CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206038Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	July 2, 2015
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	206038
Applicant Name	Vertex pharmaceuticals, Inc.
Proprietary / Established (USAN) Names	Orkambi/ Lumacaftor/ivacaftor combination tablet
Dosage Forms / Strength	Lumacaftor 200 mg/ivacaftor 125 mg oral tablets Two tablets every 12 hours
Proposed Indication(s)	For the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding lumacaftor/ivacaftor (LUM/IVA) and the reader should review the action package for more detail. Lumacaftor is a first in class new molecular entity for cystic fibrosis (CF) that is theorized to work by stabilizing and promoting folding of the defective F508del cystic fibrosis transmembrane conductance regulator (CFTR) protein during processing in the endoplasmic reticulum such that the protein is able to exit and move to the apical surface of the epithelial cell membrane. Ivacaftor is an approved product for patients with CF with specific genetic mutations in the *CFTR* gene, potentiating the function of the (CFTR) protein at the cell-surface membrane. The sponsor has proposed that the two drugs will be complementary such that the use of lumacaftor will enable more protein, even in a defective form, to exist on the cell surface, and that ivacaftor will allow for improved chloride ion transport of the defective protein resulting in clinical benefit.

CF is a serious, debilitating, autosomal recessive genetic disease leading to premature mortality that affects ≈ 30,000 patients in the United States. Since CF is autosomal recessive, disease will only be expressed if both alleles are affected with a mutation causing decrease function of the CFTR protein. Approximately one in every 3,500 children in the United States is born with CF each year. While the disease can be found in all ethnic and racial groups, it is most common in Caucasians. CF is caused by a defective gene (over 1800 known mutations) that code for the CFTR protein. The CFTR protein provides a cell-surface chloride ion channel that allows for the regulation of salt and water absorption. Lack of properly functioning CFTR protein leads to decrease chloride ion transport resulting in tenacious secretions that progressively affects mainly the pulmonary tract (infection, inflammation, bronchiectasis-leading to fibrosis and respiratory failure) and gastrointestinal tract (malabsorption of nutrients-poor weight gain). There is no cure for cystic fibrosis and affected

patients have a median age of survival of the mid-30s. Present therapies for the F508D mutation only treat symptoms and sequelae of the disease and include antibiotics (both systemic and inhaled) for pulmonary infections, mucolytics to thin secretions, oral pancreatic enzymes to aid in nutrient absorption and bronchodilators to aid in breathing.

Mutations in the CFTR gene can result in reduced quantity and/or quality of the CFTR protein. They have been loosely categorized into classes based on how they affect the CFTR. TheF508del mutation has been designated as a Class 2 mutation; it results in improper folding and processing of the CFTR protein leading to degradation in the endoplasmic reticulum and failure of the majority of protein to reach the cell-surface membrane. It is the most common mutation in the *CFTR* gene with 87% of all patients in United States having at least one allele affected and 50% having both affected.

A person with F508del CFTR mutation on one or both alleles has deletion of the three nucleotides that code for phenylalanine at position 508. It is thought that the F508del mutation results in a truncated protein that does not fold correctly with resultant degradation of the majority of the protein. The small amount of protein that does reach the cell surface has reduced function with decreased open-ion channel probability.

The efficacy of LUM/IVA was demonstrated in two trials. Both trials were of 24 weeks duration and demonstrated improvement in lung function (FEV1) which was the primary endpoint. Clinically important secondary endpoints such as delayed time to first pulmonary exacerbation supported efficacy. Adverse events were generally well-tolerated.

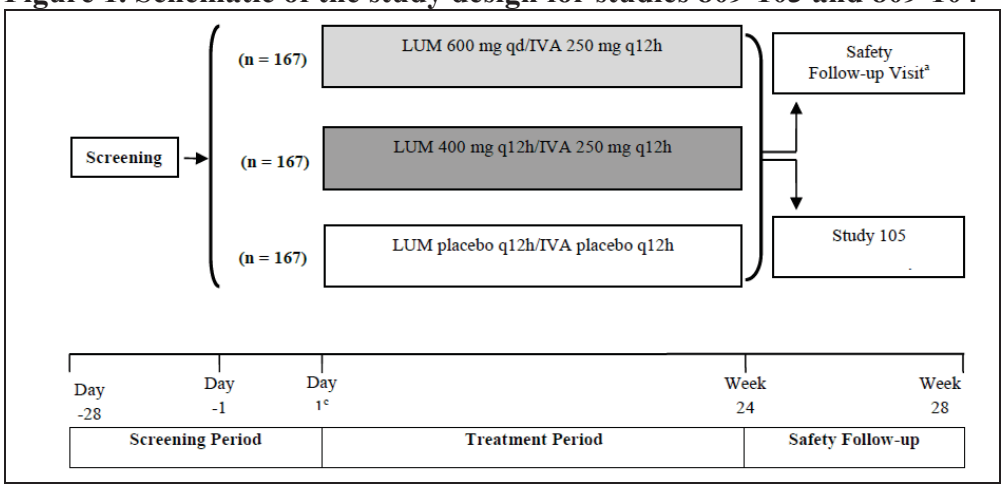
Overall, there is clinical benefit for LUM/IVA. It is unclear whether each component is contributing to this effect, which will be discussed in detail later. The effect size is minimal when compared to that demonstrated with IVA in the G551D mutation, a CF population for which ivacaftor monotherapy has already been approved. However, any benefit provided to this patient population is readily welcomed as patients with the F508del mutation at present only have therapies that manage downstream consequences of CF (the result of diminished CFTR function) and without any effect on the underlying cause and LUM/IVA is targeted to have effect on the cause of CF. There clearly is a favorable risk:benefit consideration that allows approval and marketing.

Efficacy

Efficacy has been thoroughly covered by Drs. Zeng, Petullo, Lim, Durmowicz and Chowdhury and I will not present this in detail. There were two replicated randomized parallel arm trials, VX12-809-103 (103) and VX12-809-104 (104). Two different doses were explored (LUM 400mg/IVA 250mg q 12h, LUM 600mg qd/IVA 250mg q 12h) and both doses and trials provided statistically significant benefits over placebo on the primary endpoint of absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) at Week 24[1]. Secondary endpoints provided supportive evidence of efficacy. The study design and primary endpoint results are summarized below (from Dr. Zeng's review, pages 9 and 16).

[1] Average of treatment effects at Week 16 and Week 24.

Figure 1. Schematic of the study design for studies 809-103 and 809-104



Source: Clinical Overview, Figure 1

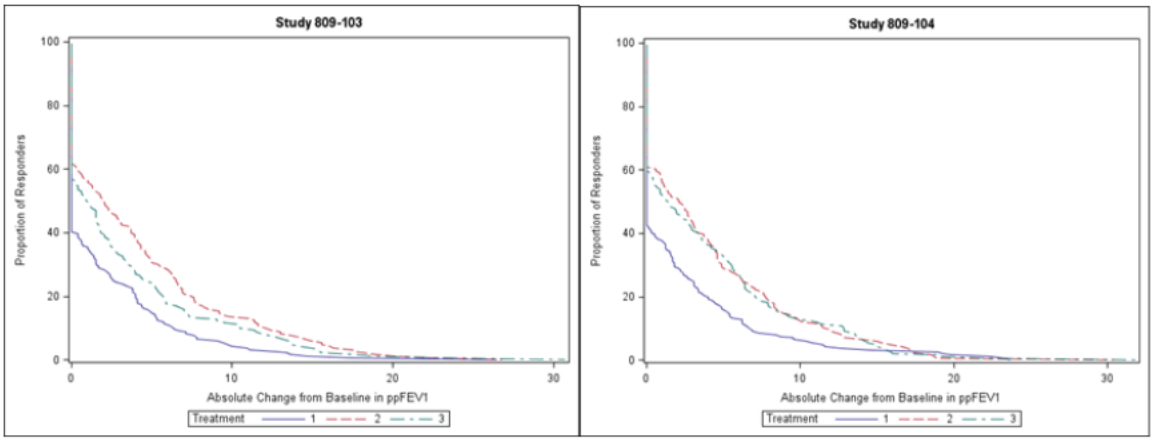
Table 1. Absolute change from baseline in ppFEV1 at Week 24*, FAS

Statistics	Study 809-103			Study 809-104		
	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
Baseline						
N	181	182	180	185	184	185
Mean (SD)	60.5 (13.2)	61.2 (13.3)	60.5 (14.3)	60.4 (14.3)	60.5 (13.8)	60.6 (14.0)
Absolute Δ from baseline at Week 24*						
N	180	176	172	183	181	180
Mean (SD)	-0.6 (6.5)	3.5 (7.0)	2.1 (7.1)	-0.5 (6.6)	2.2 (7.5)	2.6 (6.7)
Applicant						
LS mean within-group change (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)
LS mean difference vs placebo (95% CI)	NA	4.0 (2.6, 5.4) *P*<0.0001	2.6 (1.2, 4.0) *P*=0.0003	NA	2.6 (1.2, 4.1) *P*=0.0004	3.0 (1.6, 4.4) *P*<0.0001
Reviewer						
LS mean within-group change (SE)	-0.5 (0.5)	3.6 (0.5)	2.1 (0.5)	-0.2 (0.5)	2.3 (0.6)	2.8 (0.5)
LS mean difference vs placebo (95% CI)	NA	4.1 (2.7, 5.5) *P*<0.0001	2.7 (1.2, 4.1) *P*=0.0003	NA	2.5 (1.0, 4.0) *P*=0.0008	3.0 (1.5, 4.4) *P*<0.0001

*Assessed as the average of the treatment effects at Week 16 and at Week 24
Source: Reviewer

In study 809-103, the average treatment effect over placebo was 4.0% for LUM 600mg qd/IVA 250mg q12h and 2.6% for LUM 400mg /IVA 250mg q12h, respectively. In study 809-104, the average treatment effect above placebo was 2.6% for LUM 600mg qd/IVA 250mg q12h and 3.0% for LUM 400mg /IVA 250mg q12h, respectively. A responder analysis generated by Dr. Zeng (page 17) demonstrates a greater percentage of subjects taking LUM/IVA at all levels of response.

Figure 1. Absolute change from baseline in $ppFEV_1$ at Week 24, FAS



1: Placebo; 2: LUM 600 mg qd/IVA 250 mg q12h; 3: LUM 400mg/IVA 250 mg q12h
Source: Reviewer

In looking at those that have a decrease in FEV1, the effect of LUM/IVA is also evident (e-mail exchange with Dr. Zeng 6-1-2015).

Study 809-103	Treatment							
	Placebo		LUM 600 /IVA 250		LUM 400 /IVA 250		Total	
	N	%	N	%	N	%	N	%
Total	176	100.0	171	100.0	167	100.0	514	100.0
Absolute Change from baseline in ppFEV1 at Week 24								
<= -20%	2	1.1	2	1.2	2	1.2	6	1.2
-20% to -15%	3	1.7	2	1.2	3	1.8	8	1.6
-15% to -10%	3	1.7	4	2.3	6	3.6	13	2.5
-10% to -5%	27	15.3	12	7.0	9	5.4	48	9.3
-5% to 0%	64	36.4	37	21.6	43	25.7	144	28.0
Improved	74	42.0	113	66.1	103	61.7	290	56.4
Missing	3	1.7	1	0.6	1	0.6	5	1.0

Study 809-104	Treatment							
	Placebo		LUM 600 /IVA 250		LUM 400 /IVA 250		Total	
	N	%	N	%	N	%	N	%
Total	178	100.0	176	100.0	174	100.0	528	100.0

Study 809-104	Treatment						Total	
	Placebo		LUM 600 /IVA 250		LUM 400 /IVA 250			
	N	%	N	%	N	%	N	%
Absolute Change from baseline in ppFEV1 at Week 24								
<= -20%	-	0.0	3	1.7	1	0.6	4	0.8
-20% to -15%	2	1.1	-	0.0	1	0.6	3	0.6
-15% to -10%	13	7.3	9	5.1	4	2.3	26	4.9
-10% to -5%	18	10.1	18	10.2	19	10.9	55	10.4
-5% to 0%	65	36.5	34	19.3	37	21.3	136	25.8
Improved	79	44.4	112	63.6	111	63.8	302	57.2
Missing	1	0.6	-	0.0	1	0.6	2	0.4

As demonstrated above the percentage of those exposed to LUM/IVA who have decreases in FEV1 is less than those receiving placebo.

Key secondary endpoints are summarized below in tables from Dr. Zeng's review (page 20). These should be viewed somewhat cautiously as statistical testing (based on hierarchical specification) should not occur past BMI for trial 103 and CFQ-R respiratory domain score for trial 104.

Table 2. Summary of key secondary endpoints (Reviewer's analysis), FAS

Analysis	Statistics	Trial 809-103			Trial 809-104		
		Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
1) Relative Δ from baseline in $ppFEV_1$ at Week 24* (%)	Mean	-0.5	6.3	3.9	-0.1	4.1	5.1
	Difference	NA	6.8	4.4	NA	4.2	5.2
	(95% CI)		(4.3, 9.3)	(1.9, 7.0)		(1.6, 6.8)	(2.6, 7.8)
2) Absolute Δ from baseline in BMI at Week 24 (kg/m^2)	Mean	0.2	0.4	0.3	0.1	0.5	0.4
	Difference	NA	0.1	0.1	NA	0.4	0.4
	(95% CI)		(-0.1, 0.3)	(-0.1, 0.3)		(0.2, 0.6)	(0.2, 0.6)
3) Absolute Δ from baseline in CFQ-R respiratory domain score at Week 24 (points)	Mean	1.2	5.5	2.9	3.1	5.5	6.2
	Difference	NA	4.3	1.6	NA	2.4	3.1
	(95% CI)		(1.0,7.5)	(-1.6, 4.9)		(-0.7, 5.6)	(-0.1, 6.2)
4) Response of ≥5% in relative Δ from baseline in $ppFEV_1$ at Week 24*	Yes, n(%)	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)
	Odds ratio	NA	2.9	2.1		2.8	2.3
	(95% CI)		(1.9,4.6)	(1.3, 3.4)	NA	(1.8, 4.4)	(1.5, 3.6)

5) Number of pulmonary exacerbations from baseline through Week 24	No. events	112	79	73	139	94	79
	Event rate/year	1.1	0.8	0.7	1.2	0.8	0.7
	Rate ratio (95% CI)	NA	0.7 (0.5, 1.0)	0.7 (0.5, 0.9)	NA	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)

*Assessed as the average of the treatment effects at Week 16 and at Week 24

Source: Reviewer

Secondary endpoints support the conclusion demonstrated by FEV1 that LUM/IVA has efficacy for subjects in the trials homozygous for F508del.

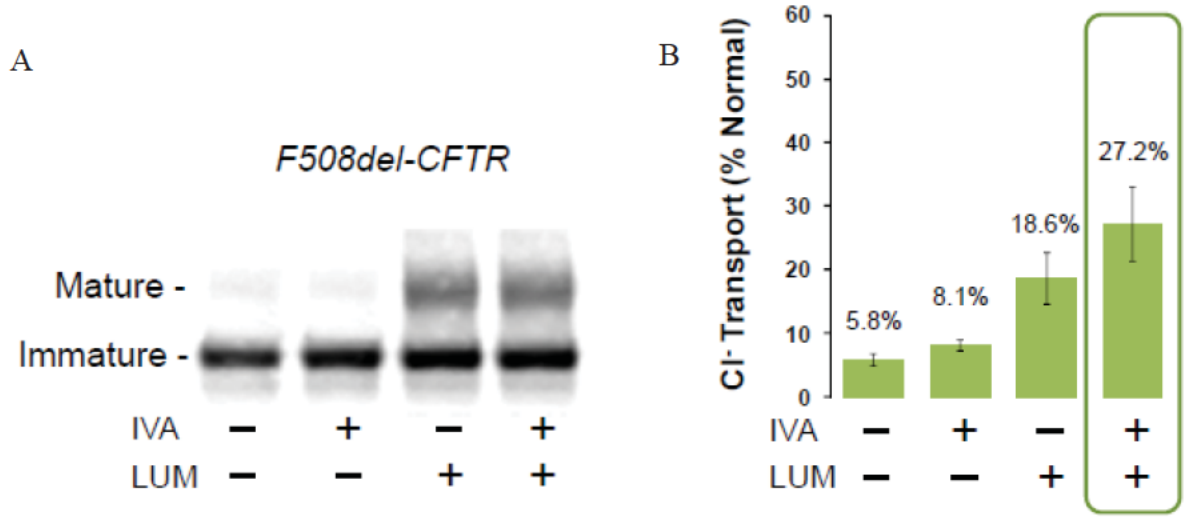
Combination therapy

For combination products the contribution of each individual drug of the combination should usually be demonstrated. This is typically done by designing clinical trial/s with factorial design comparing the combination to each component and sometimes to placebo on a clinically important endpoint. However, this was not done for this application and it is instructive to review the timeline of results occurring during development and decision making that led to not having clinical factorial evaluation upon which to make decisions.

Before reviewing the clinical data however, it is useful to review the in vitro and pre-Phase 3 data that had been generated that held the promise that each component of LUM/IVA should be contributory.

LUM had been demonstrated to facilitate the processing of mutant CFTR to the cell surface resulting in improved overall chloride ion transport in cell cultures (Figure 1 from Dr. Durmowicz review, page 3).

Figure 1. In vitro data suggesting that lumacaftor facilitates processing of mutant CFTR to the cell surface (A) where chloride transport can be potentiated by ivacaftor (B)



Source: Slide CA-12 Vertex Pharmaceuticals May 12, 2015 PADAC presentation

Phase 2 clinical evaluations demonstration reductions in sweat chloride for LUM/IVA that were greater than either LUM or IVA alone (Table 2, Dr. Drumowicz's review, page 12).

Table 2. Study 809-102 Cohorts 2 and 3: change in sweat chloride compared to placebo

	Placebo (combined)	LUM 200mg qd	LUM 400mg qd	LUM 600mg qd	LUM 400mg q12h
Δ in sweat chloride (mmol/L) vs. placebo					
# of patients	26	21	19	20	10
Baseline to day 28 (lumacaftor alone) (95% CI)	--	-4.9 (-9.5, -0.28)	-8.3 (-13.0, -3.6	-6.1 (-11.0, -1.4)	-8.2 (-14.1, -2.3)
Days 28-56 (+ 250 mg ivacaftor) (95% CI)	--	-1.0 (-7.2, 5.3)	-2.5 (-8.9, 4.0)	-4.3 (-10.7, 2.1	-3.9 (-12.2, 4.4)
Baseline to day 56 (lumacaftor+ivacaftor) (95% CI)	--	-5.0 (-10.5, 0.48)	-9.8 (-15.3, -4.2)	-9.5 (-15.1, -3.9)	-11.0 (-18.3, -3.7)

Source: Module 2.7.2, Summary of Clinical Pharmacology; tables 15 and 16; p68

These promising results supported the working hypothesis that the combination should perform better than either single component. Even with these results, under typical situations we may want further clinical validation, which in normal situations would take place in late Phase 2 or Phase 3. This was not done in the case and I will outline the reasons.

Monotherapy evaluation of LUM during Phase 2 development demonstrated a dose dependent decrease in FEV1 in CF patients homozygous for the F508del mutation as noted in the table below (Dr. Lim's review page 20-21).

Table 3. Study 809-102 Cohorts 2 and 3. Absolute change percent predicted FEV_1 versus placebo between treatment periods in *F508del* homozygous patients (cohorts 2 and 3)

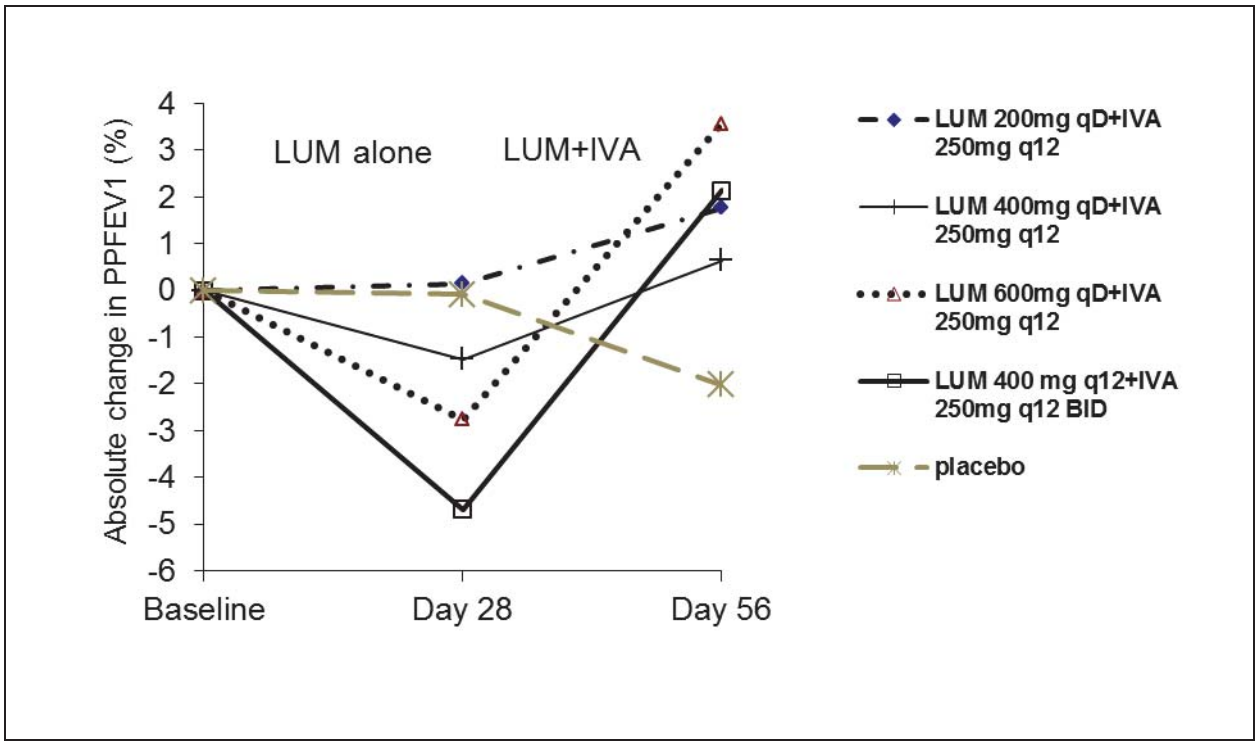
	Placebo (combined)[a]	LUM 200mg qD	LUM 400mg qD	LUM 600mg qD	LUM 400mg q12
Δ in percent predicted FEV1 vs. placebo					
# of patients	27	21	20	20	11
Baseline to day 28[b] (95% CI)	--	0.24 (-3.7, 4.2)	-1.4 (-5.4, 2.6)	-2.7 (-6.7, 1.4)	-4.6 (-9.6, 0.36)
Day 28-56[c] (95% CI)	--	3.52 (-0.45, 7.5)	3.6 (-0.43, 7.6)	7.8 (3.7, 11.9)	7.7 (2.6, 12.8)
Baseline to day 56[c] (95% CI)	--	3.8 (-0.5, 8.1)	2.7 (-1.7, 7.0)	5.6 (1.2, 10.0)	4.2 (-1.3, 9.7)

[a]Includes *F508del* heterozygous patients
[b]LUM alone was given from baseline to day 28 in all groups
[c]All LUM therapy doses were given in combination with IVA 250mg q12 from day 29-56
Source: Module 2.7.2, Summary of Clinical Pharmacology, tables 15 and 16, pp70-71

In contrast, during the 28-day treatment period with LUM (200mg qD, 400mg qD, 600 qD, and 400mg q12) in combination with IVA 250mg q12 (baseline to day 56), an increase of 5.6% and 4.2% compared to placebo in FEV1 was observed in the LUM 600mg qD/IVA

250mg q12 and LUM 400mg/IVA 250mg q12 groups, respectively. This is represented graphically below (from Dr. Lim's review, page 22).

Figure 2. Study 809-102, Cohorts 2 and 3. Absolute change from baseline in percent predicted FEV_1 ($ppEFV_1$) at days 28 and 56 in *F508del* homozygous patients



Source: FDA generated from data from module 2.7.2, Summary of Clinical Pharmacology, table 16,pg 70

Because of the safety concerns related to decrease in FEV1 demonstrated in this study, further comparison of LUM monotherapy to LUM/IVA was not required.[2]

During the development of IVA for patients with the G551D mutation (NDA 203,188), subjects homozygous for the *F508del* mutation (study 770-104)[3] were also evaluated. IVA demonstrated robust efficacy in CF patients who carried at least one G551D mutation in the CFTR gene. In contrast, subjects homozygous for the F508del mutation had effect sizes that were small in magnitude, although some point estimates were positive (e.g., FEV_1 and exacerbation). Key results from these studies summarized in Table 4 (Dr. Lim's review, page 26).

[2] It is perplexing that LUM monotherapy treatment decreased sweat chloride values but caused dose-dependent worsening (statistically significant) FEV1. This demonstrates that improvements (decreases) in sweat chloride as a result of lumacaftor were not associated with clinical benefit (increase in FEV1). The cause of the LUM mediated dose-dependent in FEV1 is not known but LUM may have off-target effects not necessarily related to CFTR function.

[3] This trial was not designed with formal power analysis to determine a sample size and has much less power than trials 103 and 104.

Table 4. Treatment effect of ivacaftor monotherapy in patients with the *G551D*mutation and homozygous for the *F508del* mutation

	Δ from baseline **IVA** alone (n=83) versus placebo (n=78) through week 24 (95% CI)				
G551D **≥12 years old**	$ppFEV_1$ (%)	CFQ-R Respiratory Domain (score)	Sweat (mmol/L)	Weight (kg)	Exacerbation (rate ratio)
IVA 150mg q12	10.6% (8.6, 12.6)	8.1 (4.7, 11.4)	-47.9 (-51.3, -44.5)	2.8 (1.8, 3.7)	0.43[a] (0.27, 0.68)
F508del **homozygous ≥12 years old Study 770-104**	Δ from baseline **IVA** alone (n=112) versus placebo (n=28) through week 16 (95% CI)				
IVA 150mg q12	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-2.9 (-5.6, -0.15)	-0.16 (-1.1, -0.7)	0.68 (0.3, 1.4)

[a]exacerbation rate ratio through week 48
Source: NDA 203188 statistical review, table 4 and 10, pp13 and 30; & clinical review section 6.1.5, pg.63

The profound difference between the results for the *G551D* population compared to the F508del homozygous population led to a statement in the Limitations of Use section of the IVA label stating 'Not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene'.[4]

Also, as noted in the table above reviewing the results of Study 809-102, phase II results of FEV1 evaluation of LUM/IVA indicated changes of 5.6 % and 4.2% depending upon dose. This change was more impressive than that demonstrated in Study 770-104 with IVA alone (1.7%) and seemed to provide circumstantial evidence that the combination had a greater effect than IVA alone.

Because of the sequence of data production and results (minimal change in FEV1 with IVA in study 770-104 and moderate effect of LUM/IVA on FEV1 in phase 2 study) an IVA monotherapy comparator arm was also not required during the planning of the Phase 3 trials.

However, the surprising results of the adequately powered LUM/IVA studies 809-103 and 809-104, in which statistically significant but small improvements for the primary endpoint FEV_1 were noted, approximated the FEV_1 point estimate for the previous IVA alone study

[4] While this wording was inserted into labeling, it does not mean that IVA does not have an effect. It was not adequately studied, and had we anticipated the small effect on FEV1 that the LUM/IVA combination had in phase 3 (the new bar for expected efficacy compared to G551del) and the trials of IVA alone been powered to the same level that as 103 and 104 perhaps we would come to a different conclusion.

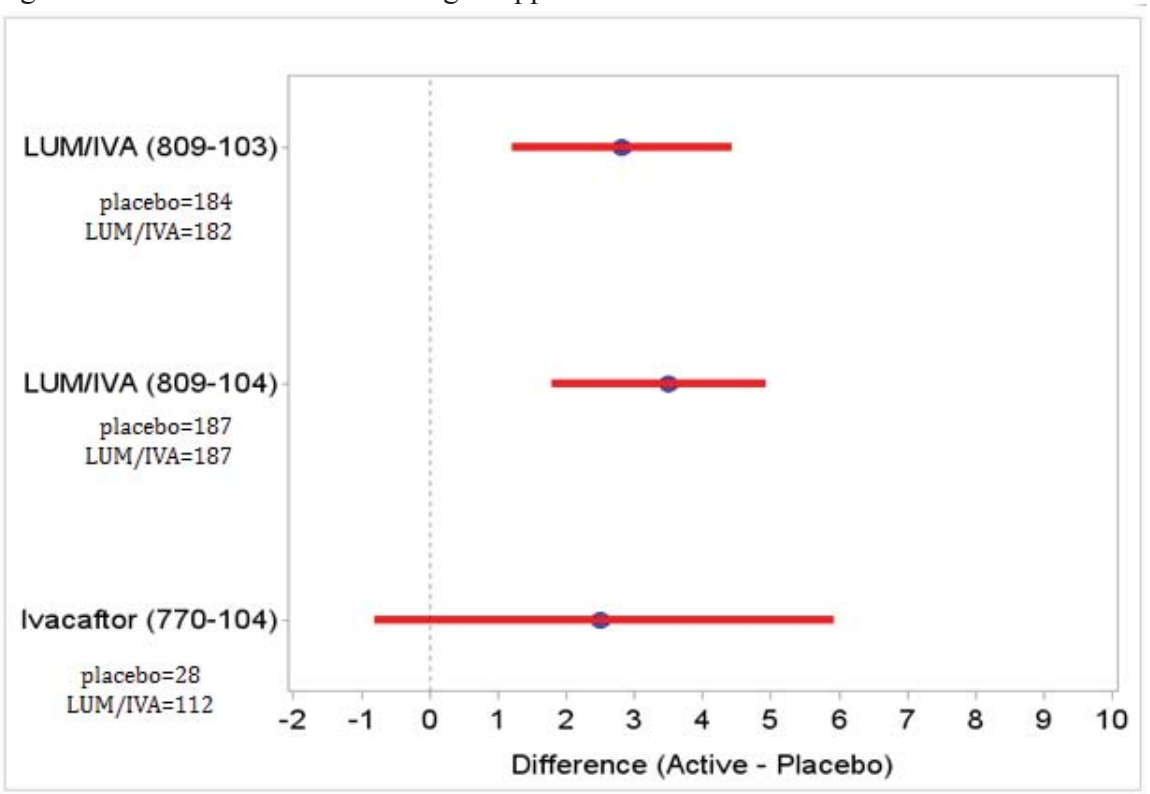
(770-104) and were well below those demonstrated in Phase 2 evaluations. This is demonstrated below in a table and figure from Dr. Petullo's review (page 8).

Table 4. Summary of $ppFEV_1$ at week 16 for all randomized and treated subjects

Study	Time Point	$ppFEV_1$, LSMEAN* (SE)		
		placebo	Ivacaftor (150 mg q12h)	LUM 400mg / IVA 250mg q12h
770-104	Baseline	73.2 (4.5)	76.9 (2.2)	-
	Absolute Change*	-0.3 (1.5)	2.2 (0.8)	-
	Relative change#*	-0.4 (2.1)	3.2 (1.1)	-
809-103	Baseline	60.3 (1.0)	-	60.5 (1.1)
	Absolute Change	-0.2 (0.6)	-	2.6 (0.6)
	Relative change#	0.3 (1.0)	-	4.7 (1.0)
809-104	Baseline	60.2 (1.0)	-	60.3 (1.1)
	Absolute Change	-0.7 (0.6)	-	2.8 (0.6)
	Relative change#	-0.7 (1.0)	-	5.4 (1.0)

Source: Reviewer
*ANCOVA with baseline $ppFEV_1$, # Relative change is define as % change from baseline

Figure 1. Treatment effect for change in ppFEV1



The same is also seen for pulmonary exacerbations (Dr. Petullo's review, page 10)

Table 6. Summary of pulmonary exacerbations

Study	Statistics	Exacerbations		
		placebo	Ivacaftor (150 mg q12h)	LUM 400mg / IVA 250mg q12h
770-104	n	28	112	-
	days on study	3038	12504	-
	Annual rate	1.2	0.73	-
	Rate ratio	-	0.61	-
	SE		0.37	-
Integrated*	n	371	-	369
	days on study	62427	-	61,057
	Annual rate	1.5	-	0.91
	Rate ratio	-	-	0.62
	SE	-	-	0.1

Source: Reviewer
*Studies 809-103 and 809-104

While this is a cross study comparison, it is difficult based on these results to confirm whether the treatment effect for the LUM/IVA combination is different than that observed for IVA monotherapy. In an exploratory statistical analysis, Dr. Petullo concluded that the contribution of LUM to the efficacy of the proposed combination product had not been shown. I agree this was an exploratory analysis and that it does raise concerns regarding the contribution of lumacaftor. However this leaves us in a quandary where we have a completed program demonstrating efficacy of a combination drug product, while not perhaps having all the assurance that we would have typically developed during the program for inclusion with the submission. Such assurance would have been developed during Phase 3, but for the reasons above, was not. Considering the disease and available therapies, delaying submission for further evaluation of a product that demonstrated efficacy does not seem reasonable.

Safety

Most serious adverse events (SAEs) were related to pulmonary exacerbations of CF which occurred in approximately 13% of subjects receiving LUM/IVA and 24% of subjects receiving placebo. Other SAEs were infrequent and did not appear to be drug related. It is interesting to note, considering the adverse pulmonary effects that treatment with LUM alone expressed, that discontinuations that were pulmonary related were more frequent in the LUM/IVA group compared to placebo including bronchospasm (0.3% vs 0%) and dyspnea (0.3% vs 0%). Also noted were increased frequency of respiratory symptoms and dyspnea of 23% and 10% compared to 8% and 3% in those receiving placebo.

IVA therapy alone is known to be associated with potential liver toxicity. This was also demonstrated with IVA/LUM therapy in the form of more liver-related SAEs, AEs leading to discontinuation and transaminase elevations associated with bilirubin elevations. There were three cases of ALT elevations greater than or equal to 3x and total bilirubin elevations greater than or equal to 2 times. Two of these cases had reasons to account for this elevation. The third case also had underlying considerations, making the diagnosis of Hy's law difficult.

Considering the severity of the disease, lack of other effective therapies and ability to monitor for possible adverse liver effects, this finding does not impact approvability.

Common adverse events demonstrated increases with LUM/IVA therapy for dyspnea, abnormal respiration, flatulence and rash.

Advisory Committee Meeting

A Pulmonary Advisory Committee (PADAC) meeting was held on May 12, 2015. The majority of committee members agreed that there was not adequate evidence to establish the contribution of each ingredient in the combination product. Members voted for approval 12-1 as they felt the overall program did demonstrate efficacy, with a unique mechanism of action, in a population in desperate need. However, some members advised the agency that future combination products for CF should have a program that evaluates the contribution of each component.

Conclusions and Recommendations

LUM/IVA has demonstrated clinical efficacy for patient homozygous for the F508del mutation as measured by lung function and supported by secondary endpoints. The mean effect size is small relative to that demonstrated by IVA for the G551D genetic defect. However there is a desperate need for those homozygous for the F508del defect, the action of the combination product is novel compared to what is available now and works upstream such that even though the effect is modest, any improvement is welcomed. It is important also as the F508del defect affects the majority of patients with CF so this will impact a large portion afflicted with this disease.

There has been a great deal of internal discussion at all levels regarding whether the combination regulation has been met. There is good reason for this concern, as it would be an extreme disservice to patients to allow exposure to an ineffective drug. Such a situation would expose patients to a drug where they would not receive any benefit, but would be exposed to all the risk and expense associated with the drug's use. This is more than theoretical in this case as we know from Phase 2 studies that LUM by itself has a detrimental effect on pulmonary function. Therefore, it is not unreasonable that someone might hypothesize that IVA could be driving all the favorable results demonstrated in the two trials, and LUM could actual be hindering IVA's effect, which would be unfortunate if the case. On the other hand, counterbalancing this concern is that there is compelling scientific theory, supportive in vitro data, and clear beneficial effect of LUM/IVA for those homozygous for F508del who have few other options. Therefore, considering that the product is producing clinical benefit in a population in desperate need, I will recommend approval.

However, once approved, there will be an effective therapy for patients homozygous for the F508del such that any further combination therapy being developed should evaluate the contribution of each component to the product using clinical data to support preclinical results, unless there is a compelling reason not to do so.

I recommend Approval with appropriate labeling.

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/s/

CURTIS J ROSEBRAUGH
07/02/2015