Sucroferric Oxyhydroxide
A novel iron-based phosphate binder

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25 Avril, 2017

Conflict of Interest Statement

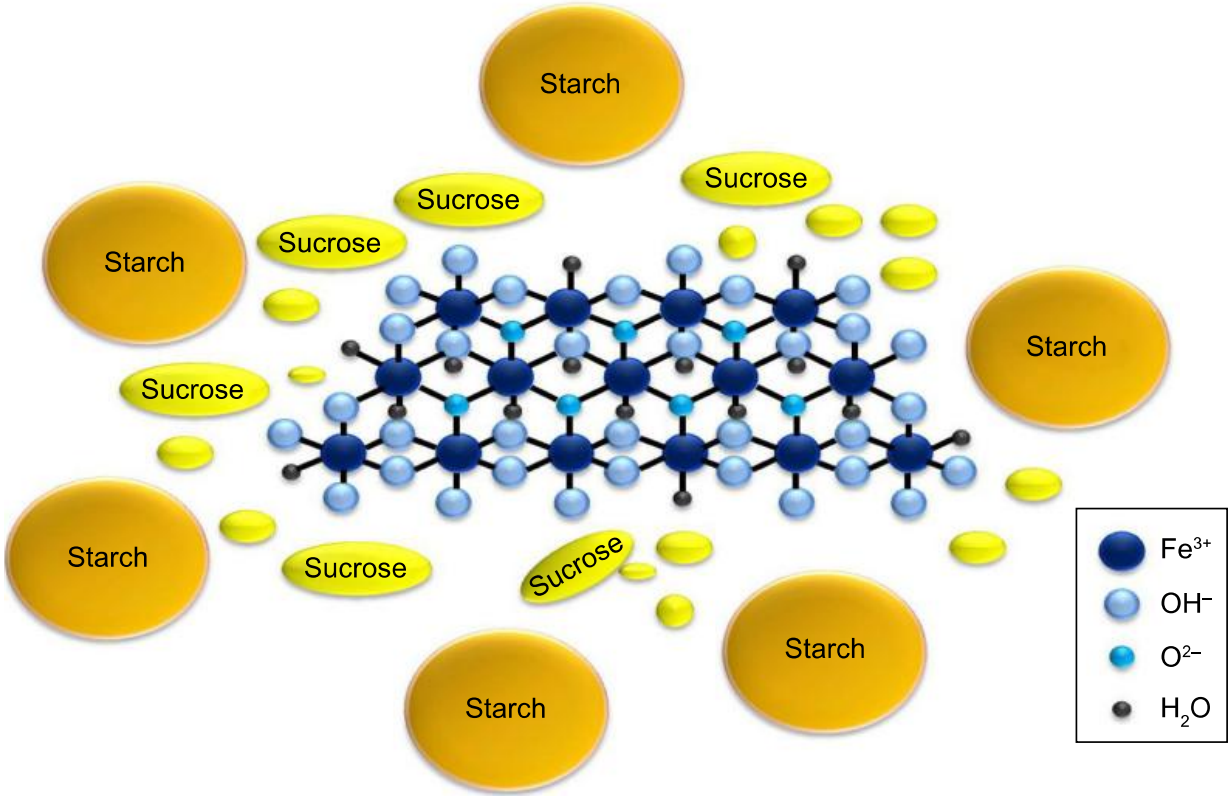
Consulting fees or lecture fees from Gilead, Amgen and Vifor-Fresenius

Research and training supports from Baxter, Bellco and Fresenius

Oxyhydroxide Iron

Goethite (FeO(OH)) hydroxide mineral found in
Cornwall, England and in the Martian crater Gusev (Nasa'Spirit rover, 2004)
Paint pigment in the caves of Lascaux

Mixture of polynuclear-iron (III-oxydroxide), sucrose and starch



Starch for drug processing

Sucrose to stabilize iron and to prevent ageing

pn-FeOOH 33% (Fe^{+++} 21%)
Sucrose 30%
Starch 28%
Water < 10%

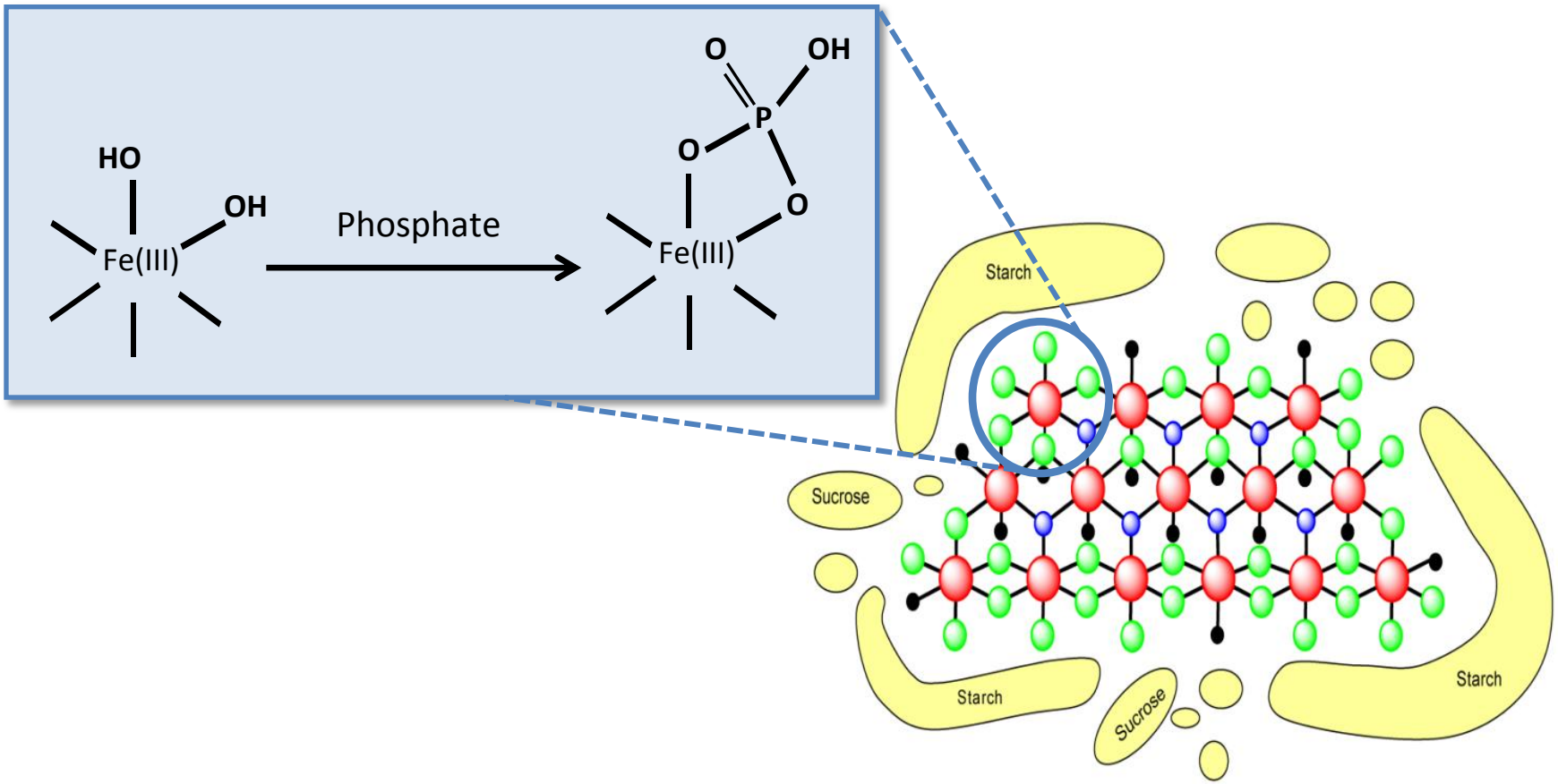
Sucroferric oxyhydroxide

Chewability > to Lanthanum

Spontaneous disintegration after contact with water

Floege J , J Nephrol, 2016

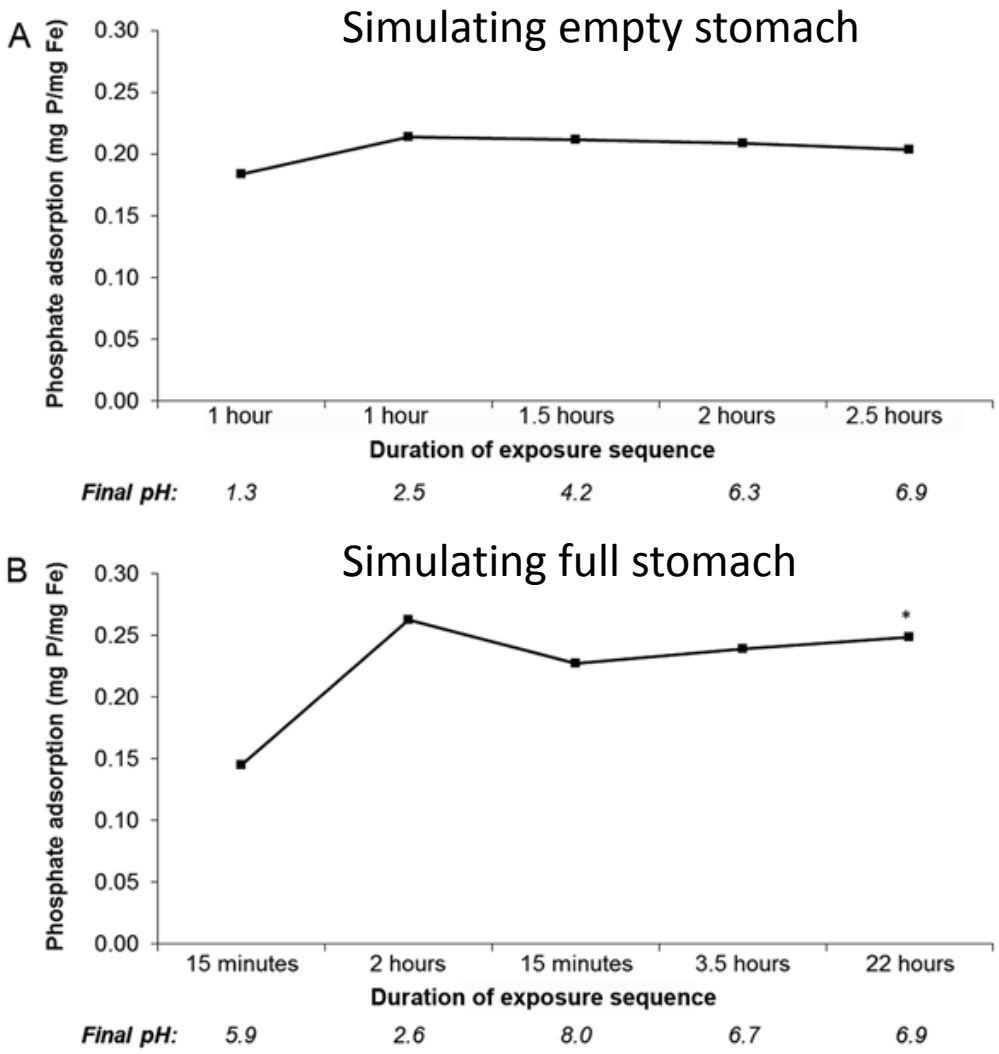
Phosphate Binding Mechanisms



Acidic ph:chemical reaction , ie formation of iron phosphate

Less acidic ph: adsorption of phosphate to the iron complex (pn –FeOOH)

Phosphate Binding Capacity



Stoichiometric ratio of P:Fe
to peak at 0.47 mmolP:mmol Fe

Bindign capacity
0,26 mg of P bound by 1mg of Fe

Weak influence of pH change

3 tablets of 500 mg iron equals binding 390 mg of P

Wilhelm M, Clin Nephrol, 2014

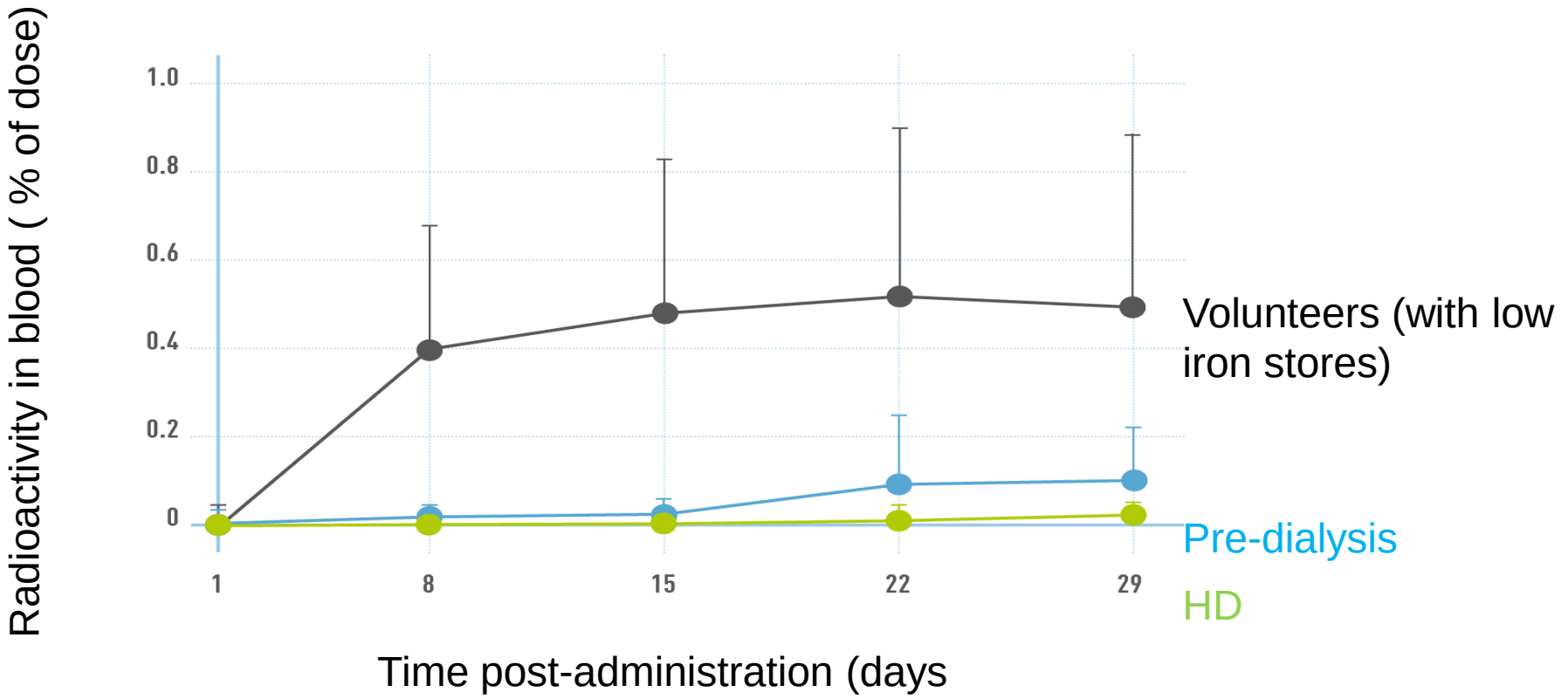
Phosphate binding Potency

	Dose Size mg	Estimated PO_4 binding capacity /gr	RBPC	PBED/tablet to 1gr $CaCO_3$	Nb of tablets = to 6gr $CaCO_3$
$CaCO_3$	750	40	1	0,75	8
Ca Acetate	667	45	1	0,67	9
Sevelamer HCl	800	21	0,75	0,6	10
Sevelamer carbonate	800	21	0,75	0,6	10
Lanthanum	500	135 ou 90	2	1	6
Sucroferric Oxyhydroxide	500	130	1,6	1,6	3,75
Ferric Citrate	1000	46	≈ 1	0,64	9

RBPC: relative phosphate binding coefficient , ref 1gr of $CaCO_3$

PBEP : phosphate binder equivalent dose

Low iron uptake

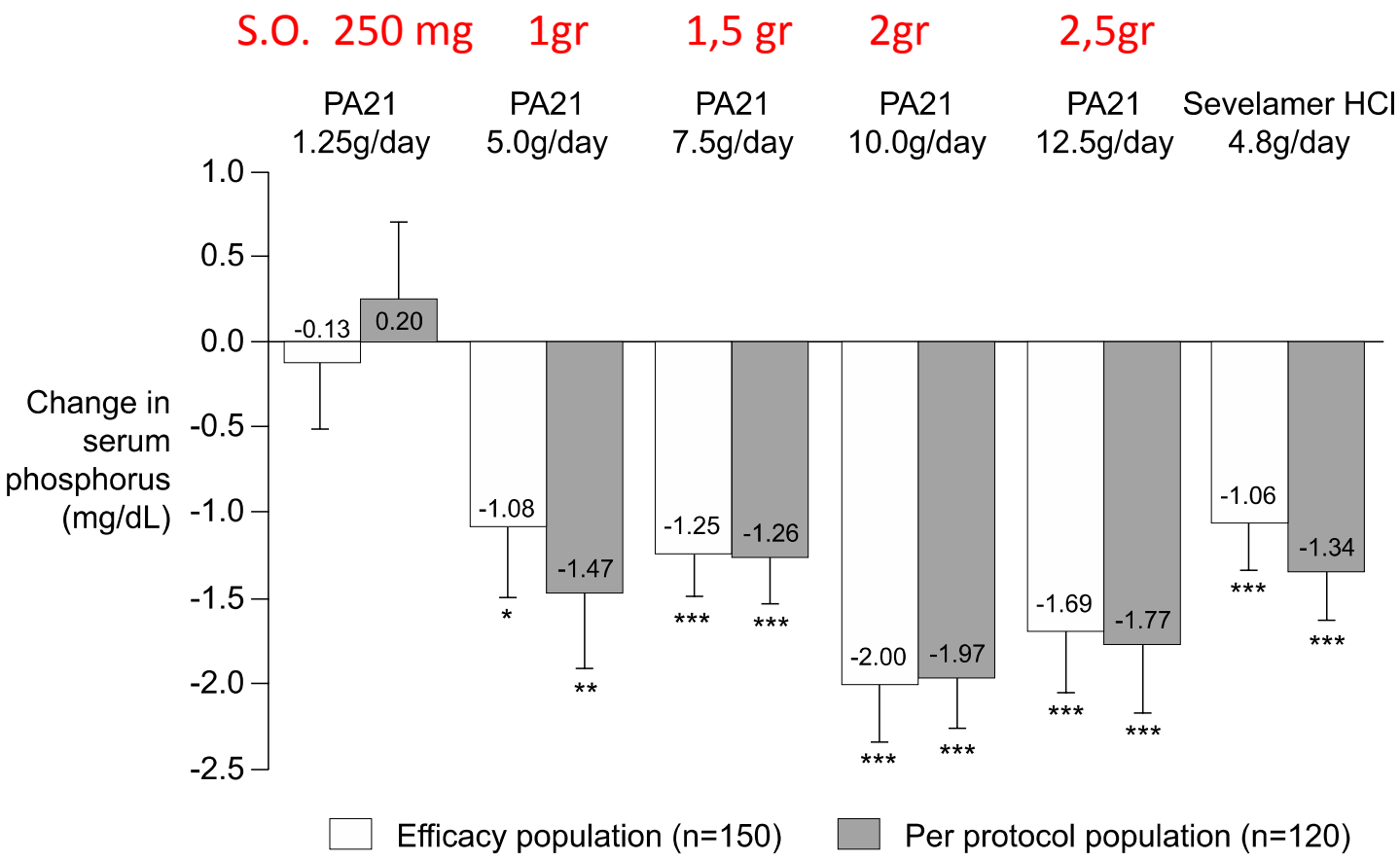


Iron uptake 10 fold lower (0.04%) in CKD compared to healthy volunteers

10 gr of PA21,ie 2 gr of iron,: daily iron absorption 1.4 mg for CKD and 0.4 mg for HD patients

Geisser P, Clin Nephro, 2010

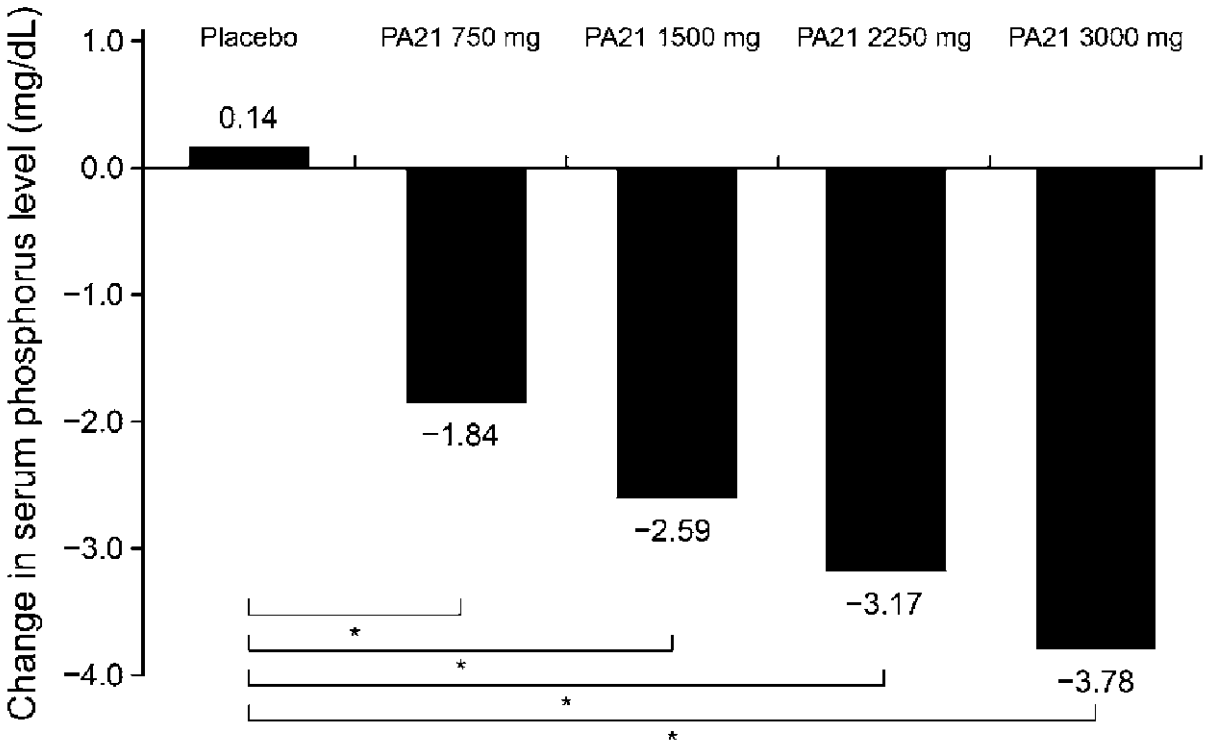
Dose-response Efficacy (1)



6 weeks , tablets of 250 mg of sucroferric iron given 1 to 3 times per day,
≈ 25 patients per group

Wüthrich R, Clin J Am Soc Nephrol, 2013

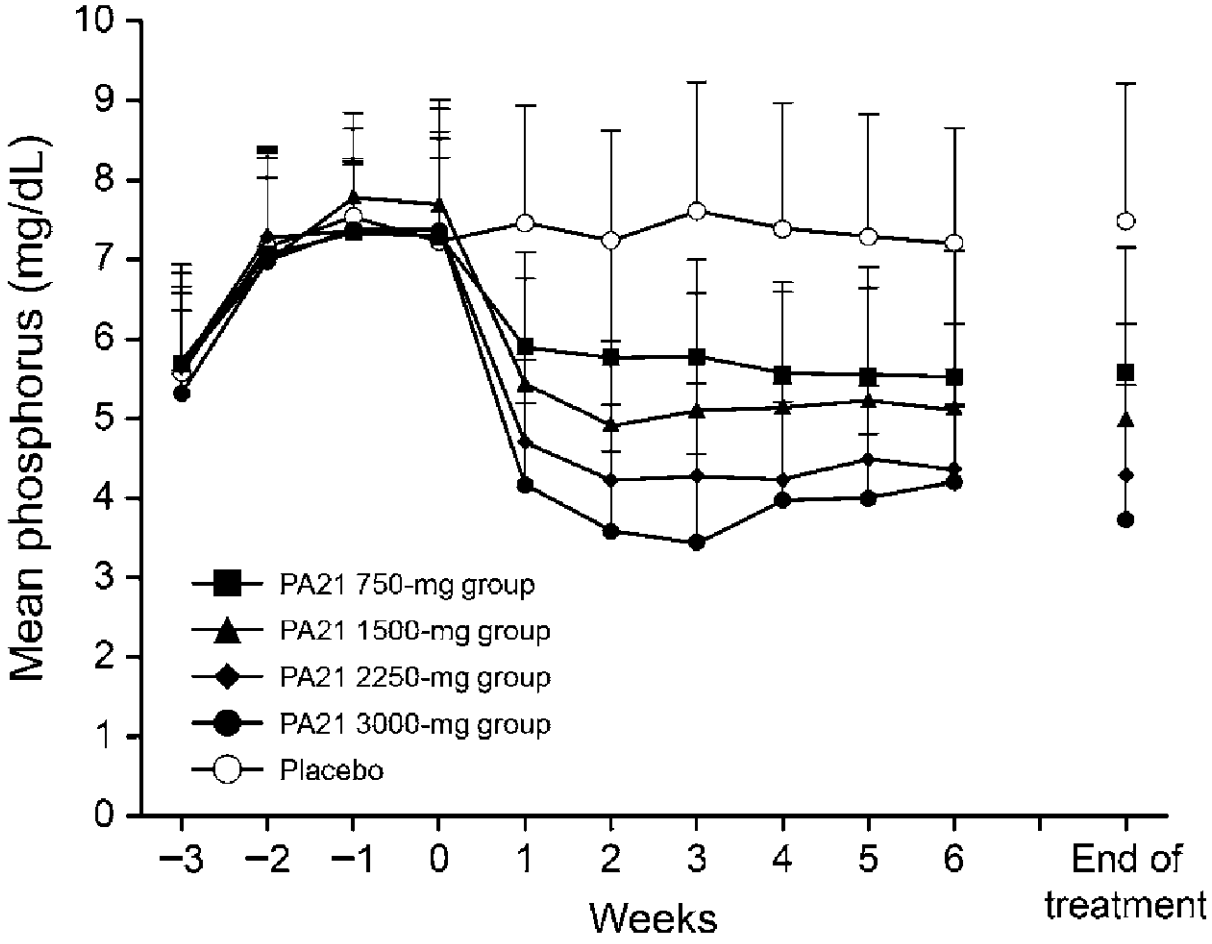
Dose-response Efficacy (2)



6 weeks, tablets of 250 mg given 3 times per day, 35 patients per group,

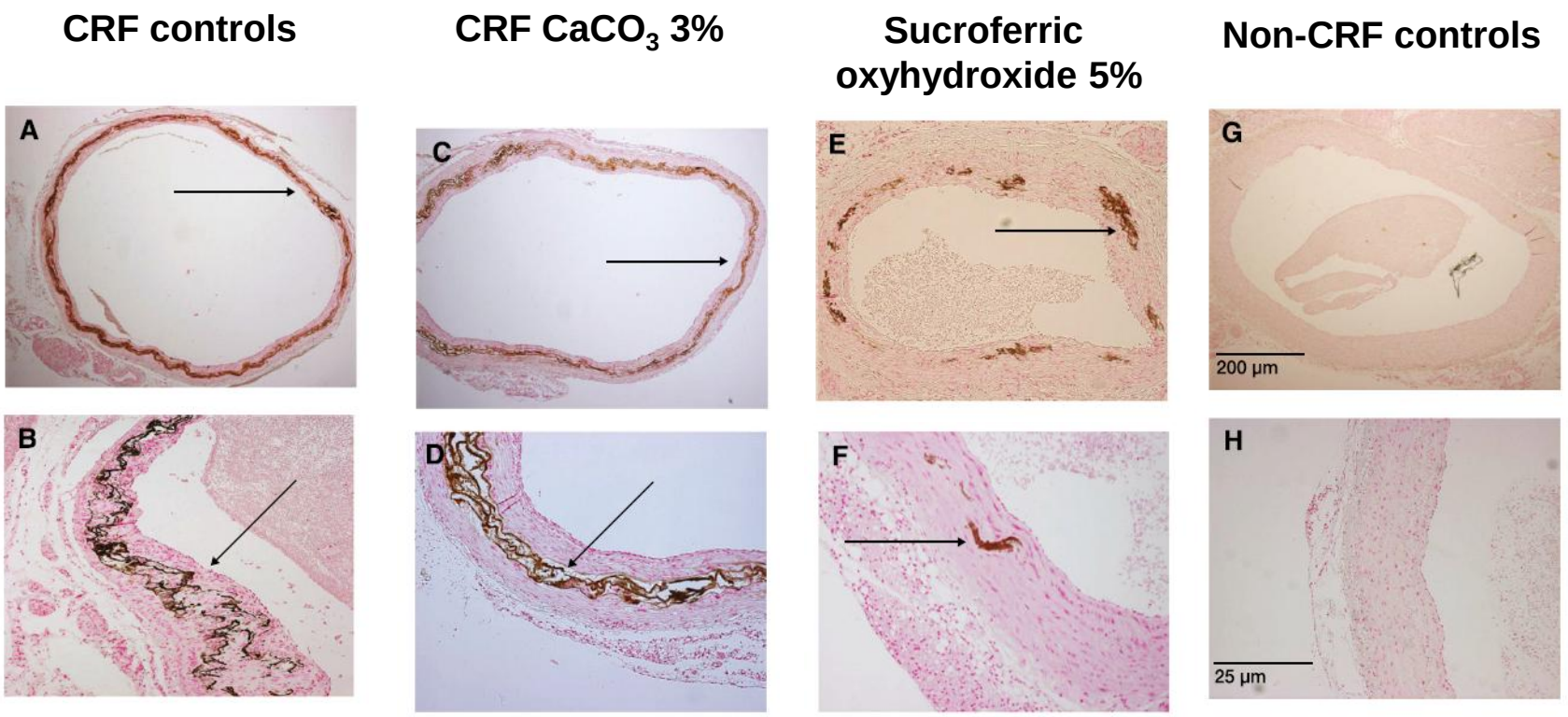
Koiwa F, Clin Exp Nephrol, 2017

Dose-response efficacy (3)



Koiwa F, Clin Exp Nephrol, 2017

Sucroferric Oxyhydroxide and Vascular calcifications

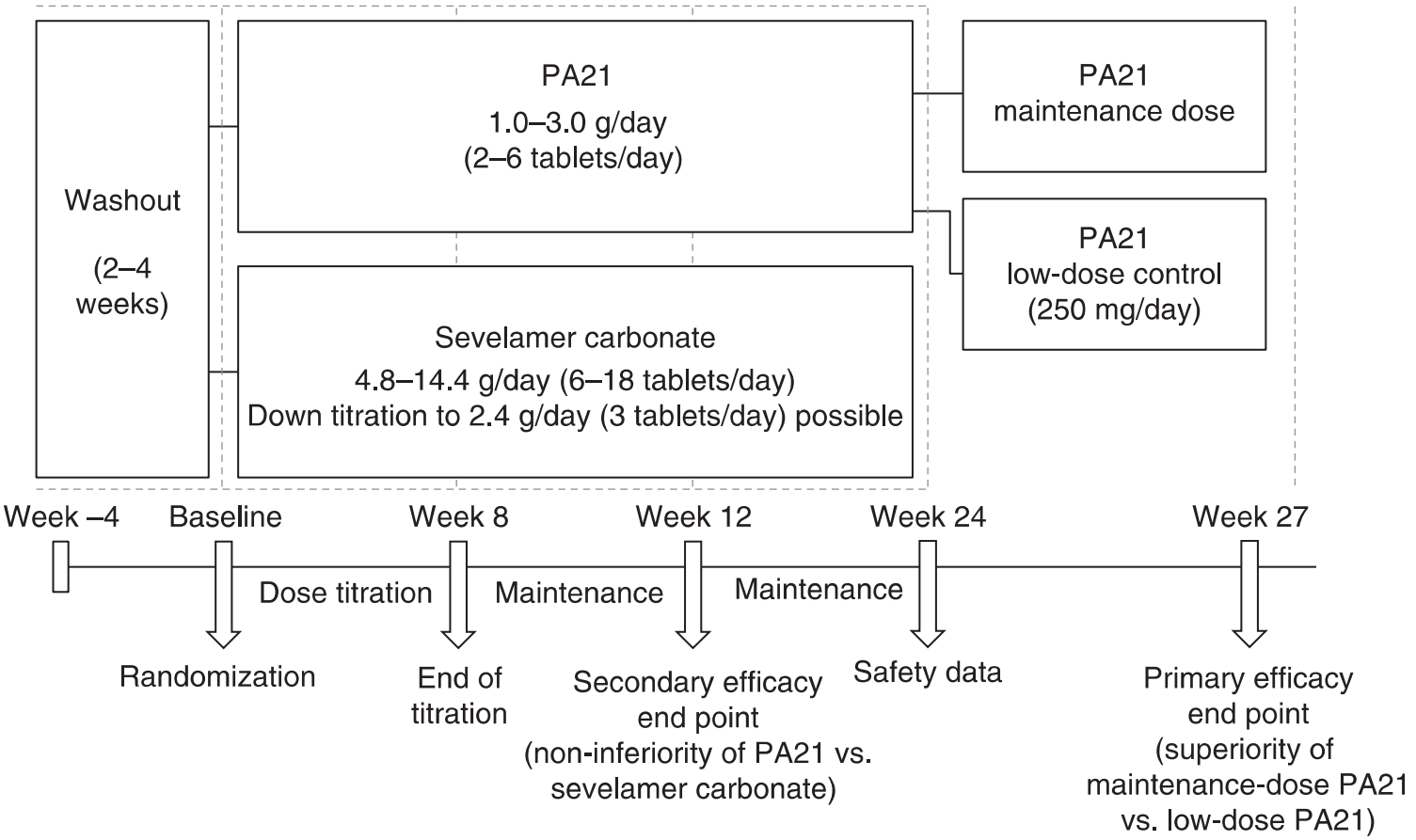


Male Wistar rats: diet 0.75% adenine and high phosphorus content (1.3%)

Von Kossa staining

Phan Q, J Pharmacol Exp Ther, 2013

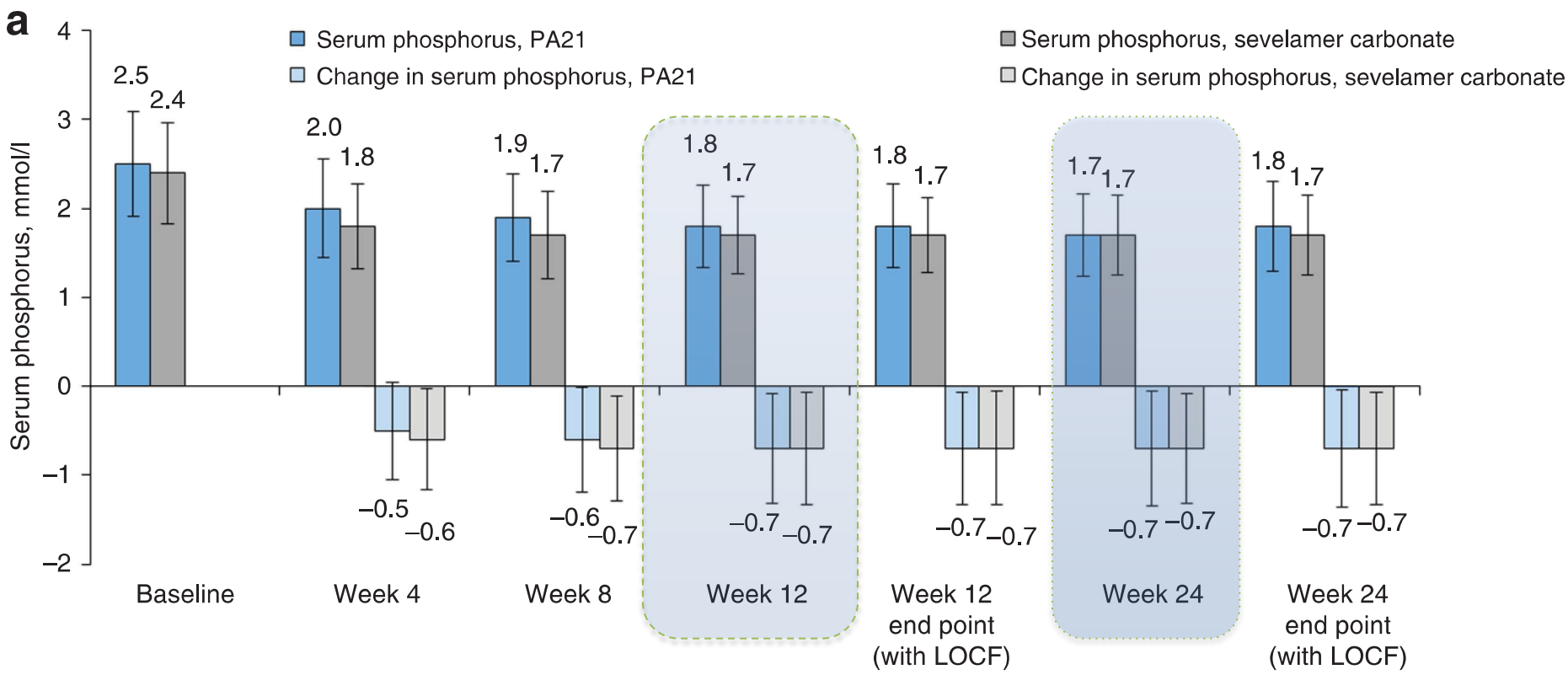
PA-CL-05A Study



710 patients with PA-21
349 patients with sevelamer

Floege J Kidney Int, 2014

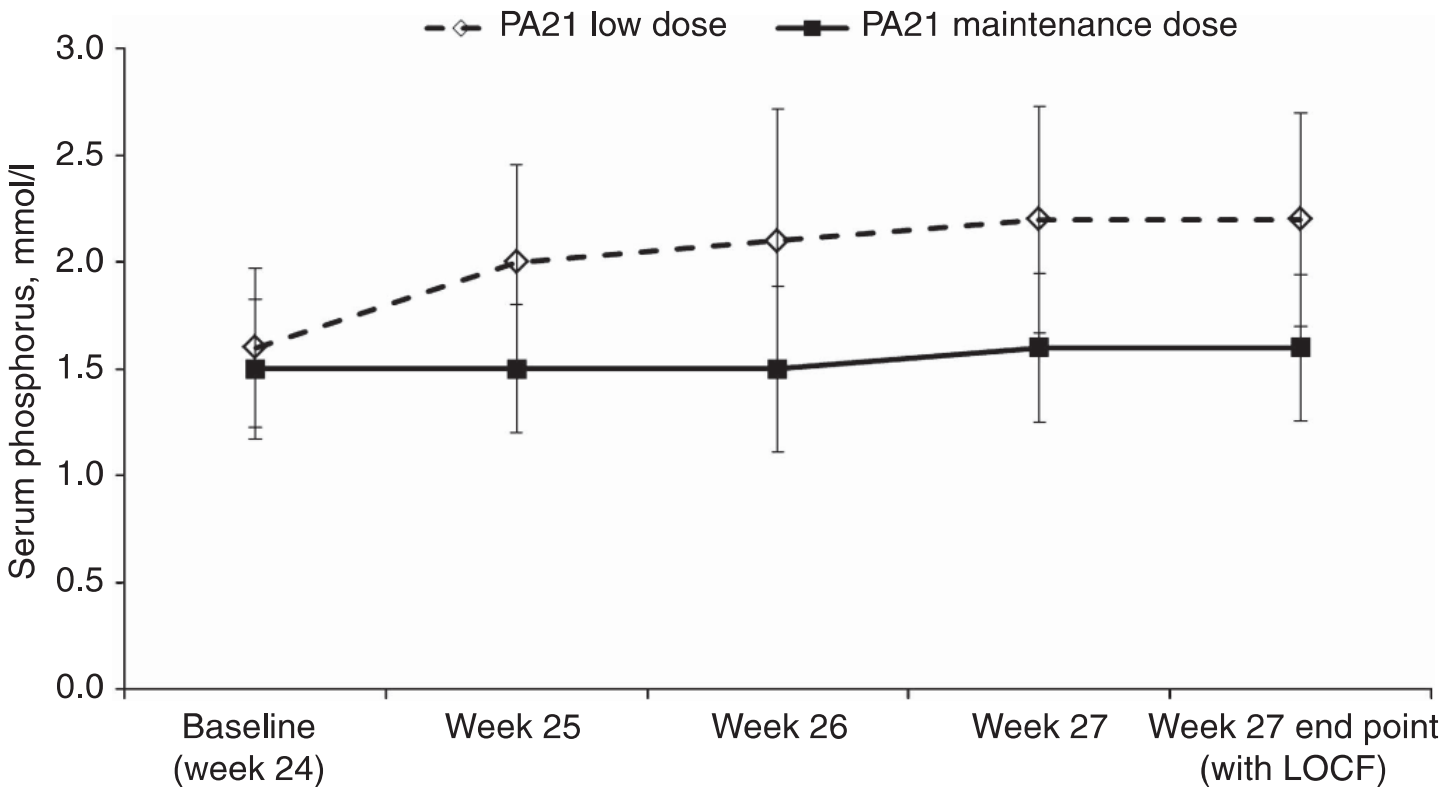
Phosphorus concentrations and Changes



1.8 gr / day S.O.
6.96 gr / day Sevelamer

Floege J, Kidney Int, 2014

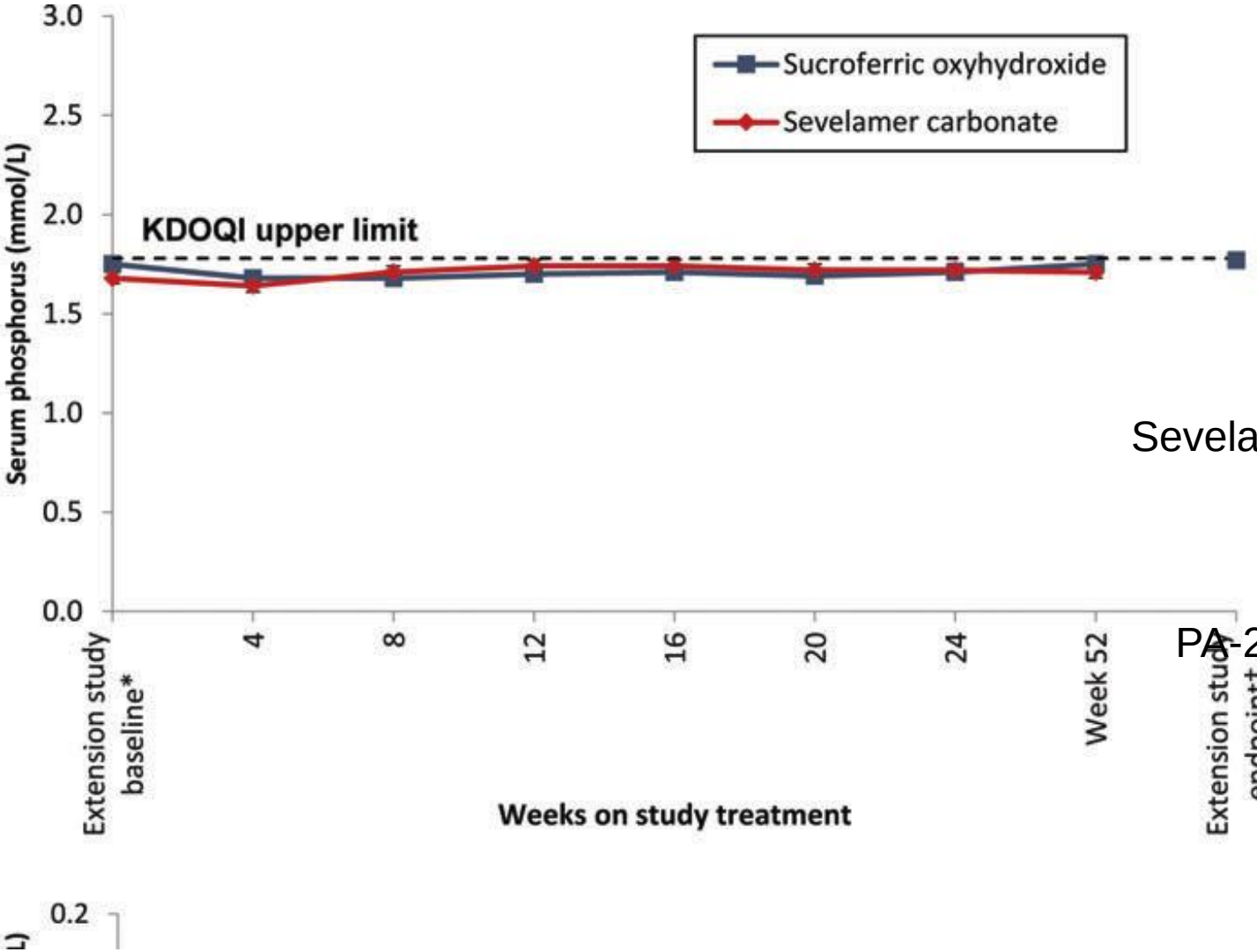
Sucroferric Oxyhydroxide Low Dose



100 patients with phosphatemia < 1,78 mmol/L

Floege J, Kidney Inter, 2014

Serum Phosphorus over 1 year

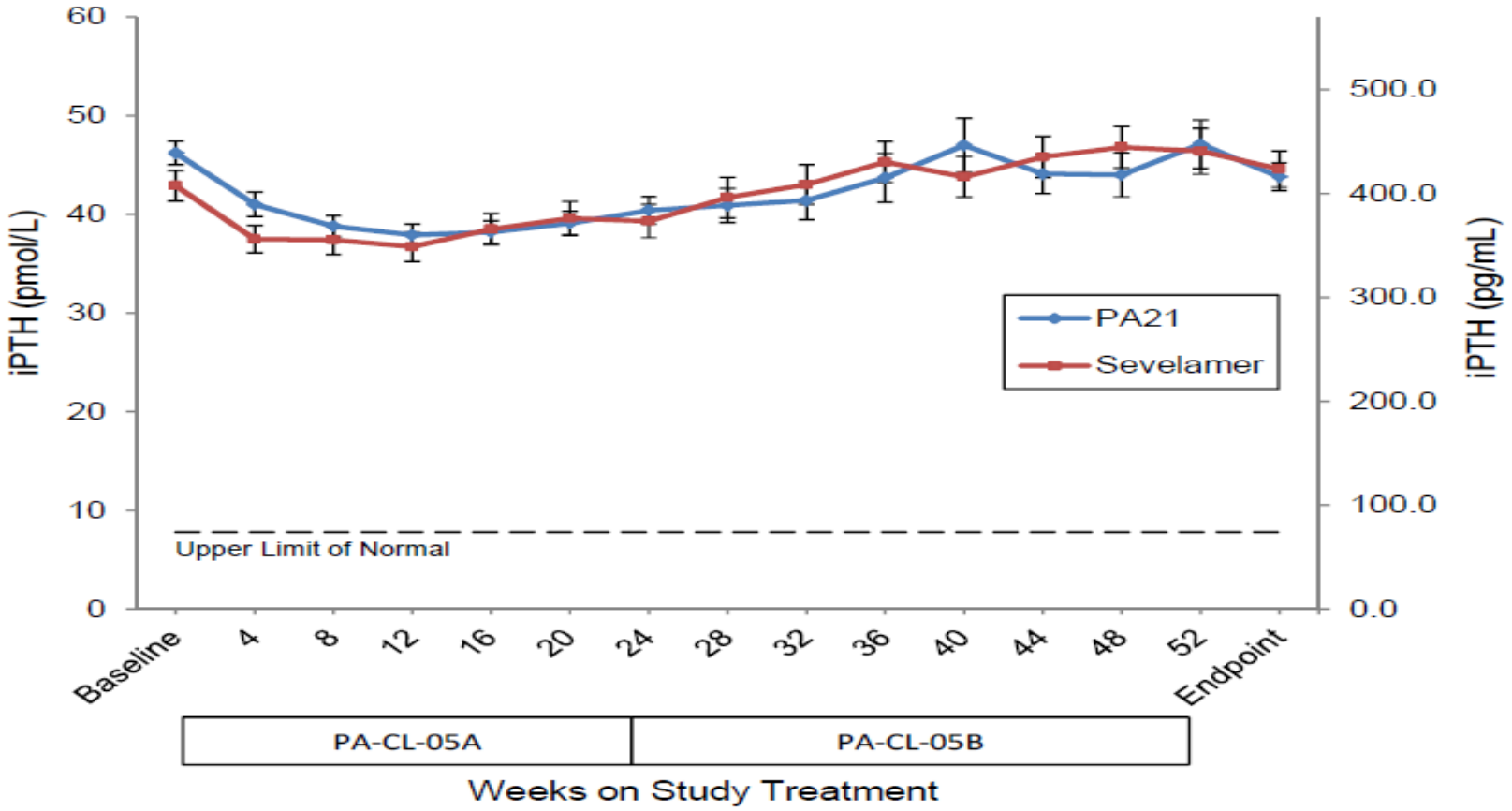


Sevelamer, 268 pts

PA-21, 391 pts

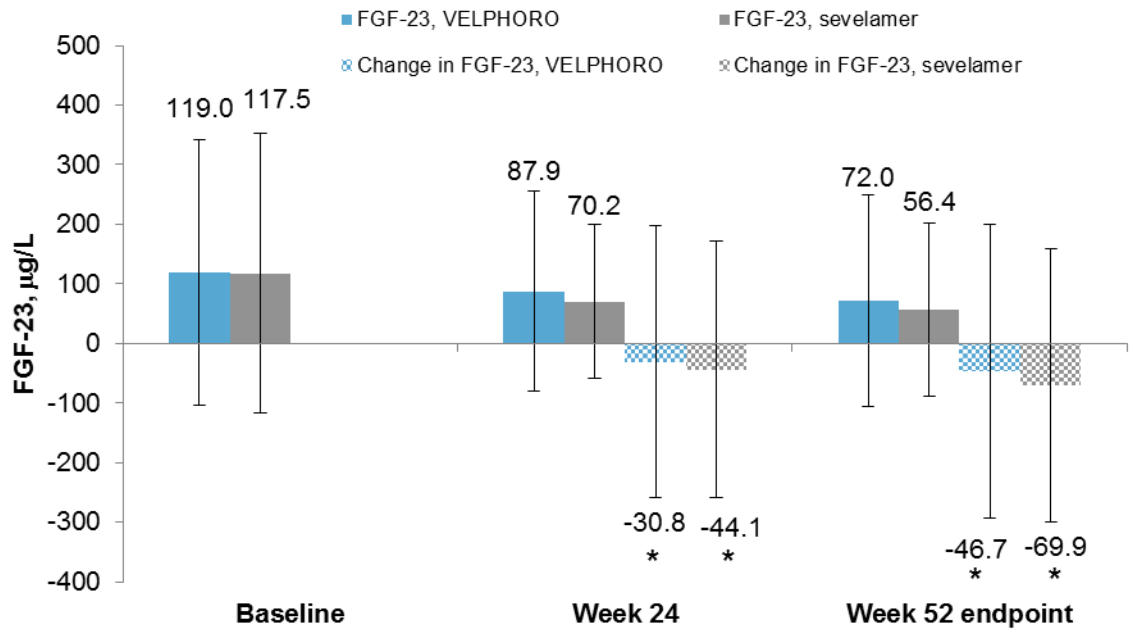
Floege J, Nephrol Dial Transplant, 2015

Serum PTH concentration over 1 year



Floege J, Nephrol Dial Transplant, 2015

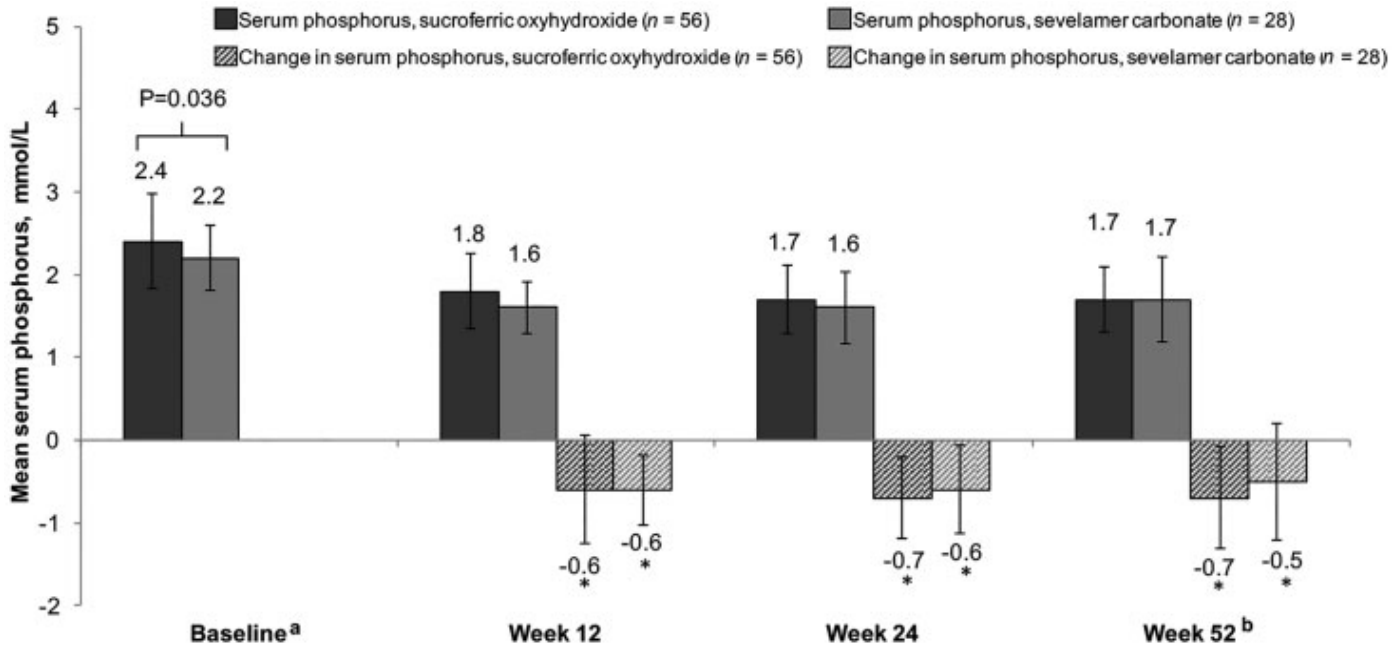
FGF 23 Changes



Integrated analysis of mean (SD) serum FGF23 concentrations and changes from baseline over 1 year

Ketteler M, ISN-WCN, 2015

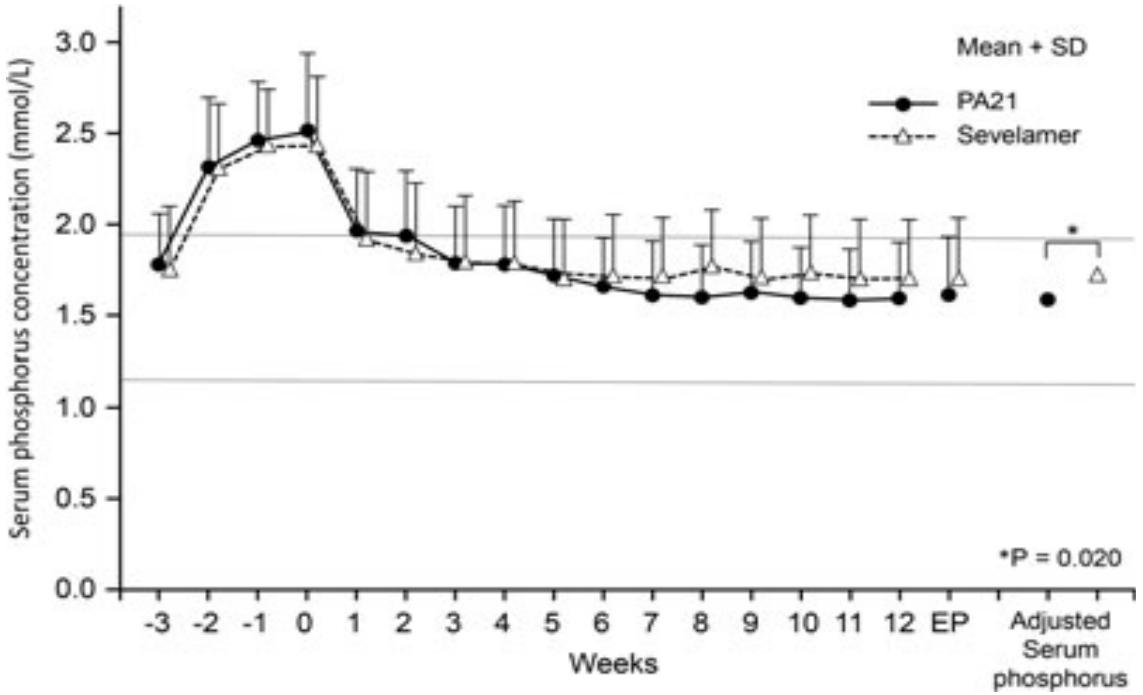
PA-CL-05A PD Patients



57 pts Oxyhydroxide sucroferric , 1.7 gr /day
29 pts Sevelamer Carbonate, 6.5 gr / day

Floege J, Nephrol Dial Transplant, 2017

Japanese Study 12 Weeks



Changes from W1 to W12: -0.9 mmol /L for PA21 et -0.73 for Sevelamer

1.4 gr / day S.O.
4.7 gr / day Sevelamer

Koiwa F, Nephrology, 2017

PA-CL-05A, Adverse Events

	PA21 (*N* = 707) (%)	Sevelamer (*N* = 348) (%)
Any TEAE	83.2	76.1
Any severe TEAE	11.5	10.9
Any serious TEAE	18.2	19.8
Withdrawals due to TEAEs	15.7	6.6
Death	1.8	2.0
Any GI TEAE	45.1	33.6
Any GI TEAE, excluding isolated discolored feces	39.0	33.3
Diarrhea	20.1	7.5
Feces discolored	15.4	0.3
Hyperphosphatemia	11.2	7.8
Nausea	7.2	11.2
Hypertension	6.4	7.5
Vomiting	4.4	5.5
Constipation	3.8	7.2

Floege J, Kidney Int, 2014

PA-CL-05A PD Patients : Adverse Events

TEAE	Sucroferric oxyhydroxide ($n = 57$), n (%)	Sevelamer carbonate ($n = 29$), n (%)	Total ($n = 86$), n (%)
Any TEAE	49 (86.0)	27 (93.1)	76 (88.4)
Any severe TEAE	12 (21.1)	3 (10.3)	15 (17.4)
Any serious TEAE	21 (36.8)	7 (24.1)	28 (32.6)
Any treatment-related TEAE	26 (45.6)	7 (24.1)	33 (38.4)
Death[a]	2 (3.5)	1 (3.4)	3 (3.5)
Any TEAE leading to discontinuation	10 (17.5)	3 (10.3)	13 (15.1)
Any TEAE leading to hospitalization	15 (26.3)	5 (17.2)	20 (23.3)
Any GI TEAE	28 (49.1)	12 (41.4)	40 (46.5)
Diarrhea	8 (14.0)	2 (6.9)	10 (11.6)
Discolored feces	10 (17.5)	0 (0)	10 (11.6)
Nausea	2 (3.5)	6 (20.7)	8 (11.3)
Vomiting	1 (1.8)	3 (10.3)	4 (4.7)
Constipation	3 (5.3)	4 (13.8)	7 (8.1)
Abdominal pain[b]	4 (7.0)	2 (6.9)	6 (7.0)
Dyspepsia	3 (5.3)	2 (6.9)	5 (5.8)
Peritonitis[c]	10 (17.5)	5 (17.2)	15 (17.4)

Floege J, Nephrol Dial Transplant, 2017

Japanese study, Adverse Events

	PA21 group *n* = 108	Sevelamer group *n* = 105
Adverse events, *n* (%)	81 (75.0)	70 (66.7)
Nasopharyngitis	24 (22.2)	24 (22.9)
Diarrhoea	27 (25.0)	3 (2.9)
Constipation	2 (1.9)	19 (18.1)
Adverse drug reactions, *n* (%)	29 (26.9)	28 (26.7)
Diarrhoea	23 (21.3)	1 (1.0)
Constipation	0 (0.0)	19 (18.1)
Abdominal discomfort	0 (0.0)	3 (2.9)
Abdominal distension	0 (0.0)	3 (2.9)
Adverse events that led to withdrawal, *n* (%)	7 (6.5)	10 (9.5)
Diarrhoea	4 (3.7)	1 (1.0)
Constipation	0 (0.0)	3 (2.9)

Koiwa F, Nephrology, 2017

Adverse Events in relation to Sucroferric Oxyhydroxide dose

	PA21 750-mg group ($N = 39$)	PA21 1500-mg group ($N = 36$)	PA21 2250-mg group ($N = 35$)	PA21 3000-mg group ($N = 36$)	Placebo group ($N = 37$)
Adverse events					
Diarrhea	6 (15.4)	6 (16.7)	13 (37.1)	15 (41.7)	7 (18.9)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.1)	0 (0.0)
Nasopharyngitis	5 (12.8)	5 (13.9)	3 (8.6)	3 (8.3)	4 (10.8)
Constipation	0 (0.0)	1 (2.8)	2 (5.7)	2 (5.6)	1 (2.7)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)
Pain in extremity	0 (0.0)	1 (2.8)	2 (5.7)	0 (0.0)	0 (0.0)
Hemorrhoids	0 (0.0)	0 (0.0)	2 (5.7)	0 (0.0)	0 (0.0)
Insomnia	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse drug reactions					
Diarrhea	4 (10.3)	4 (11.1)	12 (34.3)	12 (33.3)	3 (8.1)
Constipation	0 (0.0)	1 (2.8)	2 (5.7)	1 (2.8)	0 (0.0)

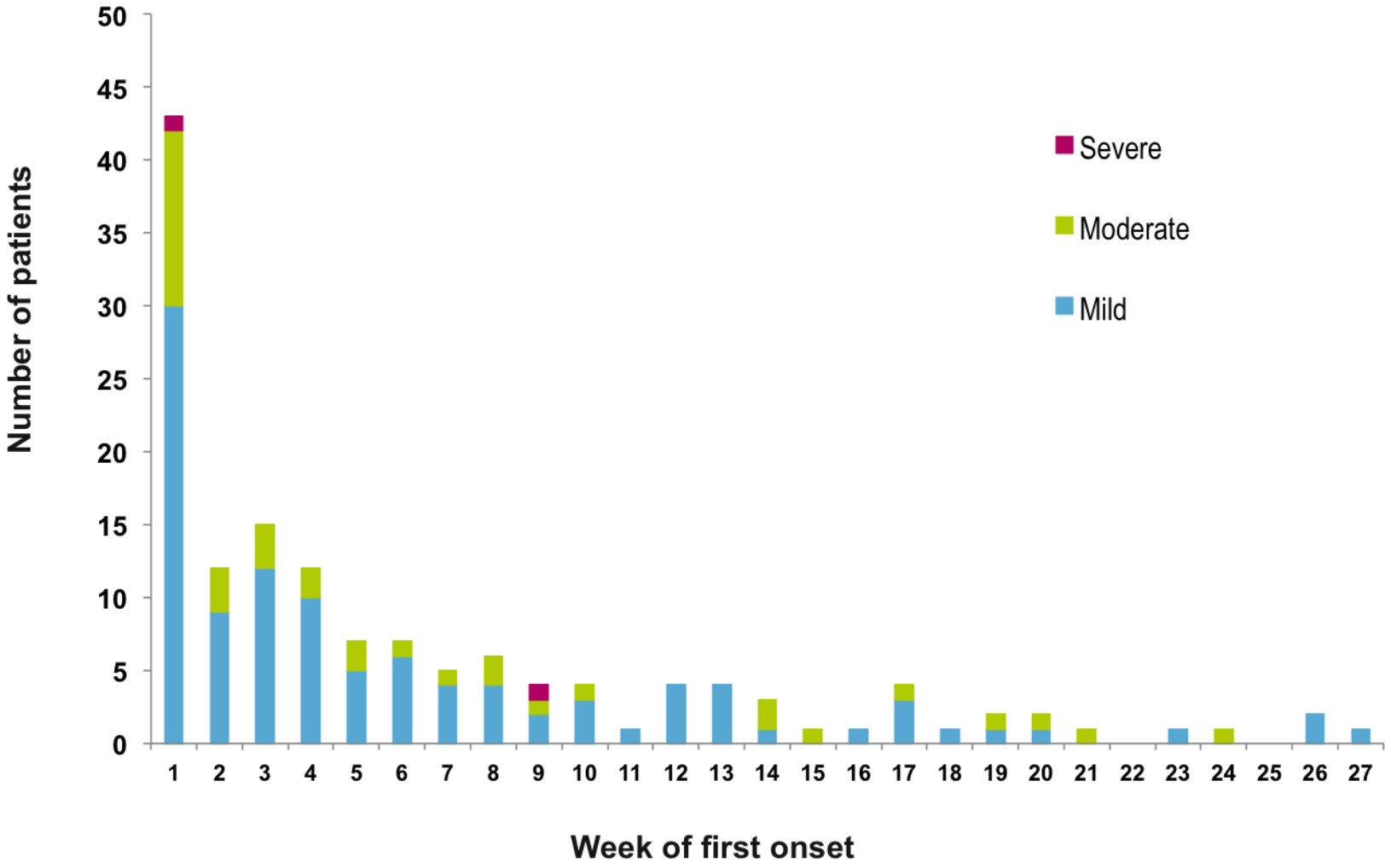
Koiwa F, Clin Exp Nephrol, 2017

Time to onset of diarrhea

Time to onset	PA21 groups	Placebo group
1–7 days	31	4
1st day	6	0
2nd day	10	1
3rd day	8	1
4th day	2	0
5th day	5	1
6th day	0	1
7th day	0	0
8–14 days	3	0
15–21 days	2	2
22–28 days	2	0
29–35 days	0	0
36–42 days	2	1

Koiwa F, Clin Exp Nephrol, 2017

PA-CL-05A



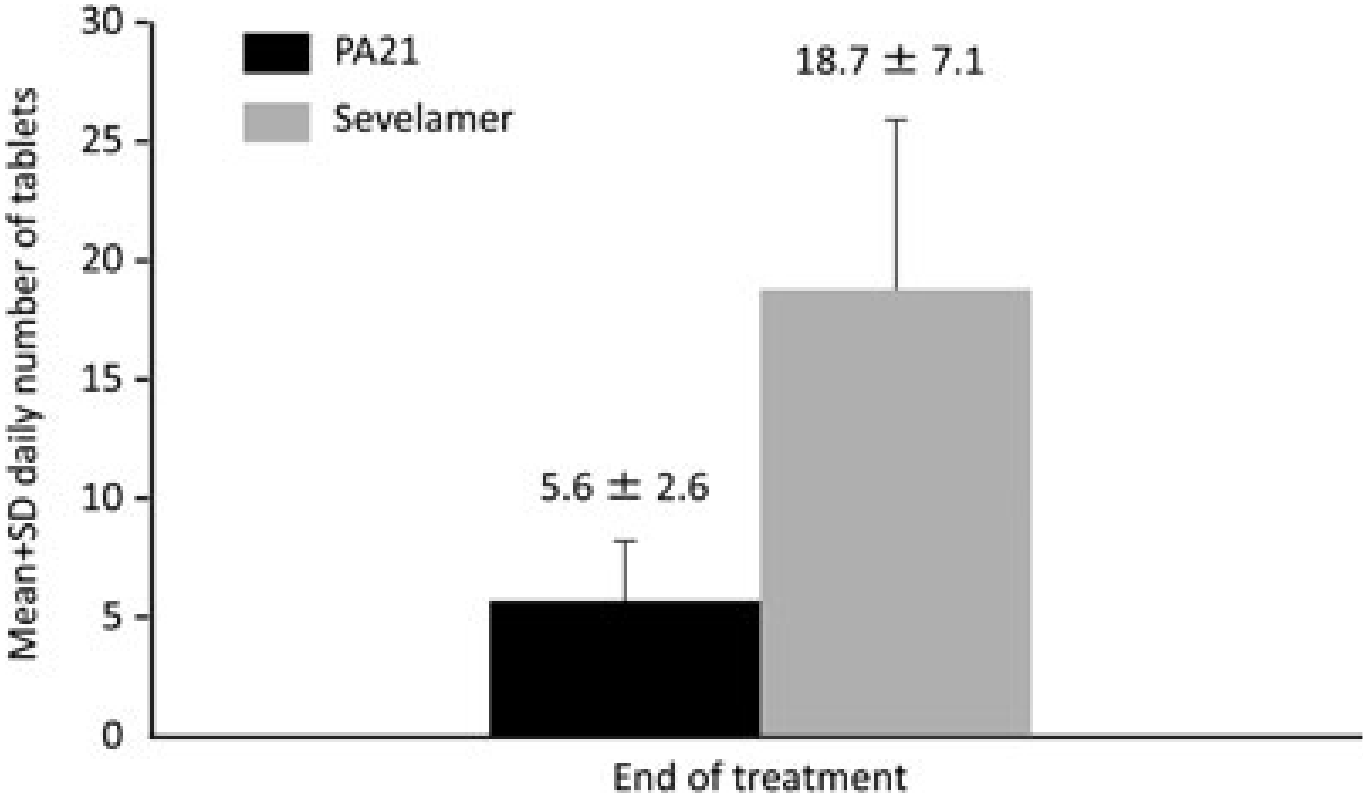
Withdraw for diarrhea 2,8%

Floege J , Kidney Int, 2014

Withdrawal Rate (%) due to A.E.

	Sucroferric Oxyhydroxide	Sevelamer
PA-CL-05A	15,7 (diarrhea 2,8)	6,6
PA-CL-05B (Extension Study)	8,2	4,9
Japanese Study	3,7	3,9

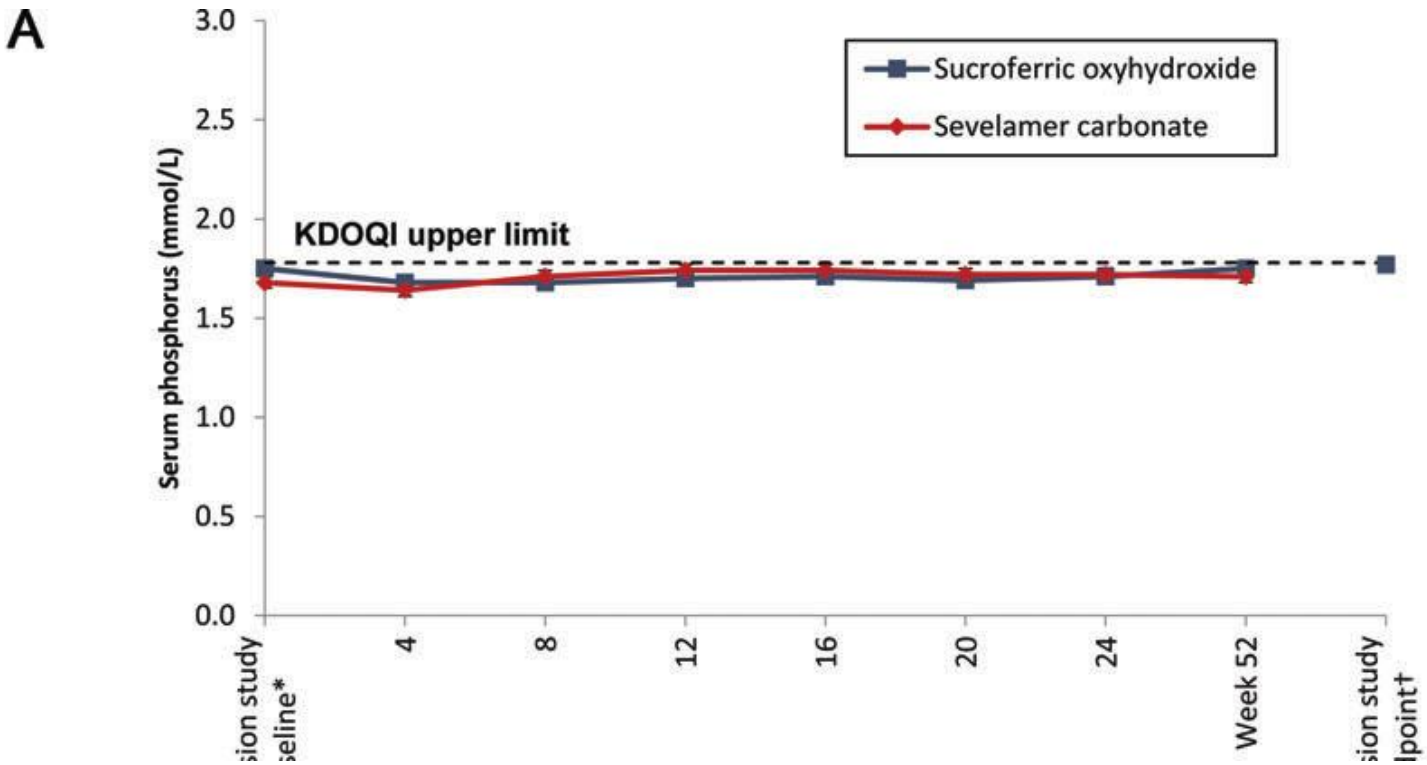
Mean number of tablets per day



Tablets 250 mg S.O.

Koiwa F, Nephrology, 2017

Mean number of tablets per day



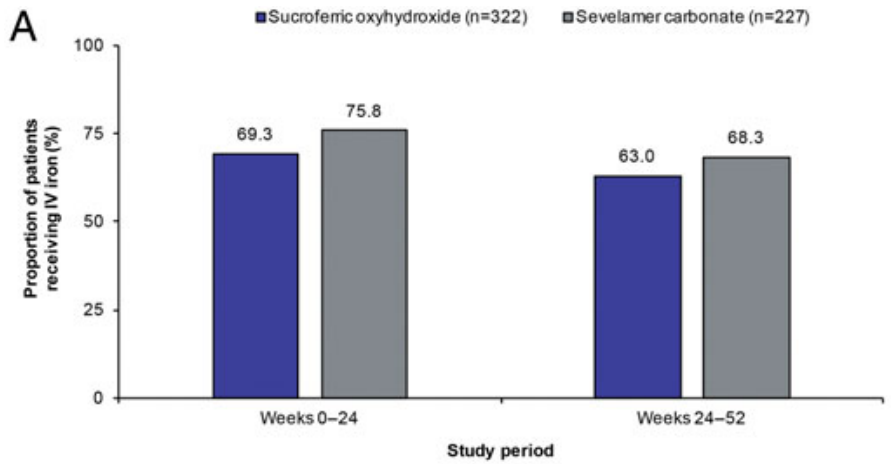
Floege J ,Nephrol Dial Transplant, 2015

Adherence to treatment (%)

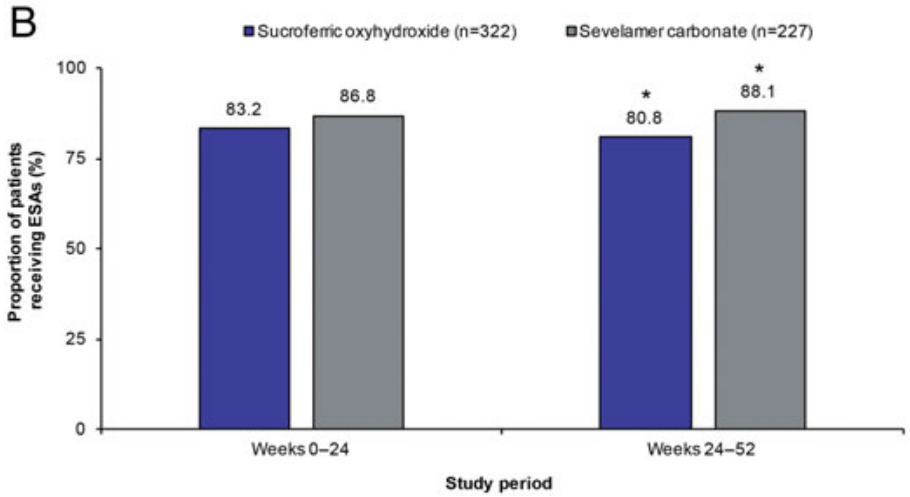
	Sucroferric Oxyhydroxide	Sevelamer
PA-CL-05A	82,6	77,2
PA-CL-05B	86,7	78,8
PD patients (PA-CL-05A et 05B)	91,2	79,3

Adherence defined as taking < 70 % of the expected number of tablets

Anti-anaemic products during PA-CL-05A



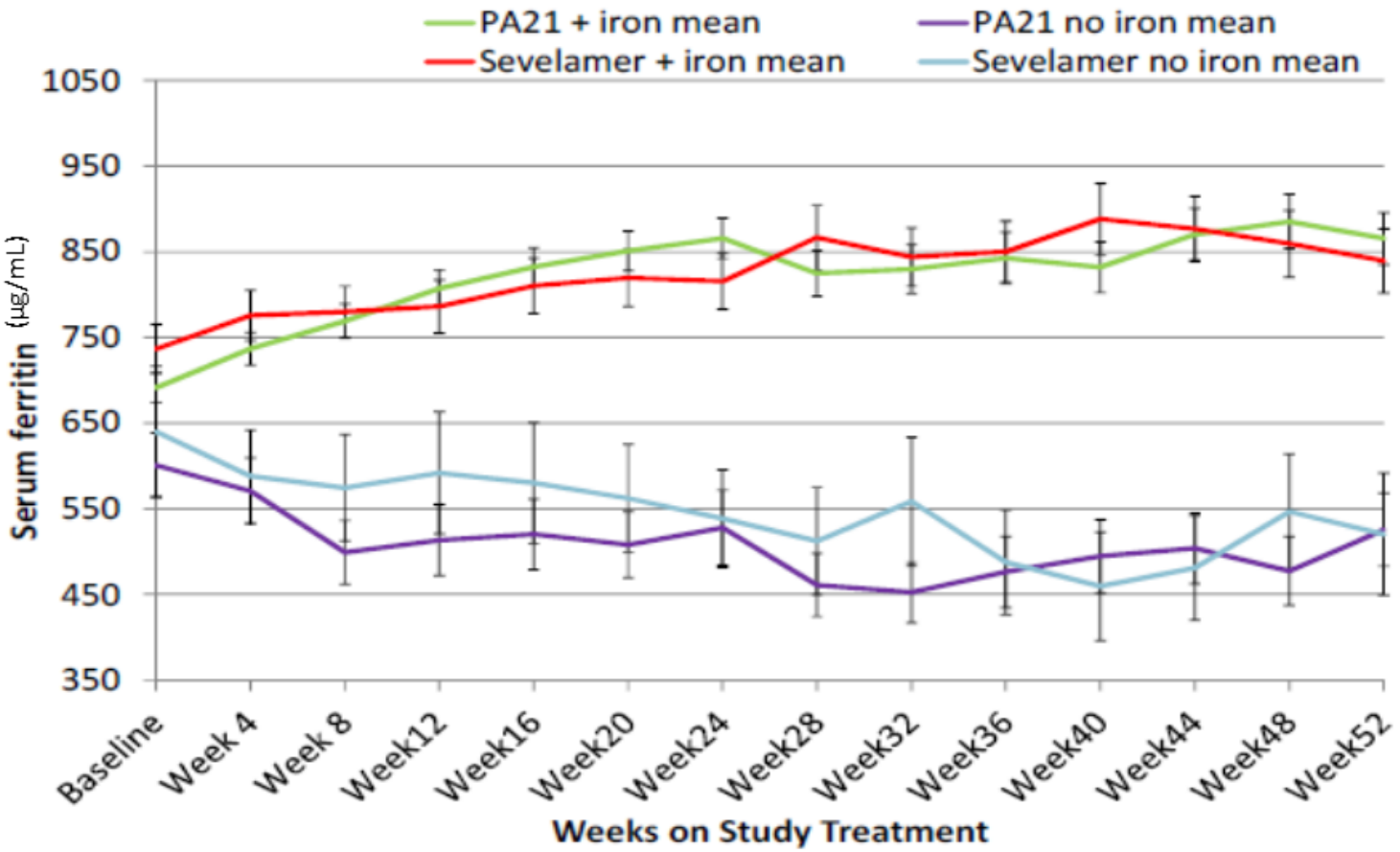
IV Iron



ESA

Covic A, Nephrol Dial Transplant,2016

Ferritin concentrations during PA-CL-05A Study



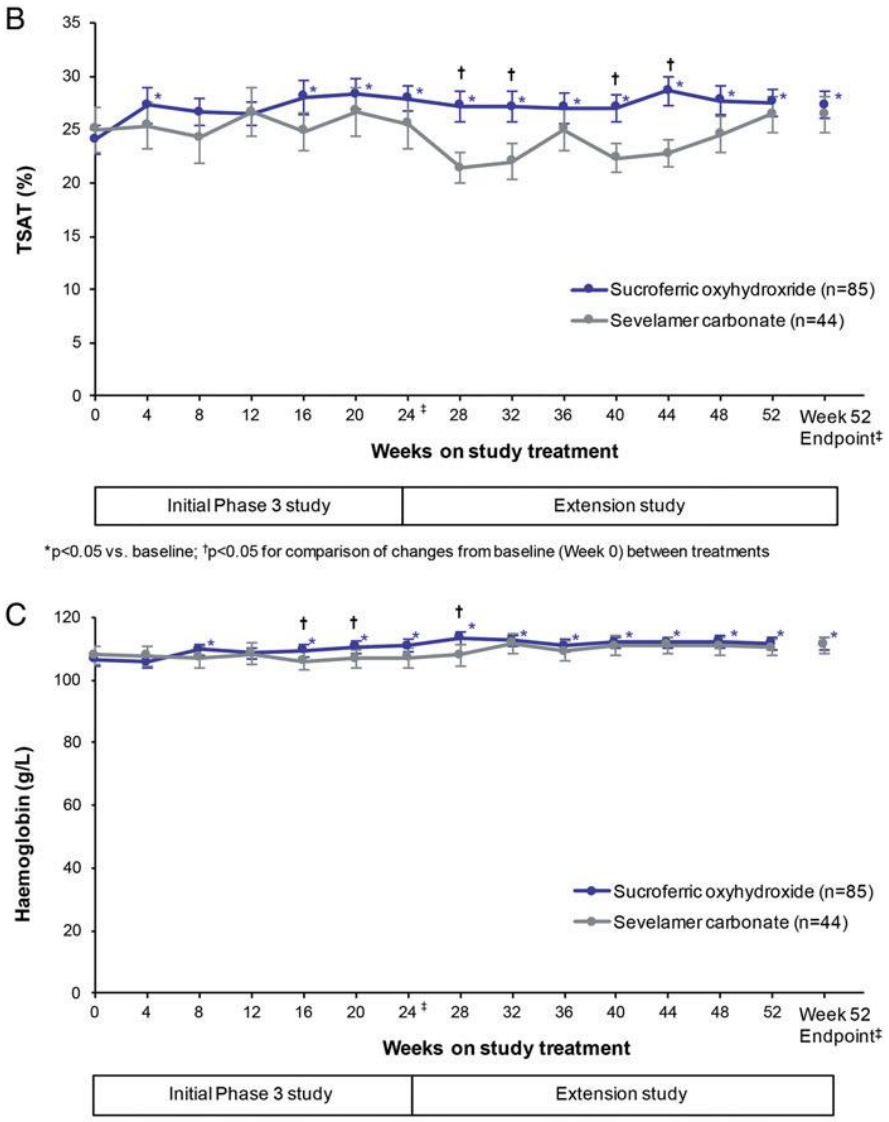
IV Iron

No IV Iron

Note: SS = Safety set.
Source: Module 5, Section 5.3.5.3, Table E.76.1.2.

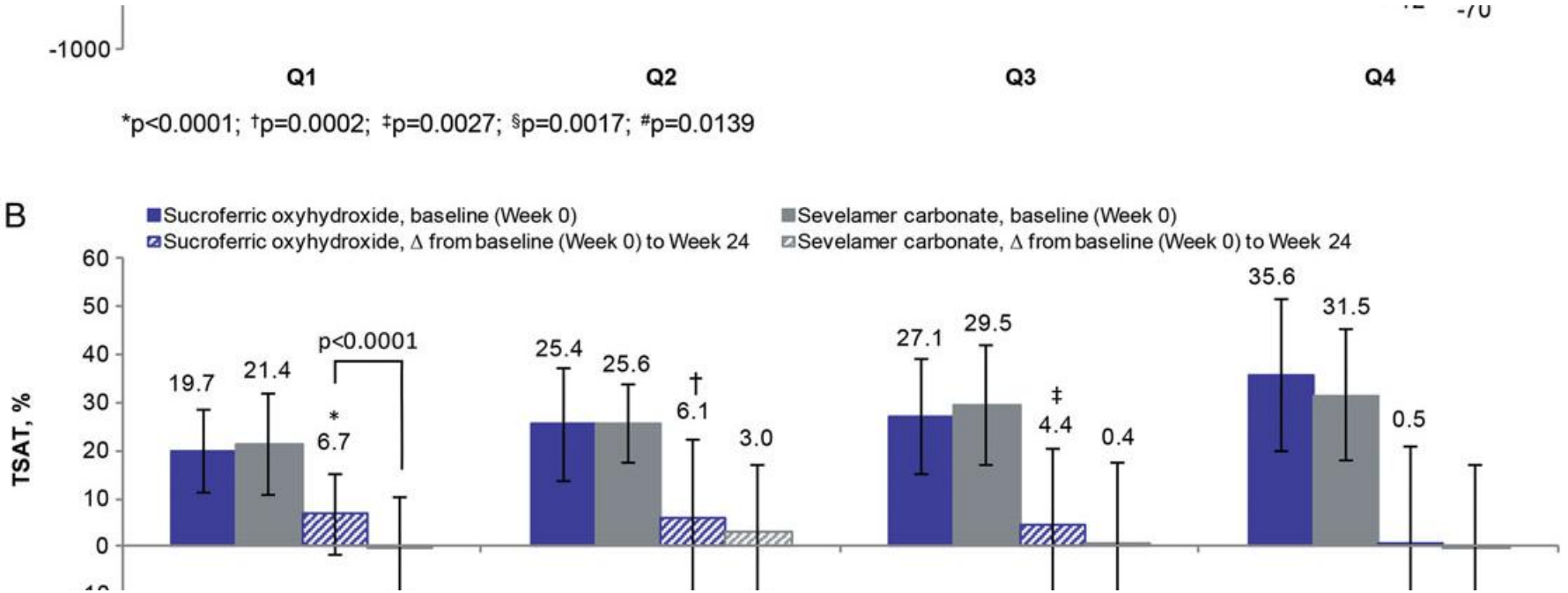
Covic A, Nephrol Dial Transplant,2016

TSAT and hemoglobin in patients without IV Iron



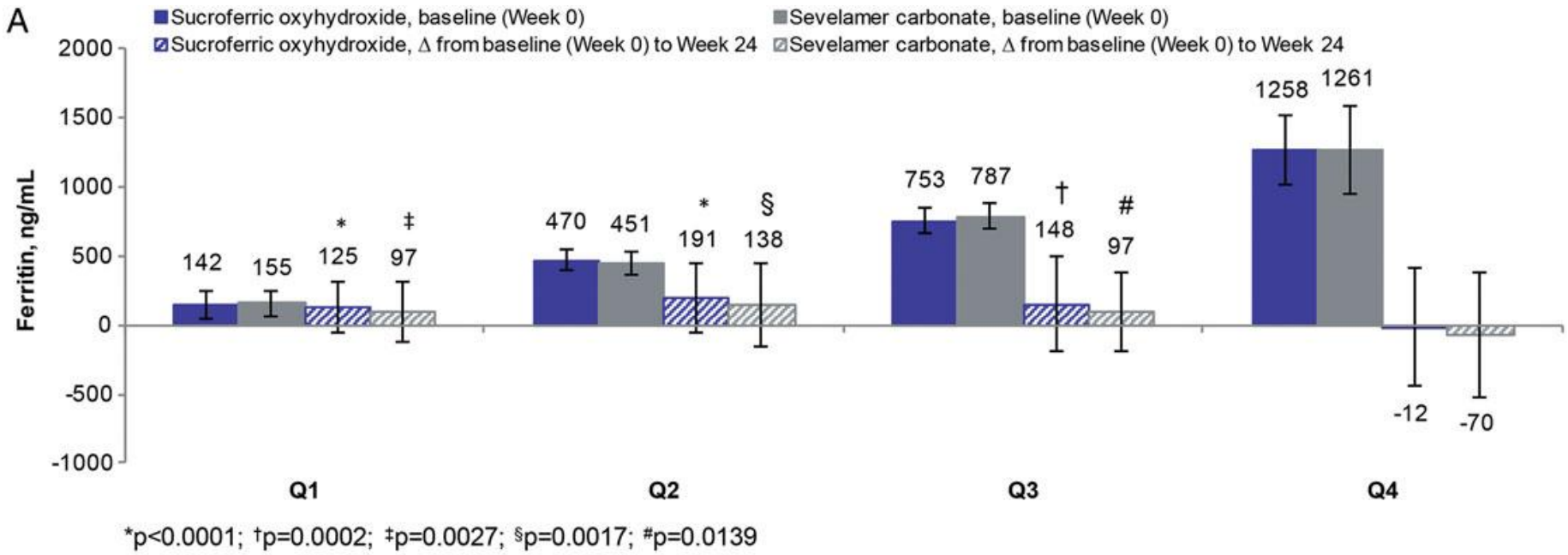
Covic A, Nephrol Dial Transplant,2016

Ferritin changes by baseline ferritin levels



Covic A, Nephrol Dial Transplant,2016

Hemoglobin changes by baseline ferritin levels



Covic A, Nephrol Dial Transplant,2016

Iron phosphate binders

	Sucroferric Oxyhydroxide	Ferric Citrate
PO_4 binding capacity mg/gr	260	46
Dose size mg	500	1000
Tablets /day	≈ 3	≈ 6
Diarrhea	10 à 15 %	5 à 20 %
PTH and FGF23	↓	↓
Iron absorption	low	high
ASE needs	No change	- 20 %
IV Iron needs	No change	- 50 %
Hazards	Impact on gut microbiotome	Impact on gut microbiotome Aluminium absorption and iron overload

No Drug interactions

Atorvastatine, simvastatine

Digoxine

Warfarine

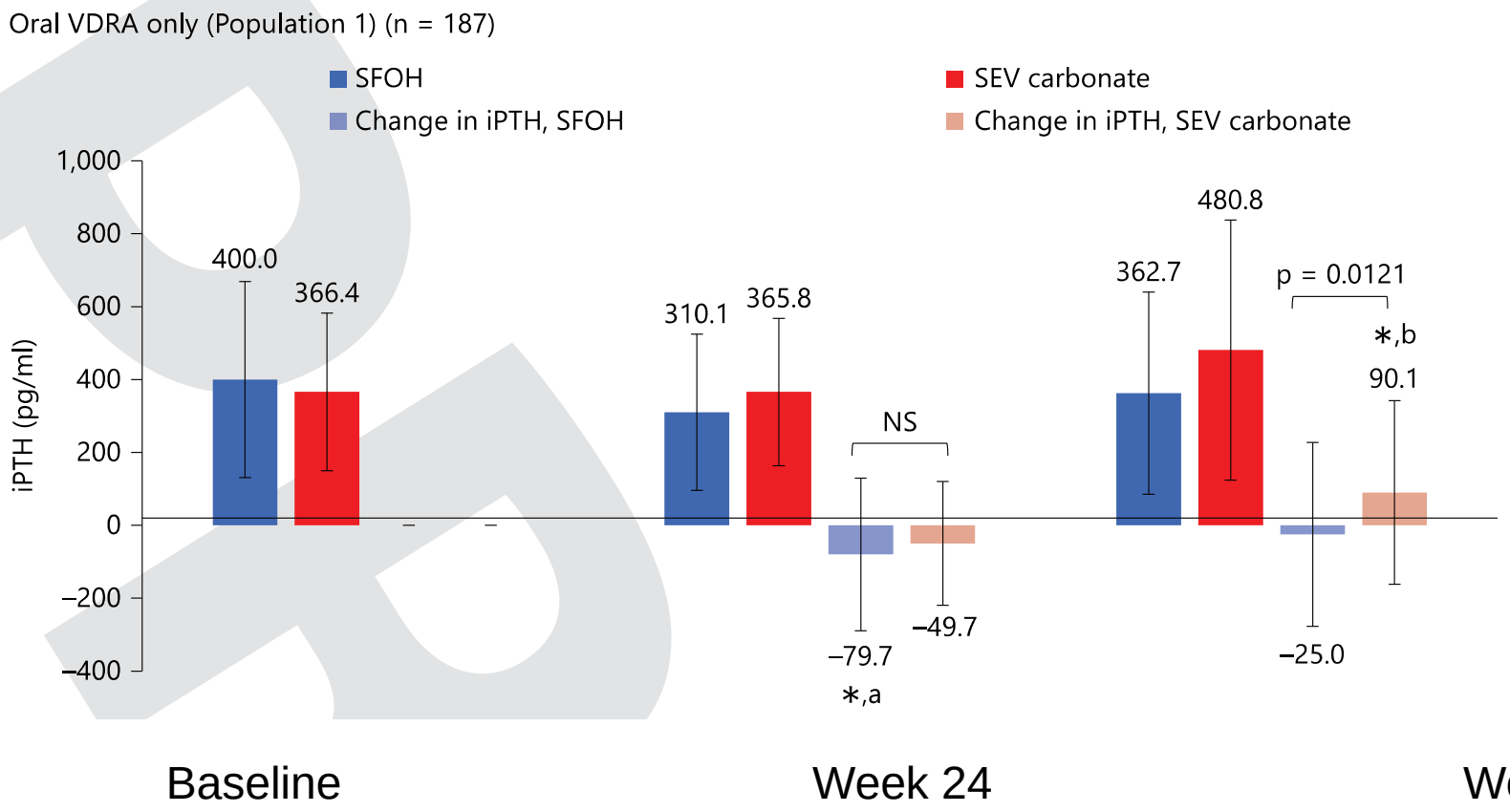
Oméprazole

Losartan

Furosemid

Oral VDR activator

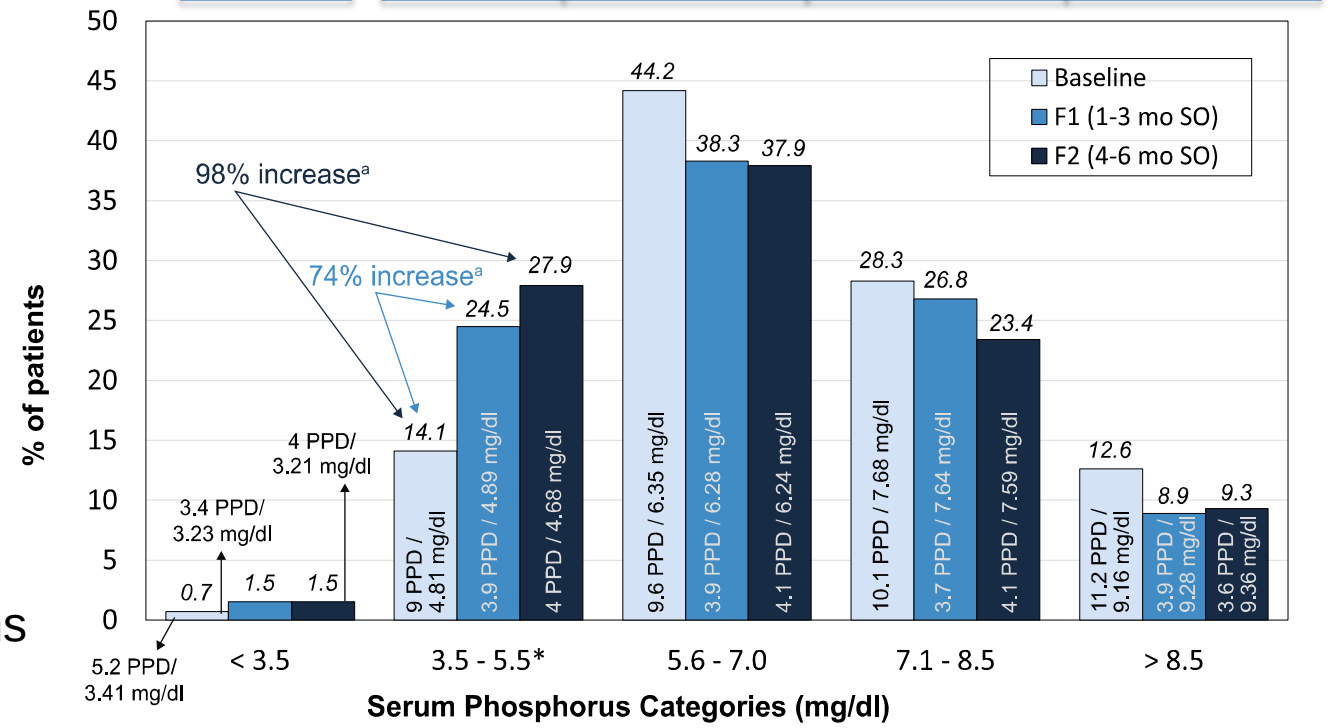
Interaction with oral VDRA



Sprague SM, Am J Nephrol, in Press

Switch Sevelamer-S.O. M6

5,2 3,4 4	9 3,9 4	9,6 3,9 4,1	10.1 3.7 4.1	12.6 8.9 9.3



259 pts HD
51 ans, vintage 4,6 ans

Pills per day:
M0, 10,1
M3, 3.8, *P < 0.0001*
M6, 3.9, *P < 0.0001*

Ficociello LH, EDTA 2016

Patients treated in our unit

	M0	M1	M3	M6
N	42	34	22	16
PPO4 mmol/L	1.53	1.2	1.17	1.06
PPO4 Change mmol/L		-0.36	-0.4	-0.44

42 patients (4 PD patients): S.O. 2.07 pills per day
Switch of phosphate binder to S.O. in 10 patients
Reduction of pills per day 4,6 ➔ 3,6

TEAE leading to withdrawal, 8 patients
- Diarrhea 5 patients
- Abdominal discomfort 3
- Constipation 1

Sucroferric Oxyhydroxide in addition to other binders

	M0	M1	M3	M6
N	29	22	17	11
PPO4 mmol/L	1.52	1.27	1.18	1.08
PPO4 change mmol/L		-0.28	-0.33	-0.35

PPO4 > 1.75 mmol/L

	M0	M1	M3	M6
N	24	19	12	8
PPO4 mmol/L	1.66	1.34	1.29	1.19
PPO4 change mmol/L		-0.32	-0.38	-0.46

S.O pills per day : 2.14.

Sucroferric Oxyhydroxide as a unique binder

	M0	M1	M3	M6
N	13	12	7	5
PPO4 mmol/L	1.51	1.08	1.17	1.17
PPO4 change mmol/L		-0.44	-0.54	-0.64

PPO4 > 1.75 mmol/L

	M0	M1	M3	M6
N	11	10	6	4
PPO4 mmol/L	1.63	1.11	1.09	1.03
PPO4 change mmol/L		-0.44	-0.54	-0.64

Number of S.O. pills per day: M1 1.8 to M3 2.3

Pratical Use of Sucroferric Oxyhydroxide

- Patient information
  - Discolored feces
  - Potential occurrence of diarrhea (frequently ending within 4 weeks)
  - Drug interaction (unfrequent, to be careful, levothyroxine, doxycycline,or alendronate given 1 or 2 hours before phosphate binder)
- Dose titration
  - 1tablet first week, 2 tablets 2nd week, 3 tablets third week)
  - Better G.I. tolerance ?

Phosphate binders in France in 2017

	Calcium-based P.B.	Sevelamer	Lanthanum	Sucroferric Oxyhydroxide
Efficacy	++	++	++++	++++
Adverse Events (AE)	G.I. AE	G.I. AE	G.I. AE	Diarrhea
Bone metabolism parameters	HCa^{++} ↓ PTH ↑ FGF23	≈PTH ↓ FGF23	≈PTH ↓ FGF23	≈ PTH ↓ FGF23
Lipid parameters	neutral	↓ cholestérol	neutral	neutral
Vascular Ca^{++}	↑ (?)	↓ or neutral	?	↓ or neutral
Cost	+	+++	+++	++(+)

Conclusions

1) Sucroferric oxyhydroxide, a very powerful phosphate binding agent with a low pill burden

2) Main adverse events are gastrointestinal in nature (diarrhea) mostly transient (one month)

3) No risk of iron overload

4) A new drug for customizing the treatment
   - good choice for patients with vascular calcification and adynamic bone disease
   - a reduced number of pills
   - intolerance to other binders