

**Errata to the FDA Briefing Document
Joint PADAC and DSaRM Advisory Committee Meeting
March 19, 2015**

Page numbers refer to PDF page number

Division Memorandum

1. On page 12, 2nd paragraph, 2nd sentence should be: “An end-of-phase 2 meeting for Breo Ellipta for asthma was held in ~~March~~ April 2009...”
2. On page 13, Table 5, Relevant dose-ranging and dose-regimen selection studies for fluticasone furoate in patients with asthma
 - Trial 109685, 6th column, add South Africa
 - Trial 109687, 3rd column, FP 100 mcg BID
 - Trial 109687, 6th column, US, Canada, EU, ~~EU, S Africa~~, Other; note, study not performed in S Africa and EU listed twice.
3. On page 14, Table 5, Relevant dose-ranging and dose-regimen selection studies for fluticasone furoate in patients with asthma
 - Trial 112202, 1st column, 2007~~8~~-2008~~9~~
 - Trial 112202, 5th column, end of **each** 28-day treatment period
 - Footnote ¶ should be deleted as there are no secondary efficacy variables listed or studies of 6 or 48 weeks of duration
 - Footnote // should be EU included ~~UK~~, Germany, ~~Italy~~, Netherlands, Sweden, Denmark, ~~Spain~~, Estonia, Poland, Czech Republic Romania; Other included Chile, ~~Argentina~~, Peru, Mexico, Philippines, Thailand, ~~Japan~~, S Korea, Russia, Ukraine; note, studies were not performed in countries that are crossed out
4. Page 14, Figure 2, Adjusted treatment difference from placebo for change from baseline in trough FEV₁ in liters at week 8 from three dose ranging studies in asthma
 - Trial FFA109685, Mid Dose, Low Med ICS
 - Trial FFA109684, High Dose, Medium High ICS
5. Page 16, Table 6, Relevant dose-ranging and dose-regimen selection studies for vilanterol in patients with asthma
 - Footnote ¶ should be deleted as there are no secondary efficacy variables listed or studies of 6 or 48 weeks of duration
6. On page 18, Table 7, Relevant clinical studies with Breo Ellipta in patients with asthma

- Trial 116863, 5th column, 1^o: FEV₁ 0-24 hr on day 84 ~~in a subset~~
 - Trial 106837, 2nd column, Asthma, FEV₁ ≥60% **50-90%**
 - Trial 113091, 3rd column, FP/Sal **250/50** ~~500/50~~ BID
 - Trial 113091, 6th column, ~~EU~~ **US**, EU, Other
 - Footnote ‡ should be: “...~~Vilanterol = vilanterol in Ellipta~~; FP/Sal...”
7. On page 18, Design and conduct of the studies, 2nd sentence should be: “...on a stable dose of ICS or LABA or both **ICS** ~~ICA~~ and LABA prior to entry...”
 8. On page 19, 2nd paragraph, 2nd sentence should be: “Eligible patients ~~had a lower cut-off of FEV₁~~, were on mid- to high dose...” Note, subjects had baseline FEV₁ of 50% to 90% compared with 40% to 80%/90% in other studies.
 9. On page 19, 2nd paragraph, 5th sentence should be: “Treatment duration for patients was at least **24** ~~26~~ weeks and did not exceed 76 weeks for any completed subject.”
 10. On page 19, 4th paragraph, 2nd sentence should be: “Eligible patients entered a **24**-week run-in period when ~~baseline ICS was allowed~~ **all subjects received FP 250 BID**...”
 11. On page 21, Table 9 Bronchodilator studies 106827, 106829, and 116863, footnote * should be: “...FF = fluticasone furoate in Ellipta device; ~~VI = vilanterol in Ellipta~~; ...”
 12. On page 23, 1st sentence should be: “...favoring the fluticasone **furoate** treatment arm over the Breo Ellipta treatment arm.”
 13. On page 23, 2nd paragraph, 4th sentence should be: “The fluticasone **furoate** treatment arms also had smaller number of patients...”
 14. Page 23, Table 11 Bronchodilator studies 106827, 106829, and 116863, footnote * should be: “...FF = fluticasone furoate in Ellipta device; ~~VI = vilanterol in Ellipta~~; ...”
 15. On page 23, Table 11, Column 3 (Change mL) for FF 100 should be: 96**1**~~7~~
 16. On page 23, 3rd paragraph, 3rd sentence should be: “Breo Ellipta 100/25 tended to show numerically smaller response compared to Advair **250/50** ~~500/50~~...”
 17. On page 25, Laboratory findings and ECGs, 2nd sentence should be: “There were some reports of elevated glucose and **decreased** potassium...”

18. On page 38, 1st paragraph, 2nd sentence should be: “Compared with FF 100 alone, FF/VI **100/25** significantly improved...”
19. On page 38, 2nd paragraph, 1st sentence should be: “Trial HZA116863 also provided an opportunity to evaluate the benefit of the higher dose (FF/**VI** 200/25) over the lower dose (FF/**VI** 100/25).”
20. On page 41, Section 2.1 Product Information, 1st paragraph, 3rd sentence should be: “Within the foil packs, for **FF/VI 100/25** one strip contains 100 mcg of FF and the second contains 25 mcg of VI **and for FF/VI 200/25 one strip contains 200 mcg of FF and the second contains 25 mcg of VI.**”
21. On page 46, Table 4 Vilanterol Dose-Ranging Trials should be:
- Trial B2C109575, 5th column, VI 3 QD ~~101~~, VI 6.25 QD ~~101~~, VI 12.5 QD ~~100~~, VI 25 QD ~~101~~, Placebo QD ~~102~~ **102**
22. On page 47, Table 5 Clinical Development Program, Trial HZA113091, 5th column, FEV1 should be: 40-90 **85%**
23. On page 49, Section 4.2 Vilanterol (VI) Dose Selection, 1st paragraph, 2nd sentence should be: “Trial **B2C109575** was a randomized...”
24. On page 50, 2nd bullet – Comparison to salmeterol, 3rd sentence should be: “While patients treated with VI 25 mcg QD demonstrated a higher **weighted mean 0-24 hr FEV₁ (L)** LS mean treatment increase...”
25. On page 51, Figure 4 title should be: “Trial HZA113091: ~~LS~~ **Raw** mean change from baseline in FEV1 (0-4h) at Day 1”
26. On page 55, Inclusion Criteria, 2nd bullet, 3rd sub-bullet should be: “On a stable dose of **ICS** or ICS/LABA for at least 4 weeks prior to visit 1”
27. On Page 55, Exclusion Criteria, 8th bullet should be:
- ~~Within 4 weeks of visit 1 and during the study:~~
 - i. ~~Inhaled, oral, or transdermal long-acting beta 2-agonist~~
 - ii. ~~Combination therapy containing long-acting beta 2-agonists and ICS for asthma~~
 - ~~Following the morning of visit 1~~ **Within 1 day of visit 1** and during the study:
 - i. **Inhaled, oral, or transdermal long-acting beta 2-agonist**
28. On page 55, Exclusion Criteria, last bullet should be: “...or affect ICS metabolism (visit 1 to visit ~~97~~ inclusive)...”

29. On page 60, Overview, 2nd sentence should be: “Subjects entered a 4-week run-in and then stratified according to their Visit 3 baseline FEV1 (greater than **65%** or less than **and equal** to 65%)...”
30. On page 79, Inclusion Criteria, first bullet should be: “Subjects were to be on a dose of ICS equivalent to FP ~~200~~ **500**-1000 mcg/day...”
31. On page 85, 3rd paragraph, 1st sentence should be: “Trial HZA116863 also provided an opportunity to evaluate the benefit of the higher dose (FF/**VI** 200/25) over the lower dose (FF/**VI** 100/25).”
32. On page 89, Table 12 Demographics and Baseline Characteristics: HZA106827
 - a. ICS/LABA for Placebo (2nd column) should be: 84 (~~42~~**1**)
 - b. ICS/LABA or FF (3rd column) should be: 83 (~~41~~**0**)
 - c. **Baseline Screening** Lung Function (Mean)
33. On page 90, Table 13 Demographics and Baseline Characteristics: HZA116863
 - d. **Baseline Screening** Lung Function (Mean)
 - e. Mid-dose **ICAS** alone
34. On page 90, Table 14 Demographics and Baseline Characteristics: HZA106829
 - f. header for 4th column should be FF/**VI** 200/25
 - g. ≥5 to <10 years for FF 200 (2nd column) should be: 49 (~~250~~)
 - h. **Baseline Screening** Lung Function (Mean)
35. On page 91, Table 14 Demographics and Baseline Characteristics: HZA106829, on ICS+LABA for FF 200 should be: 150 (~~787~~)
36. On page 91, Table 15 Demographic and Baseline Characteristics: HZA106837
 - i. On any asthma medication should be: “FF 100 ~~188~~ (~~19~~) **1010 (100)**, FF/VI 100/25 ~~157~~ (~~16~~) **1009 (100)**, Total ~~345~~ (~~17~~) **2019 (100)**”
 - j. **Baseline Screening** Lung Function (Mean)
37. On page 92, Table 16 Demographic and Baseline Characteristics: HZA11390**91**
 - k. Race, ~~Amer. Indian or Alaska~~ **Native Hawaiian or other Pacific Islander**
 - l. **Baseline Screening** Lung Function (Mean)
38. On page 93, Table 17 Patient Disposition: HZA106827, Exacerbation is a sub-reason for withdrawal of Lack of Efficacy and should be footnoted as such.
39. On page 94, Table 19 Patient Disposition: HZA106829, Exacerbation is a sub-reason for withdrawal of Lack of Efficacy and should be footnoted as such.
40. On page 94, Table 20 Patient Disposition: HZA106837
 - m. Exacerbation is a sub-reason for withdrawal of Lack of Efficacy and should be footnoted as such.
 - n. Exacerbation FF 100 ~~3~~ (~~1~~) **16 (2)**, FF/VI 100/25 ~~2~~ (~~1~~) **11 (1)**, Total ~~5~~ (~~1~~) **27 (1)**

41. On page 95, Table 21
 - o. Patient Disposition: HZA1139091
 - p. Exacerbation is a sub-reason for withdrawal of Lack of Efficacy and should be footnoted as such.
42. On page 98, Table 24 Co-Primary Endpoints: Trial HZA106829 (ITT population), Difference vs. FP500 BID for Weighted Mean (0-24h) FEV₁ (mL) for FF 200 (5th column) should be 70
43. On page 103, Table 29 Trial HZA113091: Weighted Mean Serial FEV₁, footnote should be: FP=fluticasone propionate, SAL=salmeterol
44. On page 105, Section 6.1.5.2 Trial HZA116863, first sentence should be: “The change from baseline in trough FEV₁ was an important secondary endpoint in trial HZA113091 HZA116863.”
45. On page 105, 2nd paragraph, 3rd sentence should be: “...the change from baseline in trough FEV₁ for FF/VI 200/25 vs. FF/VI 100/25...”
46. On page 107, Table 33 Trial HZA113091: Trough FEV₁, footnote should be: FP=fluticasone propionate, SAL=salmeterol
47. On pages 108 and 109, Table 34 Secondary Endpoints, for trial HZA116863 throughout table should be “difference vs. FF/VI 100/25”
48. On page 110, Section 6.1.6, 1st paragraph, 1st sentence should be: “The Agency conducted subgroup analyses for weighted mean serial FEV₁ and trough FEV₁ for trials HZA106827, HZA116863, HZA1062829, and HZA1134091.”
49. On page 112, Figure 9 Subgroup Analysis of Trial HZA116863 for Weighted Mean FEV₁; Estimated Difference of FF/VI ~~200~~100/25 vs. FF ~~200~~100 with 95% CI
50. On page 112, Figure 10 Subgroup Analysis of Trial HZA116863 for Trough FEV₁; Estimated Difference of FF/VI ~~200~~100/25 vs. FF ~~200~~100 with 95% CI
51. On page 116, Section 6.1.6.1.1, 1st paragraph, 1st sentence should be: “...in studies HZA106827, HZA116863, and HZA1068289...”
52. On page 118, Section 6.1.6.1.2, 1st paragraph, 1st sentence should be: “...in studies HZA106827, HZA116863, and HZA1068289...”
53. On page 124, Section 6.1.6.1.3, 1st paragraph, 1st sentence should be: “...for the subgroup of patients in Trial HZA113091...”
54. On page 126, Table 44 Rate of Asthma Exacerbation: Trial HZA106837, FF/VI 100/25 vs. FF 100 p-value for ITT Population (3rd column) should be: 0.014

55. On page 130, 1st paragraph, 3rd sentence should be: "...HZA106837, HZA106839, and HZA106851 (see Table ~~33~~ **46**)
56. On page 130, 1st paragraph, 5th sentence should be: "...as listed in Table 5 and shown ~~below~~ in Table ~~33~~ **46**..."
57. On page 132, 2nd paragraph, sentence should be: "...in the large, long-term exacerbation study, HZA106837, for up to 76 weeks (see Figure 7 **20**)."
58. On page 134, Table 50 Number of Subjects Exposed in Trials Including an FF/VI Treatment Group
- Total for FP 500 mcg BID should be ~~254~~ **449**
 - HZA106829 FP 500 BID should be **195**
59. On page 134, 2nd paragraph, 1st sentence should be: "A total of ~~2,396~~ **9** subjects were exposed to FF/**VI** 100/25 mcg, and 956 subjects in FF/**VI** 200/25 mcg."
60. Page 134, 2nd paragraph, 2nd sentence should be: "A total of ~~204~~ **1371** subjects were exposed to FF/**VI** 100/25 for ~~at least~~ **over** six months, and ~~399~~ 283 subjects to FF/VI 200/25 for ~~at least~~ **over** six months."
61. Page 134, 2nd paragraph, 3rd sentence should be: "A total of at least ~~204~~ **645** subjects were exposed to FF/VI 100/25 for **over** one year, and a total of ~~202~~ **100** subjects were exposed to FF/VI 200/25 for **over** one year."
62. On page 134, 3rd paragraph, 2nd sentence should be: "The mean exposure for FF/**VI** 100/25 was 237 days and for FF/VI 200/25 was 146.3."
63. On page 135, Table 51 Extent of Exposure to FF/VI 100/25 and FF/VI 200/25, columns 2 and 3 of header should be FF/**VI** 100/25 and FF/**VI** 200/25, respectively.
64. On page 136, 1st paragraph, 2nd sentence should be: "...compared with the other age groups (9% adults, 7% elderly) and the overall population (10%) (See Table ~~37~~ **52**)."
65. On page 138, Section 7.2.1, 1st paragraph, 2nd sentence should be: "Other testing, depending on the study, included ~~serum IgE~~, pharmacogenetics..." Note, serum IgE analyses were not performed in any study.
66. On page 139, Section 7.3, 1st sentence should be: "For review of major safety results, this review will focus on the studies as outlined above in Table ~~35~~ **50**..."
67. On page 139, Section 7.3.2 Nonfatal Serious Adverse Events, 3rd sentence should be: "Individual SAEs occurred in <3 patients across these trials, **with the exception of asthma and pneumonia in Trial HZA106837.**"

68. On page 140, Trial HZA106829, 1st sentence should be: "...a higher number of SAEs occurred in the FF/VI 200/25 group than the FF 200 or FP 500 groups..."
69. On page 141, Trial HZA106837, 1st paragraph, 1st sentence should be: "A total of ~~70~~ **86** non-fatal SAEs were reported in 68 subjects during the treatment period (~~29~~ **38** SAEs [3%] in 28 subjects in the FF 100 group and ~~41~~ **48** SAEs [4%] in 40 subjects in the FF/VI 100/25 group)."
70. On page 141, Trial HZA106837, 1st paragraph, 2nd sentence should be: "~~Nine (9)~~ **Twelve (12) non-fatal** SAEs were reported for eight (8) subjects during the post-treatment period (~~5~~ **4** SAEs [$<1\%$] in 4 subjects in the FF 100 group and ~~4~~ **8** SAEs [$<1\%$] in 4 subjects in the FF/VI 100/25 group)."
71. On page 141, Trial HZA106837, 2nd paragraph, 1st sentence should be: "Of the ~~70~~ **86** non-fatal SAEs reported..."
72. On page 141, Trial HZA106837, 3rd paragraph, 1st sentence should be: "~~Seven~~ **Eight** subjects had SAEs that resolved with sequelae: ~~2~~ **3** subjects in the FF 100 group...and 5 subjects in the FF/VI 100/25 group (Subject ~~285~~ **343**..."
73. On page 141, Trial HZA106837, 3rd paragraph, 3rd sentence should be: "Of the ~~9~~ **12** non-fatal SAEs reported during the post-treatment period..."
74. On page 144, Trial HZA116863, 1st sentence should be: "The incidence of events leading to withdrawal ranged from ~~0~~ $<1\%$ **1%**"
75. On page 145, Trial HZA106837, 3rd sentence should be: "...1) FF 100 – asthma (n=3), pneumonia (n=2), oral candidiasis (n=~~3~~ **1**); 2) FF/VI 100/25 – asthma (n=2), muscle spasms (n=~~3~~ **2**), **dysphonia (n=2)**."
76. On page 145, Table 59 Trial HZA106827: Adverse Events of Special Interest
- Oral candidiasis for FF/VI 100/25 (4th column) ~~1~~(<1) **4 (2)**
 - **Oropharyngeal candidiasis: Placebo 0, FF 100 2 (<1), FF/VI 100/25 1 (<1)**
77. On page 146, Trial HZA116863, 3rd sentence should be: "The most common adverse event of special interest was oropharyngeal pain; ~~more subjects in the high dose group experienced this AESI.~~" Note, details deleted because the incidence of oropharyngeal pain was the same in both FF/VI groups.
78. On page 146, Table 60 Trial HZA116863: Adverse Events of Special Interest
- Oral candidiasis for FF/VI 100/25 (3rd column) ~~0~~ **2 (<1)**
 - Oral candidiasis for FF/VI 200/25 (4th column) ~~1~~(<1) **4 (1)**
 - **Hypertension for FF 100 (2nd column) 2 (<1), FF/VI 100/25 (3rd column) 2 (<1), FF/VI 200/25 (4th column) 0**
 - **Pneumonia for FF 100 (2nd column) 2 (<1), FF/VI 100/25 (3rd column) 1 (<1), FF/VI 200/25 (4th column) 0**

79. On page 146, Trial HZA106829 states that the sponsor did not specifically examine adverse events of special interest. This statement is incorrect and the details of these are presented in the CSR.
80. On page 146, Trial HZA106837, 2nd sentence should be: “The only AEs of special interest that occurred in $\geq 1\%$ of subjects in either treatment group were oropharyngeal pain (5% of subjects in the FF 100 group and 4% of subjects in the FF/VI 100/25 group), dysphonia (2% of subjects in the FF 100 and FF/VI 100/25 groups), bronchitis (7% of subjects in the FF 100 group and 6% of subjects in the FF/VI 100/25 group) ~~and~~ hypertension (2% of subjects in the FF 100 and FF/VI 100/25 groups) **and blood pressure increased (1% of subjects in FF 100 and <1% of subjects in FF/VI 100/25).**”
81. On page 147, Table 61 Trial HZA106837: Adverse Events of Special Interest, Source should be CSR HZA1068237 Table 7.12, p. 572
82. On Page 150, Section 7.4.5, the meta-analysis results presented in the last 3 sentences of the first paragraph for the COPD population –Results for the asthma population are presented in the GSK Advisory Committee Briefing Document, Section 13.3.3 and are excerpted here:
- Based on the models, an FF AUC₍₀₋₂₄₎ of 1000 pg.h/mL would be required to reduce 24-hour serum cortisol or 24-hour urinary cortisol excretion by 20% and 17%, respectively; the proposed doses of FF (100 and 200 mcg) in BREO ELLIPTA achieve model predicted systemic exposure of FF AUC₍₀₋₂₄₎ of 244.25 and 495.33 pg.h/mL, respectively in subjects with asthma.\
83. On page 151, Trial HZA116863, 3rd sentence should be: “The pregnancy in the FF/VI 200/25 group let to fetal loss...”
84. On page 153, Table 67 Patient Disposition: HZA106839
- Lack of Efficacy for FF/VI 200/25 (3rd column) 4 (~~2~~)
 - Exacerbation is a sub-reason for withdrawal of Lack of Efficacy and should be footnoted as such.
 - Exacerbation for FF/VI 200/25 (3rd column) ~~0~~ **4 (2)** and for Total (5th column) ~~3~~ (~~1~~) **6 (1)**
85. On page 153, Adverse Events of Special Interest, 3rd sentence should be: “Other AESI that occurred in $\geq 3\%$ of the subjects were lower respiratory tract infections excluding pneumonia (FF/VI 100/25: 3%, FF/VI 200/25: 5%, and FP: ~~3%~~ **5%**)...”
86. Page 153, Common Adverse Events, 2nd sentence should be: “Other AEs occurring in $\geq 3\%$ in either FF/VI group included cough, **dysphonia**, oropharyngeal pain...”

87. On page 179, Table 2 Age Subgroup IRD Results from Trial HZA106837, FF events in 18-65 years the number should read: (~~65~~/826) to be consistent with does the number of FF events in 18-65 years (6/826) in Figure 2 Plot of Subgroup Results in Trial HZA106837 on page 169.