CAPTAIN: Effects of age of asthma onset as a continuous variable on treatment outcomes

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*At the time of the study
Conflict of interest disclosures

- This study was funded by GlaxoSmithKline (205715/NCT02924688).
- ELLIPTA and DISKUS are owned by or licensed to the GSK group of companies.
- On behalf of all authors, an audio recording of this presentation was prepared by NL, who did not receive any payment for this recording.
- NL has served on advisory boards for AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi, and Teva; has participated in clinical trials for which the institution received funding from AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi and Teva; has a consultancy agreement with AstraZeneca; and has received funds for developing CME presentations from AKH and Medscape.
- ZB, NB, FG, EP and DS are employees of GSK and hold stocks/shares in GSK.
- L-PB has received research grants for participation in multicenter clinical research trials and support for research projects from AstraZeneca, Boston Scientific, GSK, Hoffman La Roche, Ono Pharma, Novartis, Sanofi, Takeda, Boehringer Ingelheim, and Merck. L-PB has also received fees for consulting and advisory boards, conference fees, and support for participation in conferences and meetings from AstraZeneca, GSK, Merck, Metapharm, Novartis, and Takeda, and non-profit grants for the production of educational materials from AstraZeneca, Boehringer Ingelheim, GSK, Merck, and Novartis.
- NAH received personal fees from AstraZeneca, Genentech, GSK, Mylan, Sanofi, Regeneron, Amgen, and Teva and research support from Boehringer Ingelheim, GSK, Novartis, Sanofi Genzyme, and Genentech.
- HI has received research/educational grants from Boehringer Ingelheim, Chugai, GSK, Kyorin, MSD, Novartis, Ono Pharma, Pfizer, Sanofi, Shionogi, Taiho, Teijin-Pharma. He has received speaker's honoraria and/or fees for advisory boards from Astellas, AstraZeneca, Boehringer Ingelheim, Chugai, GSK, Kyorin, MSD, Novartis, and Sanofi.
- PWJ is a contractor to GSK and holds stocks/shares in GSK
- HK has received research grants and served on advisory boards for Boehringer Ingelheim, Chiesi, GSK, and Novartis.
- EK was an employee of Crisor LLC Research at the time of the study and has served on advisory boards, speaker panels, or received travel reimbursement from Amphastar, AstraZeneca, Boehringer Ingelheim, Cipla, Connect Biopharma, Chiesi, Forest, GSK, Mylan, Novartis, Pearl, Sunovion, Teva, and Theravance.
- RAP Jr has served on scientific advisory boards and/or speaker boards and/or has received research support from AstraZeneca, Genentech, GSK, Sanofi, Novartis, and Teva.
- RN is a non-paid instructor and clinical professor at the University of Colorado Health Sciences Center (Denver CO, USA); was an employee of Asthma and Allergy Associates, PC and Research Center at the time of the study; and has received speaker's fees and honoraria for advisory boards from GSK and Boehringer Ingelheim.
- Editorial support in the form of preparation of the first draft based on input from all authors, and collation and incorporation of author feedback to develop subsequent drafts, was provided by Evelin O. Szalai, BSc, of Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.
The CAPTAIN study showed that adding UMEC to FF/VI improved lung function and symptom control and led to numerical reductions in the annualized rate of moderate/severe exacerbations in patients with uncontrolled asthma despite ICS/LABA therapy.\(^1\)

Previous categorical subgroup analysis of CAPTAIN showed that response to FF/UMEC/VI may vary according to the age at which a patient develops asthma (<18 vs ≥18 years of age).\(^2\)

- Continuous analyses help understand the relationship across the entire range and avoid the loss of information introduced when using a cut-off.

The objective of this post hoc analysis of CAPTAIN was to further explore potential differential treatment responses using age of asthma onset as a continuous variable.

**Introduction and objectives**

- FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β\(_2\)-agonist; LAMA, long-acting muscarinic antagonist; UMEC, umeclidinium; VI, vilanterol.

Methods

- CAPTAIN was a Phase IIIA, randomized, 24–52-week, parallel-group study (GSK study 205715, NCT02924688).

≥18 years old with an asthma diagnosis
Uncontrolled on ICS/LABA (dose equivalent to fluticasone propionate >250 mcg/day)
FEV₁ ≥30% to <85% predicted with demonstrated reversibility
HRU contact for asthma in previous 12 months

*Provided as a fixed-dose via the DISKUS DPI; †provided as a fixed-dose via the ELLIPTA DPI; ‡randomization stratified by pre-study ICS dose (medium vs high); §all participants in the study had a safety follow-up contact approximately 7 days after the End of Study Visit (dependent on actual transition date) or Early Withdrawal Visit. All doses are mcg.

BID, twice a day; DPI, dry powder inhaler; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; HRU, healthcare resource utilization; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β₂-agonist; QD, once daily; R, randomization; UMEC, umeclidinium; VI, vilanterol.
Methods (cont.)

- Post hoc analysis of CAPTAIN for treatment groups pooled by addition of UMEC 62.5 mcg or FF dose:

<table>
<thead>
<tr>
<th>Pooling strategy</th>
<th>Pooled treatment group</th>
<th>Individual treatment groups</th>
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<tbody>
<tr>
<td>Adding UMEC 62.5 mcg to FF/VI</td>
<td>FF/VI</td>
<td>FF/VI 200/25 + FF/VI 100/25</td>
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<tr>
<td></td>
<td>FF/UMEC 62.5/VI</td>
<td>FF/UMEC/VI 100/62.5/25 + FF/UMEC/VI 200/62.5/25</td>
</tr>
<tr>
<td>Doubling FF dose</td>
<td>FF 100</td>
<td>FF/UMEC/VI 100/62.5/25 + FF/UMEC/VI 100/31.25/25 + FF/VI 100/25</td>
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- Endpoints are reported by the age of asthma onset* as a continuous variable:
  - Change from baseline in clinic trough FEV₁ at Week 24 (primary endpoint) analyzed using MMRM.
  - Annualized rate of moderate/severe asthma exacerbations (Weeks 1–52; key secondary endpoint) analyzed using a negative binomial model.

- FP models adjusted for two FP transformations of age of asthma onset and their interactions with treatment.
  - The best fitting model from 36 pre-defined models was selected based on likelihood.¹
  - Prior to modeling, age of asthma onset were pre-transformed using the approach suggested by Royston and Sauerbrei.²

All doses are mcg. *Age of asthma onset was derived as age at pre-screening – duration of asthma.
FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fractional polynomial; MMRM, mixed model repeated measures; UMEC, umeclidinium; VI, vilanterol.
## Demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total* (N=2436)</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, years, mean (SD)</td>
<td>53.2 (13.11)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>922 (38)</td>
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<td>BMI, kg/m², mean (SD)</td>
<td>29.35 (6.642)</td>
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<tr>
<th>Clinical characteristics</th>
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<tr>
<td>Age of asthma onset, years, mean (SD)</td>
<td>32.0 (18.74)</td>
</tr>
<tr>
<td>Duration of asthma, years, mean (SD)</td>
<td>21.2 (15.31)</td>
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<tr>
<td>Total number of exacerbations in 12 months prior to screening, n (%)</td>
<td></td>
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<tr>
<td>0</td>
<td>364 (15)</td>
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<tr>
<td>1</td>
<td>1390 (57)</td>
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<tr>
<td>≥2</td>
<td>682 (28)</td>
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<tr>
<td>Pre-study ICS dose – medium dose†, n (%)</td>
<td>1621 (67)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁ ‡, % predicted, mean (SD)</td>
<td>68.2 (14.76) [n=2420]</td>
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<td>Pre-bronchodilator FEV₁ ‡, mL, mean (SD)</td>
<td>2023 (678.2) [n=2420]</td>
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<tr>
<td>Reversibility to salbutamol†, %, mean (SD)</td>
<td>29.9 (18.12) [n=2418]</td>
</tr>
<tr>
<td>ACQ-7 score‡, mL, mean (SD)</td>
<td>2.1 (0.70) [n=2383]</td>
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*ITT population, including all six treatment groups; †at screening; medium dose defined as >250 to ≤500 mcg/day fluticasone propionate (or equivalent); ‡at randomization; Note: n=patients with analyzable data.

ACQ, Asthma Control Questionnaire; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITT, intent-to-treat; SD, standard deviation
Addition of UMEC 62.5 mcg to FF/VI was associated with improvements in trough FEV₁ independent of age of asthma onset

- Although the higher FF dose was associated with small numerical improvements in trough FEV₁ irrespective of age of asthma onset, there was considerable overlap in CIs.
- Improvements in trough FEV₁ from increasing FF dose were less pronounced than adding UMEC.

A. Impact of adding UMEC (pooled treatments)

B. Impact of increasing FF (pooled treatments)

All doses are mcg. Note: best fitting FP model presented. Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, baseline value, pre-study ICS dosage at screening, FP1, FP2, and visit, interaction terms for baseline value by visit, treatment by visit, FP1 by treatment and FP2 by treatment. FP1 and FP2 represent continuous transformations of age of onset. Prior to modeling, age of onset values were pre-transformed using the approach suggested by Royston and Sauerbrei. CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fractional polynomial; LS, least squares. UMEC, umeclidinium; VI, vilanterol.

The higher FF dose was associated with numerical reductions in moderate/severe exacerbations independent of age of asthma onset

- There was some indication that addition of UMEC was effective at reducing the moderate/severe exacerbation rate with advancing age of asthma onset, but there was considerable overlap in CIs.
- Greater uncertainty exists at the extremes of the age range due fewer patients.

A. Impact of adding UMEC (pooled treatments)

B. Impact of increasing FF (pooled treatments)

All doses are mcg. Note: best fitting FP model presented. Analysis performed using a negative binomial model with covariates of treatment, age, sex, region, pre-study ICS dosage at screening, severe asthma exacerbations in the previous year (0, 1, ≥2), FP1, FP2, interaction terms for FP1 by treatment, FP2 by treatment, and with logarithm of time (year) on-study as an offset variable. FP1 and FP2 represent continuous transformations of age of onset. Prior to modeling, age of onset values were pre-transformed using the approach suggested by Royston and Sauerbrei. CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fractional polynomial; LS, least squares. UMEC, umeclidinium; VI, vilanterol.

Conclusions

- Improvements in trough FEV₁ following addition of UMEC to FF/VI or from using the higher FF dose were generally independent of age of asthma onset.
  - The magnitude of improvement in trough FEV₁ was greater following addition of UMEC to FF/VI compared with increasing the dose of FF.

- Numerical reductions in the annualized rate of moderate/severe exacerbations were observed following an increase in FF dose which were generally independent of age of asthma onset.
  - Addition of UMEC to FF/VI appeared to have a greater effect on reducing the annualized rate of moderate/severe exacerbations with advancing age of asthma onset, but there was considerable overlap in CIs.

- Patients whose asthma is inadequately controlled on ICS/LABA benefit from the addition of UMEC in FF/UMEC/VI triple therapy or from the use of the higher FF dose irrespective of age of asthma onset.

CI, confidence interval; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; UMEC, umeclidinium; VI, vilanterol.