IVACAFTOR

ONE PATIENT TELLS IT ALL

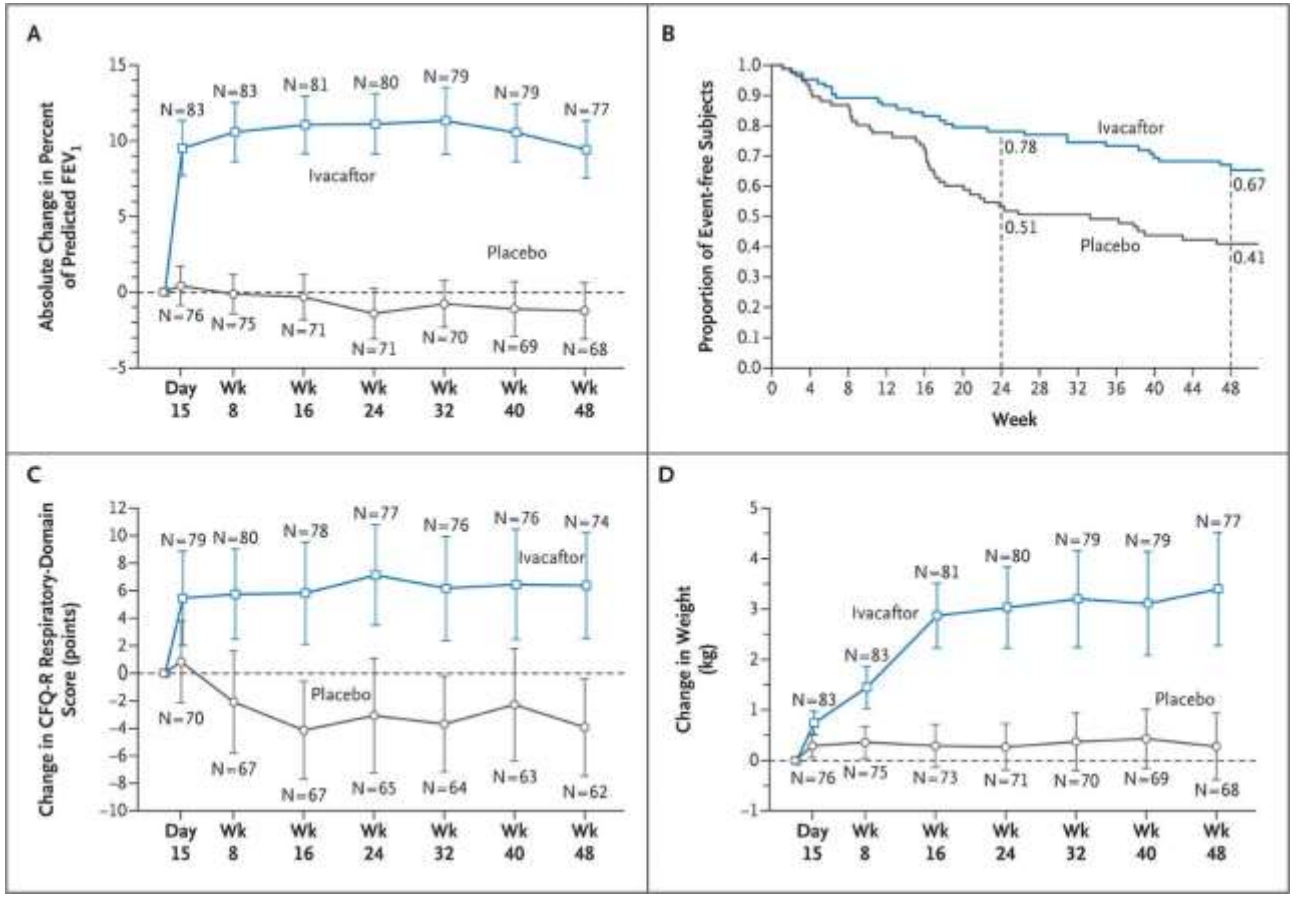
ALEX GILELES-HILLEL, MD

CF CENTER- HADASSAH- HEBREW UNIVERSITY MEDICAL CENTER

JERUSALEM

ANNUAL ISRAELI CF CONFERENCE, NOVEMBER 19-21 2017

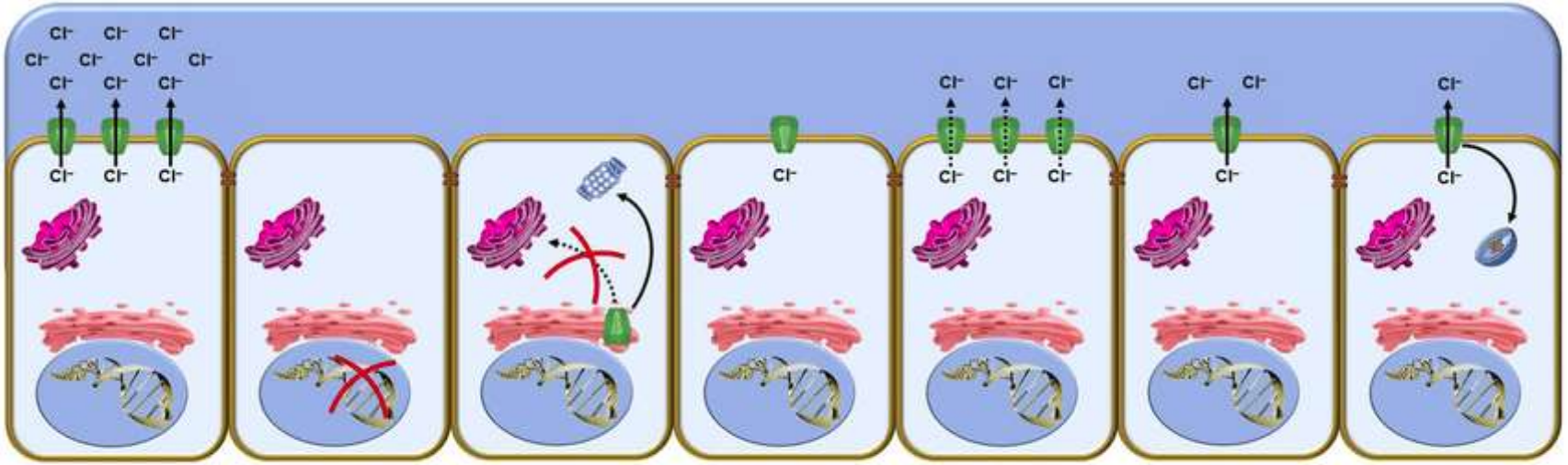
SOME HISTORY – IVACAFTOR FOR G551D



Ramsey BW et al. N Engl J Med 2011

The NEW ENGLAND JOURNAL of MEDICINE

In Israel, Kalydeco (ivacaftor) is indicated for the treatment of CF in patients ≥6 years who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*

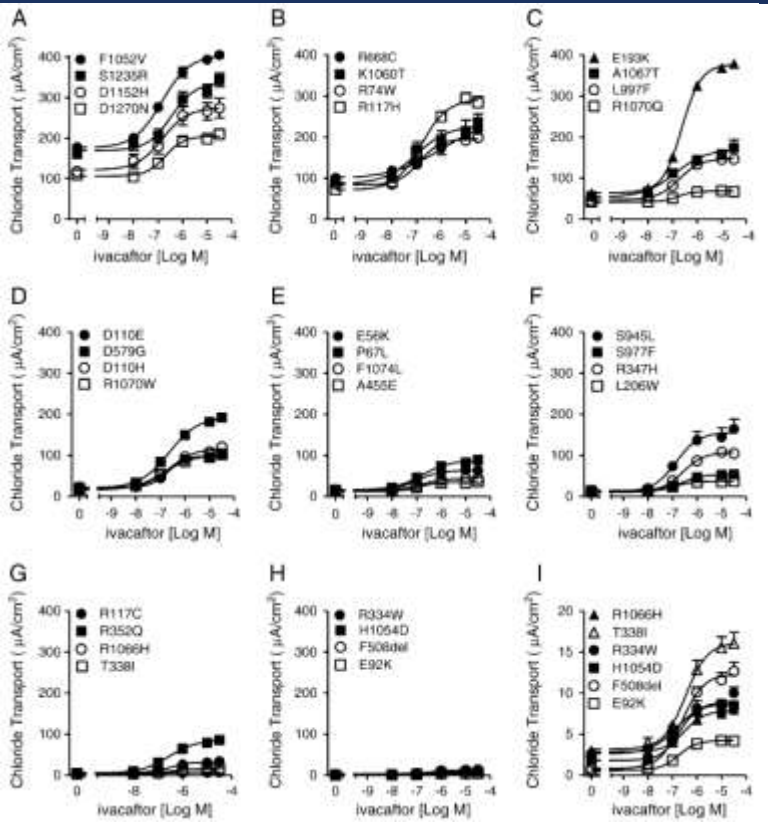


	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

Lopes-Pacheco M, CFTR Modulators: Shedding Light on Precision Medicine for Cystic Fibrosis. Front Pharmacol. 2016

IS IVACAFTOR JUST FOR CLASS III?

- Clinical phenotype of patients with "residual function" mutations is characterized by a later diagnosis, preserved pancreatic function and a slower disease progression
- Preclinical in vitro have shown promise in Ivacaftor treatment for residual function CFTR mutations



* Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. *J Cyst Fibros*. 2014

Guigui S, Wang J, Cohen RI. The use of ivacaftor in CFTR mutations resulting in residual functioning protein. *Respiratory Medicine Case Reports*. 2016

* Pilewski J, Higgins M, Cooke J, et al. A phase 3 extension study evaluating the safety and efficacy of long term ivacaftor (IVA) in patients with cystic fibrosis (CF) and phenotypic or molecular evidence of residual CFTR function [EPS1.5]. Presented at the 40th Annual European Cystic Fibrosis Conference, 07-10 June 2017, Seville, Spain.

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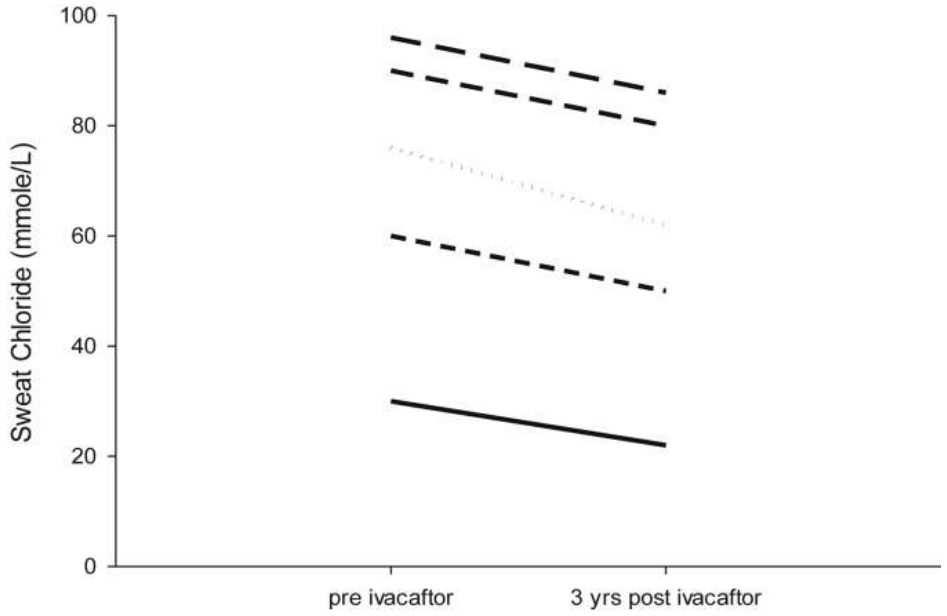

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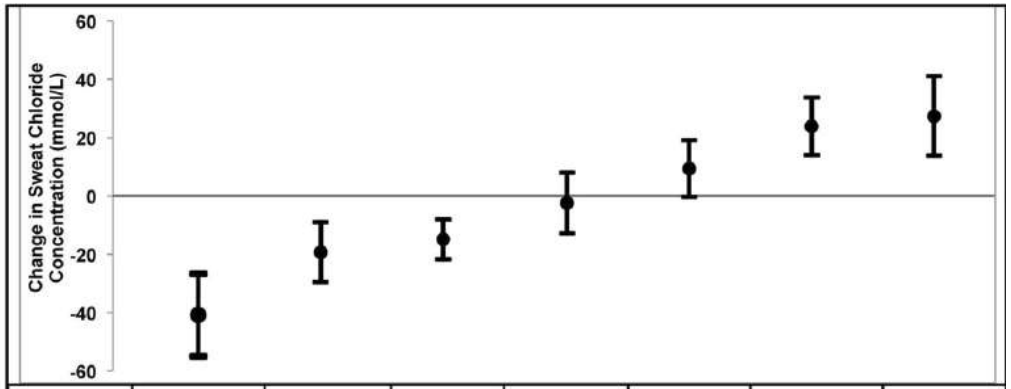
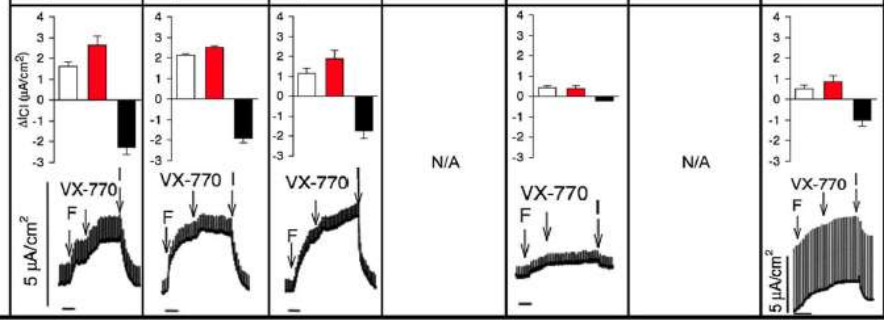
- A recent study reported the sweat chloride changes in 7 subjects with "residual function" mutations treated with Ivacaftor for 2 weeks – all with stable clinical status.

Subject	1	2	3	4	5	6	7
CFTR genotype	F508del	G542X	F508del	R334W	1717-1G->A	1717-1G->A	F508del
	1154insTC	3849 +10kbC->T	Y563N	681delC	G85E	A455E	A455E
Age (years)	20	59	16	25	27	20	19
Sex	Male	Male	Female	Male	Female	Female	Female
Race/ethnicity	White	White	White	Persian	Latino	White	White
Pancreatic sufficient	No	Yes	Yes	Yes	No	Yes	Yes
Sweat chloride concentration (mmol/L)	134	56	108	109	106	78	66
Baseline FVC (%)	N/A	69%	71%	58%	101%	92%	116%
Baseline FEV_1 (%)	N/A	50%	50%	54%	77%	67%	115%

McGarry ME, et al. In vivo and in vitro ivacaftor response in cystic fibrosis patients with residual CFTR function: N-of-1 studies. Pediatr Pulmonol. 2017 Apr;52(4):472-479.



Subject	1	2	3	4	5	6	7
CFTR Genotype	F508del 1154insTC	G542X 3849+10kbC->T	F508del Y563N	R334W 681delC	1717-1G->A G85E	1717-1G->A A455E	F508del A455E
Sweat Chloride Concentration Change	-40.8 (-55.0 to -26.6) p<0.001	-19.3 (-29.5 to -9.0) p<0.001	-14.8 (-21.7 to -8.0) p<0.001	-2.5 (-12.9 to +7.9) p=0.6	+9.3 (-0.3 to +19.0) p=0.06	+23.8 (+13.9 to +33.7) p<0.001	+27.3 (+13.7 to +41.0) p<0.001
	1.6 fold increase p=0.003	1.2 fold increase p=0.002	1.7 fold increase p=0.007	N/A	No change P=0.7	N/A	No change p=0.06
Chloride Current Change In Nasal Epithelium Cultures				N/A		N/A	

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List of CFTR mutation currently approved for Ivacaftor treatment

E56K	*G178R*	*S549R*	*K1060T*	*G1244E*
P67L	*E193K*	*G551D*	*A1067T*	*S1251N*
R74W	*L206W*	*G551S*	*G1069R*	*S1255P*
D110E	*R347H*	*D579G*	*R1070Q*	*D1270N*
D110H	*R352Q*	*S945L*	*R1070W*	*G1349D*
R117C	*A455E*	*S977F*	*F1074L*	
R117H	*S549N*	*F1052V*	*D1152H*	

A455E

CASE REPORT

- 44 year old CF-PS patient, married + 6
- Compound heterozygote for: A455E / F508
- Baseline Sweat Chloride test – 88 mmol/l
- Chronic mucoid Pseudomonas aeruginosa in sputum
- Good nutritional status
- Recurrent pancreatitis
- Frequent pulmonary exacerbations (4-6 / year).
- Baseline pulmonary function FEV_1 ~ 37% predicted

Ivacaftor – 1.12.2016

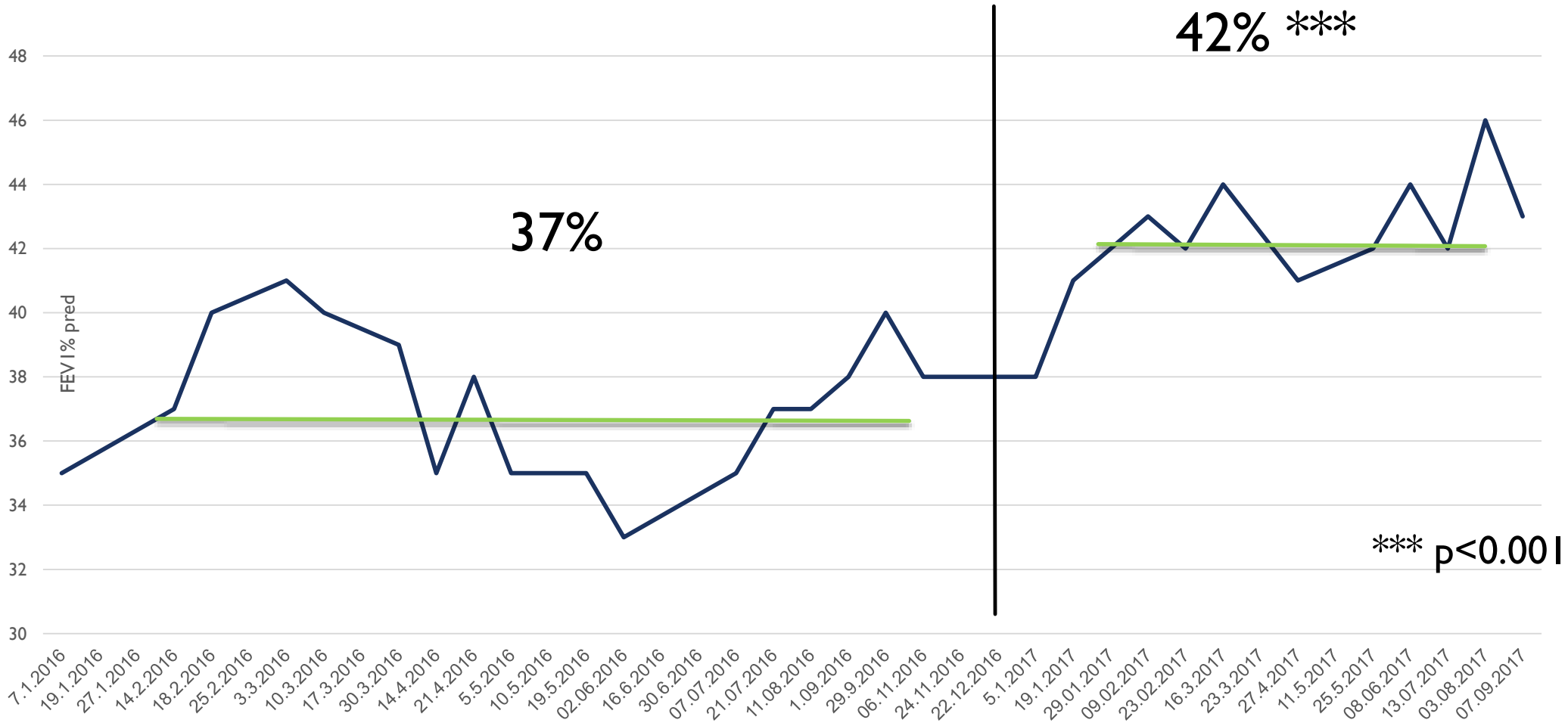
CHLORIDE TRANSPORT – NO CHANGE…

	Baseline	8 weeks post	44 weeks post
Basal	-30	-31	-33
Amiloride	-19	-21	-11
Chloride free	-16	-17	-9
Isoproterenol	-13	-15	-8

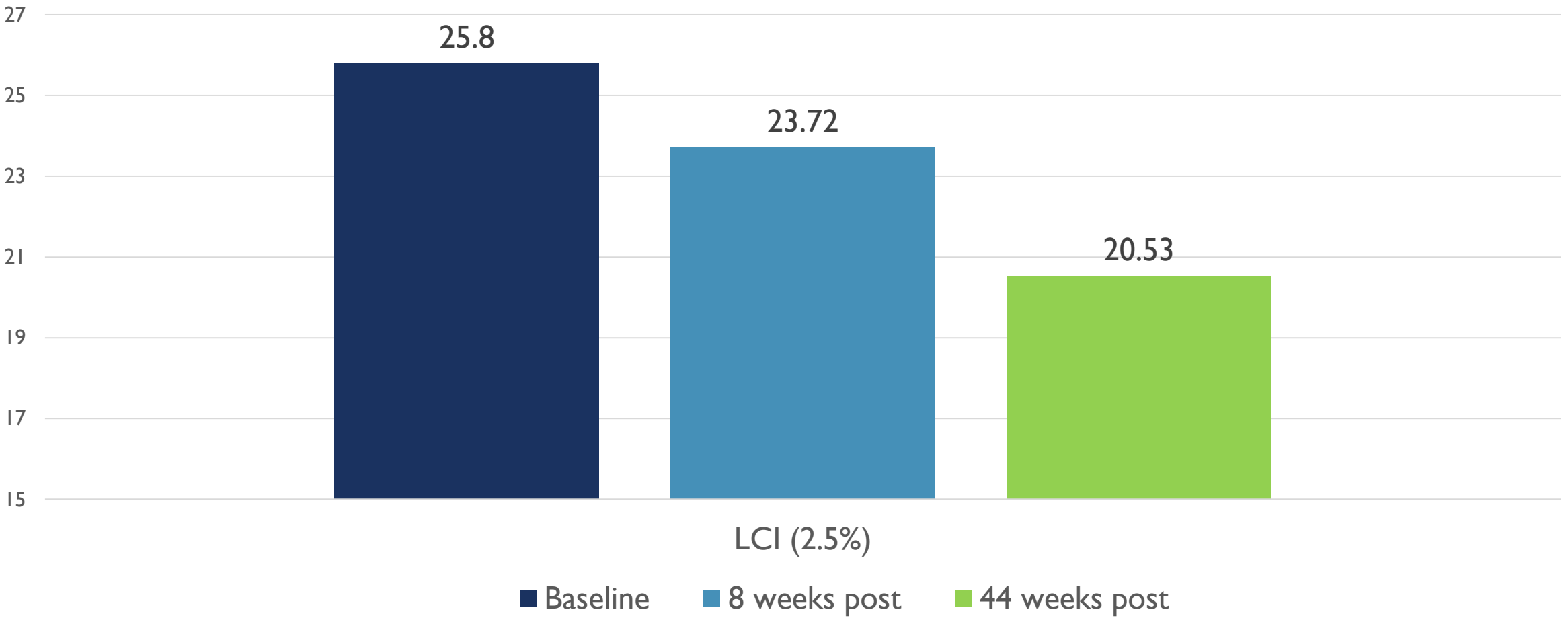
Sweat test (baseline) – 88 mmol/l

Sweat test (44 weeks post) – 103 mmol/l

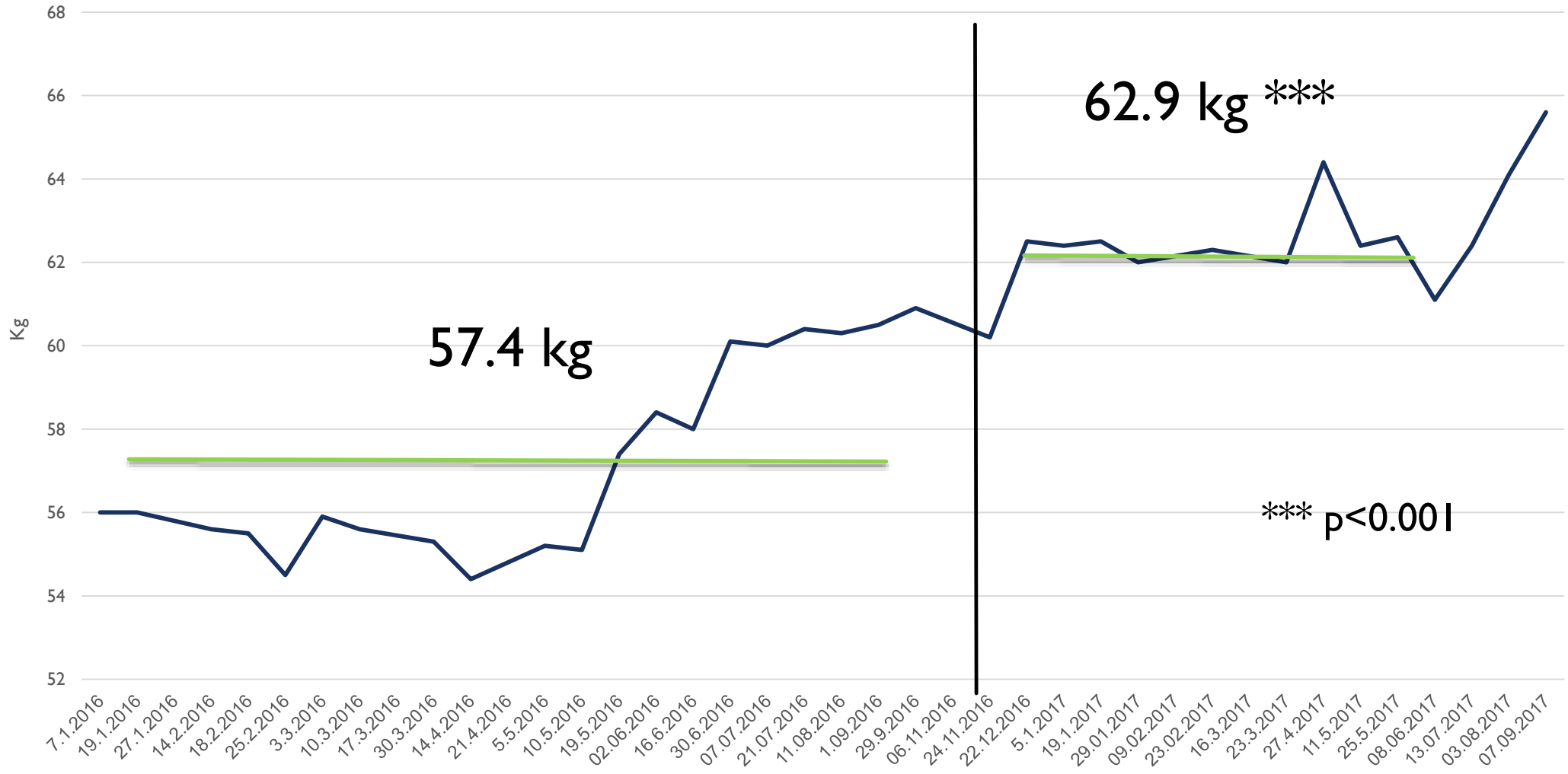
FEV1%


42% ***
37%
*** p<0.001
FEV1% pred
48
46
44
42
40
38
36
34
32
30
7.1.2016
19.1.2016
27.1.2016
14.2.2016
18.2.2016
25.2.2016
3.3.2016
10.3.2016
17.3.2016
30.3.2016
14.4.2016
21.4.2016
5.5.2016
10.5.2016
19.5.2016
02.06.2016
16.6.2016
30.6.2016
07.07.2016
21.07.2016
11.08.2016
1.09.2016
29.9.2016
06.11.2016
24.11.2016
22.12.2016
5.1.2017
19.1.2017
29.01.2017
09.02.2017
23.02.2017
16.3.2017
23.3.2017
27.4.2017
11.5.2017
25.5.2017
08.06.2017
13.07.2017
03.08.2017
07.09.2017

MULTIPLE BREATH WASHOUT TEST



WEIGHT


68
66
64
62
60
58
56
54
52
Kg
57.4 kg
62.9 kg ***
*** p<0.001
7.1.2016
19.1.2016
27.1.2016
14.2.2016
18.2.2016
25.2.2016
3.3.2016
10.3.2016
17.3.2016
30.3.2016
14.4.2016
21.4.2016
5.5.2016
10.5.2016
19.5.2016
02.06.2016
16.6.2016
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07.07.2016
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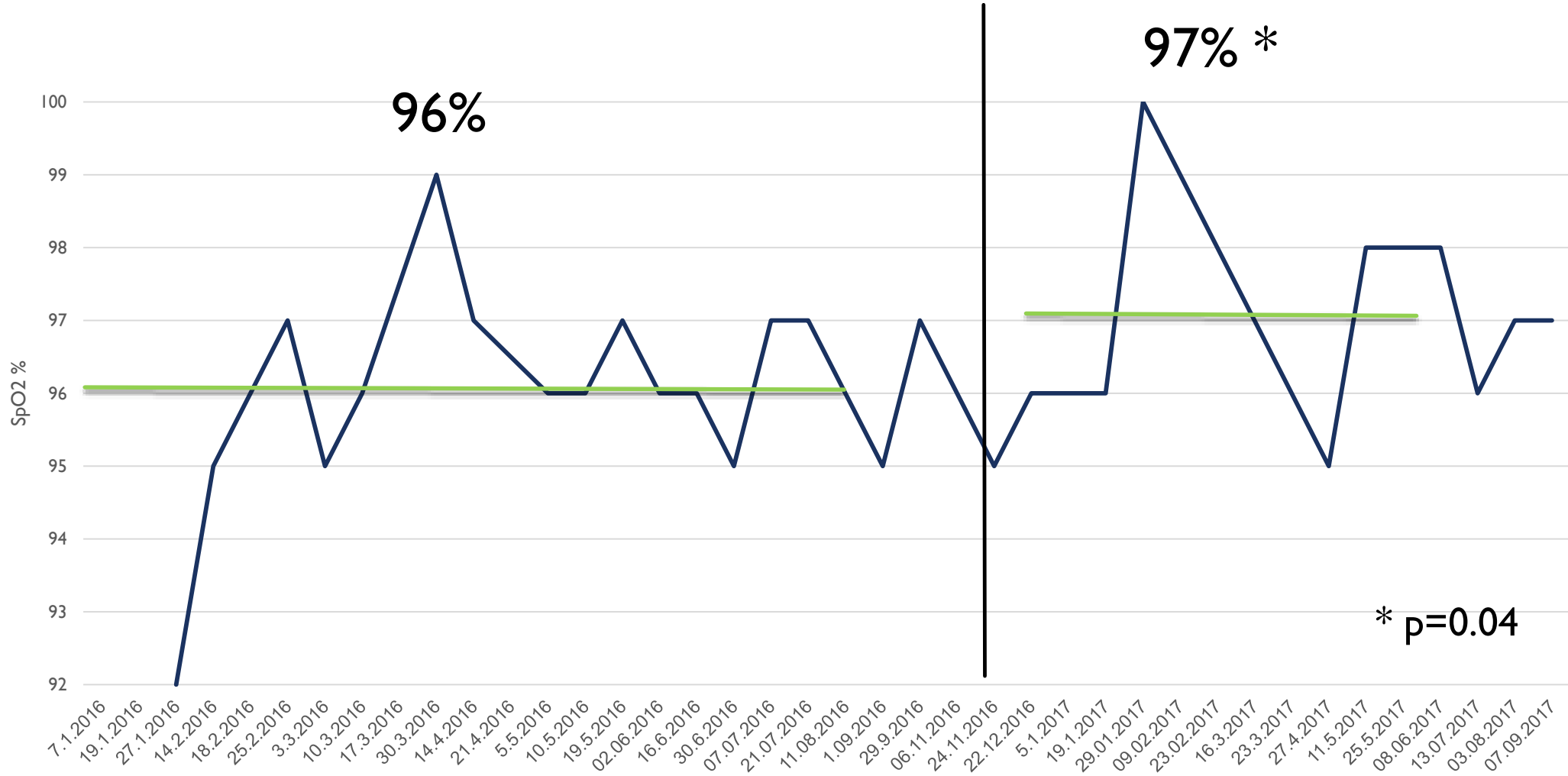
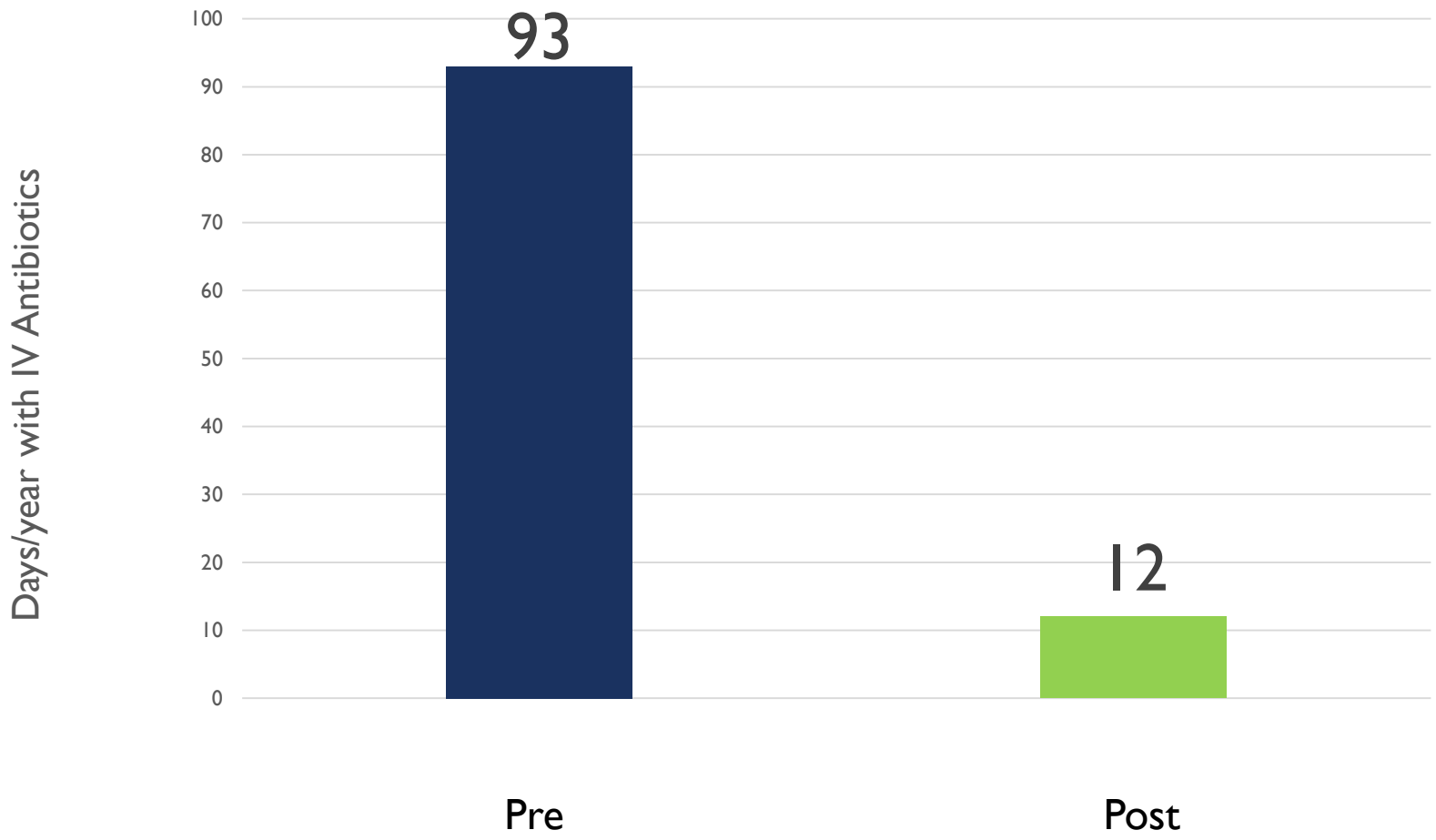
1.09.2016
29.9.2016
06.11.2016
24.11.2016
22.12.2016
5.1.2017
19.1.2017
29.01.2017
09.02.2017
23.02.2017
16.3.2017
23.3.2017
27.4.2017
11.5.2017
25.5.2017
08.06.2017
13.07.2017
03.08.2017
07.09.2017

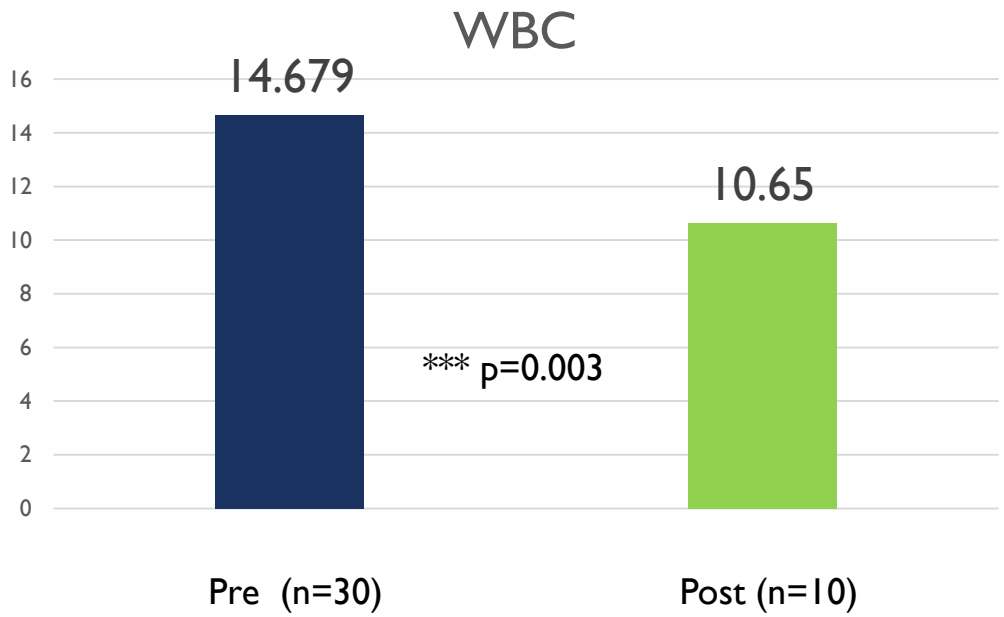
OXYGEN SATURATION

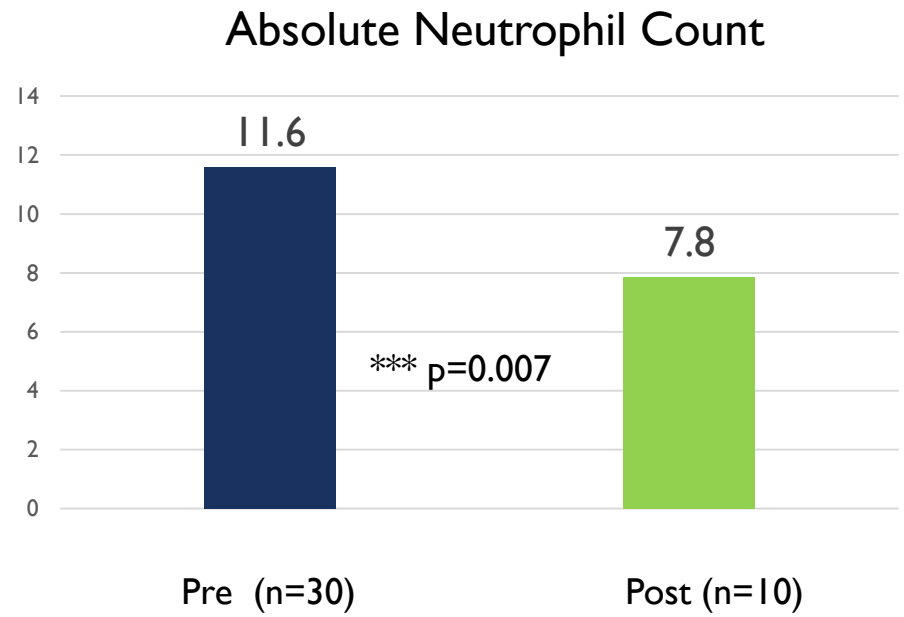


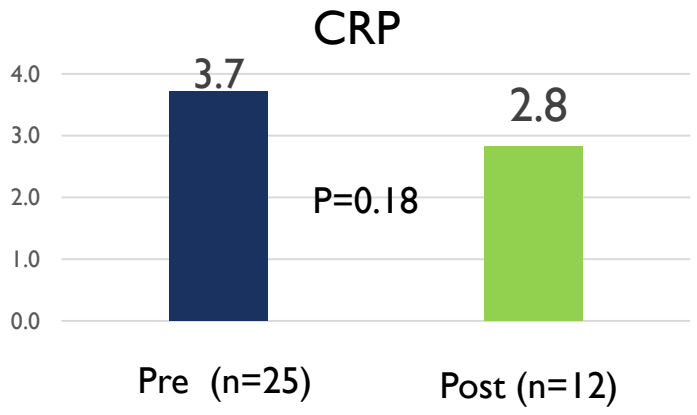
IV ANTIBIOTICS



SYSTEMIC INFLAMMATION







PANCREATITIS

- During the pre-Ivacaftor period the patient had 2-4 bouts of acute pancreatitis per year, some necessitating admission.
- Since Ivacaftor therapy was started – none.

SELF REPORT

- Speech dyspnea completely resolved
- Walking is easier
- Less cough
- No bouts of abdominal pain
- Less sputum production
- Substantial improvement in quality of life

SUMMARY

- In our small experience, our patient with residual function mutation A455E (Class V), demonstrate a clinically significant improvement following initiation of Ivacaftor therapy (PFT, weight, inflammation, pulmonary exacerbations) and significant improvement in quality of life

- This report is unique in demonstrating an effect of Ivacaftor in a patient with severely impaired lung function (FEV_1 <40% pred.)

- To the best of our knowledge, this is the first report of improvement of pancreatic function following Ivacaftor therapy

Questions?