of LABA-related Discussions

1990-1992
SEREVENT
Nationwide Surveillance (SNS)
Conducted N=25,180

1996-2003
Salmeterol Multicenter Asthma Research Trial (SMART)
Conducted

● Concomitant use of LABA increased serious asthma-related outcomes
  - not mandated or monitored

● Increase in serious asthma-related outcomes with salmeterol

● Risk of serious asthma-related outcomes was mitigated when patients reported ICS use at baseline

RD (95% CI) [Sample Sizes]*

<table>
<thead>
<tr>
<th>Drug</th>
<th>RD (95% CI)</th>
<th>[Sample Sizes]</th>
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</thead>
<tbody>
<tr>
<td>Advair</td>
<td>-0.15 (-2.01, 1.70)</td>
<td>[21/6648 20/6564]</td>
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<tr>
<td>Serevent</td>
<td>3.49 (1.27, 5.71)</td>
<td>[336/21108 270/22716]</td>
</tr>
<tr>
<td>Foradil</td>
<td>3.80 (-1.80, 940)</td>
<td>[18/1626 14/2139]</td>
</tr>
<tr>
<td>Symbicort</td>
<td>7.49 (-1.47, 16.44)</td>
<td>[6/766 1/504]</td>
</tr>
<tr>
<td>Overall</td>
<td>2.80 (1.11, 4.49)</td>
<td>[381/30148 304/30806]</td>
</tr>
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</table>

Figure 3: Risk Difference Estimates: Asthma Composite by Drug.

2008 FDA Brief Document
Timeline of LABA-related Discussions

- Concomitant use of inhaled corticosteroids not mandated or monitored
- Increase in serious asthma-related outcomes with salmeterol, including asthma-related death
- Risk of serious asthma-related outcomes was mitigated when patients reported ICS use at baseline
Ongoing LABA Safety Program

● To evaluate whether the addition of a LABA to ICS therapy is non-inferior in the risk of serious asthma-related events vs. ICS alone

● Externally adjudicated composite endpoint of serious asthma-related events including:
  – Hospitalization
  – Endotracheal intubation
  – Death

● Approximately 50,000 subjects to be enrolled across 4 sponsors
Ongoing LABA Safety Program: Adult and Adolescent (as of December 30, 2014)

- **Adult/adolescent study**
  - N=11,664 planned
  - expected 87 subjects with an event

- 11,724 randomized
  - 1228 adolescents

- 58 subjects have experienced an asthma-related outcome:
  - 58 hospitalizations
  - 2 intubations*
  - 0 deaths

*during hospitalization
SAS115359 available at: [https://clinicaltrials.gov/ct2/show/NCT01475721](https://clinicaltrials.gov/ct2/show/NCT01475721)
ADVAIR=fluticasone propionate/salmeterol: FLOVENT=fluticasone propionate

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Treatment Arms

- **ADVAIR 100/50**
- **FLOVENT 100**
- **ADVAIR 250/50**
- **FLOVENT 250**
- **ADVAIR 500/50**
- **FLOVENT 500**

≥12 years
26-week treatment
Ongoing LABA Safety Program: Pediatric
(as of December 30, 2014)

- Pediatric study
  - N=6,200 planned
  - expected 44 subjects with an event

- 5,602 randomized

- 38 subjects have experienced an asthma-related outcome:
  - 38 hospitalizations
  - 0 intubations
  - 0 deaths

Treatment Arms

- ADVAIR 100/50
- FLOVENT 100
- ADVAIR 250/50
- FLOVENT 250

4-11 years 26-week treatment

SAS115358 available at: https://clinicaltrials.gov/ct2/show/NCT01462344
ADVAIR=fluticasone propionate/salmeterol: FLOVENT=fluticasone propionate
Topics for Discussion

- Large complex program of over 12,000 adults and adolescents with asthma in Phase II and III
  - Well characterized efficacy and safety profile
- Efficacy profile of BREO ELLIPTA
  - Contribution of VI to the BREO ELLIPTA combination
  - Examination of adolescent subgroup
- Safety profile of BREO ELLIPTA
  - Serious asthma events
- Benefit: risk assessment
Advisors

Eugene Bleecker, MD
Professor and Director, Genomics and Personalized Medicine
Wake Forest School of Medicine
Winston-Salem, NC

H. William Kelly, PharmD
Professor Emeritus, Pediatrics
University of New Mexico Health Sciences Center
Albuquerque, NM

Gary G. Koch, PhD
Professor, Biostatistics
Director, Biometric Consulting Laboratory
University of North Carolina at Chapel Hill
# Agenda

<table>
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<tr>
<th>Topic</th>
<th>Speaker</th>
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<td>Clinical Efficacy and Safety</td>
<td>Courtney Crim, MD</td>
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<tr>
<td></td>
<td>Director, Project Physician Lead</td>
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<td>GlaxoSmithKline</td>
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<td>Physician's Perspective</td>
<td>Eugene Bleecker, MD</td>
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<td>Professor and Director, Genomics</td>
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<td>and Personalized Medicine</td>
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<td>Wake Forest School of Medicine</td>
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<td>Winston-Salem, NC</td>
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<td>Closing Comments</td>
<td>Katharine Knobil, MD</td>
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<td>Senior Vice President, Research</td>
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<td></td>
<td>and Development</td>
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<td>GlaxoSmithKline</td>
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BREO ELLIPTA 100/25 and 200/25 (Fluticasone furoate / Vilanterol) 
Asthma

Efficacy
Courtney Crim, MD
Director of Clinical Development
GlaxoSmithKline
Asthma Clinical Development Program
Phase I/II Studies

Clinical Pharmacology Development Program
(48 Phase I/II Studies; N = 1328)

HZA114624
2-week crossover trial FF/VI and PBO (N = 26)

Phase II Dose Ranging and Interval Studies

**FF**
(N = 3246)

- FFA109687
  8-week trial FF, FP†, and PBO (N = 598)
- FFA109685
  8-week trial FF, FP†, and PBO (N = 615)
- FFA109684
  8-week trial FF, FP†, and PBO (N = 622)

- FFA112202
  4-week crossover trial FF, FP† and PBO (N = 190)
- FFA106783†
  8-week trial FF and PBO (N = 646)
- FFA20001*
  4-week trial FF and PBO (N = 575)

**VI**
(N = 682)

- B2C109575‡
  4-week trial VI and PBO (N = 607)
- HZA113310‡
  1-week crossover trial VI and PBO (N = 75)

**FFA109685**
8-week trial FF, FP†, and PBO (N = 615)

**FFA109684**
8-week trial FF, FP†, and PBO (N = 622)

**FFA106783†**
8-week trial FF and PBO (N = 646)

**FFA20001***
4-week trial FF and PBO (N = 575)

FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; VI=vilanterol
*administered via Diskhaler
†administered via Diskus
‡subjects continued background ICS
Asthma Clinical Development Program
Phase III

Efficacy and Safety Studies
(15 Phase III Studies; N= 8123)

FF/VI
(N =6606)

FF Efficacy & Safety
(N = 1170)

FFA112059
24-week trial
FF 100, FP 250†
and PBO
(N = 343)

FFA114496
24-week trial
FF 100 & FF 200
(N = 238)

FFA115285
24-week trial
FF 50, FP† and PBO
(N = 347)

FFA115283
12-week trial
FF 50 and PBO
(N = 242)

Supportive Clinical Pharmacology
HZA113126
3-week crossover trial
FF/VI, FF, VI and PBO
(N = 242)

Primary
HZA106827
12-week trial
FF/VI, FF and PBO†
(N = 609)

Supportive
HZA113719
12-week trial
FF/VI and PBO
(N = 307)

Primary
HZA106829
24-week trial
FF/VI, FF and FP†
(N = 586)

Supportive
HZA113714
12-week trial
FF/VI and FP† 500
(N = 309)

Primary
HZA116863
12-week trial
FF/VI and FF
(N = 1039)

Exacerbation
HZA106837
24-76-week trial
FF/VI and FF 100
(N = 2019)

Primary
HZA106839
52-week trial
FF/VI and FP†
(N = 503)

Supportive
HZA113989
6-week trial
FF/VI, prednisolone
10mg and PBO
(N = 185)

Comparat
HZA113091
24-week trial
FF/VI and FP/SAL†
250/50
(N = 806)

B2C112060‡
12-week trial
VI 25, SAL 50†
and PBO
(N = 347)

FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol
†administered via Diskus
‡subjects continued background ICS
§subjects not included in total N for FF/VI

BREO Phase II/III COPD
(11 Studies, N=7851)

VI Efficacy & Safety
(N = 347)

VI 25, SAL 50†
and PBO
(N = 347)
Efficacy of Fluticasone furoate / Vilanterol

- Selection of Doses for Phase III
  - Fluticasone furoate (FF)
  - Vilanterol (VI)

- Phase III Program for FF/VI
  - Efficacy of FF monotherapy: FEV$_1$ trough
  - Efficacy of FF/VI 100/25: FEV$_1$ trough and WM (0-24 hr)
  - Contribution of VI in the combination: FEV$_1$ trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25

- Efficacy Data from Adolescent Sub-population

- Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID
Phase IIb Asthma Studies Showed a Plateau at FF 200mcg in Trough FEV$_1$ Response

Baseline Therapy

<table>
<thead>
<tr>
<th>Treatment (mcg)</th>
<th>Non-ICS</th>
<th>Low ICS</th>
<th>Medium ICS</th>
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<tr>
<td>FF 25</td>
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<td>FF 200</td>
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<td>FF 100 BID</td>
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<td>FF 200 BID</td>
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<td>FP 500 BID</td>
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<td>FFA109685</td>
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Last Observation Carried Forward (LOCF)

Dose Selection of Vilanterol (VI)

- Dose of VI (25mcg) selected for testing in Phase IIIa asthma program was based on a Phase II dose-ranging study in subjects with asthma (Study 575)
  - VI doses of 3, 6.25, 12.5, 25 and 50mcg once daily were evaluated

- Phase II dose-ranging study in COPD also supported 25mcg as appropriate dose of VI to take into Phase III

Vilanterol Dose Ranging in Patients with Asthma: 24-hr Trough FEV$_1$ (Study 575)

Diff = 162 mL, p = 0.001
Diff = 121 mL, p = 0.016
Diff = 130 mL, p = 0.011
Diff = 69 mL, p = 0.169
Diff = 64 mL, p = 0.208

Vilanterol Dose
All Patients on Background ICS

Last Observation Carried Forward (LOCF)

**Comparative Effects between VI 25mcg and 12.5mcg (Study 575)**

**Rescue-free 24-hr periods (%)**
- 12.5mcg vs Placebo: Diff = 14.7, 95% CI (5.4, 24.0)
- 25mcg vs Placebo: Diff = 28.4, 95% CI (19.3, 37.6)

**Symptom-free 24-hr periods (%)**
- 12.5mcg vs Placebo: Diff = 12.7, 95% CI (3.6, 21.8)
- 25mcg vs Placebo: Diff = 22.2, 95% CI (13.3, 31.2)

Phase IIb Dosing Conclusions

- FF 100mcg and 200mcg identified as doses to evaluate in Phase III asthma program
- VI 25mcg once daily determined as optimal dose in patients with asthma
- Additional Phase IIb studies comparing once with twice daily dosing confirmed both VI and FF as once daily products
Asthma Clinical Development Program
Phase III

Efficacy and Safety Studies
(15 Phase III Studies; N= 8,123)

FF/VI (N = 6606)

FF Efficacy & Safety (N = 1170)
- FFA112059 24-week trial FF 100, FP 250† and PBO (N = 343)
- FFA114496 24-week trial FF 100 & FF 200 (N = 238)
- FFA115285 12-week trial FF 50, FP† and PBO (N = 347)
- FFA115283 12-week trial FF 50 and PBO (N = 242)

Efficacy & Safety
- Primary HZAI06827 12-week trial FF/VI, FF and PBO (N = 609)
- Supportive HZAI113719 12-week trial FF/VI, FF and FP† (N = 307)
- Supportive Clinical Pharmacology HZAI113126 3-week crossover trial FF/VI, FF, VI and PBO (N = 27)

FF/VI 100/25
- Primary HZAI06829 24-week trial FF/VI, FF and FP† (N = 586)
- Supportive HZAI113714 12-week trial FF/VI and FF† (N = 309)

FF/VI 200/25
- Primary HZAI118663 12-week trial FF/VI and FF (N = 1039)

FF/VI 100/25 & 200/25
- Exacerbation HZAI06837 24-76-week trial FF/VI and FF 100 (N = 2019)
- LT Safety HZAI106839 52-week trial FF/VI and FP† (N = 503)
- LT Safety HZAI113989 52-week trial FF/VI and FF (N = 243)

Safety
- Exacerbation HZAI106837 24-76-week trial FF/VI and FF 100 (N = 2019)
- LT Safety HZAI113989 52-week trial FF/VI and FF (N = 243)

FFA115285 12-week trial FF 50 and PBO (N = 242)

FFA112059 24-week trial FF 100, FP 250† and PBO (N = 343)

BREO COPD
(11 Studies, N=7851)

VI Efficacy & Safety (N = 347)
- B2C112060† 12-week trial VI 25, SAL 50 and PBO (N = 347)

FF=fluticasone furoate; FP=fluticasone propionate; PBO=placebo; SAL=salmeterol; VI=vilanterol
†administered via Diskus
‡subjects continued background ICS
**Demographic and Baseline Characteristics**
(Studies 827, 829 and 863)

<table>
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<tr>
<th>Age (yrs): Mean (Min-Max)</th>
<th>Total (N=2234)</th>
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<tbody>
<tr>
<td></td>
<td>44.2 (12-84)</td>
</tr>
<tr>
<td>12-17 yrs, n (%)</td>
<td>170 (8)</td>
</tr>
<tr>
<td>18-64 yrs, n (%)</td>
<td>1869 (84)</td>
</tr>
<tr>
<td>≥65 yrs, n (%)</td>
<td>195 (9)</td>
</tr>
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</table>

| Female/Male, n (%)       | 1326 (59) / 908 (41) |

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<tr>
<th>Race, n (%)</th>
<th>ITT</th>
<th>US</th>
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<tbody>
<tr>
<td>Caucasian</td>
<td>1916 (86)</td>
<td>400 (68)</td>
</tr>
<tr>
<td>African American/African Heritage</td>
<td>168 (8)</td>
<td>166 (28)</td>
</tr>
<tr>
<td>Asian</td>
<td>99 (4)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Other*</td>
<td>50 (2)</td>
<td>9 (2)</td>
</tr>
</tbody>
</table>

| Percent Predicted FEV₁ (Screening): Mean (Min-Max) | 64.1 (37.0 – 89.6) |
| Percent Reversibility: Mean (SD)                   | 29.4 (17.6)        |
| Absolute Reversibility (mL): Mean (SD)             | 579.3 (346.6)      |

*Includes: American Indian or Alaska Native and Mixed Race
Efficacy of FF Change from Baseline in Trough FEV$_1$ (mL)

**HZA106827**
- Diff = 136mL*
- 95% CI (51, 222)
- p=0.002

**FFA112059**
- Diff = 146mL*
- 95% CI (36, 257)
- p=0.009

*Last Observation Carried Forward (LOCF)

Efficacy of Fluticasone furoate / Vilanterol

● **Selection of Doses for Phase III**
  – Fluticasone furoate (FF)
  – Vilanterol (VI)

● **Phase III Program for FF/VI**
  – Efficacy of FF monotherapy: FEV$_1$ trough
  – **Efficacy of FF/VI 100/25: FEV$_1$ trough and WM (0-24 hr)**
  – Contribution of VI in the combination: FEV$_1$ trough and WM (0-24 hr)
  – Clinical benefit of FF/VI 200/25 over 100/25

● **Efficacy Data from Adolescent Sub-population**

● **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**
Efficacy of FF/VI 100/25
Change from Baseline in FEV₁ (mL) (Study 827)

**Trough FEV₁**

![Graph showing change in Trough FEV₁ over weeks of study.]

**24 hour serial FEV₁ at Week 12**

![Graph showing change in 24 hour serial FEV₁ over planned time since dose.]

- **Diff = 172 mL**
- **95% CI (87, 258)**
- **p < 0.001**

*Last Observation Carried Forward (LOCF)
FF/VI 100/25 Improves Symptomatic Endpoints (Study 827)

Weeks 1-12

**Rescue-free 24-hr periods (%)**
- FF/VI 100/25 vs Placebo
  - FF/VI 100/25 vs Placebo
  - Diff = 19.3
  - 95% CI (13.0, 25.6)
  - p < 0.001*

**Symptom-free 24-hr periods (%)**
- FF/VI 100/25 vs Placebo
  - FF/VI 100/25 vs Placebo
  - Diff = 18.0
  - 95% CI (12.0, 23.9)
  - p < 0.001*

**ACT Score**
- FF/VI 100/25 vs Placebo
  - FF/VI 100/25 vs Placebo
  - Diff = 1.9
  - 95% CI (1.2, 2.6)
  - p < 0.001*

**Total AQLQ Score**
- FF/VI 100/25 vs Placebo
  - FF/VI 100/25 vs Placebo
  - Diff = 0.30
  - 95% CI (0.13, 0.46)
  - p < 0.001*

*p value is nominal
Efficacy of Fluticasone furoate / Vilanterol

- **Selection of Doses for Phase III**
  - Fluticasone furoate (FF)
  - Vilanterol (VI)

- **Phase III Program for FF/VI**
  - Efficacy of FF monotherapy: FEV₁ trough
  - Efficacy of FF/VI 100/25: FEV₁ trough and WM (0-24 hr)
  - **Contribution of VI in the combination: FEV₁ trough and WM (0-24 hr)**
  - Clinical benefit of FF/VI 200/25 over 100/25

- **Efficacy Data from Adolescent Sub-population**

- **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**
FF/VI vs. FF for Trough and Weighted Mean (0-24 hr) FEV\textsubscript{1} (mL)

**Trough FEV\textsubscript{1}**
- **Study 827 (Week 12)**
  - FF/VI 100/25 vs FF 100
  - Diff = 36mL
  - 95% CI (-48, 120)
  - p = 0.405
- **Study 863 (Week 12)**
  - FF/VI 100/25 vs FF 100
  - Diff = 77mL
  - 95% CI (16, 138)
  - p = 0.014
- **Study 837 (Week 36)**
  - FF/VI 100/25 vs FF 100
  - Diff = 83mL
  - 95% CI (44, 123)
  - p < 0.001
- **Study 829 (Week 24)**
  - FF/VI 200/25 vs FF 200
  - Diff = 193mL
  - 95% CI (108, 277)
  - p < 0.001

**Weighted Mean FEV\textsubscript{1}**
- **Study 827 (Week 12)**
  - FF/VI 100/25 vs FF 100
  - Diff = 116mL
  - 95% CI (-5, 236)
  - p = 0.060
- **Study 863 (Week 12)**
  - FF/VI 100/25 vs FF 100
  - Diff = 108mL
  - 95% CI (45, 171)
  - p < 0.001
- **Study 829 (Week 24)**
  - FF/VI 200/25 vs FF 200
  - Diff = 136mL
  - 95% CI (1, 270)
  - p = 0.048

**FF/VI vs. FF: Change from Baseline in Rescue- and Symptom-Free 24-Hour Periods**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Comparison</th>
<th>Improvement</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 827 (Weeks 1-12)</td>
<td>FF/VI 100/25 vs FF 100</td>
<td>Favors FF</td>
<td>Diff=10.6</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (4.3, 16.8)</td>
<td></td>
</tr>
<tr>
<td>Study 863 (Weeks 1-12)</td>
<td>FF/VI 100/25 vs FF 100</td>
<td>Favors FF</td>
<td>Diff=12.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (7.1, 17.3)</td>
<td></td>
</tr>
<tr>
<td>Study 829 (Weeks 1-24)</td>
<td>FF/VI 200/25 vs FF 200</td>
<td>Favors FF</td>
<td>Diff=11.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (4.9, 18.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: p value is nominal*
FF/VI Increases Time to First Asthma Exacerbation (Study 837)

ATS/ERS Task Force Definition: Exacerbation defined as one requiring systemic corticosteroids for at least 3 days or an hospitalization/ED visit that required treatment with systemic corticosteroids.

FF/VI Maintained Improved FEV\textsubscript{1} Compared with FF over the Course of the Study (Study 837)
Efficacy of Fluticasone furoate / Vilanterol

● Selection of Doses for Phase III
  – Fluticasone furoate (FF)
  – Vilanterol (VI)

● Phase III Program for FF/VI
  – Efficacy of FF monotherapy: $\text{FEV}_1$ trough
  – Efficacy of FF/VI 100/25: $\text{FEV}_1$ trough and WM (0-24 hr)
  – Contribution of VI in the combination: $\text{FEV}_1$ trough and WM 0-24 hr
  – **Clinical benefit of FF/VI 200/25 over 100/25**

● Efficacy Data from Adolescent Sub-population

● Efficacy of FF/VI 100/25 compared with FP/SAL 250/50
Relative Comparison of FF 200 and FF 100 for Efficacy Endpoints (Study 496)

**Week 24**

**Trough FEV₁ (mL)**
- Favors FF 100: 
- Favors FF 200: 77 (-39, 192)
- Diff (95% CI): 77 (-39, 192)

**Weeks 1-24**

- Rescue-free 24-hr periods (%): 1.8 (-6.7, 10.3)
- Symptom-free 24-hr periods (%): 2.1 (-5.7, 9.9)

**Week 24**

- PM PEF (L/min): 1.3 (-7.8, 10.4)
- AM PEF (L/min): -0.2 (-9.2, 8.8)

- Change from Baseline ACT Score:
  - Adjusted Treatment Difference and 95% CI: 0.2 (-0.7, 1.2)
  - % Patients with ACT Score ≥20:
    - Adjusted Odds Ratio and 95% CI: 1.42 (0.76, 2.68)

Woodcock et al, BMC Pulm Med 2014;14:113
Relative Comparison of FF/VI 200/25 and FF/VI 100/25 for Efficacy Endpoints (Study 863)

### Week 12

**Weighted Mean (0-24 hr) FEV₁ (mL)**
- Favors FF/VI 100/25: 24 (-37, 86)
- Favors FF/VI 200/25: 16 (-46, 77)

**Trough FEV₁ (mL)**
- Favors FF/VI 100/25: 16 (-46, 77)
- Favors FF/VI 200/25: 0.9 (-4.2, 6.1)

**Weeks 1-12**

**Rescue-free 24-hr periods (%)**
- Favors FF/VI 100/25: 0.9 (-4.2, 6.1)
- Favors FF/VI 200/25: 1.9 (-3.0, 6.7)

**Symptom-free 24-hr periods (%)**
- Favors FF/VI 100/25: 0.9 (-3.0, 6.7)
- Favors FF/VI 200/25: 1.9 (-3.0, 6.7)

**PM PEF (L/min)**
- Favors FF/VI 100/25: 2.0 (-4.2, 8.2)
- Favors FF/VI 200/25: 3.4 (-2.8, 9.7)

**AM PEF (L/min)**
- Favors FF/VI 100/25: 3.4 (-2.8, 9.7)
- Favors FF/VI 200/25: 4.8 (-1.3, 10.9)

### Week 12

**Total AQLQ Score**
- Favors FF/VI 100/25: 0.14 (-0.01, 0.28)
- Favors FF/VI 200/25: 0.7 (0.1, 1.2)

**ACT Score**
- Favors FF/VI 100/25: 0.7 (0.1, 1.2)
- Favors FF/VI 200/25: 1.55 (1.12, 2.16)

**Percentage of Subjects Controlled (ACT Score ≥20)**
- Favors FF/VI 100/25: 1.55 (1.12, 2.16)
- Favors FF/VI 200/25: 1.55 (1.12, 2.16)
Efficacy of Fluticasone furoate / Vilanterol

- **Selection of Doses for Phase III**
  - Fluticasone furoate (FF)
  - Vilanterol (VI)

- **Phase III Program for FF/VI**
  - Efficacy of FF monotherapy: FEV\(_1\) trough
  - Efficacy of FF/VI 100/25: FEV\(_1\) trough and WM (0-24 hr)
  - Contribution of VI in the combination: FEV\(_1\) trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25

- **Efficacy Data from Adolescent Sub-population**

- **Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID**
Change from Baseline in Trough FEV$_1$ in Adolescents

Week 12

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Favors FF</th>
<th>Favors FF/VI</th>
<th>Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>829</td>
<td>5</td>
<td>130 (-955, 1214)</td>
<td>N=6</td>
<td></td>
</tr>
<tr>
<td>863</td>
<td>23</td>
<td>-213 (-527, 101)</td>
<td>N=21</td>
<td>-9 (-307, 288)</td>
</tr>
<tr>
<td>827</td>
<td>28</td>
<td>-9 (-307, 288)</td>
<td>N=21</td>
<td></td>
</tr>
<tr>
<td>837</td>
<td>126</td>
<td>93 (-24, 211)</td>
<td>N=142</td>
<td></td>
</tr>
</tbody>
</table>

Change from Baseline (mL) and 95% CI
Mean Change from Baseline in Trough FEV$_1$ (mL) at Week 12 by Age (Study 837)

12-17 years
- FF 100 (n=126)
- FF/VI 100/25 (n=142)

18-64 years
- FF 100 (n=770)
- FF/VI 100/25 (n=768)

≥65 years
- FF 100 (n=67)
- FF/VI 100/25 (n=64)
## Rate of Asthma Exacerbations by Age (Study 837)

<table>
<thead>
<tr>
<th></th>
<th>ITT Population</th>
<th>12-17 years</th>
<th>≥18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FF 100 N=1010</td>
<td>FF/VI 100/25 N=1009</td>
<td>FF 100 N=130</td>
</tr>
<tr>
<td>Number (events) of subjects with ≥1 asthma exacerbation</td>
<td>186 (271)</td>
<td>154 (200)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Mean asthma exacerbation rate per subject year</td>
<td>0.19</td>
<td>0.14</td>
<td>0.0008</td>
</tr>
<tr>
<td>FF/VI 100/25 vs. FF 100</td>
<td>0.755 (0.603, 0.945)</td>
<td>1.904 (0.793, 4.573)</td>
<td>0.717 (0.567, 0.906)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.014</td>
<td>0.150</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Probability of Best Response to Step-up Therapies (Children Aged 6-17 Uncontrolled on FP 100 BID)

- FP/SAL100/50 BID
- FP 250 BID
- Montelukast + FP 100 BID

LABA step-up therapy was the most likely to provide the best response

Efficacy of Fluticasone furoate / Vilanterol

- Selection of Doses for Phase III
  - Fluticasone furoate (FF)
  - Vilanterol (VI)

- Phase III Program for FF/VI
  - Efficacy of FF monotherapy: FEV₁ trough
  - Efficacy of FF/VI 100/25: FEV₁ trough and WM (0-24 hr)
  - Contribution of VI in the combination: FEV₁ trough and WM (0-24 hr)
  - Clinical benefit of FF/VI 200/25 over 100/25

- Efficacy Data from Adolescent Sub-population

- Efficacy of FF/VI 100/25 QD vs. FP/SAL 250/50 BID
Comparison of FF/VI 100/25 QD and ADVAIR 250/50 BID (Study 091)

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Favors ADVAIR 250/50</th>
<th>Favors FF/VI 100/25</th>
<th>Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted Mean 0-24 hr FEV₁ (mL)</td>
<td>-37 (-88, 15)</td>
<td>-19 (-73, 34)</td>
<td></td>
</tr>
<tr>
<td>Trough FEV₁ (mL) (LOCF)</td>
<td>-37 (-88, 15)</td>
<td>-19 (-73, 34)</td>
<td></td>
</tr>
<tr>
<td>Total AQLQ Score</td>
<td>0.09 (-0.03, 0.21)</td>
<td>0.09 (-0.03, 0.21)</td>
<td></td>
</tr>
<tr>
<td>ACT Score</td>
<td>0.2 (-0.2, 0.7)</td>
<td>0.2 (-0.2, 0.7)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D Visual Analog Scale Score</td>
<td>1.4 (-0.3, 3.0)</td>
<td>1.4 (-0.3, 3.0)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted Treatment Difference and 95% CI

Adapted from Woodcock et al, Chest 2013;144:1222-29.
Summary of Efficacy

- FF/VI provides sustained improvement in lung function.

- Contribution of VI was demonstrated by the incremental improvement in lung function and symptoms:
  - In one study, there was also a reduction in asthma exacerbations for FF/VI 100/25 compared with FF 100.

- Efficacy of FF was demonstrated in the ARNUITY development program.

- FF/VI 200/25 showed numerical improvements in lung function and symptoms compared with FF/VI 100/25.

- No difference in treatment effects of FF/VI 100/25 QD and ADVAIR 250/50 BID.
Conclusion

The breadth of data from our clinical development program demonstrates that FF/VI 100/25 is efficacious in the management of patients with asthma. Recognizing the need to titrate therapy to manage patients with different asthma severities, the data also supports the clinical utility of FF/VI 200/25.
Safety of Fluticasone furoate / Vilanterol

- Adverse and serious adverse events and deaths
- Adverse events of special interest
  - ICS
    - HPA and ocular effects
  - LABA
    - Cardiovascular effects
- Asthma composite endpoint
  - Hospitalization, intubation and death
- Overall benefit : risk
**Integrated Studies for Safety**

**Efficacy and Safety Studies**  
(18 Studies; N= 10,322)

- **FF Efficacy & Safety**  
  (N = 3005)
  - FFA112059  
    24-week trial  
    FF 100, FP 250† and PBO  
    (N = 343)
  - FFA114496  
    24-week trial  
    FF 100 & FF 200  
    (N = 238)
  - FFA115285  
    24-week trial  
    FF 50, FP† and PBO  
    (N = 347)
  - FFA115283  
    12-week trial  
    FF 50 and PBO  
    (N = 242)
  - FFA109687  
    8-week trial  
    FF, FP†, and PBO  
    (N = 598)
  - FFA109685  
    8-week trial  
    FF, FP†, and PBO  
    (N = 615)
  - FFA109684  
    8-week trial  
    FF, FP†, and PBO  
    (N = 622)

- **FF/VI (N = 6363)**
  - Primary HZA106827  
    12-week trial  
    FF/VI, FF and PBO  
    (N = 609)
  - Primary HZA106829  
    24-week trial  
    FF/VI, FF and FP†  
    (N = 586)
  - Supportive HZA113719  
    12-week trial  
    FF/VI and PBO  
    (N = 307)
  - Supportive HZA113714  
    12-week trial  
    FF/VI and FP† 500  
    (N = 309)
  - Comparator HZA113091  
    24-week trial  
    FF/VI and FP/SAL†  
    250/50  
    (N = 808)

- **VI Efficacy & Safety**  
  (N = 954)
  - B2C112060†  
    12-week trial  
    VI 25, SAL† 50 and PBO  
    (N = 347)
  - B2C109575‡  
    4-week trial  
    VI and PBO  
    (N = 607)

**Efficacy & Safety**

- FF/VI 100/25  
- FF/VI 200/25  
- FF/VI 100/25 & 200/25  
- FF/VI 100/25

**Safety**

- Primary HZA116863  
  12-week trial  
  FF/VI and FF  
  (N = 1039)
- Exacerbation HZA106837  
  24-76-week trial  
  FF/VI and FF 100  
  (N = 2019)
- LT Safety HZA106839  
  52-week trial  
  FF/VI and FP†  
  (N = 503)
- HPA Axis HZA106851  
  6-week trial  
  FF/VI, prednisolone 10mg and PBO  
  (N = 185)

**Supportive**

- HZA113719  
  12-week trial  
  FF/VI, FF and FP†  
  (N = 1039)
- HZA113091  
  24-week trial  
  FF/VI and FP/SAL†  
  250/50  
  (N = 808)
- HZA106829  
  24-week trial  
  FF/VI, FF and FP†  
  (N = 309)
- HZA106827  
  12-week trial  
  FF/VI, FF and PBO  
  (N = 307)

**Comparator**

- FF/VI and FP/SAL†  
  12-week trial  
  (N = 586)
- FF/VI and FP†  
  500  
  (N = 309)
- FF/VI and PBO  
  (N = 307)

**Exacerbation**

- HZA106837  
  24-76-week trial  
  FF/VI and FF 100  
  (N = 2019)

**Comparator**

- HZA106839  
  52-week trial  
  FF/VI and FP†  
  (N = 503)
- HZA106851  
  6-week trial  
  FF/VI, prednisolone 10mg and PBO  
  (N = 185)

**Other**

- FFA109687  
  8-week trial  
  FF, FP†, and PBO  
  (N = 622)
- FFA109685  
  8-week trial  
  FF, FP†, and PBO  
  (N = 615)
- FFA109684  
  8-week trial  
  FF, FP†, and PBO  
  (N = 622)

**Notes:**

- FF = fluticasone furoate; FP = fluticasone propionate; PBO = placebo; SAL = salmeterol; VI = vilanterol
- †administered via Diskus
- ‡subjects continued background ICS

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A-50
## Common Adverse Events
### Integrated Data

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo N = 1070</th>
<th>FF/VI 100/25 N = 2369</th>
<th>FF/VI 200/25 N = 956</th>
<th>FF 100 N = 2010</th>
<th>FF 200 N = 608</th>
<th>VI 25 N = 216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>74 (7)</td>
<td>322 (14)</td>
<td>85 (9)</td>
<td>260 (13)</td>
<td>44 (7)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>59 (6)</td>
<td>277 (12)</td>
<td>76 (8)</td>
<td>207 (10)</td>
<td>53 (9)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>30 (3)</td>
<td>155 (7)</td>
<td>52 (5)</td>
<td>123 (6)</td>
<td>15 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16 (1)</td>
<td>80 (3)</td>
<td>24 (3)</td>
<td>104 (5)</td>
<td>15 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (1)</td>
<td>72 (3)</td>
<td>27 (3)</td>
<td>75 (4)</td>
<td>19 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (1)</td>
<td>86 (4)</td>
<td>18 (2)</td>
<td>74 (4)</td>
<td>13 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8 (&lt;1)</td>
<td>70 (3)</td>
<td>16 (2)</td>
<td>55 (3)</td>
<td>15 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (&lt;1)</td>
<td>66 (3)</td>
<td>22 (2)</td>
<td>59 (3)</td>
<td>11 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Influenza</td>
<td>9 (&lt;1)</td>
<td>64 (3)</td>
<td>19 (2)</td>
<td>49 (2)</td>
<td>17 (3)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Note: Table lists preferred terms of AEs seen in ≥3% in FF/VI 100/25 and FF/VI 200/25 groups
# Exposure Adjusted Common Adverse Events
## Integrated Data

<table>
<thead>
<tr>
<th>Event per Subject Year (SY)</th>
<th>Placebo SY = 214.9</th>
<th>FF/VI 100/25 SY = 1537.3</th>
<th>FF/VI 200/25 SY = 382.2</th>
<th>FF 100 SY = 1253.1</th>
<th>FF 200 SY = 169.2</th>
<th>VI 25 SY = 32.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>344.3</td>
<td>209.5</td>
<td>222.4</td>
<td>207.5</td>
<td>260.1</td>
<td>524.4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>274.5</td>
<td>180.2</td>
<td>198.9</td>
<td>165.2</td>
<td>313.3</td>
<td>277.6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>139.6</td>
<td>100.8</td>
<td>136.1</td>
<td>98.2</td>
<td>88.7</td>
<td>123.4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>74.4</td>
<td>52.0</td>
<td>62.8</td>
<td>83.0</td>
<td>88.7</td>
<td>0</td>
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<tr>
<td>Oropharyngeal pain</td>
<td>60.5</td>
<td>46.8</td>
<td>70.7</td>
<td>59.8</td>
<td>112.3</td>
<td>215.9</td>
</tr>
<tr>
<td>Cough</td>
<td>60.5</td>
<td>55.9</td>
<td>47.1</td>
<td>59.1</td>
<td>76.9</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>37.2</td>
<td>45.5</td>
<td>41.9</td>
<td>43.9</td>
<td>88.7</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>18.6</td>
<td>42.9</td>
<td>57.6</td>
<td>47.1</td>
<td>65.0</td>
<td>61.7</td>
</tr>
<tr>
<td>Influenza</td>
<td>41.9</td>
<td>41.6</td>
<td>49.7</td>
<td>39.1</td>
<td>100.5</td>
<td>30.8</td>
</tr>
</tbody>
</table>

SY = subject years
On-Treatment Serious Adverse Events in >1 Subject Integrated Data

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo N = 1070</th>
<th>FF/VI 100/25 N = 2369</th>
<th>FF/VI 200/25 N = 956</th>
<th>FF 100 N = 2010</th>
<th>FF 200 N = 608</th>
<th>VI 25 N = 216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>7 (&lt;1)</td>
<td>54 (2)</td>
<td>9 (&lt;1)</td>
<td>41 (2)</td>
<td>7 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>1 (&lt;1)</td>
<td>13 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>9 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>6 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abscess</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intervertebral disc protrusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Limb traumatic amputation</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Fatal Events

- FF/VI 100/25
  - Car accident
- FF 100
  - Stage IV lung cancer (post-treatment)
  - Pneumonia
- Placebo (on a background of ICS)
  - Sudden death, cause unknown
Safety of Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
- **Adverse events of special interest**
  - ICS
    - HPA and ocular effects
  - LABA
    - Cardiovascular effects
- Asthma composite endpoint
  - Hospitalization, intubation and death
- Overall benefit : risk
### Other Tolerability: Adverse Events of Special Interest

**Integrated Data**

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Placebo N = 1070</th>
<th>FF/VI 100/25 N = 2369</th>
<th>FF/VI 200/25 N = 956</th>
<th>FF 100 N = 2010</th>
<th>FF 200 N = 608</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICS-associated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic steroid effects</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Local steroid effects*</td>
<td>17 (2)</td>
<td>155 (7)</td>
<td>70 (7)</td>
<td>131 (7)</td>
<td>48 (8)</td>
</tr>
<tr>
<td>Effects on glucose†</td>
<td>0</td>
<td>10 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>12 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Effects on bone</td>
<td>0</td>
<td>18 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>20 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>LABA-associated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (&lt;1)</td>
<td>45 (2)</td>
<td>6 (&lt;1)</td>
<td>39 (2)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Effects on potassium</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*oropharyngeal pain, dysphonia, oral and oral pharyngeal candidiasis, throat irritation, candida infection, oral fungal infection, oropharyngitis, fungal

†Both ICS and LABA have potential effects on glucose
Geometric Mean Serum Cortisol Concentration (Study 851)

Ocular-associated Adverse Events of Special Interest
Integrated Data

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Placebo N = 1070</th>
<th>FF/VI 100/25 N = 2369</th>
<th>FF/VI 200/25 N = 956</th>
<th>FF 100 N = 2010</th>
<th>FF 200 N = 608</th>
<th>VI 25 N = 216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>6 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye pain</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>4 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cataract</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cataract cortical</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Evaluation of Lens Opacification Classification System (LOCS III) in the year long safety study (Study 839) did not show any appreciable effects in cataracts or other lens opacities.
### Pre-Defined Arrhythmias of Potential Clinical Importance

#### 24-hour Holter Monitoring

(Study 839)

<table>
<thead>
<tr>
<th>Arrhythmia, n (%)</th>
<th>FF/VI 100/25, N=201</th>
<th>FF/VI 200/25, N=202</th>
<th>FP 500 BID, N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with Holter</td>
<td>111</td>
<td>115</td>
<td>50</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Non sustained VT</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Idioventricular rhythm</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Supraventricular arrhythmias</strong></td>
<td>0</td>
<td>4 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Sustained supraventricular tachycardia</td>
<td>0</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation (rate &gt;100 bpm)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Junctional tachycardia</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinus pause (≥2 sec)</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abnormalities of repolarization</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>ST elevation</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ST depression</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>
Studies in the Asthma Composite Assessment

Clinical Pharmacology, Efficacy and Safety Studies (17 Studies; N=7766)

**FF/VI** (N=6606)

- **Clinical Pharmacology** (N = 131)
  - HZA113126: 3-week crossover trial FF/VI, FF, VI and PBO (N = 27)
  - HZA114624: 2-week crossover trial FF/VI and FF (N = 26)
  - HZA112777: 2-week crossover trial FF/VI and FF (N = 26)
  - HZA113090: 4-week crossover trial FF/VI, FF and PBO (N = 52)

**Efficacy & Safety**

- FF/VI 100/25
  - Primary: HZA106627 12-week trial FF/VI, FF and PBO (N = 609)
  - Supportive: HZA113719 12-week trial FF/VI and PBO (N = 307)
  - Comparator: HZA113091 24-week trial FF/VI and FP/‡ 250/50 (N = 806)

- FF/VI 200/25
  - Primary: HZA106629 24-week trial FF/VI, FF and FP/‡ (N = 586)
  - Supportive: HZA113714 12-week trial FF/VI and FP/‡ 500 (N = 309)

- FF/VI 100/25 & 200/25
  - Primary: HZA116663 12-week trial FF/VI and FF (N = 1039)
  - Exacerbation: HZA106837 24-76-week trial FF/VI and FF (N = 2019)
  - Comparator: HZA113090 24-week trial FF/VI and FP/SAL/‡ 250/50 (N = 806)

**Safety**

- FF/VI 100/25
  - LT Safety: HZA113989 52-week trial FF/VI and FF (N = 243)

- VI (N=1029)
  - B2C112060 ‡: 12-week trial VI 25, SAL 50 and PBO (N = 347)

- FF (N=1029)
  - B2C109575 ‡: 4-week trial FF and PBO (N = 607)

- HZA113310 ‡: 1-week crossover trial VI and PBO (N = 75)

FF = fluticasone furoate; FP = fluticasone propionate; PBO = placebo; SAL = salmeterol; VI = vilanterol

‡ administered via Diskus

‡ subjects continued background ICS
Asthma Composite Endpoint Adjudication

- A committee of three independent, experienced respiratory clinicians
- All SAEs were adjudicated in a blinded fashion to determine if they resulted in a hospitalization, intubation or death
- Each SAE determined to be a hospitalization, intubation or death was assessed:
  - Respiratory-related or not
  - If respiratory-related: asthma, COPD, pneumonia or another cause
Asthma Composite Endpoint
All VI-Containing Doses vs. All Non-LABA Doses

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors VI</th>
<th>Favors Non-LABA</th>
<th>RD % (95% CI)</th>
<th>VI-Containing Doses n / N</th>
<th>Non-LABA All Doses n / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 624</td>
<td>0 / 18</td>
<td>0 / 8</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 989</td>
<td>0 / 153</td>
<td>0 / 90</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 719</td>
<td>0 / 153</td>
<td>0 / 154</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 714</td>
<td>0 / 153</td>
<td>0 / 154</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 710</td>
<td>0 / 15</td>
<td>0 / 14</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 126</td>
<td>0 / 6</td>
<td>0 / 14</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 090</td>
<td>0 / 18</td>
<td>0 / 34</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 777</td>
<td>0 / 13</td>
<td>0 / 13</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 851</td>
<td>0 / 112</td>
<td>0 / 73</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 839</td>
<td>1 / 403</td>
<td>2 / 100</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 837</td>
<td>10 / 1009</td>
<td>7 / 1010</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 827</td>
<td>0 / 197</td>
<td>1 / 389</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 829</td>
<td>0 / 201</td>
<td>0 / 408</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 060</td>
<td>0 / 115</td>
<td>0 / 116</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Study 575</td>
<td>0 / 101</td>
<td>0 / 102</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
<tr>
<td>Combined</td>
<td>13 / 3361</td>
<td>11 / 3026</td>
<td>0.018 (-0.316, 0.352)</td>
<td>1 / 155</td>
<td>1 / 154</td>
</tr>
</tbody>
</table>

- No asthma-related deaths or intubations
Asthma Composite Endpoint
All FF/VI Doses vs. All ICS Doses

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors FF/VI</th>
<th>Favors ICS</th>
<th>RD % (95% CI)</th>
<th>FF/VI All Doses n / N</th>
<th>ICS All Doses n / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 863</td>
<td>0</td>
<td>0</td>
<td>0 / 692</td>
<td>0 / 347</td>
<td></td>
</tr>
<tr>
<td>Study 989</td>
<td>0</td>
<td>0</td>
<td>0 / 153</td>
<td>0 / 90</td>
<td></td>
</tr>
<tr>
<td>Study 714</td>
<td>-0.004 (-1.792, 1.784)</td>
<td>1 / 155</td>
<td>1 / 154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 126</td>
<td>0</td>
<td>0</td>
<td>0 / 6</td>
<td>0 / 7</td>
<td></td>
</tr>
<tr>
<td>Study 090</td>
<td>0</td>
<td>0</td>
<td>0 / 18</td>
<td>0 / 17</td>
<td></td>
</tr>
<tr>
<td>Study 777</td>
<td>0</td>
<td>0</td>
<td>0 / 13</td>
<td>0 / 13</td>
<td></td>
</tr>
<tr>
<td>Study 839</td>
<td>-1.752 (-4.538, 1.035)</td>
<td>1 / 403</td>
<td>2 / 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 837</td>
<td>0.298 (-0.499, 1.095)</td>
<td>10 / 1009</td>
<td>7 / 1010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 829</td>
<td>-0.257 (-0.760, 0.246)</td>
<td>0 / 197</td>
<td>1 / 389</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 827</td>
<td>0</td>
<td>0</td>
<td>0 / 201</td>
<td>0 / 205</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>-0.020 (-0.424, 0.384)</td>
<td>12 / 2847</td>
<td>11 / 2332</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No asthma-related deaths or intubations
- 23 asthma-related hospitalizations: 12 with FF/VI and 11 with ICS
Asthma Composite Endpoint by Race

### Favors VI

**African American**
- Risk Difference: 1.149 (-0.434, 2.733)
- Doses: 2 / 174
- All VI-containing Doses: 0 / 170

**Asian**
- Risk Difference: 0.114 (-0.388, 0.615)
- Doses: 2 / 720
- All VI-containing Doses: 1 / 609

**White**
- Risk Difference: -0.083 (-0.479, 0.312)
- Doses: 9 / 2260
- All VI-containing Doses: 10 / 2076

**Other**
- Risk Difference: 0
- Doses: 1 / 609
- All VI-containing Doses: 10 / 2076

**Combined**
- Risk Difference: 0.018 (-0.316, 0.352)
- Doses: 13 / 3360
- All VI-containing Doses: 11 / 3026

### Favors Non-LABA

**African American**
- Risk Difference: -0.434 (-0.434, 2.733)
- Doses: 0 / 170
- All VI-containing Doses: 2 / 174

**Asian**
- Risk Difference: 0.615 (-0.388, 0.615)
- Doses: 1 / 609
- All VI-containing Doses: 2 / 720

**White**
- Risk Difference: 0.312 (-0.479, 0.312)
- Doses: 2076
- All VI-containing Doses: 2260

**Other**
- Risk Difference: 0
- Doses: 2076
- All VI-containing Doses: 2260

**Combined**
- Risk Difference: -0.316 (-0.316, 0.352)
- Doses: 3026
- All VI-containing Doses: 3360

### Combined

**All FF/VI All ICS**
- Risk Difference: 0.658 (-0.627, 1.943)
- Doses: 1 / 152
- All FF/VI: 1 / 152
- All ICS: 0 / 131

**Asian**
- Risk Difference: 0.046 (-0.557, 0.649)
- Doses: 2 / 711
- All FF/VI: 2 / 711
- All ICS: 1 / 425

**White**
- Risk Difference: -0.179 (-0.646, 0.288)
- Doses: 1649
- All FF/VI: 2107
- All ICS: 1649

**Other**
- Risk Difference: 0
- Doses: 127
- All FF/VI: 127
- All ICS: 127

**Combined**
- Risk Difference: -0.020 (-0.424, 0.384)
- Doses: 2847
- All FF/VI: 2847
- All ICS: 2332
Asthma Composite Endpoint by Age

### All VI - All

<table>
<thead>
<tr>
<th>Age</th>
<th>Favors VI</th>
<th>Favors Non-LABA</th>
<th>RD % (95% CI)</th>
<th>Doses n / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 years</td>
<td></td>
<td></td>
<td>0</td>
<td>0 / 13</td>
</tr>
<tr>
<td>12-17 years</td>
<td></td>
<td></td>
<td>0.537 (-1.023, 2.096)</td>
<td>4 / 321</td>
</tr>
<tr>
<td>18-64 years</td>
<td></td>
<td></td>
<td>0.048 (-0.249, 0.344)</td>
<td>9 / 2754</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td></td>
<td></td>
<td>-0.893 (-2.125, 0.339)</td>
<td>0 / 273</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>0.018 (-0.316, 0.352)</td>
<td>13 / 3361</td>
</tr>
</tbody>
</table>

### All FF/VI

<table>
<thead>
<tr>
<th>Age</th>
<th>Favors FF/VI</th>
<th>Favors ICS</th>
<th>RD % (95% CI)</th>
<th>Doses n / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 years</td>
<td></td>
<td></td>
<td>0</td>
<td>0 / 13</td>
</tr>
<tr>
<td>12-17 years</td>
<td></td>
<td></td>
<td>0.434 (-1.391, 2.259)</td>
<td>4 / 296</td>
</tr>
<tr>
<td>18-64 years</td>
<td></td>
<td></td>
<td>-0.053 (-0.399, 0.293)</td>
<td>8 / 2564</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td></td>
<td></td>
<td>-1.093 (-2.599, 0.413)</td>
<td>0 / 257</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>-0.020 (-0.424, 0.384)</td>
<td>12 / 3130</td>
</tr>
</tbody>
</table>
Safety Summary

- AE and SAE profile consistent with classes

- Adverse events of special interest
  - No HPA-axis suppression
  - Minimal ocular effects of FF/VI
  - No clinically relevant differences for cardiovascular events

- No increase in asthma composite endpoint in VI-containing treatment arms
Benefit: Risk FF/VI vs. FF

**WM FEV₁ (mL) (Week 12)**
- Study 863
- Study 827

**% Rescue-free 24 hr Periods (Weeks 1-12)**
- Study 863
- Study 827

**Rate of Asthma Exacerbations (per subject/yr)**
- Study 837

**% Controlled ACT**
- Study 863
- Study 827

---

**Benefit Adjusted Treatment Difference with 95% CI**

**Risk Adjusted Treatment Difference with 95% CI**

**Lower risk for FF 100**

**Lower risk for FF/VI 100/25**

**Lower risk for ICS**

**Lower risk for FF/VI**

---

**Effects on glucose**
**Effects on potassium**
**Cardiovascular effects**
**Tremor**

**Serious AE**
**Withdrawal due to AE**

---

**Asthma composite endpoint**
The program was not designed to statistically demonstrate the benefit of FF/VI over FF in the adolescent subgroup.

The effect on lung function favored FF/VI over FF in pooled analysis at week 12:
- Variable lung function response in the pivotal studies that only included 6% or less adolescents.

In the 837 exacerbation study:
- 93mL treatment difference favoring FF/VI over FF in trough FEV₁ at week 12.
- Although no difference in exacerbations was observed, the exacerbation rate was 100 times less than the adult population.

For the asthma composite endpoint, there were four hospitalization events in the FF/VI arm and two in the ICS-containing arm and the confidence interval crossed zero with the upper bound risk difference just over 2%.
Benefit : Risk of 200/25 vs. 100/25

- Trough FEV₁ (mL) (Week 12)
- % Rescue-free 24 hr Periods (Weeks 1-12)
- % Controlled ACT (Week 12)

Risk

- Serious AE
- Withdrawal due to AE
- Effects on glucose
- Ocular effects
- Local steroid effects
Clinical Perspectives on Asthma Management

Eugene R. Bleecker, MD
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Genomics and Personalized Medicine
Professor of Medicine, Pediatrics and
Public Health Sciences
Wake Forest School of Medicine
Winston-Salem, NC
Disclosures

Eugene R. Bleecker, MD

Listed are all of my relationships that *may* be related to this presentation that have existed during the past 3 years:

- **Industry-sponsored Clinical Trials (Through Wake Forest Health Sciences):** Amgen, AstraZeneca-MedImmune, Boehringer-Ingelheim-Pfizer, Cephalon-TEVA, Forest, Genentech-Roche, GlaxoSmithKline, Janssen-Johnson and Johnson, Novartis, Pearl, Pfizer, Sanofi-Aventis-Regeneron

- **Consultancy:** AstraZeneca, Boehringer-Ingelheim-Pfizer, Janssen-Johnson & Johnson, Genentech-Novartis, GlaxoSmithKline, Merck, Sanofi-Adventis/Regeneron

- **NIH Grants (NHLBI):** *Severe Asthma Research Program (SARP); AsthmaNet; Spiromics; Pharmacogenetics of Asthma*; Linking Genetics, Genomics and Phenomics to Better Understand Asthma Severity; CAPPA Consortium

- No personal relationships with tobacco industry entities.
- No Off-Label Disclosure.
Asthma is a Serious Disease with Major Public Health Impact

- 18.7 million adults (8.0%) and 6.8 million children (9.3%) have asthma
- Asthma accounts yearly for:
  - 15.5 million outpatient visits
  - 1.8 million emergency department visits
  - 439,000 hospitalizations (3.6 day average stay)
- 3630 patients died from asthma in 2013
- Asthma is often poorly controlled despite available treatments (49% of adults and 58% of children have ≥1 asthma attacks)

2013 National Health Interview Survey (NHIS) Data. Available at: http://www.cdc.gov/asthma/nhis/2013/data.htm
Adult Self-Reported Current Asthma Prevalence (%) by State or Territory, 2010

The Challenge

Clinical asthma is characterized by phenotypic variation

How do we effectively manage asthma heterogeneity and differing levels of disease severity?
Important Clinical Management Issues in Asthma

• Individualized controller and preventive options in asthma

• Improved adherence and better therapeutic efficacy

• Safe and effective asthma therapies for our patients
Asthma Control Assessment

Impairment

- Symptoms
- Nighttime awakenings
- SABA use for symptom control
- FEV$_1$ or peak flow
- Interference with normal activity
- Validated questionnaires
  - ATAQ
  - ACQ
  - ACT

Risk

- Exacerbations
- Progressive loss of lung function
- Treatment-related adverse events

Adapted from Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007. NIH, NHLBI. August 2007. NIH publication no. 08-4051.
NIH / NAEPP Asthma Guidelines
Stepwise Approach for Managing Asthma (≥12 Years)

Intermittent Asthma

Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred: Low-dose ICS + LABA
OR Medium-dose ICS
Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 5
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Key: ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist

Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007. NIH, NHLBI. August 2007. NIH publication no. 08-4051.
Treating the Spectrum of Asthma

Severe Asthma Definition: Asthma which requires treatment with guidelines suggested medications: high dose ICS and LABA for the previous year or systemic CS to prevent it from becoming “uncontrolled” or asthma remains “uncontrolled” despite this therapy.

Prevalence of severe asthma is estimated as 5-10% of total asthma population.

Clinical Heterogeneity in Asthma

• Limitations of Guidelines Asthma Classification
  – Does not adequately reflect heterogeneity within and across asthma severity levels
  – Assumes all patients within a severity level respond to the same therapies

• Because of asthma heterogeneity, multiple controller therapies (e.g. ICS, ICS/LABA, etc.) with flexible dosing are required to achieve optimal management in asthma

Asthma Management: Issues

- Specific Treatment Issues
  - Adolescent asthma
  - Dosing flexibility
  - Consistent inhaler availability
  - Adherence
Asthma Management: Issues

- Specific Treatment Issues
  - Adolescent asthma
  - Dosing flexibility
  - Consistent inhaler availability
  - Adherence
Improvement in FEV₁ with Increasing Doses of Fluticasone Furoate (FF)

Δ = 77 mL*

Change from Baseline, mL

<table>
<thead>
<tr>
<th>Dose</th>
<th>Change (mL)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF 100 µg QD</td>
<td>208</td>
<td>106</td>
</tr>
<tr>
<td>FF 200 µg QD</td>
<td>284</td>
<td>109</td>
</tr>
</tbody>
</table>

*95% CI: -39,192; this was a descriptive trial therefore no p-value is available for this comparison. Woodcock, et al. BMC Pulmonary Medicine. 2014;14(1)
Too many inhalers are confusing to most asthmatics and health providers: 

*Combination inhalers with dosing flexibility are very important*

The brands listed are trademarks of their respective owners.
In chronic diseases, less frequent dosing is associated with improved adherence.

Personalized Asthma Management

- Asthma is a heterogeneous disease characterized by different severity phenotypes

Thus, appropriate asthma management requires effective and safe pharmacologic approaches that facilitate individualized therapeutic strategies.
BREO ELLIPTA Benefits in Asthma Management

• Improves lung function
• Decreases symptoms, SABA use and improves asthma control
• Decreases asthma exacerbations vs. ICS alone
• Similar safety profile to current ICS/LABA products
• Provides the ability to address asthma heterogeneity and provides titration of therapy with the same inhaler
• Once-daily therapy should improve adherence

Closing Remarks

Katharine Knobil, MD
Summary of the BREO ELLIPTA Asthma Development Program

- New, once daily treatment option for patients with asthma

- Robust clinical programs in asthma and COPD (N >20,000)

- Established class of medications for the treatment of asthma
  - ICS component approved for asthma (FF)

- Efficacy
  - 24 hour improvement in lung function with BREO ELLIPTA
  - Improvements in symptoms of asthma
  - 20% relative reduction in the risk of experiencing an asthma exacerbation

- Safety
  - Extensive safety database
  - Safety profile similar to established ICS/LABA combinations
  - No increase in serious asthma-related outcomes
Extensive Data Show No Increased Risk in Serious Asthma Outcomes with LABAs when used with ICS

- **ADVAIR**: 22,000 patients
  - No asthma-related deaths or intubations
  - No increased risk of hospitalizations

- **BREO program**: 7,766 patients included in asthma composite endpoint
  - No asthma-related deaths or intubations
  - No increased risk of hospitalizations

- Ongoing LABA safety studies: over 17,000 patients randomized
  - No asthma-related deaths
  - 2 asthma-related intubations in adult and adolescent study

- Another study for BREO to evaluate hospitalizations would be unlikely to meaningfully add to currently available evidence and ongoing studies
Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults

Intermittent Asthma

Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
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Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

Step 6
Step up if needed
(first, check adherence, inhaler technique, environmental control and comorbid conditions)

Assess control
Step down if possible (and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

Quick-Relief Medication for All Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
• Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Key: ICS, inhaled corticosteroid; LABA, inhaled long-acting beta<sub>2</sub>-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist

Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007. NIH, NHLBI. August 2007. NIH publication no. 08-4051.
BREO ELLIPTA for Asthma

- BREO ELLIPTA is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 12 years and older.

- The recommended starting dosage of BREO ELLIPTA is 100/25 or BREO ELLIPTA 200/25 administered as 1 inhalation once daily.
BACKUP SLIDES
Table 48: Total Subjects Treated in the FF/VI Asthma Clinical Program (ITT)

<table>
<thead>
<tr>
<th>Study Grouping</th>
<th>Total Subjects Treated¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT²</td>
</tr>
<tr>
<td>Integrated Studies⁴</td>
<td>10,322⁵</td>
</tr>
<tr>
<td>Non-integrated Studies⁴,⁵</td>
<td>1729</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>1328</td>
</tr>
<tr>
<td>Adult (18-75 years)</td>
<td>1247</td>
</tr>
<tr>
<td>Pediatric (5-11 years)</td>
<td>81</td>
</tr>
<tr>
<td>Program Total</td>
<td>13,379</td>
</tr>
</tbody>
</table>

Source: Table 1.02, Table 11.3, Table 11.22, Table 12.3

1. Numbers provided are not unique subjects (i.e., subjects who participated in more than one study or subjects in the Clinical Pharmacology Program who participated in multiple periods in crossover design studies are counted more than once).
2. Includes subjects treated with at least one dose of any study medication (placebo, active, or comparator) given by any route of administration.
3. All orally inhaled doses studied (regardless of inhaler used).
4. Integrated and Non-integrated Studies included adolescent and adult subjects (≥12 years of age).
5. Includes 403 subjects who were randomized to FP/SALM 250/50 BD.
6. For the two crossover studies (FFA112202 and HZA113310), only the first treatment period was used for counting subjects.
7. 135 of these subjects received the H-salt of VI

Source: Module 5.3.5.3, ISS, Table 7, pg. 50.
Heart rate population PK/PD analysis (asthma): East Asian vs. Caucasian comparison

- Higher VI exposure in East Asians was not associated with a greater effect on heart rate.
- The VI $C_{\text{max}}$ in Asian subjects with asthma is comparable to healthy subjects.
Urine cortisol excretion population PK/PD (asthma): East Asian vs. Caucasian comparison

- Higher FF exposure in East Asians was not associated with a greater effect on cortisol
## Results: Primary Endpoint

### Mean Annual Asthma Exacerbation Rate Per Patient

<table>
<thead>
<tr>
<th></th>
<th>FSC Diskus 100/50 n = 239</th>
<th>FP 100 mcg n = 236</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation Rate</td>
<td>0.449</td>
<td>0.529</td>
</tr>
<tr>
<td><em>P</em>-Value</td>
<td>0.169</td>
<td></td>
</tr>
</tbody>
</table>

## Results: Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>FSC Diskus 100/50</th>
<th>FP 100</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AM PEF (L/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>342</td>
<td>340</td>
<td>15.1 (5.5, 24.7)</td>
</tr>
<tr>
<td>Mean Change</td>
<td>15.6</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td><strong>AM Pre-dose FEV&lt;sub&gt;1&lt;/sub&gt; (L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.53</td>
<td>2.52</td>
<td>0.103 (0.041, 0.165)</td>
</tr>
<tr>
<td>Mean Change</td>
<td>0.045</td>
<td>-0.061</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom-free Days, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26.7</td>
<td>23.2</td>
<td>3.3 (-2.9, 9.6)</td>
</tr>
<tr>
<td>Mean Change</td>
<td>10.8</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td><strong>Albuterol-free Days, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>37.9</td>
<td>42.1</td>
<td>4.5 (-1.8, 10.9)</td>
</tr>
<tr>
<td>Mean Change</td>
<td>10.8</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

The *a priori* analysis plan required meeting the primary outcome as a prerequisite for declaring statistical significance of the secondary outcomes. As a result, the statistical results are provide only to help inform on the individual measures.

Figure 1: Risk Difference Estimates
Age Subgroup Analysis
Figure 3: Risk Difference Estimates: Asthma Composite by Drug

- Advair: RD = 0.15 (95% CI: -2.01, 1.70) [Sample Sizes]: 21/6648, 20/6564
- Serevent: RD = 3.49 (95% CI: 1.27, 5.71) [Sample Sizes]: 21108/270, 22716
- Foradil: RD = 3.80 (95% CI: -1.80, 9.40) [Sample Sizes]: 18/1626, 14/2139
- Symbicort: RD = 7.49 (95% CI: -1.47, 16.44) [Sample Sizes]: 16/766, 1/504
- Overall: RD = 2.80 (95% CI: 1.11, 4.49) [Sample Sizes]: 381/30148, 304/30806

*RD = Risk Difference Per 1000 Subjects [Treat. Events/Treat. n Plac. Events/Placebo n]
Pediatric Population
Asthma-related Death and Hospitalization with ADVAIR
2008 Analysis

<table>
<thead>
<tr>
<th></th>
<th>ADVAIR</th>
<th>ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1,138</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1</td>
<td>1,138</td>
</tr>
</tbody>
</table>

Risk Difference (95% CI)
-0.539 per 10,000 pts (-60.34, 49.57)

Presented at 2008 FDA Advisory Committee Meeting
ADVAIR: Results from RCTs

Asthma-related Death, Intubation and Hospitalization and OCS-requiring Exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Number of Events</th>
<th>Favors ADVAIR</th>
<th>Favors ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>31</td>
<td>29</td>
<td>0.28 (-18.51, 19.06)</td>
</tr>
<tr>
<td>Pediatric population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1</td>
<td>2</td>
<td>-5.39 (-60.34, 49.57)</td>
</tr>
<tr>
<td>Exacerbation population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>67</td>
<td>144</td>
<td>-123 (-231, -16)</td>
</tr>
</tbody>
</table>

Risk Difference per 10,000 patients

**Rate of Asthma Exacerbations by Age (Study 837)**

<table>
<thead>
<tr>
<th></th>
<th>ITT Population</th>
<th>12-17 years</th>
<th>≥18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FF 100</td>
<td>FF/VI 100/25</td>
<td>FF 100</td>
</tr>
<tr>
<td>Number (events) of subjects with ≥1 asthma exacerbation</td>
<td>N=1010</td>
<td>N=1009</td>
<td>N=130</td>
</tr>
<tr>
<td>FF 100</td>
<td>186 (271)</td>
<td>154 (200)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>FF/VI 100/25</td>
<td>1006</td>
<td>1020</td>
<td>126.5</td>
</tr>
<tr>
<td>Crude exacerbation rate per subject per year</td>
<td>0.27</td>
<td>0.20</td>
<td>0.08</td>
</tr>
<tr>
<td>FF/VI 100/25 vs. FF 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude Ratio</td>
<td>0.74</td>
<td></td>
<td>1.63</td>
</tr>
</tbody>
</table>

Note: A separate negative binomial regression model was used for each age group with covariates of treatment, FEV₁ at baseline, sex, age and region.
### SEREVENT: Results from SMART

*All Patients and Reported ICS Use at Baseline*

<table>
<thead>
<tr>
<th>Event</th>
<th>RR (95% CI)</th>
<th>SEREVENT n</th>
<th>Placebo n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma-related Death</td>
<td>4.37 (1.25, 15.33)</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.35 (0.30, 6.03)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Not estimable</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Asthma-related Death or Asthma-related Intubation</td>
<td>1.71 (1.01, 2.89)</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1.24 (0.60, 2.57)</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>2.39 (1.10, 5.21)</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Asthma-related Hospitalization</td>
<td>1.14 (0.92, 1.42)</td>
<td>176</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>1.06 (0.80, 1.40)</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>1.28 (0.92, 1.79)</td>
<td>77</td>
<td>60</td>
</tr>
</tbody>
</table>

Adapted from Nelson H, et al. Chest 2006;129:15-26

Baseline Asthma Characteristics in Caucasians and African Americans

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Caucasian (n=18,642)</th>
<th>African American (n=4685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak expiratory flow (% predicted)</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>Nocturnal symptoms present</td>
<td>57%</td>
<td>64%</td>
</tr>
<tr>
<td>≥1 ER visit last 12 months</td>
<td>22%</td>
<td>41%</td>
</tr>
<tr>
<td>≥1 ER visit lifetime</td>
<td>59%</td>
<td>72%</td>
</tr>
<tr>
<td>≥1 hospitalization last 12 months</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>≥1 hospitalization lifetime</td>
<td>30%</td>
<td>44%</td>
</tr>
<tr>
<td>≥1 intubation for asthma lifetime</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Baseline ICS Use</td>
<td>49%</td>
<td>38%</td>
</tr>
</tbody>
</table>

### Cumulative Exposure

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=1070</th>
<th>FF/VI 100/25 N=2369</th>
<th>FF/VI 200/25 N=956</th>
<th>FF 100 N=2010</th>
<th>FF 200 N=608</th>
<th>VI 25 N=216</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Exposure (n)</strong></td>
<td>1065</td>
<td>2369</td>
<td>954</td>
<td>2008</td>
<td>604</td>
<td>216</td>
</tr>
<tr>
<td>&lt;12 weeks, n (%)</td>
<td>674 (63)</td>
<td>388 (16)</td>
<td>276 (29)</td>
<td>493 (25)</td>
<td>327 (54)</td>
<td>152 (70)</td>
</tr>
<tr>
<td>≥12 weeks, n (%)</td>
<td>391 (37)</td>
<td>1981 (84)</td>
<td>678 (71)</td>
<td>1515 (75)</td>
<td>277 (46)</td>
<td>64 (30)</td>
</tr>
<tr>
<td>≥24 weeks, n (%)</td>
<td>120 (11)</td>
<td>1400 (59)</td>
<td>309 (32)</td>
<td>1081 (54)</td>
<td>180 (30)</td>
<td>0</td>
</tr>
<tr>
<td>≥52 weeks, n (%)</td>
<td>0</td>
<td>696 (29)</td>
<td>122 (13)</td>
<td>567 (28)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Patient Years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>215</td>
<td>1537</td>
<td>382</td>
<td>1253</td>
<td>169</td>
<td>32</td>
</tr>
</tbody>
</table>