Pulmonary-Allergy Drugs Advisory Committee Meeting Lumacaftor/Ivacaftor Tablets for oral use NDA 206038

FDA Opening Remarks and Regulatory History

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May 12, 2015

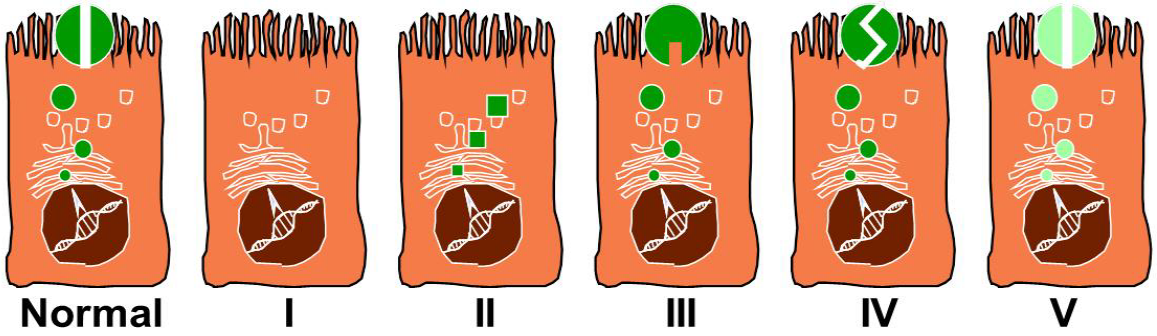
Objective

- Discuss NDA 206038 for lumacaftor/ivacaftor (LUM/IVA) tablets: for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene
- Safety
- Focus on Efficacy
  - LUM/IVA is a combination drug of a new molecular entity (LUM) with an approved product (IVA)
  - Contribution of lumacaftor to the lumacaftor/ivacaftor combination
  - Overall efficacy of the lumacaftor/ivacaftor combination

Cystic Fibrosis

CF is most common genetic disease in US, ~30,000 people

- Caused by defect in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), a chloride conducting ion channel
- Autosomal recessive, need presence of 2 CF-causing mutations
- *F508del* the most common mutation
  - 90% CF patients have on at least one allele
  - 50% CF patients homozygous



Source: adapted from P. Sosnay, 10/21/14 PADAC Presentation

Ivacaftor

Ivacaftor: small molecule ion channel “potentiator”

- Increases chloride transport through the CFTR chloride channel by increasing the “open time”
- Approved:
  - January 2012: CF subpopulation 6 years of age and older with a *G551D* mutation in the *CFTR*
  - February 2014: 8 of 9 subpopulations defined by presence of a “gating” mutation similar to *G551D* in at least one allele
  - December 2014: CF population 6 years of age and older with the *R117H* mutation in the *CFTR*
  - March 2015: CF indication extended down to age of 2 years based on availability of granule formulation, matching PK, and lack of additional safety concerns

Lumacaftor

Lumacaftor: affects CFTR processing and trafficking

- While the exact MOA is not known, lumacaftor may promote more proper folding of the defective F508del CFTR protein thereby allowing it to get to the cell surface
  - In vitro data suggest partial restoration of F508del CFTR channel function (14%)
- Actual F508 CFTR defect (deletion of the amino acid phenylalanine at position 508) is not corrected
- F508del CFTR that reaches epithelial cell membrane has deficient chloride transport

Combination Drug Development

Contribution	*Comparison of interest*		
Benefit from IVA	**Combination Product**: **LUM** + **IVA**	vs	**Single Component**: **LUM**
Benefit from LUM	Combination Product: **LUM** + **IVA**	vs	Single Component: **IVA**

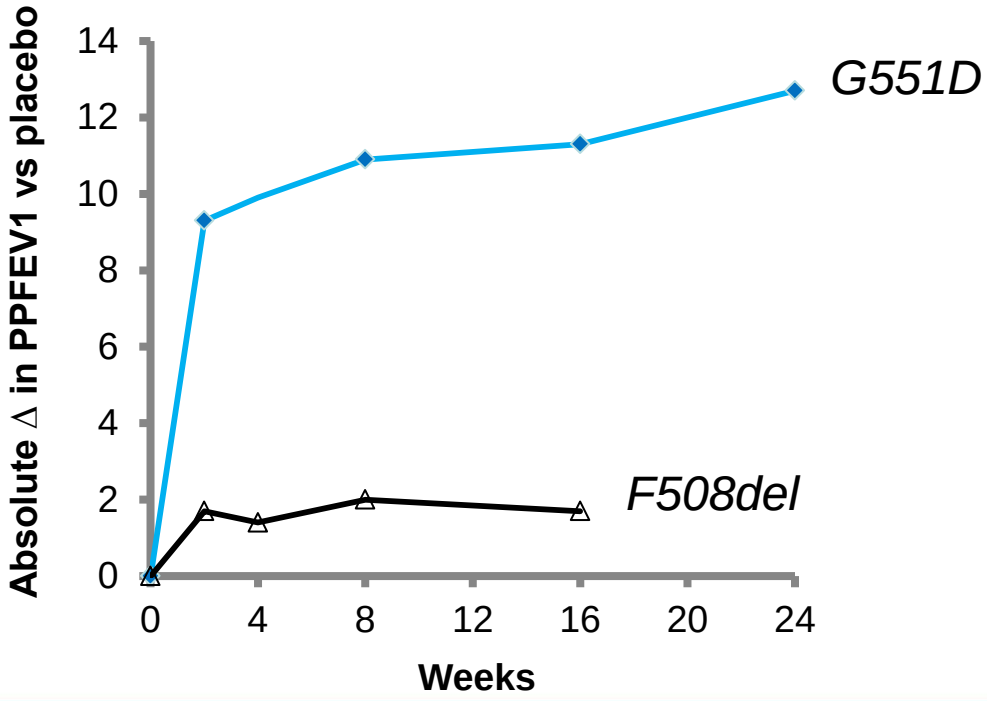
LUM/IVA Drug Development

LUM	IVA
Dose selection, dose frequency, efficacy, safety (*F508del homozygotes*) • Study 809-101 • Study 809-102 R, DB, PC, multi-cohort LUM 200, 400, 600 qd, 400 q12h, Placebo X 28 days Addition of IVA 250 q12h X 28 days	Dose selection, dose frequency, efficacy, safety • Ivacaftor monotherapy program (*G551D*) • Study 770-104 (*F508del homozygotes*) R, DB, PC, PG, Randomized 4:1 IVA 150 q12h, Placebo X 16 weeks ≈140 pts/study, 112 IVA, 28 Placebo

LUM	IVA
Efficacy and safety Studies 809-103 and 809-104 (*F508del homozygotes*) R, DB, PC, PG, Randomized 1:1:1 LUM 600qd/IVA 250 q12h, LUM 400/IVA 250 q12h, Placebo X 24 weeks ≈ 550 pts/study, ≈ 185/group	

Ivacaftor Monotherapy Program

- Ivacaftor dose (150 mg), dosing interval (q12 hours) established
- Range of effect on pulmonary function
  - Effect *G551D* vs *F508del* homozygote populations



Source: 770-104 Clinical Study Report, Table 11-11, Kalydeco PI

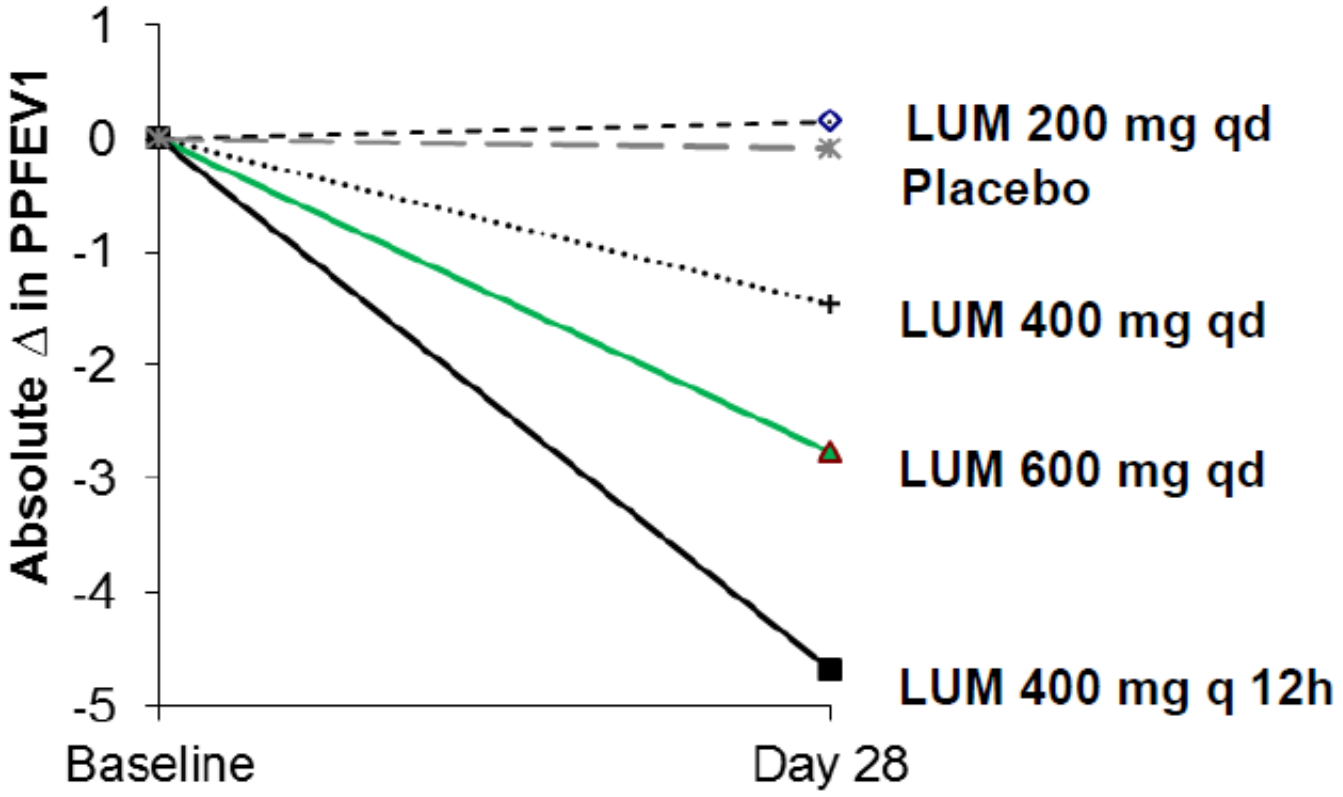
Lumacaftor Monotherapy Program

Study 809-101

- 200 mg dose no effect

Study 809-102

- Dose dependent decrease in FEV1

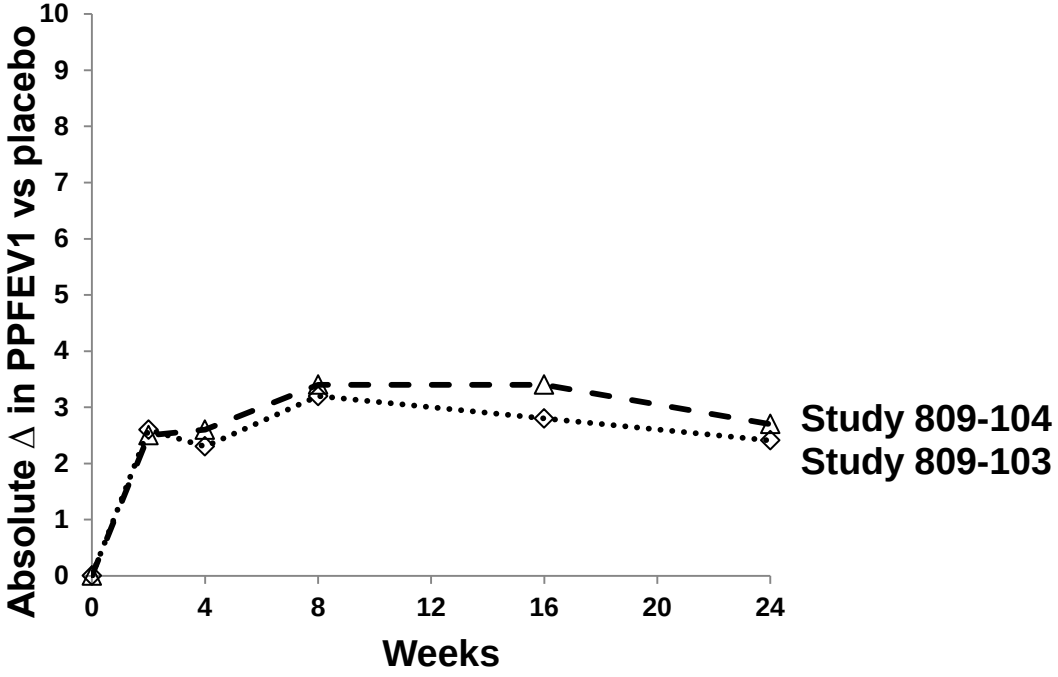


Source: adapted from FDA Briefing Document, Figure 4, p. 50

LUM/IVA Combination Program

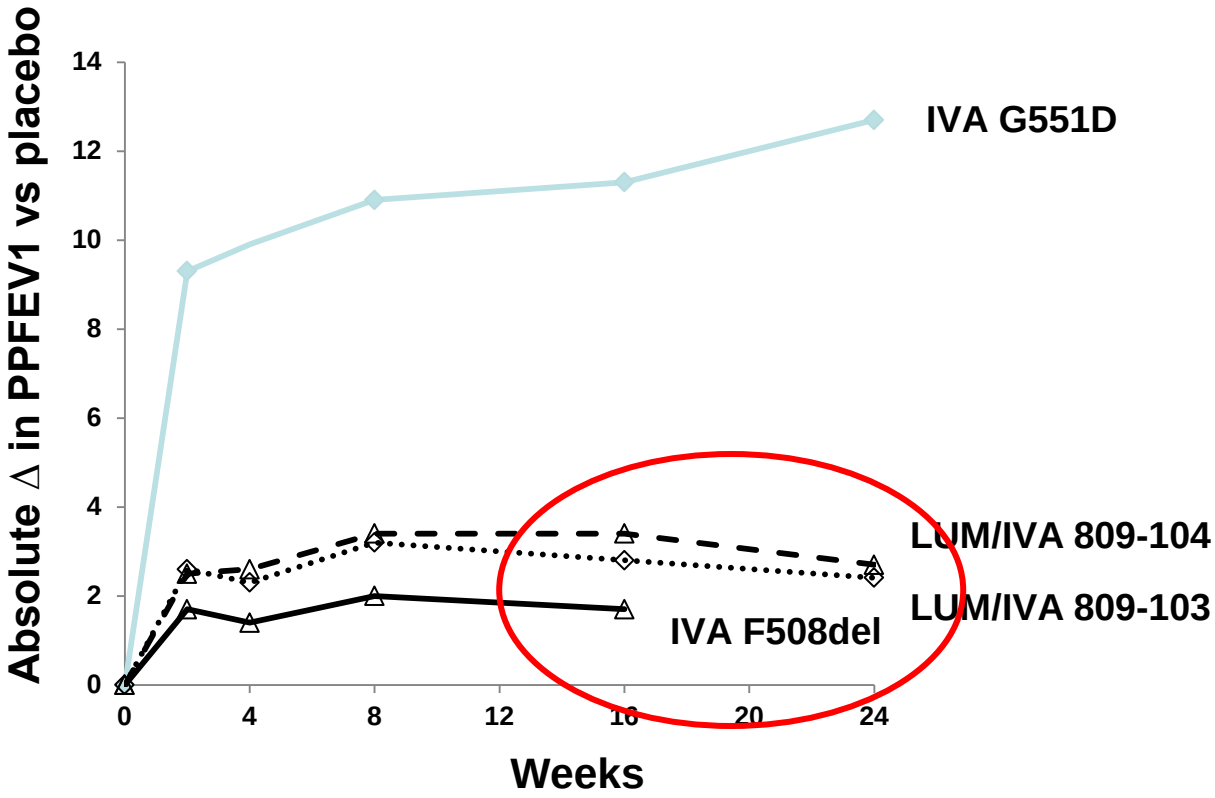
Studies 809-103, 809-104

- Lack of individual components
  - Small but significant increase in FEV1 (primary endpoint)
  - Lack of Cystic Fibrosis Questionnaire-Revised (CFQ-R) resp domain/BMI benefit
  - Nominal decrease in exacerbations



Source: adapted from Figure 6, AC Briefing document p. 71

LUM/IVA Combination and IVA Programs



Source: Figure 6, AC Briefing document p. 71, Study 770-104 Clinical Study Report, Table 11-11, Kalydeco PI

Contribution of Lumacaftor

Lumacaftor monotherapy

- Dose dependent decrease in pulmonary function
  - Safety concern: unacceptable comparator for Phase 3

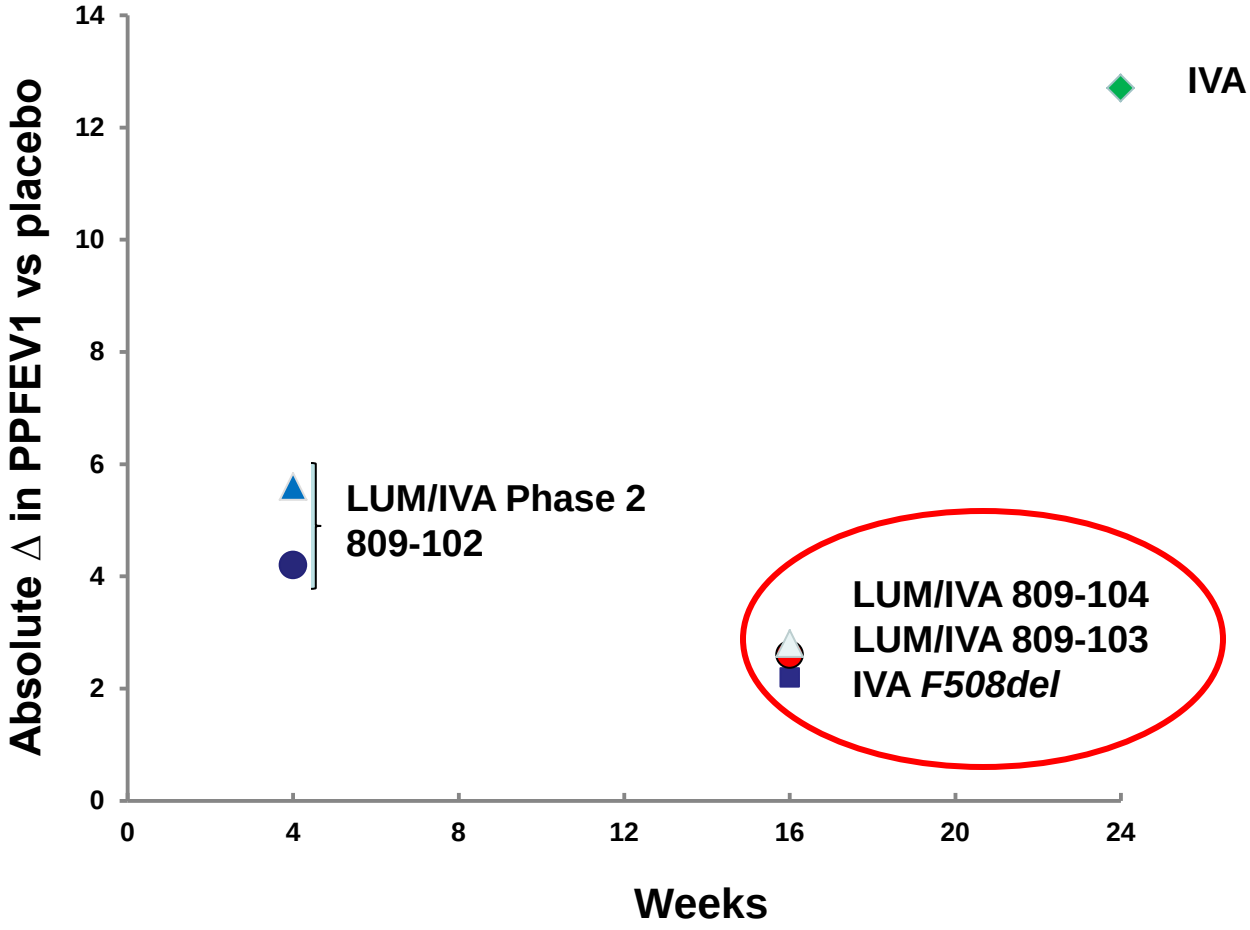
Ivacaftor monotherapy

- Small increase in pulmonary function (not statistically significant)
- "not effective" in context of G551D mutation response
  - But not without clinical activity
- Correct comparator rather than placebo

FDA analyses: LUM/IVA compared to IVA

- Does LUM/IVA impart a clinical benefit over IVA alone
- Study 770-104 (IVA in *F508del* Pts)
  - Historical control

Contribution of Lumacaftor



Exacerbation rate ratio
LUM/IVA: 0.67/0.57
IVA alone: 0.61

Source: FDA briefing document Table 4, pg 49; FDA analysis; Kalydeco PI

Summary of Issues

- Overall efficacy
  - Clinical significance of the LUM/IVA treatment effect
- Contribution of LUM to LUM/IVA combination
  - Clinical benefit over IVA alone?
  - Results of FDA analyses LUM/IVA to IVA alone
    - Small FEV1 effect similar to that for IVA alone (2-3%)
    - Exacerbation rate ratio similar (0.60)
- Benefit-Risk profile

Question 1
(Discussion Question)

Discuss the available efficacy data for LUM 400 mg/IVA 250 mg fixed-dose combination (FDC) administered twice daily in patients with cystic fibrosis (CF) 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Consider the following issues in the discussion: clinical significance of the observed treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.

Question 2
(Discussion Question)

Discuss the available efficacy data for ivacaftor monotherapy 150 mg twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

Question 3
(Voting Question)

Do the available data demonstrate that lumacaftor contributes positively to the clinical efficacy seen for the lumacaftor plus ivacaftor FDC product in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

A. Yes

B. No

C. Cannot determine

Please comment on the rationale for your vote and whether a clinical trial should be conducted to compare the LUM/IVA FDC to ivacaftor alone

Question 4
(Discussion Question)

Discuss the safety data for LUM 400 mg/IVA 250 mg FDC twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Question 5
(Voting Question)

Do the data support the safety of LUM 400 mg/IVA 250 mg FDC administered twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what further data should be obtained to more fully define the safety profile of LUM 400 mg/IVA 250 mg?

Question 6
(Voting Question)

Do the available efficacy and safety data support approval of the LUM 400 mg/IVA 250 mg FDC product administered twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what additional data should be obtained to further define the benefit risk profile of LUM 400 mg/IVA 250 mg twice daily in patients with CF who are homozygous for the F508del mutation in the CFTR gene?

Thank you

Pulmonary-Allergy Drugs Advisory Committee Meeting
Lumacaftor 400mg/Ivacaftor 250mg q12 hours
NDA 206038

Introduction to FDA Efficacy Review

Robert Lim, MD
Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
May 12, 2015

Outline of FDA presentations

- Introduction to FDA Efficacy Review

  Robert Lim, MD

  Clinical Reviewer, DPARP, CDER, FDA

- Review of Efficacy for Phase 3 Trials

  Lan Zeng, MS

  Statistical Reviewer, DB II, OTS, CDER, FDA

- Contribution of Lumacaftor and Review of Sweat Chloride Data

  David Petullo, MS

  Statistical Reviewer, DB II, OTS, CDER, FDA

- Clinical Considerations for Efficacy and Summary of Safety

  Robert Lim, MD

  Clinical Reviewer, DPARP, CDER, FDA

In vitro Support for Development Program

- LUM alone ↑ chloride (Cl^-) transport to 14% of normal[1]
- LUM+IVA ↑ chloride transport to 25% of normal[1]
  - Potentiating Cl^- transport in *F508del* CFTR
- *In vitro* data suggest that LUM and LUM/IVA exposure should result in a beneficial clinical effect
  - LUM and LUM/IVA resulted in decreases in sweat chloride (SwCl-)
- *In vitro* results not consistent with clinical findings

[1]Van Goor et al. PNAS 2011:108 (46): 18843-18848

Development Program

Study	Purpose	N	Treatments
770-104	Safety/Efficacy (IVA monotherapy)	140	IVA 150mg q12 Placebo
809-102	Dose-selection (LUM and LUM/IVA)	312	Various LUM doses followed by the addition of IVA 250mg q12
809-103	Confirmatory Safety/Efficacy (LUM/IVA)	549	LUM 600mg qD/IVA 250mg q12 LUM 400/IVA 250mg q12 Placebo
809-104	Confirmatory Safety/Efficacy (LUM/IVA)	559	LUM 600mg qD/IVA 250mg q12 LUM 400/IVA 250mg q12 Placebo

Development Program

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809-104	Confirmatory Safety/Efficacy (LUM/IVA)	559	LUM 600mg qD/IVA 250mg q12 LUM 400/IVA 250mg q12 Placebo

- Confirmatory studies only included placebo comparator arms
  - With only a placebo comparator, can one conclude that LUM/IVA provides a benefit above IVA monotherapy?

Ivacaftor Component: Study 770-104

- Evaluated IVA 150mg q12 in *F508del* homozygous patients during the *G551D* program
- Primarily meant to augment the IVA safety database
- Result: Small ppFEV1 effect – not statistically significant

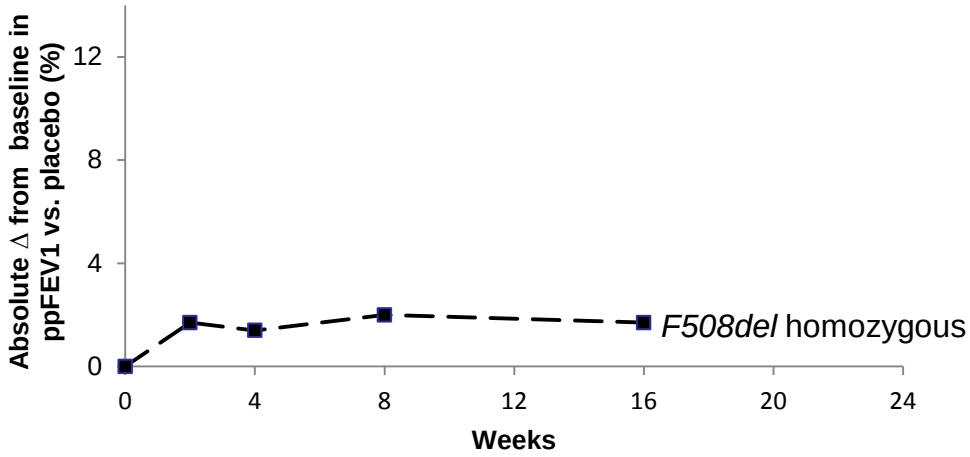

Figure source: 770-104 Clinical Study Report, Table 11-11

Ivacaftor Component: Study 770-104

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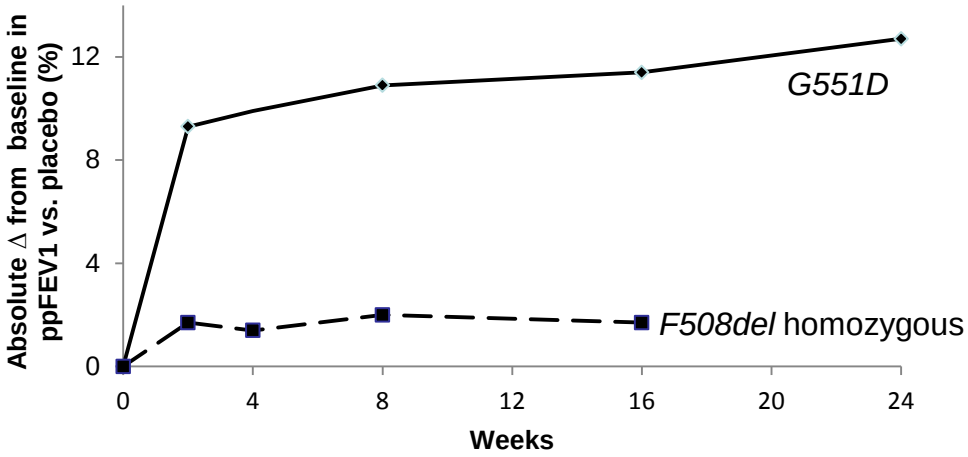

- Similar for other parameters
  - CFQ-R Resp Domain
  - Exacerbation
  - Sweat Chloride

- Interpretation: IVA *not* effective in the *F508del* homozygotes
  - Reflected in the label

Figure source: 770-104 Clinical Study Report, Table 11-11 and ivacaftor label

Lumacaftor Component: Study 809-102

- Multi-cohort study evaluating multiple doses of LUM alone and LUM/IVA

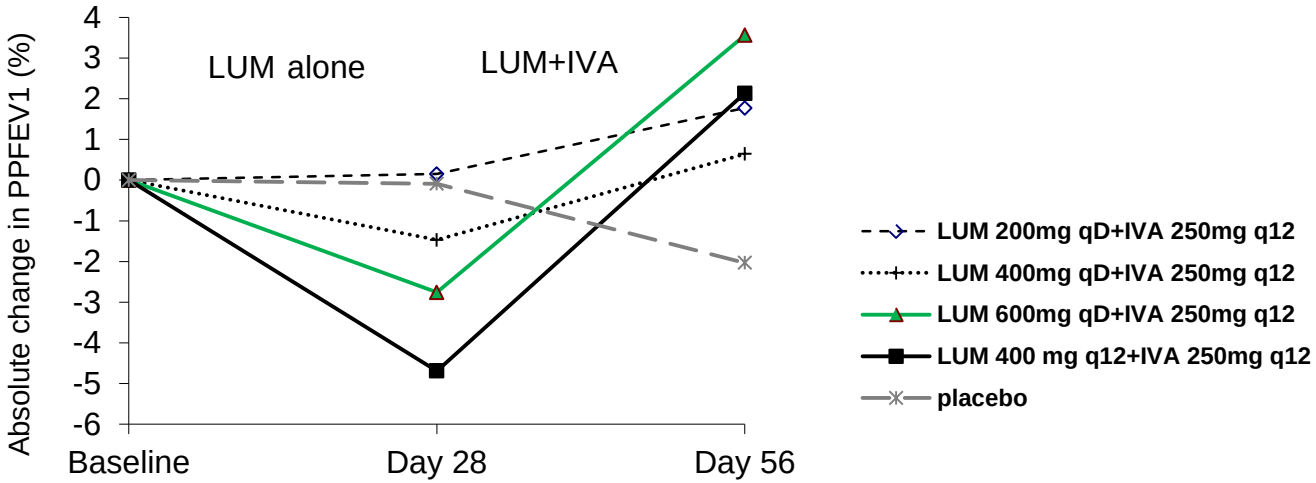

Figure source: FDA Briefing Document, Figure 4, pg50

Lumacaftor Component: Study 809-102

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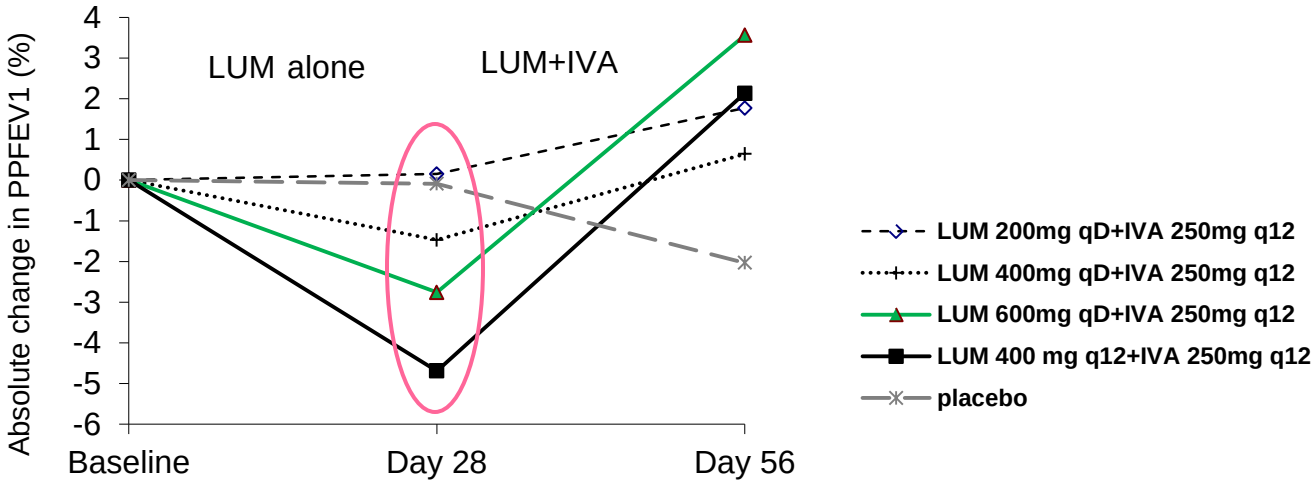
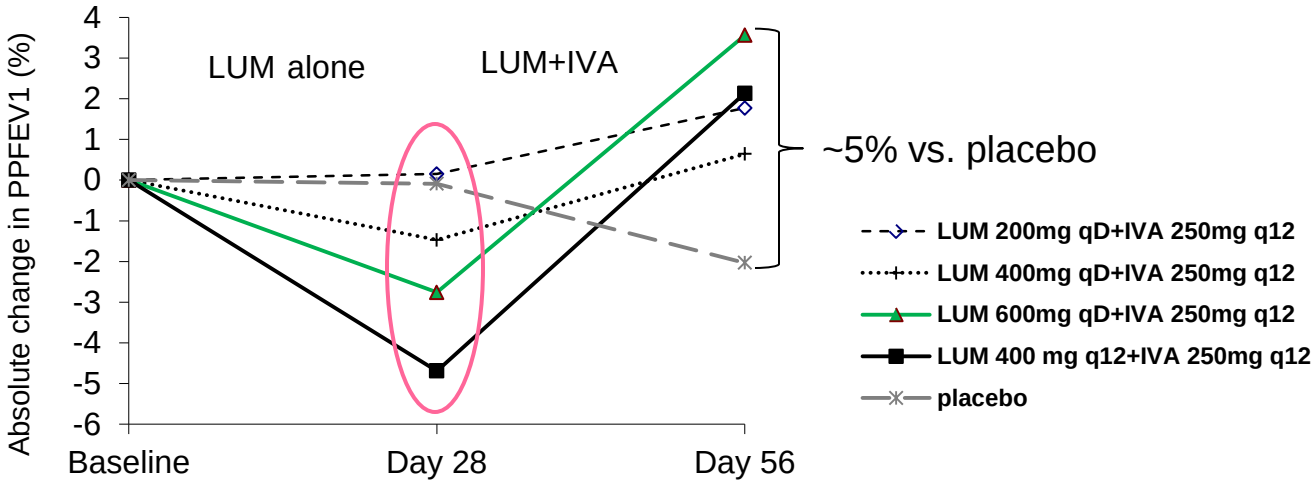


- LUM alone -dose dependent decrease in ppFEV1
- No LUM monotherapy comparator in confirmatory studies

Figure source: FDA Briefing Document, Figure 4, pg50

Lumacaftor Component: Study 809-102

- Multi-cohort study evaluating multiple doses of LUM alone and LUM/IVA



- LUM alone -dose dependent decrease in ppFEV1
- No LUM monotherapy comparator in confirmatory studies
- LUM/IVA – approximately 5%↑ in ppFEV1 vs. placebo

Figure source: FDA Briefing Document, Figure 4, pg50

Choice of Comparators

- Placebo comparator for confirmatory studies
  - Demonstration of superiority to placebo would be sufficient to conclude efficacy
    - IVA monotherapy ineffective in *F508del* homozygous patients
    - LUM monotherapy arm not feasible due to safety
    - LUM/IVA effect expected to be in line with 809-102 (~5%)

Choice of Comparators

- Results from confirmatory studies suggested the need for an IVA comparator
  - LUM/IVA treatment effect smaller than expected
  - Numerically similar to IVA monotherapy
- Direct comparison of LUM/IVA to IVA not available
- FDA conducted additional analysis assessing the contribution of LUM
  - Compared relevant endpoints from IVA study 770-104 with LUM/IVA confirmatory studies

Thank you

Pulmonary-Allergy Drugs Advisory Committee Meeting
Lumacaftor 400mg/Ivacaftor 250mg q12 hours
NDA 206038

Efficacy Evaluation for Phase 3 Trials

Lan Zeng
Statistical Reviewer
Division of Biometrics II
Center for Drug Evaluation and Research
Food and Drug Administration
May 12, 2015

Outline

- Studies 809-103 and 809-104
  - Sample Size
  - Multiplicity
  - Analysis and Results

Sample Size

- Study 809-103: placebo 184; LUM/IVA 183, 182
- Study 809-104: placebo 187; LUM/IVA 185, 187
- Type B meeting: January 8, 2014
  - Studies are powered to detect small differences in FEV1
- preNDA meeting: August 12, 2014
  - Clinical importance of effect size
  - Consider effect of ivacaftor in study 770-104

Primary Endpoint and Analysis

- Primary endpoint
  - Absolute change from baseline in ppFEV1 at Week 24
    - Assessed as average of the treatment effect at Weeks 16 and 24
- Primary analysis: mixed model repeated measures (MMRM)
  - Treatment, visit, treatment-by-visit interaction, sex, baseline age group, and ppFEV1 severity at screening
  - All randomized and treated patients
- Each trial analyzed separately
- Additional analyses
  - Sensitivity: change at Week 24, stratification error
  - Subgroup analysis: age, gender, region, disease severity at baseline

Key Secondary Endpoints

1. Relative change from baseline in ppFEV1 at Week 24
2. Absolute change from baseline in BMI at Week 24
3. Absolute change from baseline in CFQ-R respiratory domain at Week 24
4. ≥ 5% increase in relative change from baseline in ppFEV1 at Week 24
5. Number of pulmonary exacerbations through Week 24

Multiplicity

- Two doses of LUM/IVA
  - Bonferroni correction, $\alpha=0.025$
- Pre-specified hierarchical testing for key secondary endpoints:
  1. Relative change in ppFEV1
  2. Change in BMI
  3. Change in CFQ-R
  4. Responders with ≥ 5% increase in ppFEV1
  5. Pulmonary exacerbations
- If primary endpoint was significant within dose, each secondary endpoint tested in the above order at $\alpha=0.025$
- If a test failed, all subsequent tests considered not statistically significant

Pooled Analysis

- Pooling only pre-specified for exacerbations
  - Statistical Analysis Plan

    "*The primary analysis for number of pulmonary exacerbations through Week 24 will be based on the pooled data of the two pivotal studies VX12-809-103 and VX12-809-104*."

- Applicant presents pooled results for primary and key secondary endpoints
  - Does not fit into the pre-specified hierarchical testing scheme
  - Post hoc analyses

Primary Analysis – Absolute Change in ppFEV1

	Study 809-103			Study 809-104		
	Placebo	LUM/IVA 600/250	LUM//IVA 400/250	Placebo	LUM/IVA 600/250	LUM/IVA 400/250
Baseline, Mean	60.5	61.2	60.5	60.4	60.5	60.6
Δ from baseline*, mean (SE)	-0.4 (0.5)	3.6 (0.5)	2.2 (0.5)	-0.2 (0.5)	2.5 (0.5)	2.9 (0.5)
Diff. vs placebo, mean	-	4.0	2.6	-	2.6	3.0
95% CI	-	(2.6, 5.4)	(1.2, 4.0)	-	(1.2, 4.1)	(1.6, 4.4)

Source: FDA reviewer

- Additional analyses consistent with primary

Key Secondary Analysis

Endpoint	statistic	Study 809-103		Study 809-104	
		LUM/IVA 600/250	LUM/IVA 400/250	LUM/IVA 600/250	LUM/IVA 400/250
Relative Δ in ppFEV1	Diff from Placebo	6.7	4.3	4.4	5.3
	95% CI	(4.3, 9.2)	(1.9, 6.8)	(1.9, 7.0)	(2.7, 7.8)
Absolute Δ in BMI	Diff from Placebo	0.2	0.1	0.4	0.4
	95% CI	(-0.0, 0.4)	(-0.1, 0.3)	(0.2, 0.6)	(0.2, 0.5)
Absolute Δ in CFQ-R	Diff from Placebo	3.9	1.5	2.2	2.9
	95% CI	(0.7, 7.1)	(-1.7, 4.7)	(-0.9, 5.3)	(-0.3, 6.0)
≥5% increase in ppFEV1	Odds ratio	2.9	2.1	3.0	2.4
	95% CI	(1.9, 4.6)	(1.3, 3.3)	(1.9, 4.6)	(1.5, 3.7)
Exacerbations	Rate ratio	0.7	0.7	0.7	0.6
	95% CI	(0.5, 1.0)	(0.5, 0.9)	(0.5, 0.9)	(0.4, 0.8)

Source: FDA reviewer

Summary of Efficacy in Phase 3 Trials

- LUM/IVA versus placebo
  - Primary endpoint (absolute change in ppFEV1)
    - » superiority demonstrated, mean difference**:** 2.6% to 3.0%
  - Key secondary endpoints

    1. Relative change in ppFEV1: significant results
    2. BMI: significant result in study 809-104 only
    3. CFQ-R : not statistically significant
    4. Response rate: failed due to sequential testing strategy
    5. Exacerbations: failed due to sequential testing strategy

- Both studies powered to detect small differences in FEV1

- Clinical relevance of the 2.6-3.0% improvement

Pulmonary-Allergy Drugs Advisory Committee Meeting Lumacaftor 400mg/Ivacaftor 250mg q12 hours

NDA 206038

Contribution of Lumacaftor and Review on Sweat Chloride Data

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Statistics Team Leader
Division of Biometrics II
Center for Drug Evaluation and Research
Food and Drug Administration
May 12, 2015

Outline

- Contribution of individual drug components
- FDA analysis
  - Superiority of LUM/IVA versus ivacaftor
  - ppFEV1 and pulmonary exacerbations
- Effect of LUM/IVA on sweat chloride (SwCl)

Lumacaftor

- Lumacaftor demonstrated a dose-dependent decrease in lung function
- Not to be developed as monotherapy
- Type B meeting February 12 , 2013
  - Inclusion of lumacaftor arm in confirmatory studies not required

Ivacaftor

- Efficacy of ivacaftor not established in study 770-104
  - Effect on ppFEV1 at Week 16 was 2.5% (95% CI: -1.1, 5.9)
- Based on effected noted for *G551D* mutation, 10.6%, this effect was deemed not clinically meaningful
- End-of-Phase 2 meeting November 2, 2012
  - Early indication that efficacy of LUM/IVA > ivacaftor
  - Inclusion of ivacaftor arm in confirmatory studies not required

LUM/IVA Combination

- Effect of LUM/IVA in studies 809-103 and 809-104 was not greater ivacaftor

- Lack of evidence that the efficacy of LUM/IVA is more than ivacaftor alone

Non-inferiority argument

- Placebo was shown to be *similar* to ivacaftor
- LUM/IVA was superior to placebo
- LUM/IVA is *better* than ivacaftor
- However, the absence of a statistically significant difference between ivacaftor and placebo does not establish lack of an effect

FDA Analysis: LUM/IVA vs Ivacaftor

- Synthesis method
  - Test for superiority
  - Constancy assumption
- Combine variance across studies
  - Compute 95% confidence interval for the difference
- Considers LUM/IVA superior to placebo not that placebo is similar to ivacaftor

Ivacaftor: Study 770-104

- Reviewed under NDA 203188
  - Homozygous for *F508del* mutation
    - *28 placebo, 112 ivacaftor*
  - Placebo or ivacaftor 150 mg every 12 hours for 16 weeks
  - Inclusion criteria: baseline ppFEV1 > 40%
  - Use of hypertonic saline not allowed
- Results
  - Insufficient evidence to establish that ivacaftor was any different than placebo

Δ ppFEV1 (at 16 weeks):	2.5(-0.8, 5.9)
exacerbations (rate ratio):	0.61 (0.29, 1.26)

LUM/IVA - Studies 809-103 and 809-104

- Placebo or LUM 400mg/IVA 250mg every 12 hours
- 24 weeks of double-blind randomized treatment
- Inclusion criteria: baseline ppFEV1 between 40 and 90%
- Use of hypertonic saline
- Results

Δ ppFEV1 (at 24 weeks)	809-103: 2.6% (1.2, 4.0)
	809-104: 3.0% (1.6, 4.4)
exacerbations (rate ratio)	809-103: 0.7 (0.5, 0.9)
	809-104: 0.6 (0.4, 0.8)

Differences in Study Design

- 16 weeks versus 24 weeks
  - "at" rather than "through"
- Inclusion criteria – baseline FEV1
  - Baseline lung function > 90%
- Other aspects considered
  - Derivation of ppFEV1
  - Use of hypertonic saline

Percent Predicted FEV1

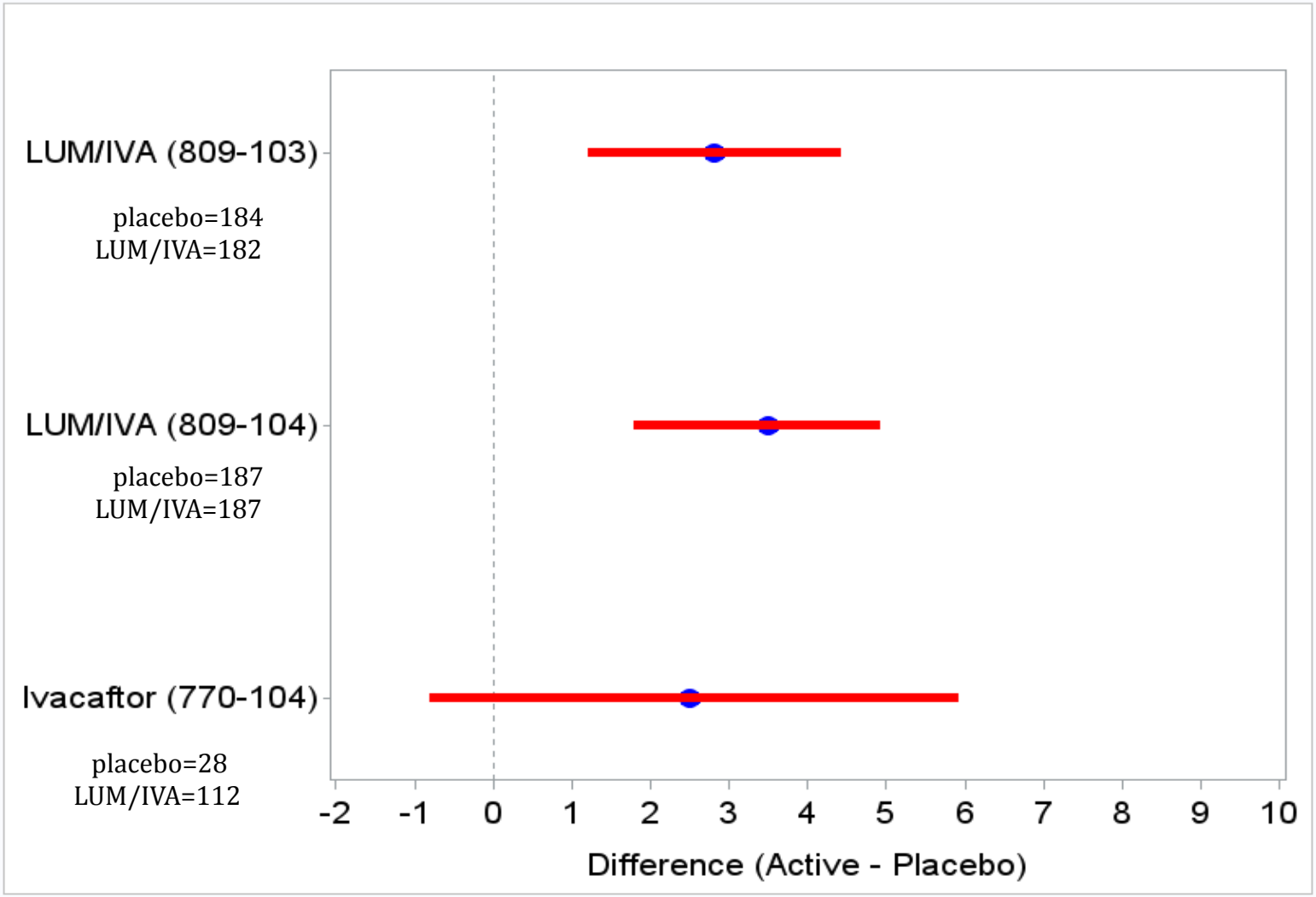
- Change at Week 16 rather than through 16 weeks
- Analysis of Covariance (ANCOVA) with baseline lung function
- Baseline lung function
  - All subjects – ITT
  - Exclude subjects > 90% at baseline

Change from Baseline at Week 16

Study	ppFEV$_1$, LSMEAN (SE)			
	endpoint	placebo	Ivacaftor	LUM/IVA
770-104	baseline	73.2 (4.5)	76.9 (2.2)	-
	Δ Week 16	-0.3 (1.5)	2.2 (0.8)	-
809-103	baseline	60.3 (1.0)	-	60.5 (1.1)
	Δ Week 16	-0.2 (0.6)	-	2.6 (1.0)
809-104	baseline	60.2 (1.0)	-	60.3 (1.0)
	Δ Week 16	-0.7 (0.6)	-	2.8 (0.6)

Source: FDA Reviewer

Percent Predicted FEV1



Source: FDA Reviewer

Test for Superiority - ppFEV1

Baseline $ppFEV_1$	Diff in $ppFEV_1$ Combo-Mono (synthesized)	95% CI	SE
40-90%	0.6	(-3.3, 4.5)	2.0
≥40%	0.7	(-2.8, 4.1)	1.8

Source: FDA Reviewer

Pulmonary Exacerbations

Defined as new, or changed, antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs or symptoms:

- change in sputum
- new or increased hemoptysis
- increased cough
- increased dyspnea
- malaise, fatigue, or lethargy
- temperature above 38°C (equivalent to approximately 100.4°F)
- anorexia or weight loss
- sinus pain or tenderness
- change in sinus discharge
- change in physical examination of the chest
- decrease in pulmonary function by 10%
- radiographic changes indicative of pulmonary infection

Exacerbations

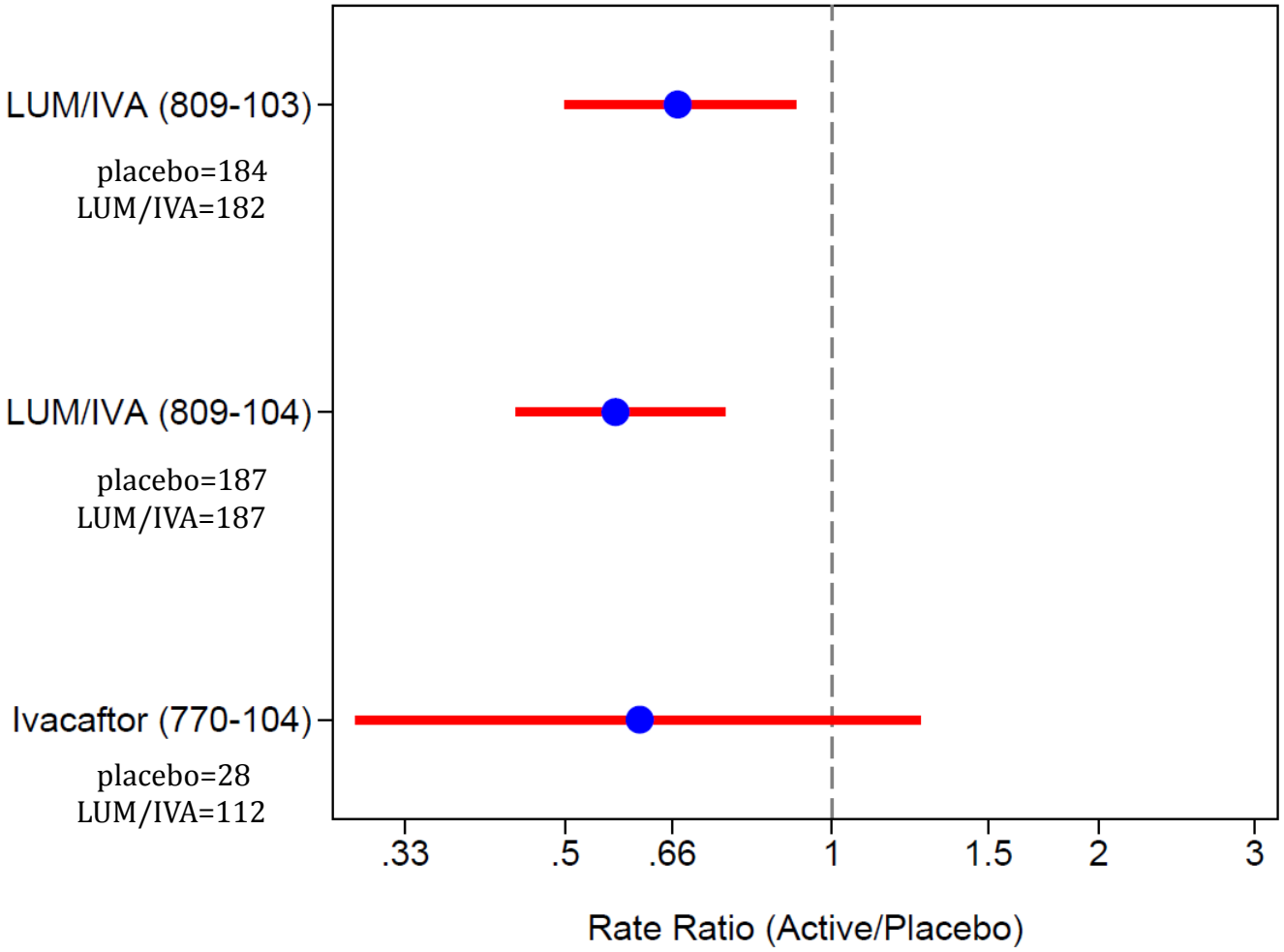
- Definition consistent across studies
- Reported as rate ratio
  - Rate defined as number of events / days on study
- Baseline lung function
  - All patients (ITT)
  - Exclude patients > 90% at baseline

Exacerbation Rate Ratio (active/placebo)

Study	Rate Ratio	95% CI	SE
Ivacaftor (770-104)	0.61	(0.29, 1.26)	0.37
LUM/IVA (809-103)	0.67	(0.50, 0.91)	0.15
LUM/IVA (809-104)	0.57	(0.44, 0.76)	0.14

Source: FDA Reviewer

Exacerbations



Source: FDA Reviewer

Test for Superiority: Exacerbations

Baseline ppFEV$_1$	Rate Ratio Combo/Mono (synthesized)	95% CI	SE
40-90%	1.11	(0.46, 2.62)	0.44
≥40%	1.02	(0.48, 2.18)	0.39

Source: FDA Reviewer

Summary – LUM/IVA versus Ivacaftor

- Lack of substantial evidence that LUM/IVA is any better than ivacaftor with respect to ppFEV1 and pulmonary exacerbations

- Results from study 770-104 did not establish that ivacaftor was ineffective, rather there was not enough evidence to conclude that it was effective

Effect of LUM/IVA on Sweat Chloride

- Study 809-102 – dose selection
  - Randomized, double-blind, placebo-controlled
- Conducted in 4 different cohorts
  - Cohort 1: 60 homozygous subjects for 37 days
  - Cohort 2: 109 subjects (82 homozygous) for 8 weeks
  - Cohort 3: 13 subjects homozygous for 8 weeks
  - Cohort 4: 125 subjects heterozygous for 8 weeks
- Focus on homozygous subjects from cohorts 2 and 3

Study Design

- Lumacaftor administered for 28 days
- LUM/IVA administered for an additional 28 days
- Sweat Chloride measured at baseline and on days 28 and 56
  - On days 28 and 56 measured at dosing and 4 hours post-dose
- Δ SwCl at Week 8
  - Change from Day 0
  - At dosing and 4 hours post-dosing
- ANCOVA model with treatment and baseline measurement

Difference from Placebo: Δ in SwCl (mmol/L)

measured	Day	LUM/IVA (mg)[c] , LSMEAN[d] [95% CI]			
		200[a]/250[b]	400[a]/250[b]	600[a]/250[b]	400[b]/250[b]
at dosing	28	-5.5	-8.8	-6.7	-8.9
	56	-4.7	-9.5	-9.2	-10.7
4-hours post-dose	28	-7.0	-6.3	-12.1	-4.2
	56	-3.5	-9.5	-9.6	-5.0

a: once daily dosing, b: twice daily dosing, c: during weeks 1-4, subjects received lumacaftor, in weeks 5-8, subjects received lumacaftor/ivacaftor, d: ANCOVA with treatment and baseline lung function

Source: FDA Reviewer

Summary - Sweat Chloride

- Small numerical decreases ~ 10 mmol/L
  - Variability depending on when measured
- Much smaller than effect observed with *G551D* and *R117H* mutations ~ 50 and 24 mmol/L, respectively

Pulmonary-Allergy Drugs Advisory Committee Meeting
Lumacaftor 400mg/Ivacaftor 250mg q12 hours
NDA 206038

Clinical Considerations for Efficacy and Summary of Safety

Robert Lim, MD
Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
May 12, 2015

Outline of FDA presentations

- Introduction to FDA Efficacy Review

  Robert Lim, MD

  Clinical Reviewer, DPARP, CDER, FDA

- Review of Efficacy for Phase 3 Trials

  Lan Zeng, MS

  Statistical Reviewer, DB II, OTS, CDER, FDA

- Contribution of Lumacaftor and Review of Sweat Chloride Data

  David Petullo, MS

  Statistical Reviewer, DB II, OTS, CDER, FDA

- Clinical Considerations for Efficacy and Summary of Safety

  Robert Lim, MD

  Clinical Reviewer, DPARP, CDER, FDA

Clinical Considerations for Efficacy and Summary of Safety

- Efficacy Summary
  - Studies 809-103 and 809-104
  - Benefit of LUM/IVA versus IVA monotherapy
  - Sweat Chloride
- Safety Review
  - All adverse events
  - Adverse events of interest

Efficacy – Studies 809-103 and 809-104

	Δ from baseline LUM/IVA 400/250mg q12 v. placebo at week 24 (95% CI)					
1º and Key 2º Endpoints	ppFEV1 (%)	Relative ppFEV1	BMI (kg/m^2)	CFQ-RRD (score)	Responder[b] (odds ratio)	Exacerbation (rate ratio)
Study 809-103	2.6% (1.2, 4.0)[a]	4.3 (1.9, 6.8)	0.1 (-0.1, 0.2)	1.5 (-1.7, 4.7)	2.1 (1.3, 3.3)[c]	0.66 (0.5, 1.0)[c]
Study 809-104	3.0% (1.6, 4.4)[a]	4.4 (1.9, 7.0)	0.4 (0.2, 0.5)	2.9 (-0.3, 6.0)	2.4 (1.5, 3.7)[c]	0.57 (0.4, 0.8)[c]

[a]assessed as the averaged of the treatment effects at week 16 and 14
[b]Responder defined as relative change in ppFEV1≥5% averaged at week 16 and 24
[c]not statistically significant due to earlier failure in the analysis hierarchy
Source: Summary of Clinical Efficacy, Table 16, p62-63

Efficacy – Studies 809-103 and 809-104

	Δ from baseline LUM/IVA 400/250mg q12 v. placebo at week 24 (95% CI)					
1º and Key 2º Endpoints	ppFEV1 (%)	Relative ppFEV1	BMI (kg/m^2)	CFQ-RRD (score)	Responder[b] (odds ratio)	Exacerbation (rate ratio)
Study 809-103	2.6% (1.2, 4.0)[a]	4.3 (1.9, 6.8)	0.1 (-0.1, 0.2)	1.5 (-1.7, 4.7)	2.1 (1.3, 3.3)[c]	0.66 (0.5, 1.0)[c]
Study 809-104	3.0% (1.6, 4.4)[a]	4.4 (1.9, 7.0)	0.4 (0.2, 0.5)	2.9 (-0.3, 6.0)	2.4 (1.5, 3.7)[c]	0.57 (0.4, 0.8)[c]

[a]assessed as the averaged of the treatment effects at week 16 and 14
[b]Responder defined as relative change in ppFEV1≥5% averaged at week 16 and 24
[c]not statistically significant due to earlier failure in the analysis hierarchy
Source: Summary of Clinical Efficacy, Table 16, p62-63

- Statistically significant benefit for absolute and relative change in ppFEV1 vs. placebo
- Inconsistent effect on BMI
- CFQ-R Respiratory Domain, responder, and exacerbations not statistically significant

Benefit of LUM/IVA versus IVA

- Typically a combination product demonstrates added benefit over monotherapy
  - Placebo or monotherapy comparator
- LUM/IVA treatment effect less than expected
  - Similar to IVA monotherapy from 770-104
- IVA monotherapy comparator more informative

Benefit of LUM/IVA versus IVA

- FDA analysis of LUM/IVA confirmatory studies and IVA study 770-104

	Δ from baseline **LUM 400mg/IVA 250mg q12** v. placebo at week 16 (95% CI)	
Study #	ppFEV1 (%)	Exacerbation (rate ratio)[a]
809-103	2.8 (1.2, 4.4)	0.67 (0.50, 0.91)
809-104	3.5 (2.1, 4.3)	0.57 (0.44, 0.76)
	Δ from baseline **IVA 150mg q12** v. placebo (95% CI)	
770-104	2.6 (-1.1, 6.4)	0.61 (0.29, 1.26)

[a]Crude ratios, FDA analysis

- Cannot conclude that LUM/IVA > IVA
  - Contrary to *in vitro* prediction
- Does IVA alone have an effect?

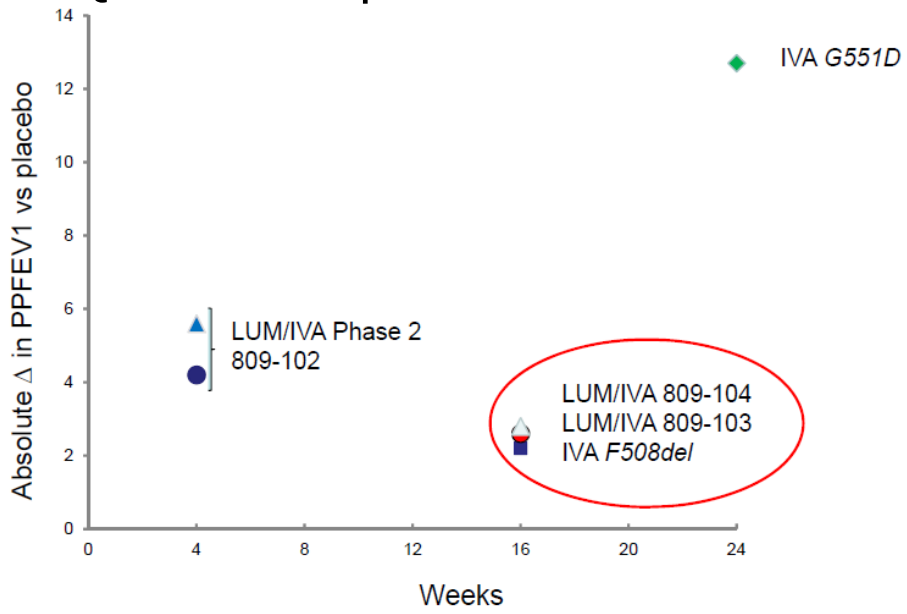
Sweat Chloride

- Not assessed in confirmatory studies
- Assessed in 809-102
- LUM and LUM/IVA results in small decreases in sweat chloride values
- Additive effect depends on when measured

Mutation	***F508 homozygous***			***G551D***	***R117H***
Sweat Chloride Δ from baseline v. placebo	LUM 400mg/ IVA 250mcg q12	LUM 400mg q12		IVA 150mcg q12	IVA 150mcg q12
Absolute(mmol/L)	-11	-9		-48	-24
Relative (%)	-11%	-9%		-48%	-34%
Source: ivacaftor approved label, FDA analysis					

Efficacy Summary

- LUM/IVA
  - Modest improvement in ppFEV1 versus placebo
  - Exacerbation reduction – not statistically significant
- Cannot conclude that LUM/IVA > IVA
  - Contrary to *in vitro* prediction
  - Question of potential benefit for IVA



Study #	Exacerbation (rate ratio)[a]
809-103	0.67 (0.50, 0.91)
809-104	0.57 (0.44, 0.76)
770-104	0.61 (0.29, 1.26)

[a]Crude ratios, FDA analysis

Figure source: FDA briefing document Table 4, pg 49; FDA analysis; ivacaftor label

Clinical Considerations for Efficacy, and Summary of Safety

- Efficacy Summary
  - Studies 809-103 and 809-104
  - Benefit of LUM/IVA versus IVA monotherapy
  - Sweat Chloride
- Safety Review
  - All adverse events
  - Adverse events of interest

Safety - Exposure

Studies 809-103 & 809-104	Placebo	LUM 600mg qd IVA 250mg q12	LUM 400mg/ IVA 250mg q12	Total LUM/IVA
Total Exposure (days)				
Patients (n)	370	369	369	738
Median	168	168	168	168
Source: Module 2.7.4; Summary of Clinical Safety; Table 7; pg39				

- 116 patients exposed in ongoing extension 809-105 for a total of 1-year

Safety – All Adverse Events

Studies 809-103 & 809-104	**PBO N=370**	**LUM 600mg qD IVA 250mg q12 N=369**	**LUM 400mg/ IVA 250mg q12 N=369**
Deaths	0	0	0
Adverse events (AE) leading to discontinuation	6 (1.6)	14 (3.8)	17 (4.6)
Serious Adverse Events (SAE)	106 (28.6)	84 (22.8)	64 (17.3)
Any Adverse Events	355 (95.9)	356 (96.5)	351 (95.1)
Source: Module 2.7.4; Summary of Clinical Safety; Table 16; pg54			

- No deaths
- AEs leading to discontinuation not driven by SOC or PT
- Difference in SAEs driven by differences in exacerbation
- No cataracts reported

Safety – Liver-related Adverse Events

Studies 809-103 and 809-104	PBO N=370	LUM 600mg qD IVA 250mg q12 N=369	LUM 400mg/ IVA 250mg q12 N=369
Liver-related AE	20 (5.4)	20 (5.4)	22 (6.0)
Elevated transaminases*	17 (4.6)	18 (4.9)	20 (5.4)
Hepatobiliary disorder	3 (0.8)	2 (0.5)	3 (0.8)
Liver-related SAEs	0	4 (1.1)	3 (0.8)
Discontinuation due to liver-related AE	0	3 (0.8)	1 (0.3)

*Applicant defined grouping
Source: Module 2.7.4; Summary of Clinical Safety; Table 25; pg71

Safety – Liver-related Adverse Events

Studies 809-103 and 809-104	PBO N=370	LUM 600mg qD IVA 250mg q12 N=369	LUM 400mg/ IVA 250mg q12 N=369
Liver-related AE	20 (5.4)	20 (5.4)	22 (6.0)
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Hepatobiliary disorder	3 (0.8)	2 (0.5)	3 (0.8)
Liver-related SAEs	0	4 (1.1)	3 (0.8)
Discontinuation due to liver-related AE	0	3 (0.8)	1 (0.3)

*Applicant defined grouping
Source: Module 2.7.4; Summary of Clinical Safety; Table 25; pg71

Safety – Liver Function Tests

Studies 809-103 and 809-104 Maximum on-treatment values	PBO N=369	LUM 600mg qD IVA 250mg q12 N=366	LUM 400mg/ IVA 250mg q12 N=368
ALT or AST >3x ULN	19 (5.1)	22 (6.0)	16 (4.3)
ALT or AST >3x ULN and Total Bilirubin >2x ULN	0	2 (0.5)	1 (0.3)

Source: Module 2.7.4; Summary of Clinical Safety; Table 29; pg78

- No cases of elevated ALT or AST with associated elevated bilirubin levels in the ivacaftor development program

Safety – Respiratory-related AEs

Studies 809-103 and 809-104	PBO N=370	LUM 600mg qD IVA 250mg q12 N=369	LUM 400mg/ IVA 250mg q12 N=369
Respiratory-related AEs	63 (17.0)	99 (26.8)	95 (25.7)
Respiratory symptoms[a]	51 (13.8)	88 (23.8)	81 (22.0)
Reactive airways[b]	20 (5.4)	24 (6.5)	24 (6.5)
Respiratory-related SAEs	0	4 (1.1)	0
Discontinuation due to respiratory-related AEs	0	5 (1.4)	0

[a]Applicant defined grouping: chest discomfort, dyspnea, respiration abnormal
[b]Applicant defined grouping: asthma, bronchial hyperreactivity, bronchospasm, wheezing
Source: Module 2.7.4; Summary of Clinical Safety; Table 36; pg98

Safety – Respiratory-related AEs

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Source: Module 2.7.4; Summary of Clinical Safety; Table 36; pg98

Summary

Efficacy

- LUM/IVA
  - Modest improvement in ppFEV1 versus placebo
  - Exacerbation reduction –not statistically significant
- Cannot conclude that LUM/IVA > IVA
  - Contrary to *in vitro* prediction
  - Question of potential benefit for IVA

Safety

- Potential liver related toxicity
- Increased respiratory symptom related adverse events

Thank you

Pulmonary-Allergy Drugs Advisory Committee Meeting Lumacaftor/Ivacaftor Tablets for oral use NDA 206038

Charge to the Committee

Anthony Durmowicz, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
May 12, 2015

Summary of Issues

- Overall efficacy
  - Clinical significance of the LUM/IVA treatment effect
- Contribution of LUM to LUM/IVA combination
  - Clinical benefit over IVA alone?
  - Results of FDA analyses LUM/IVA to IVA alone
    - Small FEV1 effect similar to that for IVA alone (2-3%)
    - Exacerbation rate ratio similar (0.60)
- Benefit-Risk profile

Questions for Discussion and Voting

- Total of 6 questions
- Questions 3, 5, and 6 require voting
- Questions 1, 2 and 4 are discussion only

Question 1
(Discussion Question)

Discuss the available efficacy data for LUM 400 mg/IVA 250 mg fixed-dose combination (FDC) administered twice daily in patients with cystic fibrosis (CF) 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Consider the following issues in the discussion: clinical significance of the observed treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.

Question 2
(Discussion Question)

Discuss the available efficacy data for ivacaftor monotherapy 150 mg twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

Question 3
(Voting Question)

Do the available data demonstrate that lumacaftor contributes positively to the clinical efficacy seen for the lumacaftor plus ivacaftor FDC product in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

A. Yes

B. No

C. Cannot determine

Please comment on the rationale for your vote and whether a clinical trial should be conducted to compare the LUM/IVA FDC to ivacaftor alone.

Question 4
(Discussion Question)

Discuss the safety data for LUM 400 mg/IVA 250 mg FDC twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Question 5
(Voting Question)

Do the data support the safety of LUM 400 mg/IVA 250 mg FDC administered twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what further data should be obtained to more fully define the safety profile of LUM 400 mg/IVA 250 mg?

Question 6
(Voting Question)

Do the available efficacy and safety data support approval of the LUM 400 mg/IVA 250 mg FDC product administered twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what additional data should be obtained to further define the benefit risk profile of LUM 400 mg/IVA 250 mg twice daily in patients with CF who are homozygous for the F508del mutation in the CFTR gene?

Thank You