

# Long term effect of Orkambi<sup>®</sup> on $\Delta$ F508 homozygous in Israel

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# Disclosure

- Principal investigator for Vertex clinical studies
  - ✓ VX14-661-107
  - ✓ VX14-661-110
  - ✓ VX16-659-101

# Orkambi® and $\Delta F508$

What's New!

**CFTR Quantity**

Number of CFTR channels  
in apical surface



**CFTR Function**

Function of CFTR channels  
in apical surface



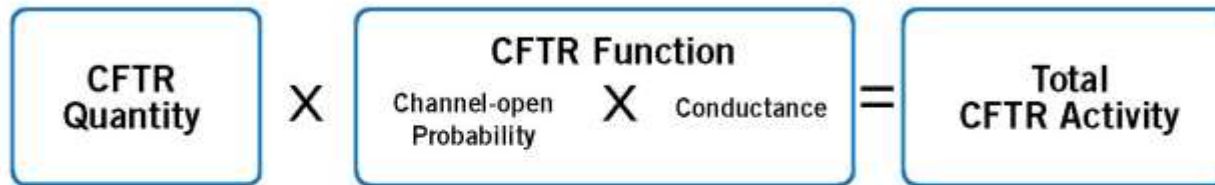
**Total CFTR Activity**

Total ion transport by epithelial cells

# The *F508del* allele results in little to no total CFTR activity<sup>1-5</sup>

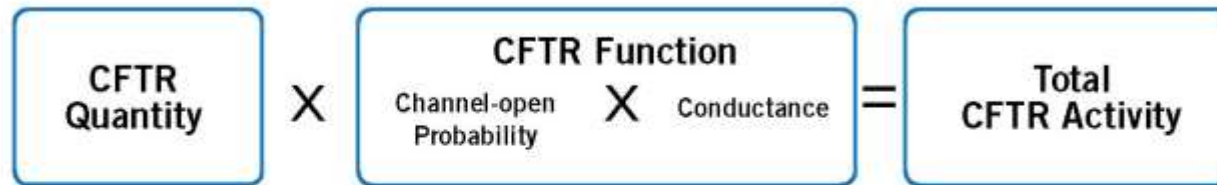
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Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein **quantity** and **function**.<sup>3</sup>



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1

Significantly reduced *F508del*-CFTR protein quantity...

*F508del* allele results in few to no CFTR channels at apical surface

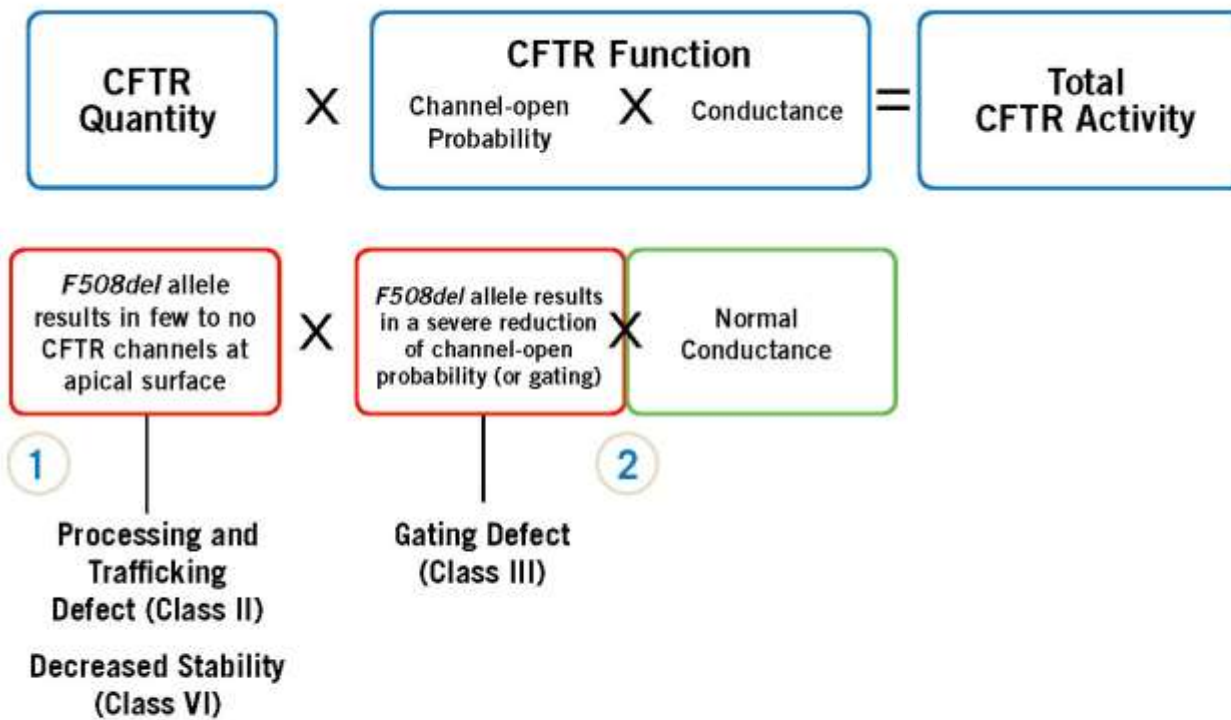
1

Processing and Trafficking Defect (Class II)

Decreased Stability (Class VI)

# The *F508del* allele results in little to no total CFTR activity<sup>1-5</sup>

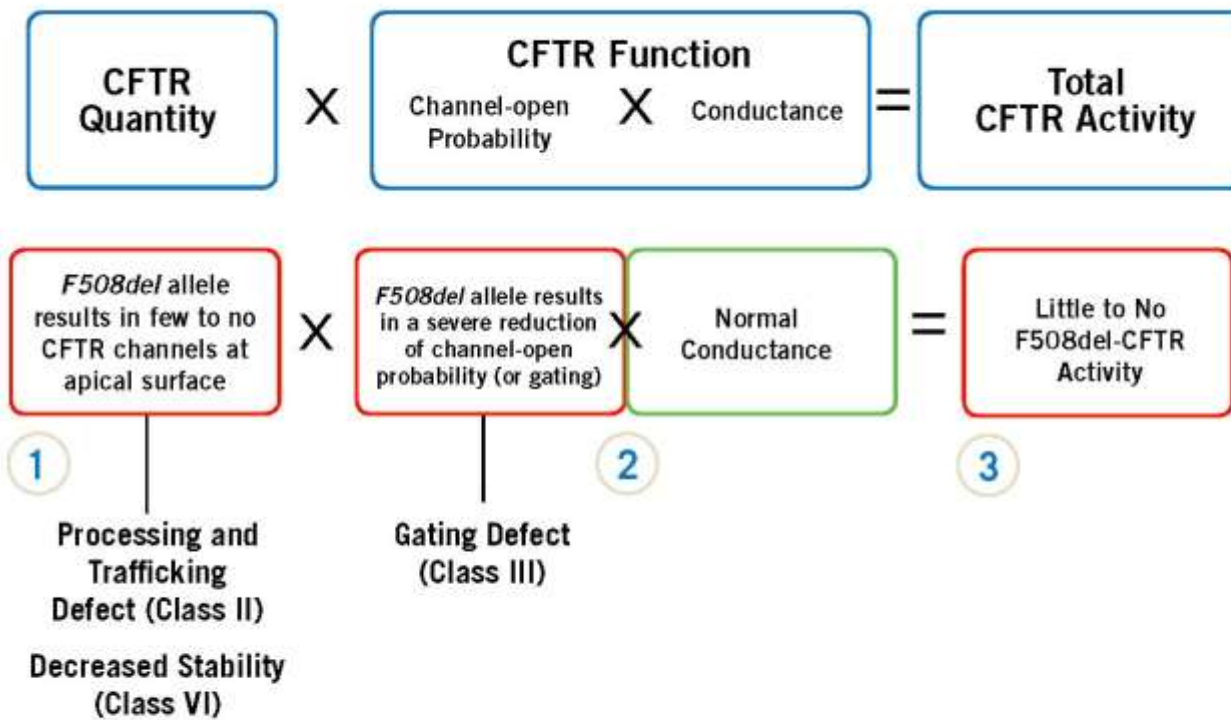
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- 1 Significantly reduced *F508del*-CFTR protein quantity...
- 2 ...and severely reduced **function** due to decreased channel-open probability...

# The *F508del* allele results in little to no total CFTR activity<sup>1-5</sup>

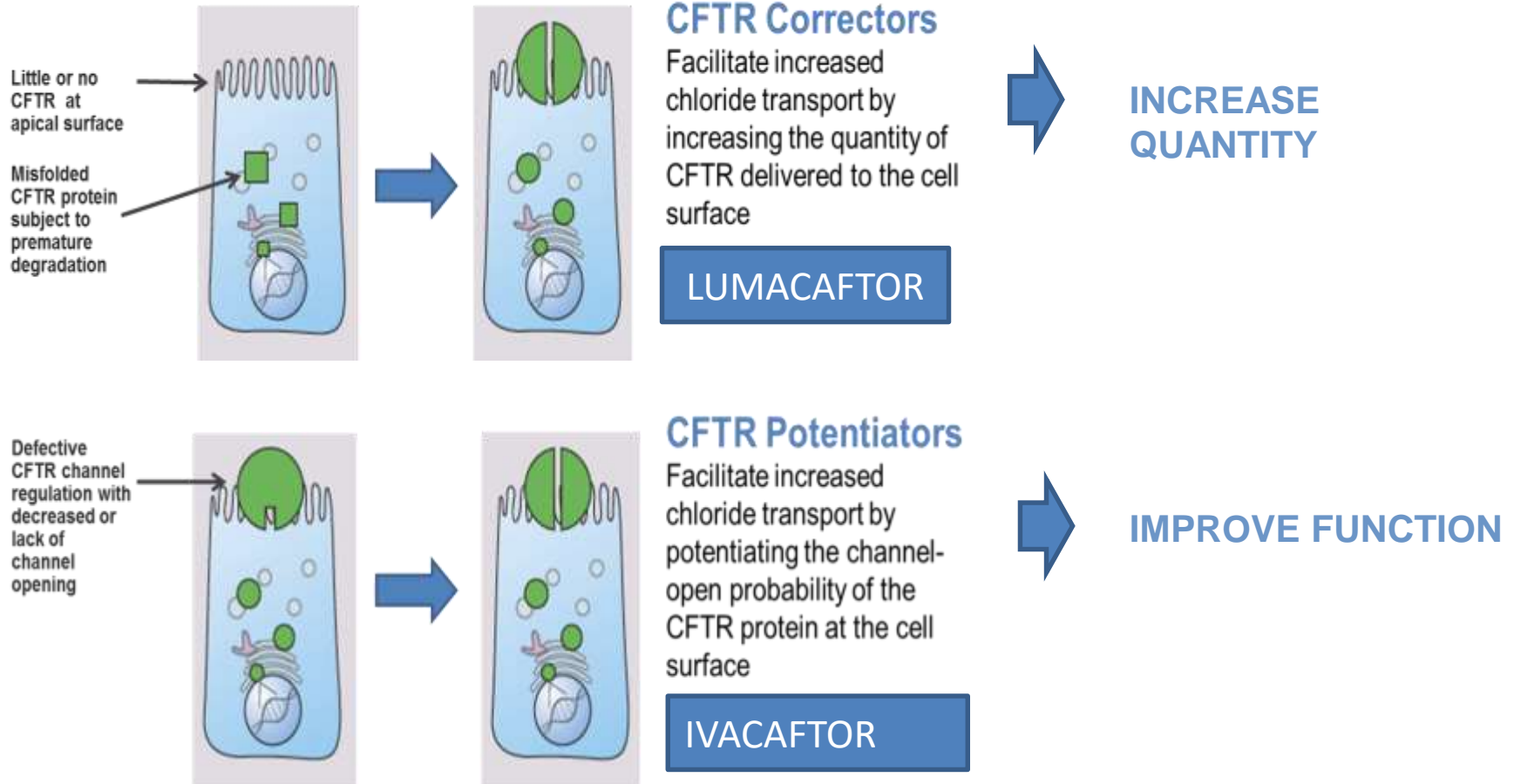
Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein **quantity** and **function**.<sup>3</sup>



- 1** Significantly reduced *F508del*-CFTR protein **quantity**...
- 2** ...and severely reduced **function** due to decreased channel-open probability...
- 3** ...results in little to no **total CFTR activity**



# ORKAMBI, the Combination of Lumacaftor and Ivacaftor, Addresses the Multiple Defects of the F508del-CFTR



1. Van Goor F et al. *Proc Natl Acad Sci U S A*. 2011;108(46):18843-18848.
2. Van Goor F et al. *Proc Natl Acad Sci U S A*. 2009;106(44):18825-18830.

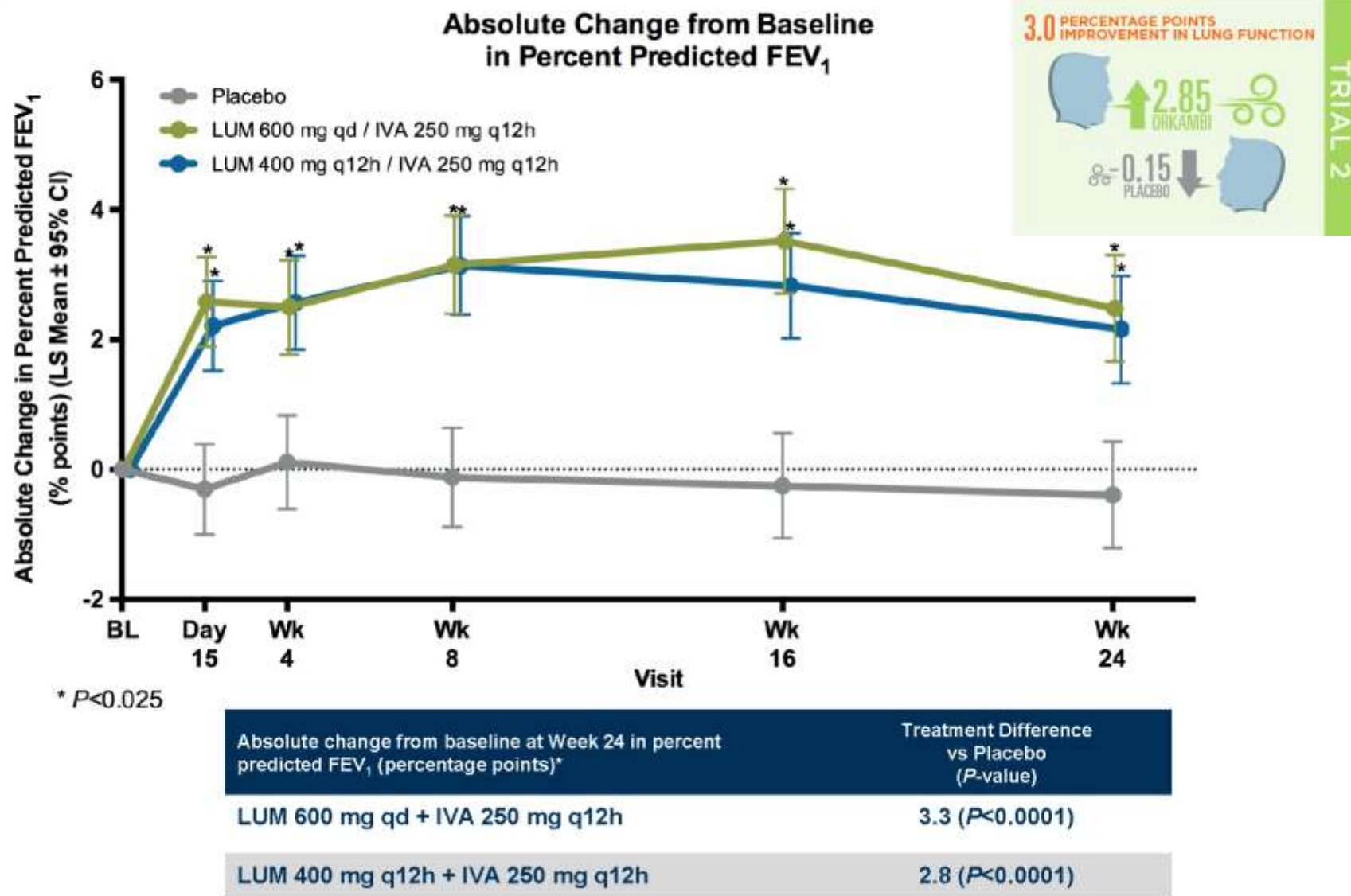
ORIGINAL ARTICLE

## Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

C.E. Wainwright, J.S. Elborn, B.W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J.C. Davies, K. De Boeck, P.A. Flume, M.W. Konstan, S.A. McColley, K. McCoy, E.F. McKone, A. Munck, F. Ratjen, S.M. Rowe, D. Waltz, and M.P. Boyle, for the TRAFFIC and TRANSPORT Study Groups.\*

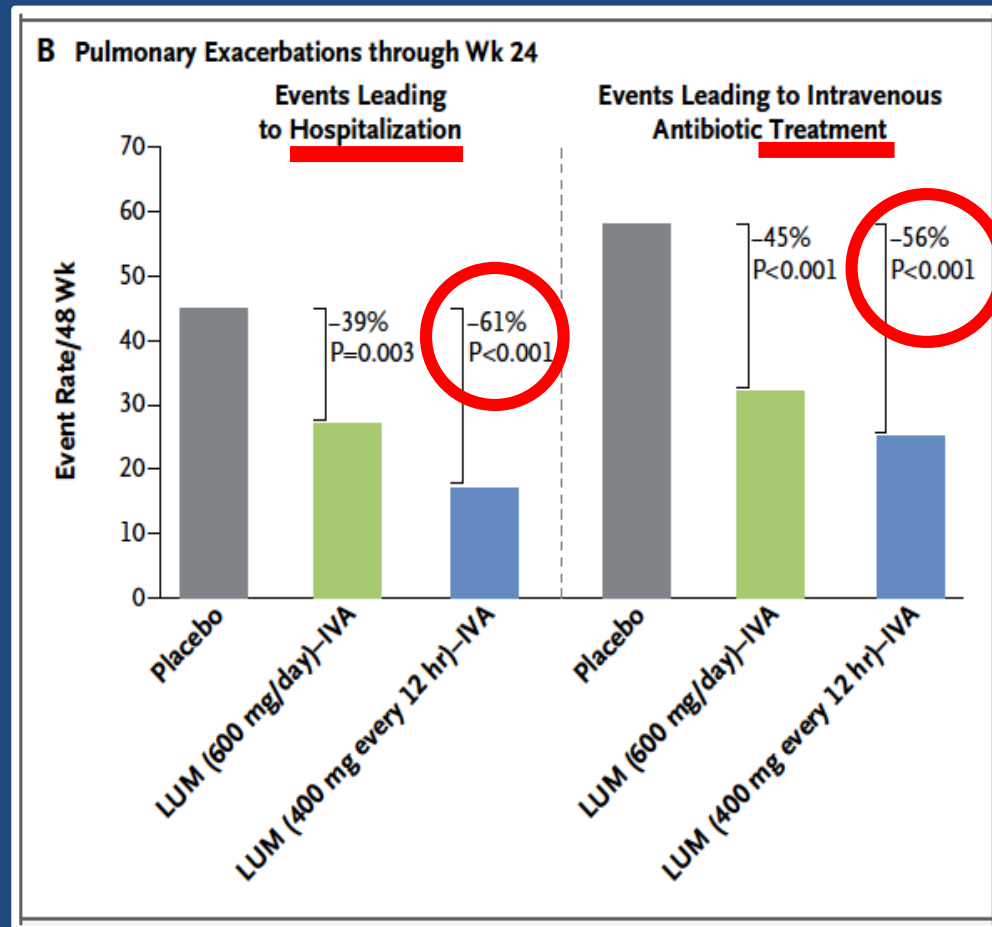
- TRAFFIC and TRANSPORT trials
- Randomized, double blind, placebo-controlled study
- 1108 patients
- Age >12 years
- 24 weeks

# Percent Predicted FEV<sub>1</sub>: Pooled TRAFFIC & TRANSPORT

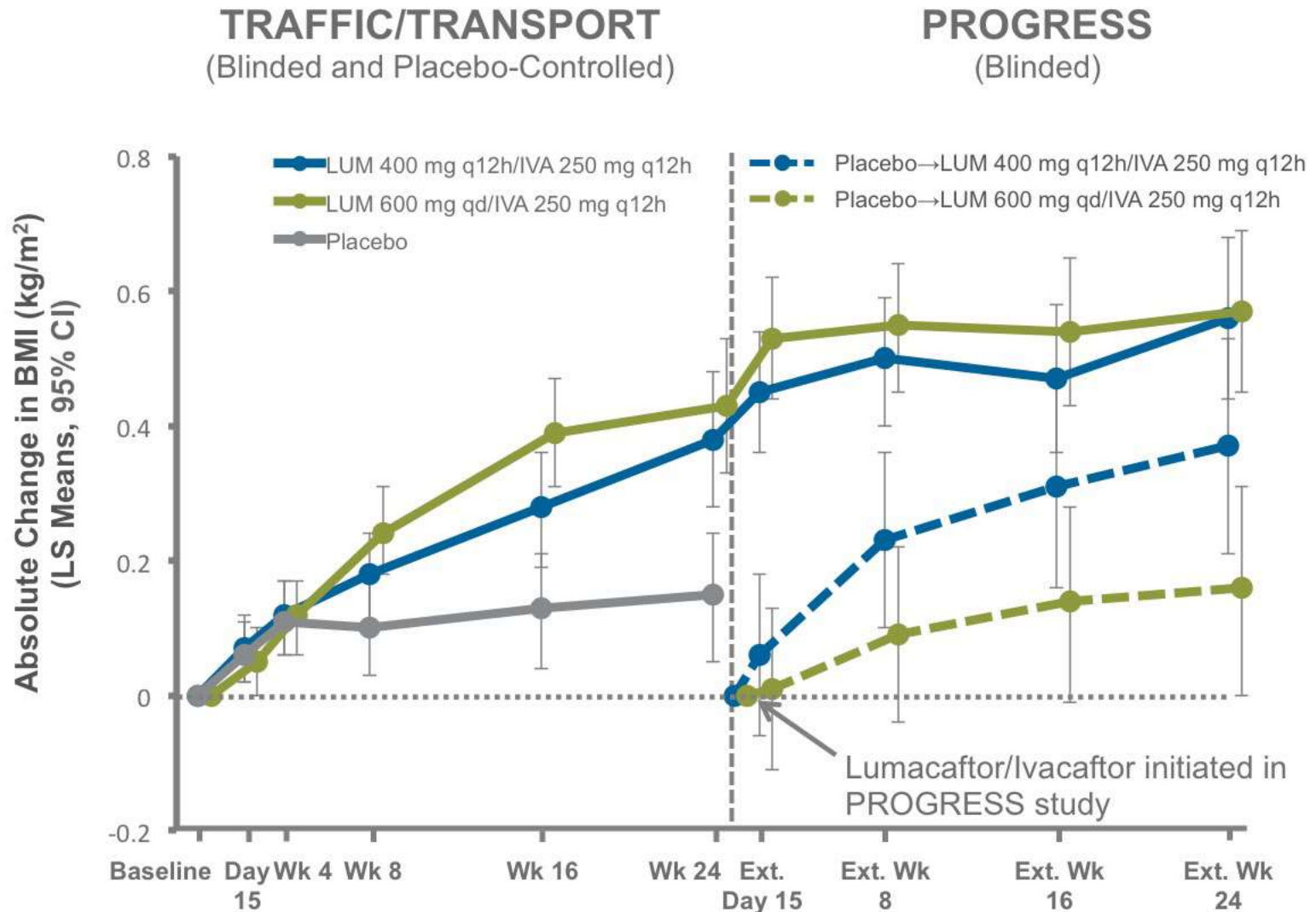


\*As assessed by the average absolute change from baseline at Weeks 16 and 24 according to the prespecified statistical analysis plan

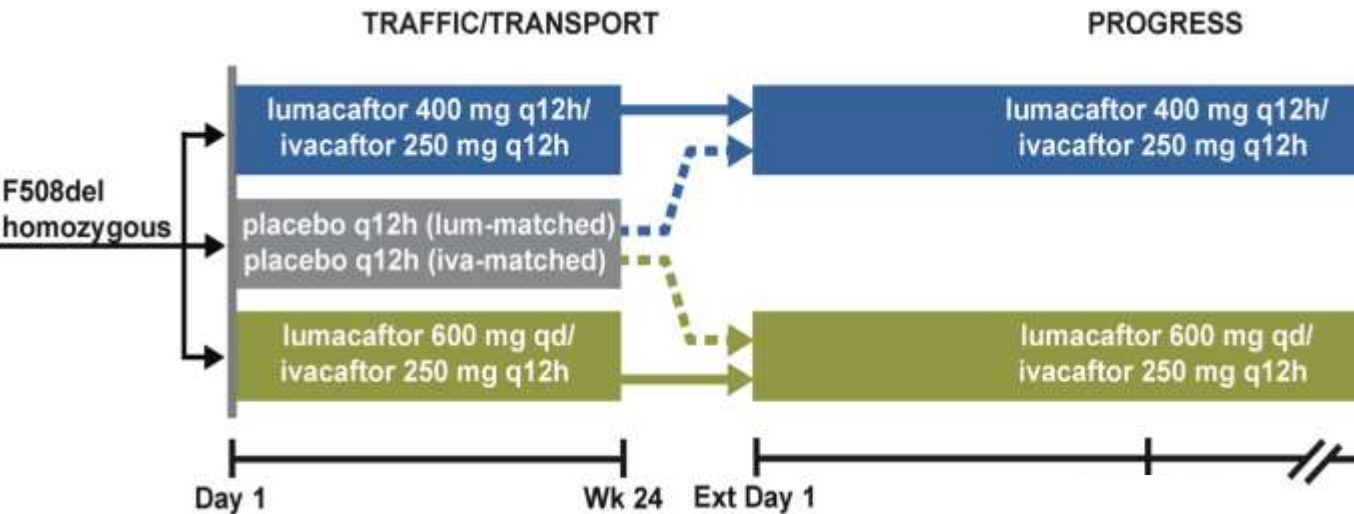
# Orkambi for F508del homozygote, >12y effect on Pulmonary Exacerbations



# BMI: Up to 48 Weeks of Treatment



# Orkambi – Study Design



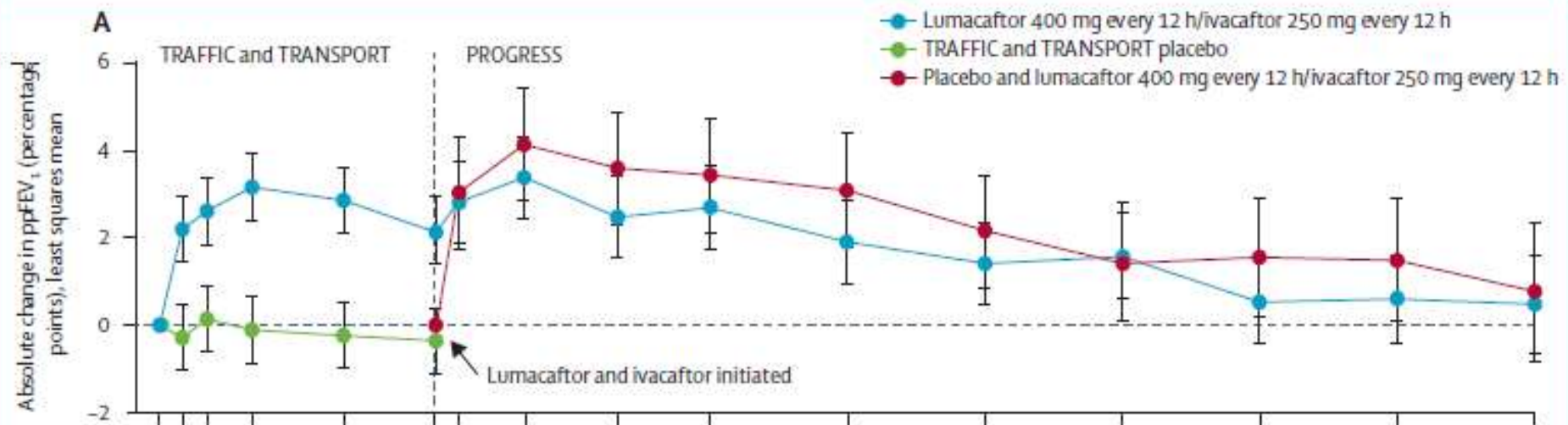
72 weeks

Total 120 weeks



# Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del*-CFTR mutation (PROGRESS): a phase 3, extension study

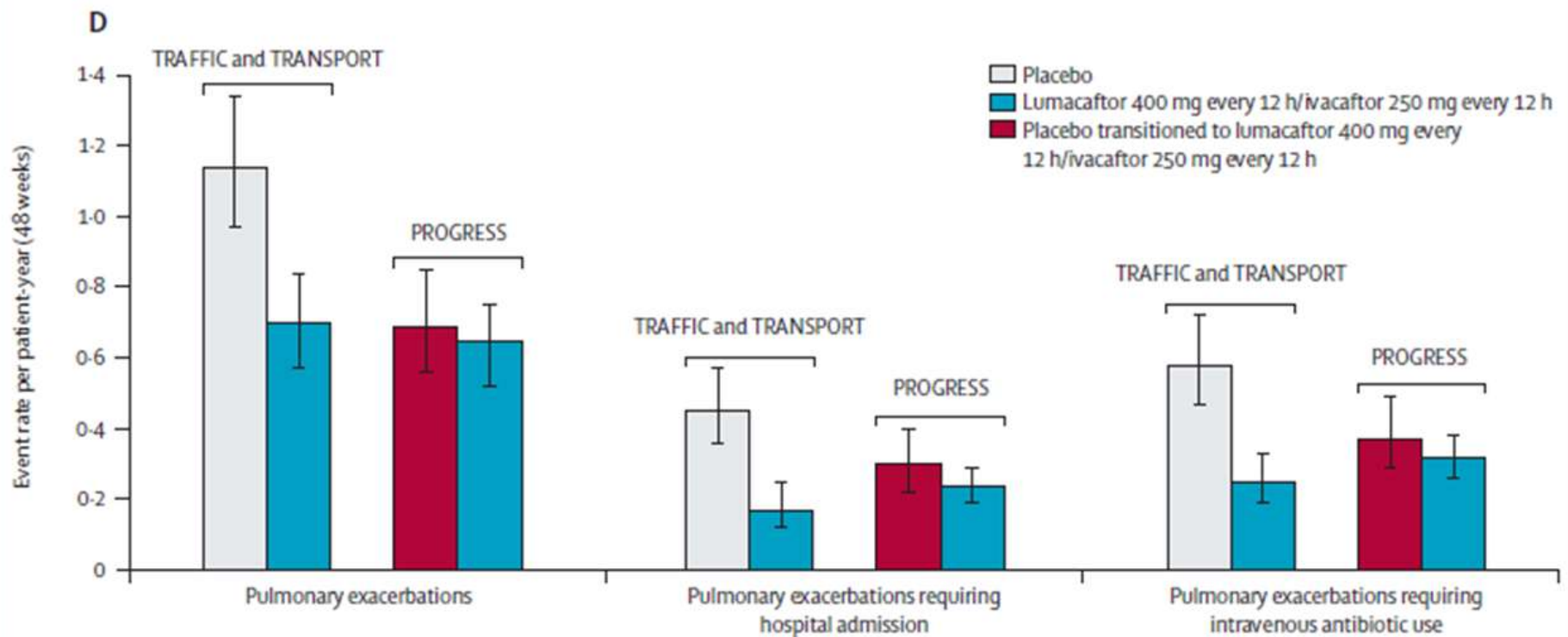
Michael W Konstan, Edward F McKone, Richard B Moss, Gautham Marigowda, Simon Tian, David Waltz, Xiaohong Huang, Barry Lubarsky, Jaime Rubin, Stefanie J Millar, David J Pasta, Nicole Mayer-Hamblett, Christopher H Goss, Wayne Morgan, Gregory S Sawicki



**LUM/IVA produced a durable treatment effect on ppFEV<sub>1</sub> through up to 120 weeks**

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Michael W Konstan, Edward F McKone, Richard B Moss, Gautham Marigowda, Simon Tian, David Waltz, Xiaohong Huang, Barry Lubarsky, Jaime Rubin, Stefanie J Millar, David J Pasta, Nicole Mayer-Hamblett, Christopher H Goss, Wayne Morgan, Gregory S Sawicki



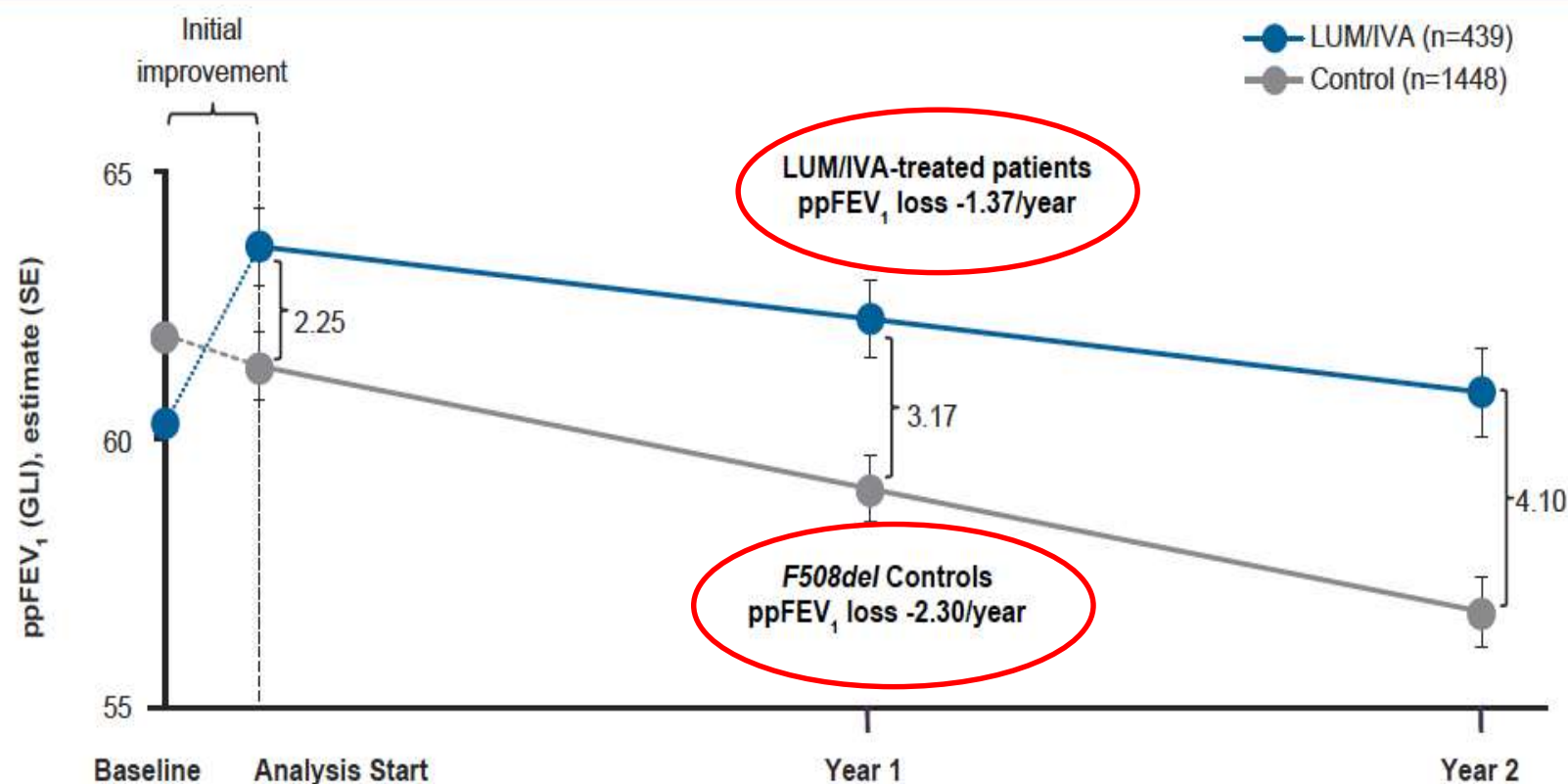


## Rate of Lung Function Decline Analysis

## Slower Lung Function Decline over 2y

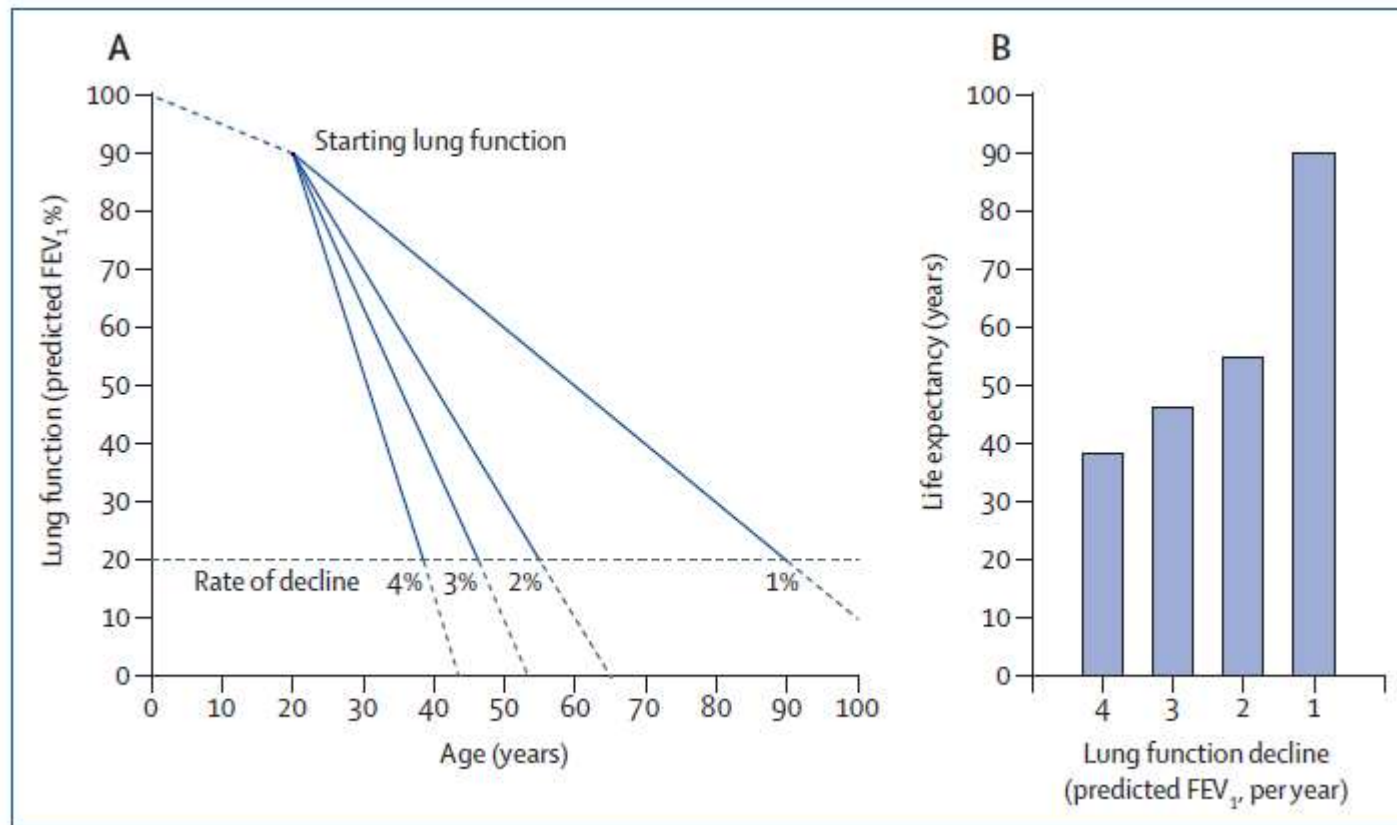
- 439 LUM/IVA-treated patients who met the inclusion criteria were matched with 1448 eligible CFFPR patients
- The annual rate of ppFEV<sub>1</sub> decline was reduced by 40.4% in LUM/IVA-treated patients compared with the propensity score matched CFFPR control group (-1.37 vs -2.30 percentage points, respectively;  $P=0.002$ ; Figure 4)

Figure 4. Estimated Annual Rate of ppFEV<sub>1</sub> Decline With LUM/IVA Compared With Propensity Score Matched Control Group of Patients Homozygous for *F508del* From the CFFPR



40% reduction in lung function decline

# A little CFTR can change a lot: slowing cystic fibrosis progress



...by reducing the average rate of decline from 4% to 3% per year starting at age 20 years, long-term mortality (or need for transplant) would be expected to be delayed by 6-8 years

# Age 6-11

AMERICAN JOURNAL OF

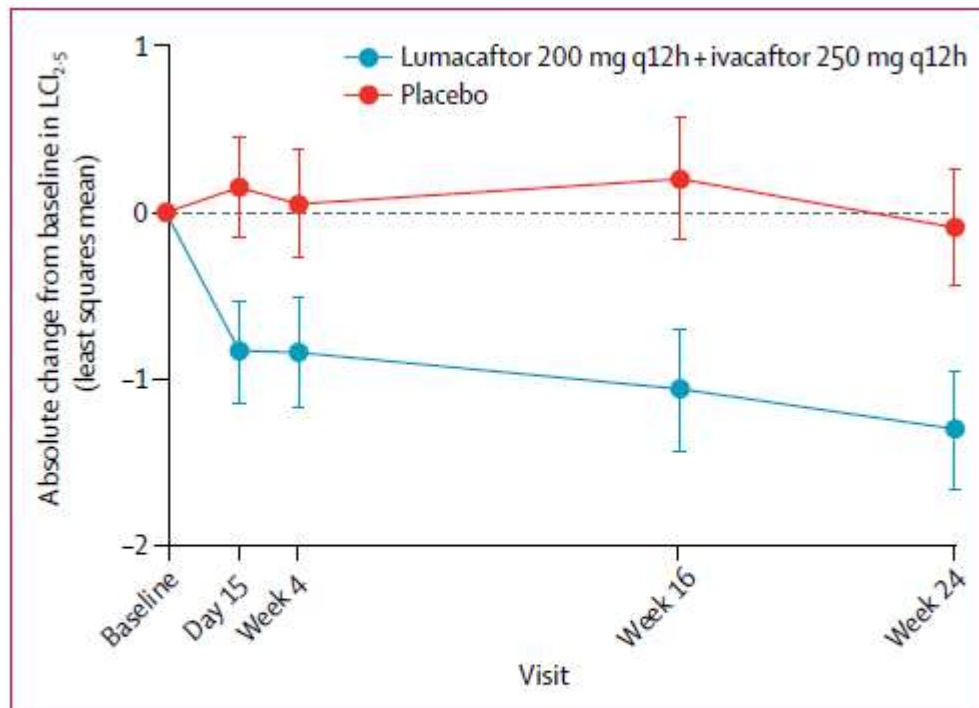
**Respiratory and  
Critical Care Medicine**

ITALIAN TRANSLATION OF SELECTED ARTICLES

**THE LANCET**  
Respiratory Medicine

# Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for *F508del*-CFTR: a randomised, placebo-controlled, phase 3 trial

Felix Ratjen, Christopher Hug, Gautham Marigowda, Simon Tian, Xiaohong Huang, Sanja Stanojević, Carlos E Milla, Paul D Robinson, David Waltz, Jane C Davies, on behalf of the VX14-809-109 investigator group\*



**Figure 2: Absolute change from baseline in  $LCI_{2.5}$**   
Values shown are adjusted for MMRM covariates. Error bars are 95% CI. Decrease in  $LCI_{2.5}$  indicates improvement.  $LCI_{2.5}$ =lung clearance index. MMRM=mixed-effects model for repeated measures. q12h=every 12 hours.

- Phase 3, randomized, double-blind, placebo-controlled, multicenter study
- 206 patients
- Primary endpoint: change in LCI
- Efficacy in the pediatric population at the early stages of disease
- The first to use LCI as a primary endpoint.

# The Israeli experience with Orkambi

# F508del homozygotes

>12 years	39
<i>On treatment</i>	<b>18</b>
Age < 12	9
<b>Total</b>	<b>48</b>

- Israeli CF patients (by database): 548
- F508del homozygotes: 9.3%

# F508del homozygotes >12y

Center	Eligible	On treatment
Carmel	13	3 (23%)
Hadassah	3	2 (67%)
Rambam	3	3 (100%)
Schneider	4	3 (75%)
Soroka	3	1 (33%)
Tel Hashomer	14	6 (43%)
<b>Total 2017</b>	<b>39</b>	<b>18 (46%)</b>
<b>Total 2016</b>	<b>39</b>	<b>12 (31%)</b>

# Israeli Patients on Orkambi

## Demographics

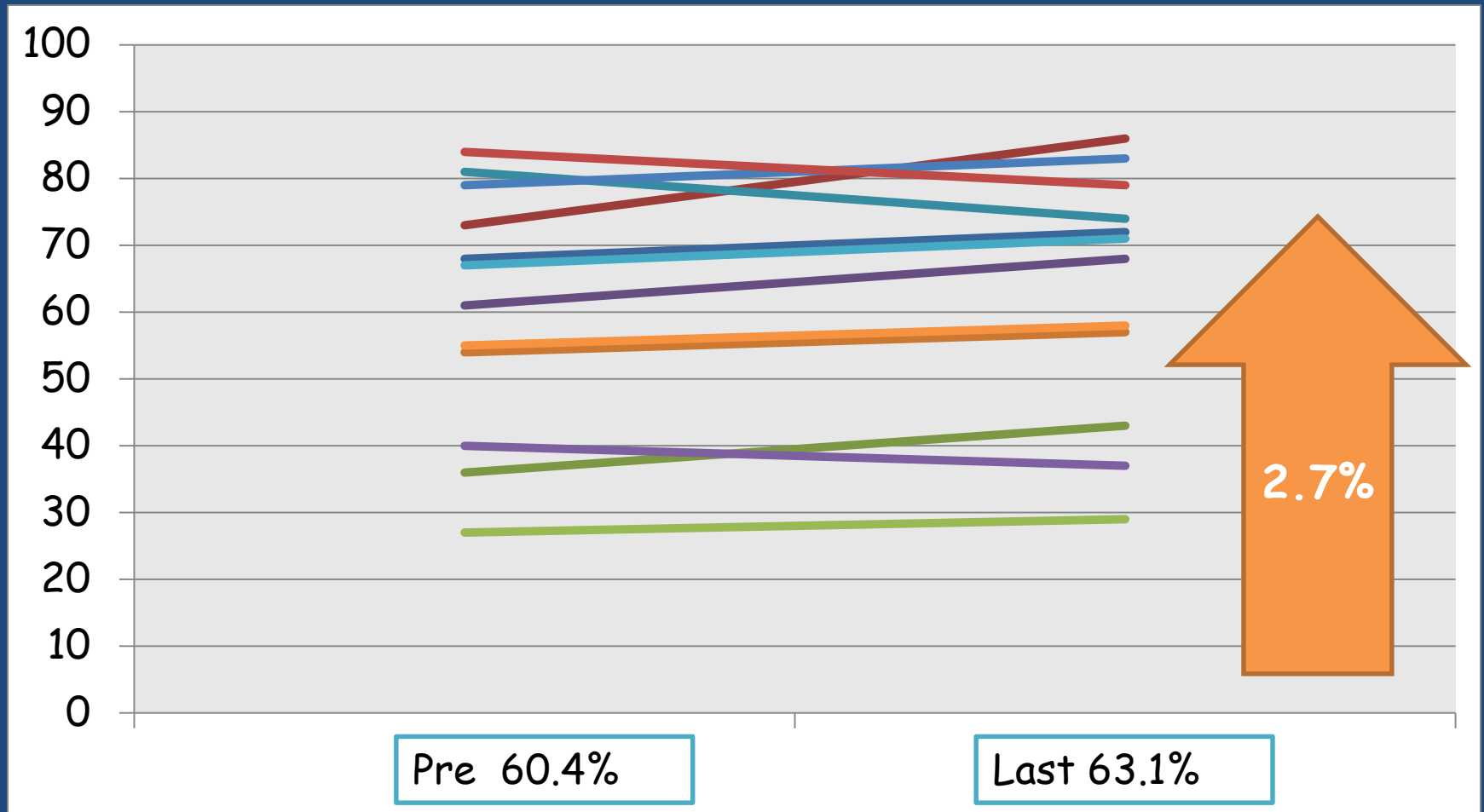
- n=18
- Starting Age
  - ✓ Mean: 23.9 ys
  - ✓ Range: 12-40 ys
- Current age
  - ✓ Mean: 25.3 ys
  - ✓ Median: 26.5 ys
- M:F 10:8
- PI: 100%
- CFRD: 50%
- Duration of treatment
  - ✓ Mean 1.3 years
  - ✓ Median 1.5 years (range 0.2-1.9 years)



# The Israeli experience

## Results

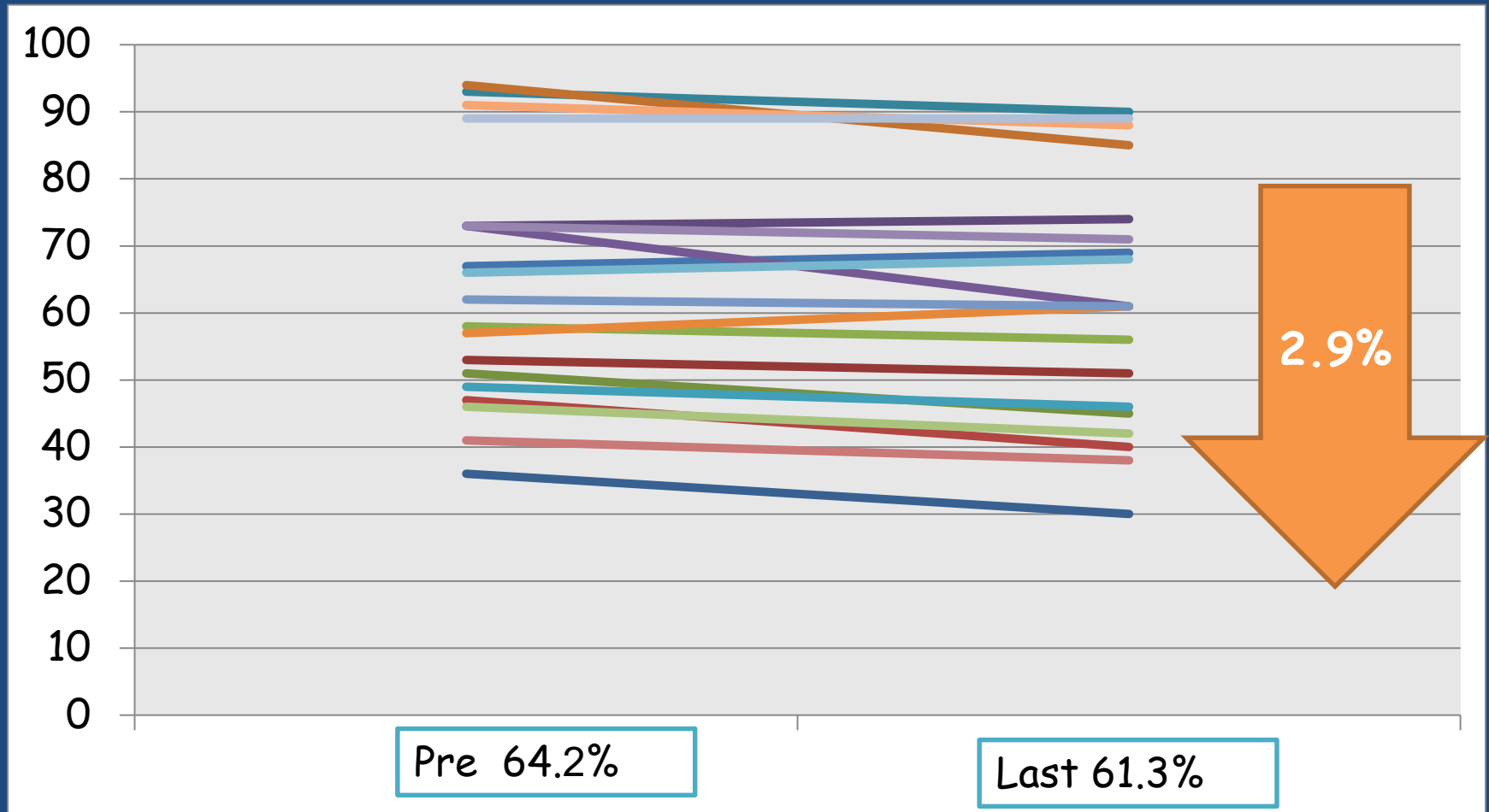
# FEV<sub>1</sub> % predicted



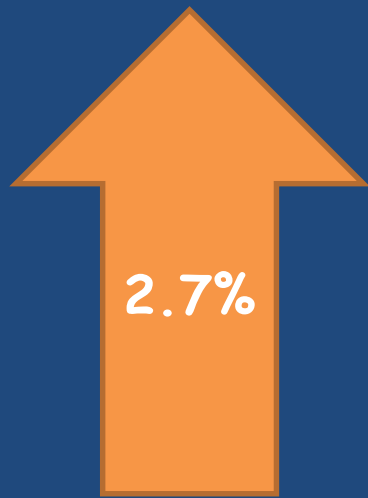
n=12

# FEV<sub>1</sub> % predicted untreated cohort

n= 18



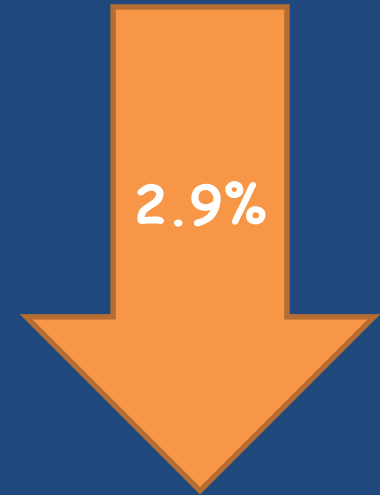
# FEV<sub>1</sub> % predicted



2.7%

Treated

Total  
improvement  
5.6%

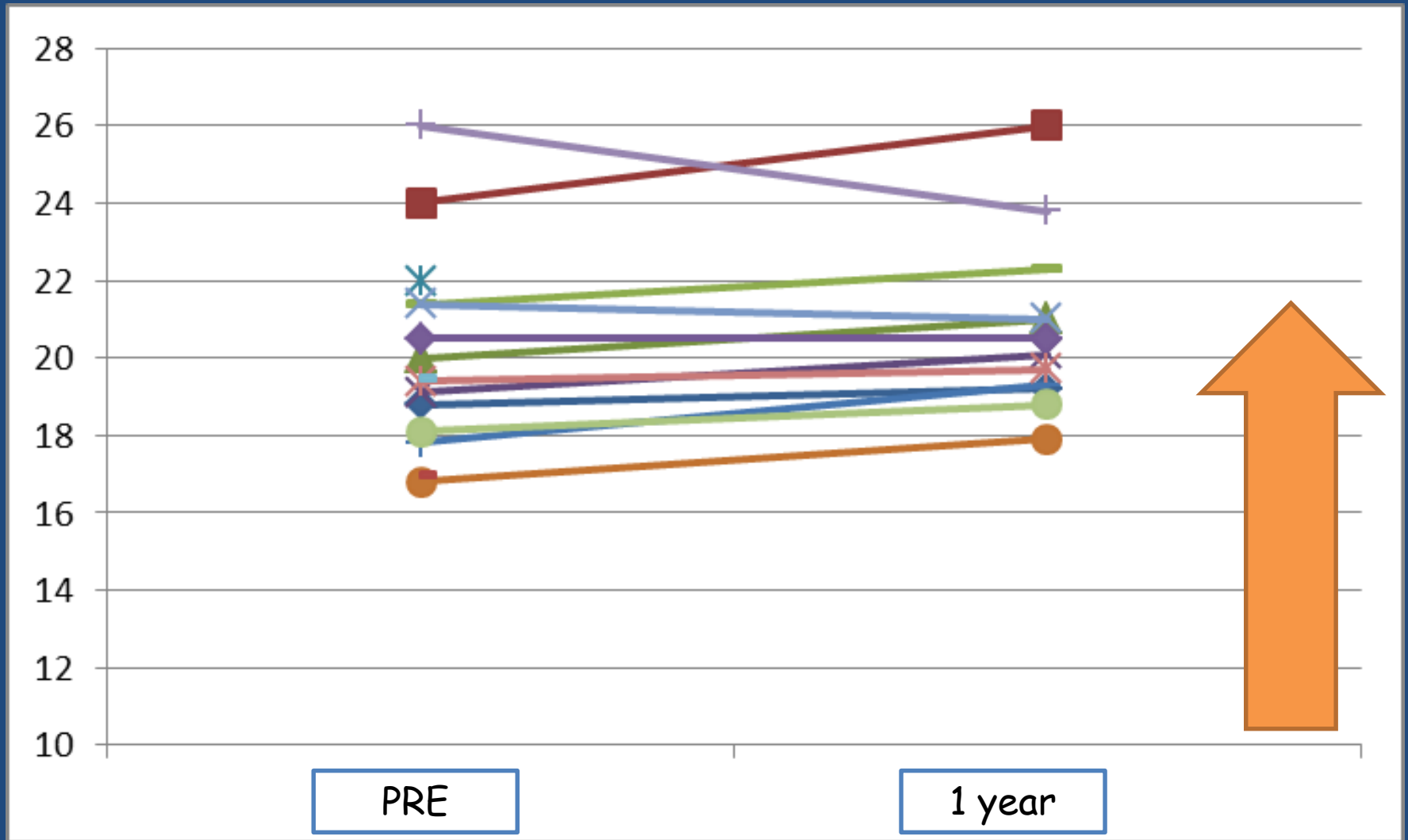


2.9%

Untreated

# BMI

n=13



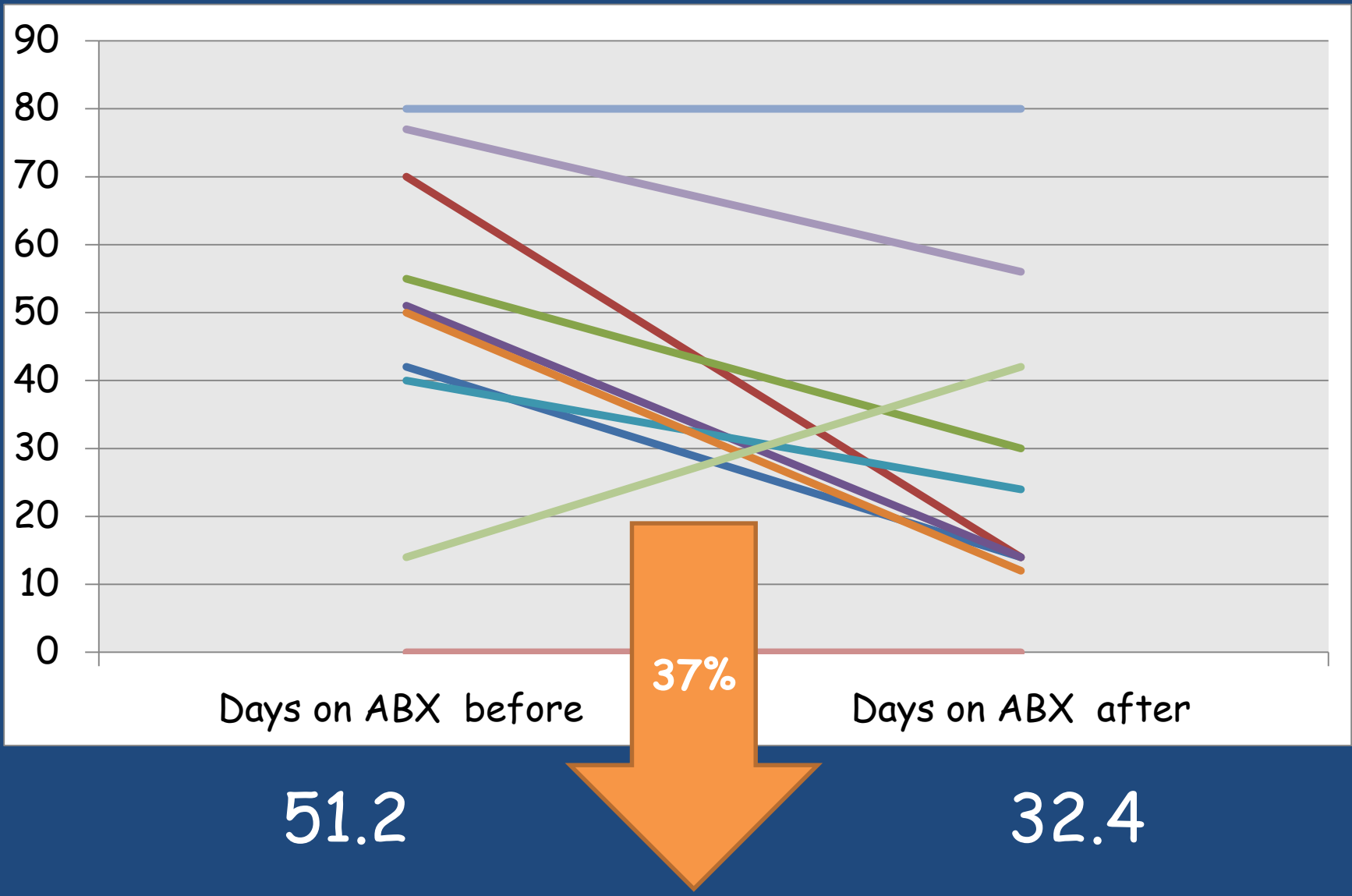
20.3 kg/m²

21.1 kg/m²

# Pulmonary exacerbations

- Modified Fuchs criteria?
- IV days?
- IV courses?
- Physician assessment?
- Patient self report?

# Days on antibiotic tx



# No effect on

- CFRD
  - ✓ CFRD:9; IGT:4; normal:5
  - ✓ HbA1C: pre 5.6% vs post 5.5%
- Pseudomonas status
- CFQ-R (?)



# Adherence

- Orkambi

**A Pilot Study to Evaluate the Use of Smart Adherence Technology to Measure Lumacaftor/Ivacaftor Adherence in CF Subjects Homozygous for the F508del CFTR Mutation**

**This study has been terminated.**

*(Study terminated early due to slow recruitment of patients.)*

**Sponsor:**

**Vertex** Pharmaceuticals Incorporated

 U.S. National Library of Medicine

*ClinicalTrials.gov*

ClinicalTrials.gov Identifier:

NCT02823470

First Posted: July 6, 2016

Last Update Posted: September 11, 2017

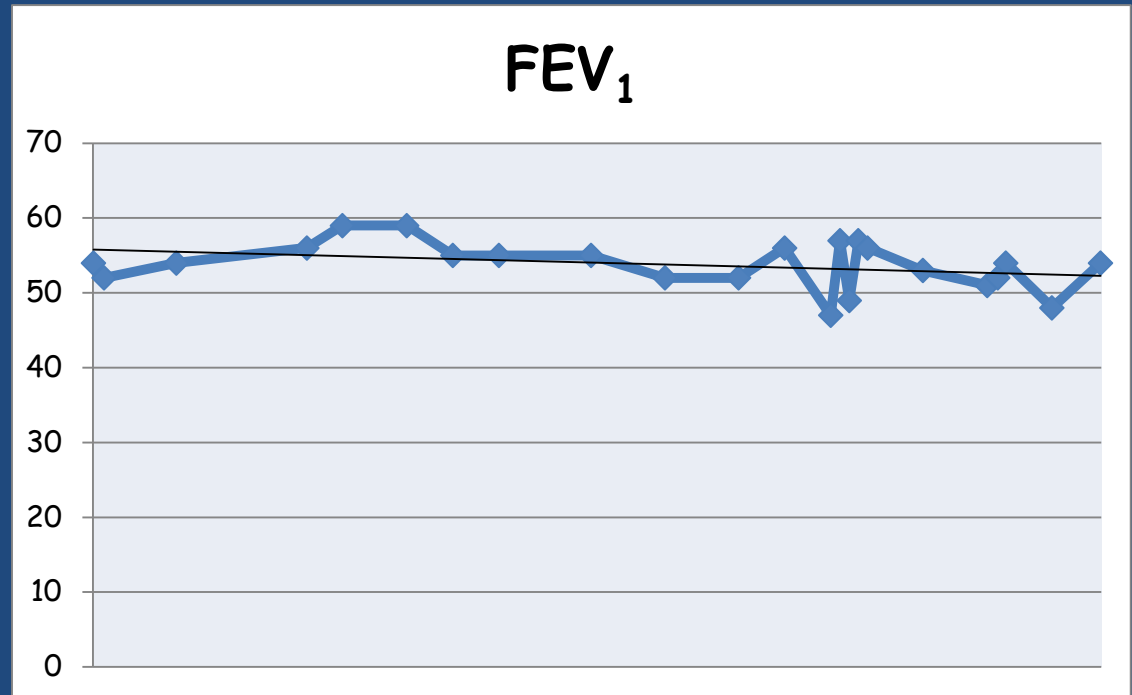
- CF treatments and therapies

# Variability in clinical response to Orkambi

- Improvement

- Stability

- No change



# Variability in clinical response to Orkambi

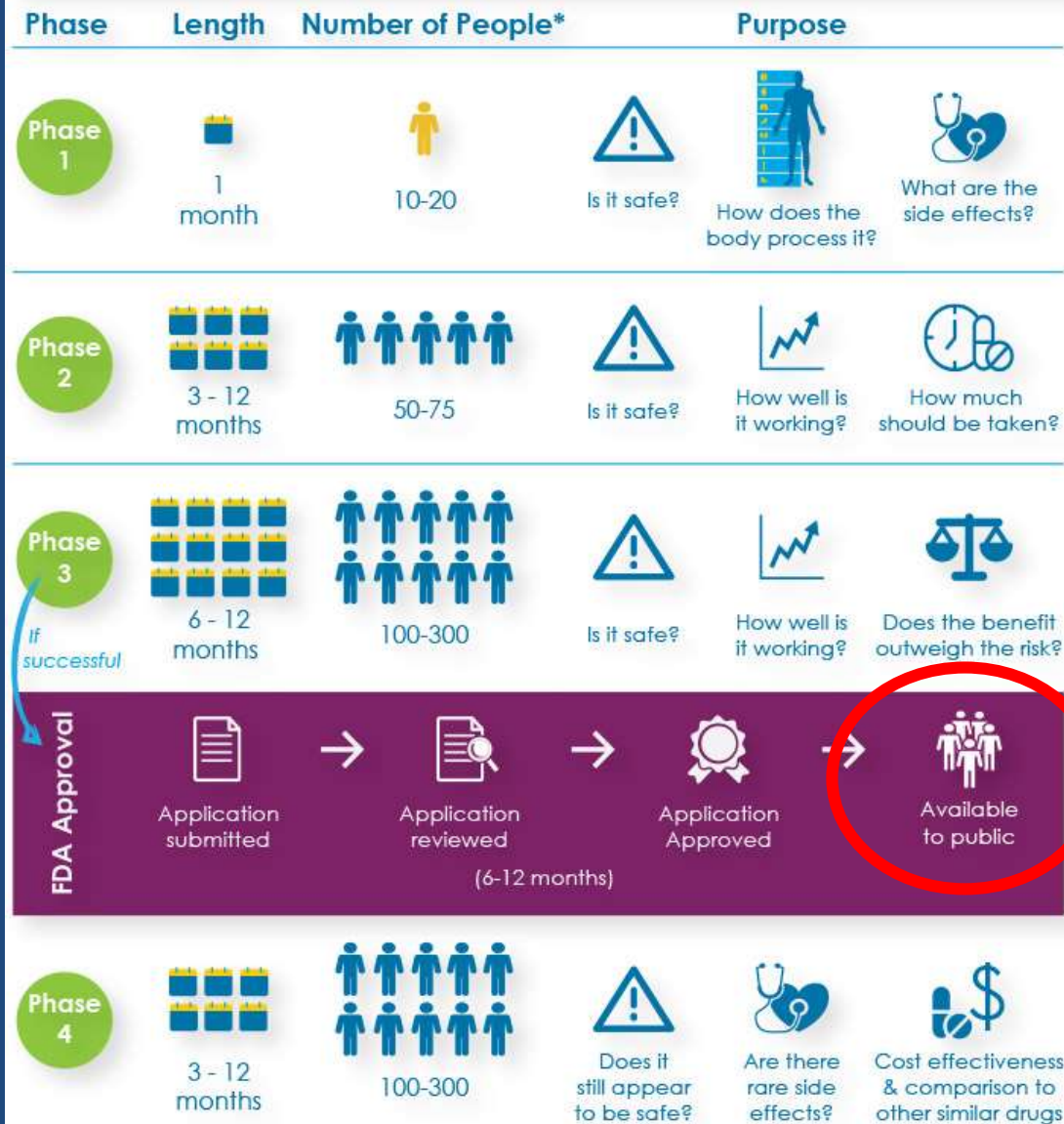
- Treatment discontinued
  - ✓ 2 patients: respiratory deterioration and severe dyspnea.
    - 1 s/p lung transplant
  - ✓ 1 patient: cataract + no improvement
- Specific / complicated subpopulations
  - ✓ ABPA
  - ✓ Severe lung disease
  - ✓ Mycobacterium Abscessus

כל מקרה הוא  
עולם ומלואו...

# Limitations

- Retrospective study
- Small number of patients
- Variability in data reporting
- Variability in measurements
  - ✓ spirometry reference values
- Lack of pre-established definitions
  - ✓ Pulmonary exacerbations
- Lack of uniformity in treatment
- ...
- ...

# CLINICAL TRIAL PROCESS



= 15 healthy participants



= 15 participants with CF



= Number of months of participant involvement

\*number of participants varies based on study characteristics

Available to public

## סל הבריאות Health basket

### התרופה שמאריכה חיי חולים בעשור ולא נכנסה לסל

תקציב הסל גדל ל-460 מיליון שקל בשנה, ואיפשר להכניס תרופות שלא נכנסו בעבר סיפורה של התרופה אורקמי לטיפול בחולי סיסטיק פיברוזיס, שנחשבת ליעילה במיוחד אך לא נכנסה לסל, היא דוגמה לדילמות הבלתי אפשריות שעומדות בפני ועדת סל התרופות



TheMarker

רוני לינדר-גנץ | התראות במייל

07:51 05.01.2017

# Thanks

- CF patients
- Israel CF centers