Efficacy and safety of Etelcalcetide in patients receiving Hemodialysis with Secondary Hyperparathyroidism: Real life data

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Therapeutics and Clinical Risk Management

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REVIEW

Treatment of secondary hyperparathyroidism: the clinical utility of etelcalcetide

Therapeutics and Clinical Risk Management 2017:13 679–689

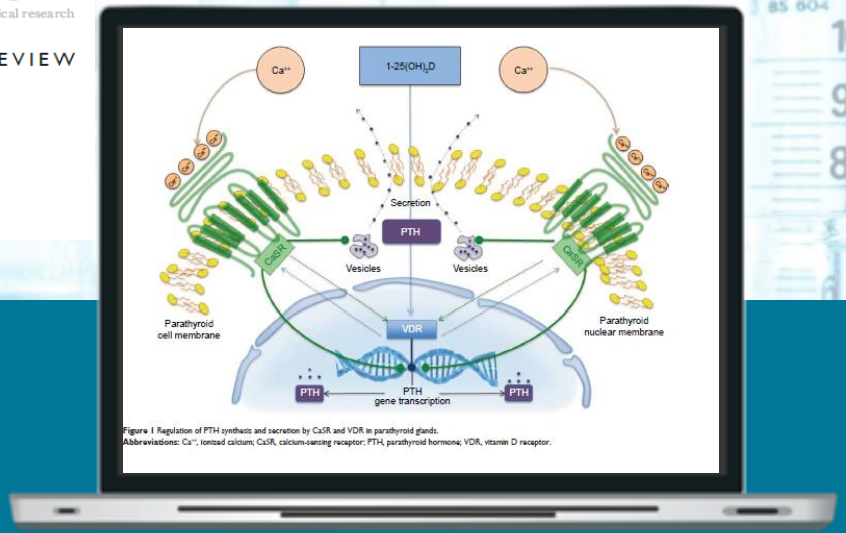
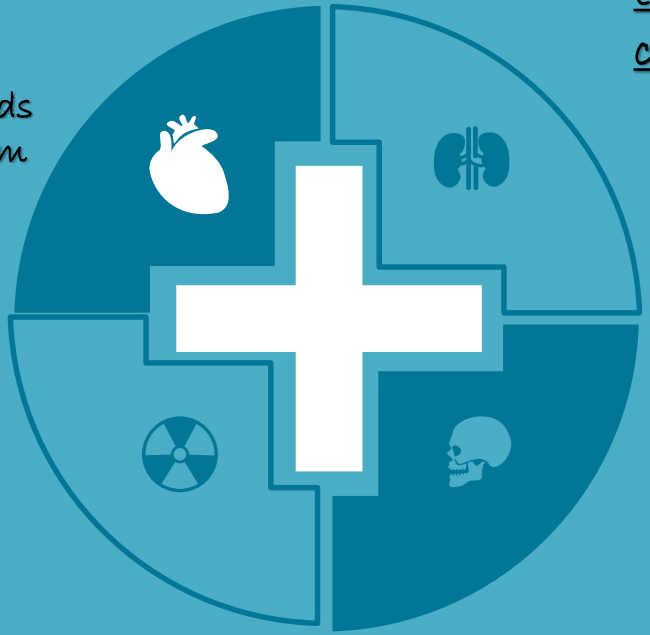


Figure 1 Regulation of PTH synthesis and secretion by CaSR and VDR in parathyroid glands.
Abbreviations: Ca^{++}, ionized calcium; CaSR, calcium-sensing receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

Under normal physiological conditions (Figure 1), the principal regulator of PTH secretion and parathyroid gland function is the calcium-sensing receptor (CaSR).[4–7] Activation of the CaSR by serum calcium rapidly inhibits PTH synthesis and secretion and parathyroid gland growth. Furthermore, the CaSR influences PTH gene expression and may also upregulate the vitamin D receptor (VDR).

Secondary hyperparathyroidism (sHPT)

Attempt to control the disturbed calcium, phosphorus, and vitamin D metabolism. sHPT causes vascular and soft-tissue calcification and leads to disturbances of mineral metabolism CKD-related mineral and bone disorder (CKD-MBD).



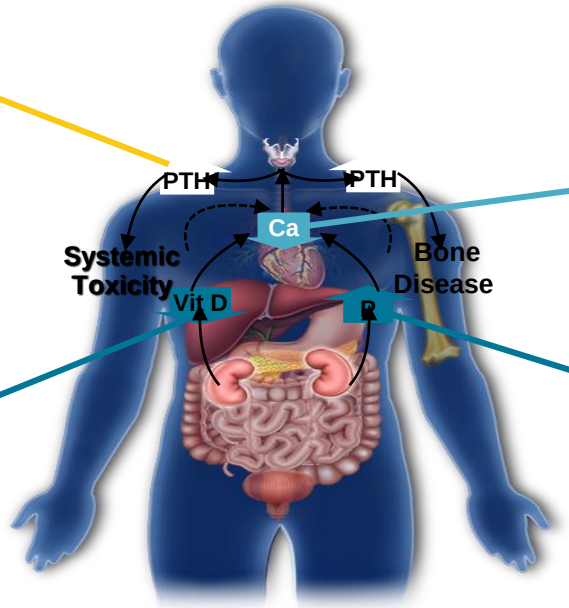
The indication for sHPT treatment results from these clinical consequences

CKD-MBD abnormalities have also been implicated as risk factors for the very rare but devastating calcific and thrombotic arteriolopathy calciphylaxis and lead to reduced health-related quality of life (HR QoL).

sHPT-associated high FGF23 is independently associated with left ventricular hypertrophy, cardiovascular events and premature death.

Abnormalities in Metabolic Parameters Are Consequences of SHPT: Management of PTH, Ca, and P

Involved in homeostasis of bone metabolism
- Maintains correct balance of Ca and P in the body



Control Ca
- Control intake
- Adjust dialysate Ca
- Use Ca supplements or vitamin D therapy (if Ca low)

Increase Vitamin D Levels
- Administer vitamin D sterols to reduce PTH

Lower Elevated Serum P
- Control dietary intake
- Use phosphate binders

Treatment approaches to the management of SHPT include Ca x P, PTH, and vitamin D.

Use of vitamin D and phosphate binders alone provide no direct way to control PTH levels without the risk of raising Ca and P levels.

Ca = calcium; P = phosphate; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism.

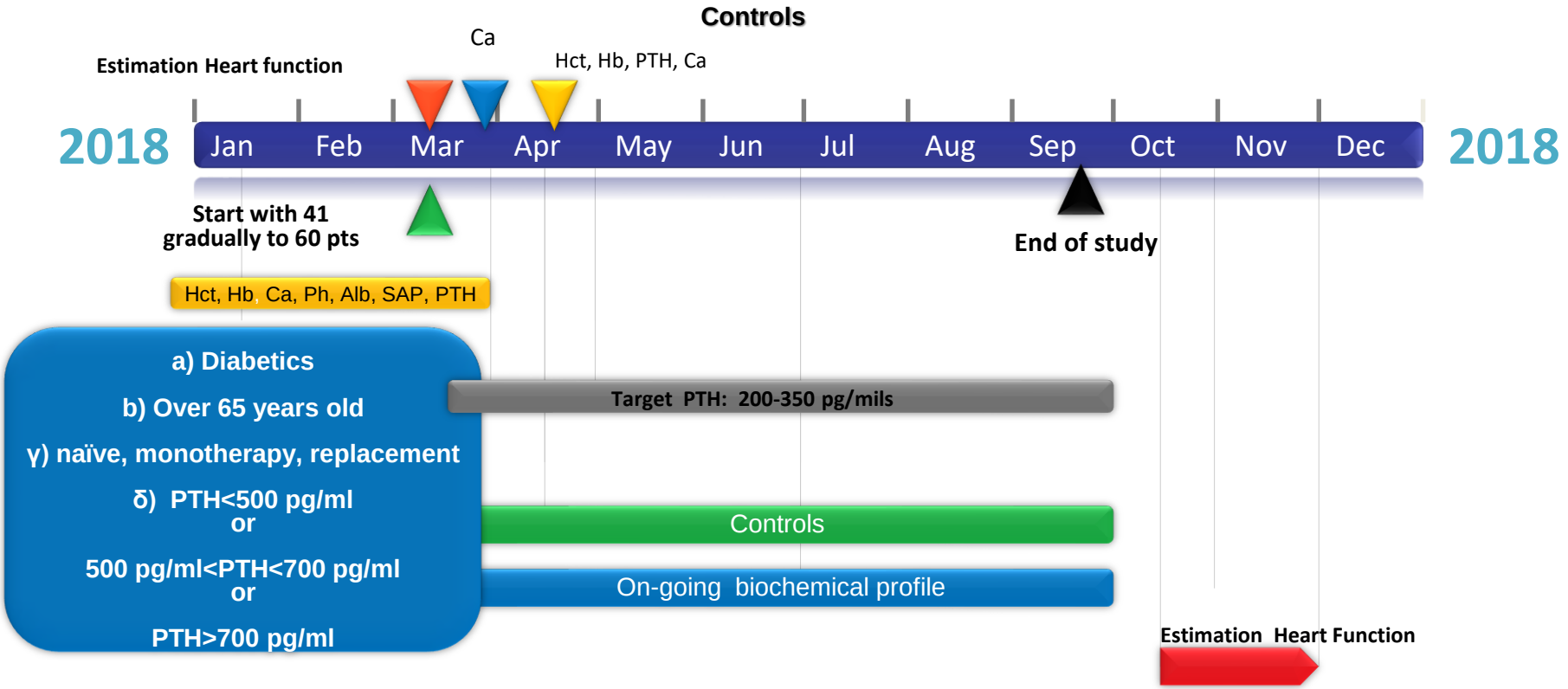
Tomasello S. Diabetes Spectrum. 2008;21:19-25

Table 1 Differences between first- and second-generation calcimimetics

	Cinacalcet	Etelcalcetide
Class	First-generation calcimimetic type II Small organic molecule	Second-generation calcimimetic type II Octapeptide
Molecular formula	$C_{22}H_{23}F_3N$	$C_{38}H_{73}N_{21}O_{10}S_2$
Molecular weight	394 Da	1,048 Da
Mode of action at CaSR	Allosteric modulator	Allosteric modulator and direct agonist
Location of interaction with CaSR	Transmembrane domain	Extracellular domain
Mode of administration	Daily oral	Thrice-weekly intravenously at the end of hemodialysis session

Abbreviation: CaSR, calcium-sensing receptor.

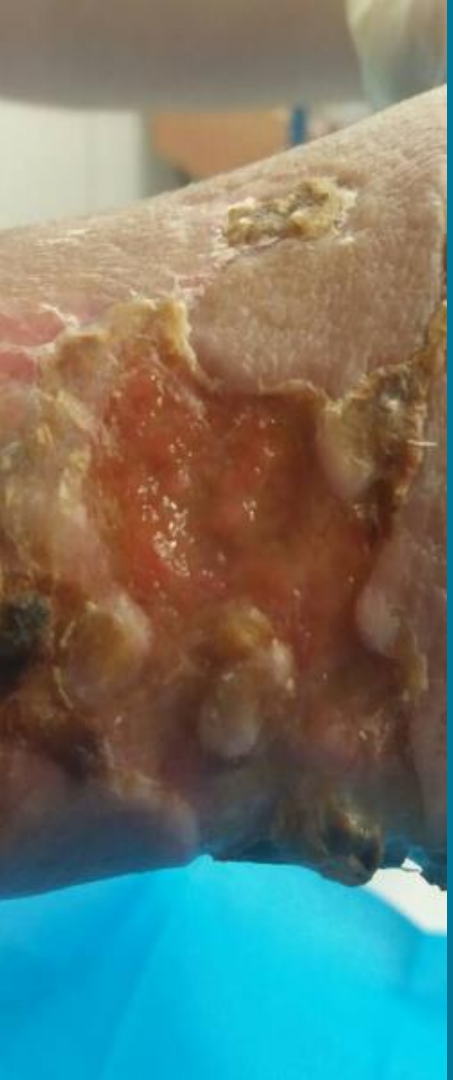
Protocol Etelcalcetide



Target PTH:
200-350
pg/ml

Management Ca

- 7,5 mg/dl<Ca<8,3 mg/dl with no symptoms:
  Dose arrangement or other maneuvers
- <7,5 mg/dl: cessation of therapy

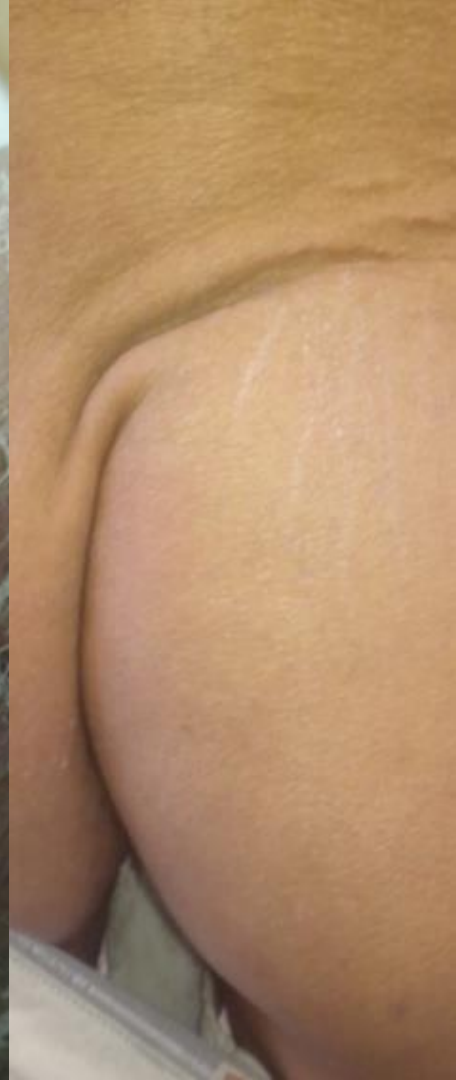


Interesting cases

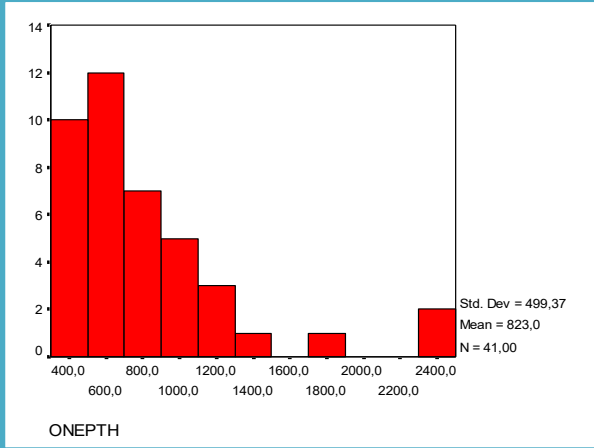
Calciphylaxis

and

Tumoral Calcinosis

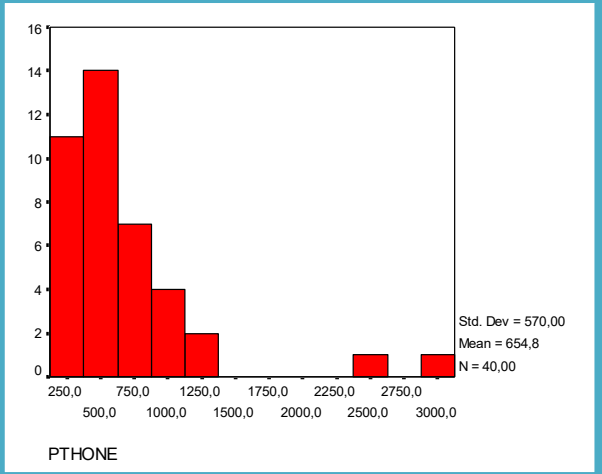


PTH behaviour

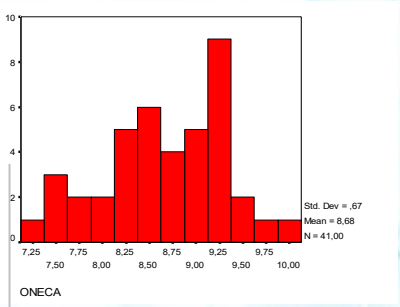


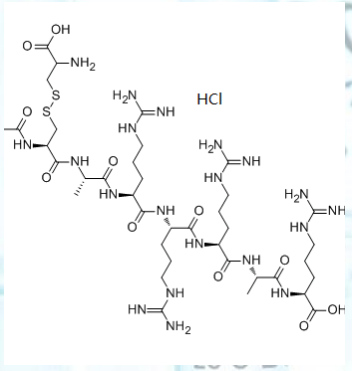
PTH before starting i.v. Etelcalcetide was **823 pg/mils**

PTH after one month therapy with i.v. Etelcalcetide was **654,8 pg/mils** ($p<0,05$).

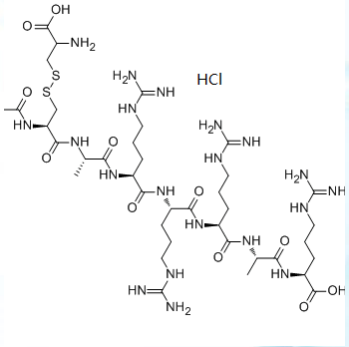


Ca before starting therapy was **8.68** mg/dl.





Ph levels were also significantly reduced from 7.28 to 5.04 mg/dl ($p<0,05$).



5 pts **Name Here**

3 in normal values in a month

1 change of doseT

1 tempor. cessation

Ca a week after was **8.61** mg/dl ($p=NS$).

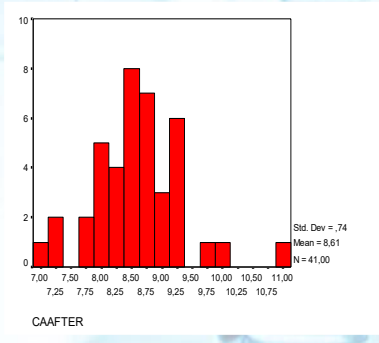


Table 3 Summary of controlled etelcalcetide Phase II and III trials

Study	Study design	Country/region	Study population (n)	Study duration	Comparator	Etelcalcetide intervention	Changes in iPTH: results of etelcalcetide vs comparator
Martin et al[44]	Double-blind, randomized placebo-controlled, multicenter	USA	28 (total) 12 (cohort 1–3) 16 (cohort 4–5)	28 days	Placebo	Single dose of study drug Cohorts 1–3: two-period crossover design with 7–14 days interdose interval: cohort 1, 5 mg; cohort 2, 10 mg; cohort 3, 20 mg Cohorts 4 and 5: 1:1 randomization; cohort 4, 40 mg; cohort 5, 60 mg	Mean change from baseline at discharge (~3 days after application): cohort 3, −48.5%; cohort 4, −49.3%; cohort 5, −62.6%
Bell et al[43]	Double-blind, randomized placebo-controlled, multicenter	USA	78	2 weeks (cohort 1), 4 weeks (cohorts 2, 3)	Placebo	Cohort 1: 5 mg thrice weekly Cohort 2: 10 mg thrice weekly Cohort 3: 5 mg thrice weekly	Mean change from baseline to efficacy period: cohort 2, −49.4% ($P<0.05$); cohort 3, −33.0% ($P<0.05$)
Block et al[44]	Two parallel, multicenter, randomized, double-blind, placebo-controlled trials	USA, Canada, Europe, Israel, Russia, Australia	1,023 (trial A 508, trial B 515)	26 weeks	Placebo	Starting dose 5 mg thrice weekly; titration in 2.5 or 5 mg increments at weeks 5, 9, 13, 17; maximum dose 15 mg thrice weekly	Proportion of patients achieving >30% reduction: trial A, 74.0% vs 8.3% ($P<0.001$); trial B, 75.3% vs 9.6% ($P<0.001$)
Block et al[45]	Randomized, double-blind, double-dummy active clinical trial	USA, Canada, Europe, Russia, New Zealand	683	26 weeks	Cinacalcet	Starting dose 5 mg thrice weekly, titration in increments of 2.5 or 5 mg at weeks 5, 9, 13, 17, maximum dose 15 mg Starting dose of oral cinacalcet 30 mg daily, titration in increments of 30 mg at weeks 5, 9, 13, 17, maximum dose 180 mg daily	Proportion of patients achieving >30% reduction: 68.2% vs 57.7% (noninferiority, $P<0.001$; superiority, $P=0.004$)
Fukagawa et al[43]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Japan	155	12 weeks	Placebo	Starting dose 5 mg thrice weekly, titration at 4-week intervals, maximum dose 15 mg thrice weekly	Proportion of patients achieving target range of 60–240 pg/mL: 59.0% vs 1.3% ($P<0.001$)

Abbreviation: iPTH, intact parathyroid hormone.

AMG 416 (velcalcetide) is a novel peptide for the treatment of secondary hyperparathyroidism in a single-dose study in hemodialysis patients

Kevin J. Martin[1], Karen Pickthorn[2], Saling Huang[2], Geoffrey A. Block[3], Andrew Vick[4], Peter F. Mount[5], David A. Power[5] and Gregory Bell[2,6]

[1]Division of Nephrology, Saint Louis University School of Medicine, Saint Louis, Missouri, USA; [2]Amgen, Inc, Thousand Oaks, California, USA; [3]Denver Nephrology, Denver, Colorado, USA; [4]WIL Research, Ashland, Ohio, USA; [5]Austin Hospital, Melbourne,

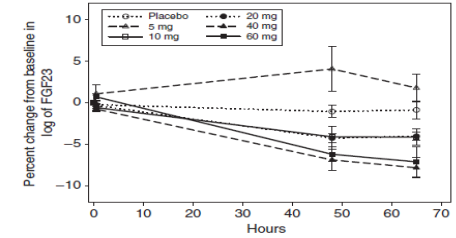


Figure 4 | Percentage change from baseline in serum log fibroblast growth factor 23 (FGF23) levels following single intravenous doses of AMG 416 or placebo. Data are shown as mean ± s.e.m.

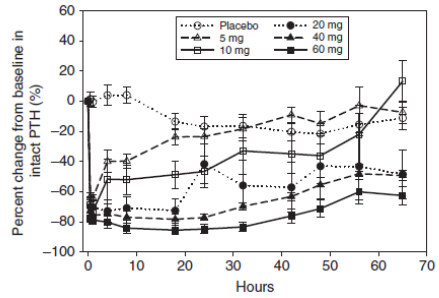


Figure 1 | Percentage change from baseline in serum intact parathyroid hormone (iPTH) levels. Time = 0 h is 2-4 h after hemodialysis and before dosing. Data are shown as mean ± s.e.m.

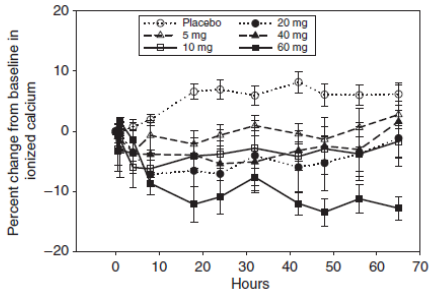


Figure 2 | Percentage change from baseline in plasma-ionized calcium following single intravenous doses of AMG 416 or placebo. Time = 0 h is 2-4 h after hemodialysis and before dosing.

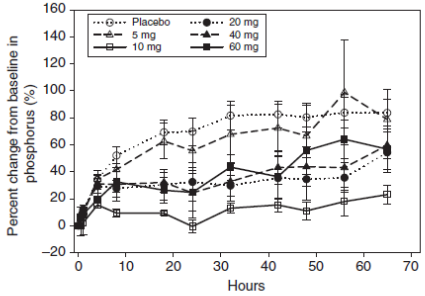


Figure 3 | Percentage change from baseline in serum phosphate levels following single intravenous doses of AMG 416 or placebo over the course of the study. Data are shown as mean ± s.e.m.

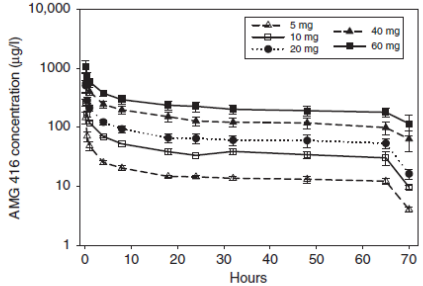
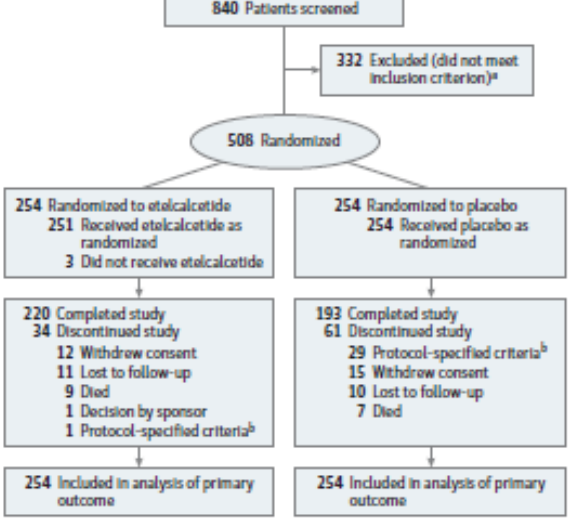
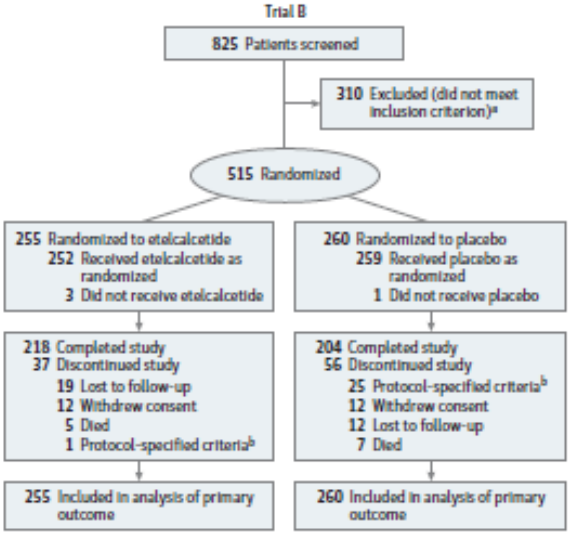
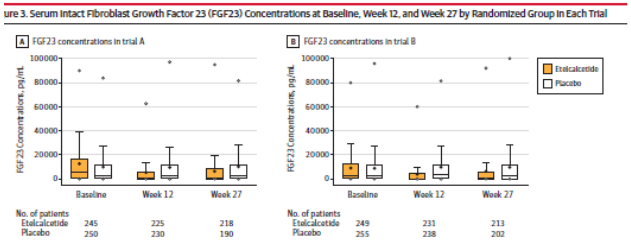


Figure 5 | Mean AMG 416 plasma concentrations (ng/ml) time course following single intravenous doses of AMG 416 to hemodialysis subjects with secondary hyperparathyroidism







ure 3. Serum Intact Fibroblast Growth Factor 23 (FGF23) Concentrations at Baseline, Week 12, and Week 27 by Randomized Group in Each Trial

sed circles represent means; solid lines, medians; boxes, interquartile ges; whiskers, 1.5 times interquartile ranges; and top and bottom open es, maximum and minimum observations. The following values were luded from the figure: in trial A, 1 (0.4%) etelcalcetide-treated and 2 (0.8%) cebo-treated patients had FGF23 values higher than 100 000 pg/mL at eline, 1 (0.4%) etelcalcetide-treated and 5 (2.2%) placebo-treated patients l FGF23 values higher than 100 000 pg/mL at week 12, and 2 (0.9%) etelcalcetide-treated and 3 (1.6%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 27; in trial B, 2 (0.8%) etelcalcetide-treated and 10 (3.9%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at baseline, 0 etelcalcetide-treated and 5 (2.1%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 12, and 2 (0.9%) 2 etelcalcetide-treated and (1.0%) placebo-treated patients had FGF23 values higher than 100 000 pg/mL at week 27.

Research

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Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

Two Randomized Clinical Trials

Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn M. Chertow, MD, MPH

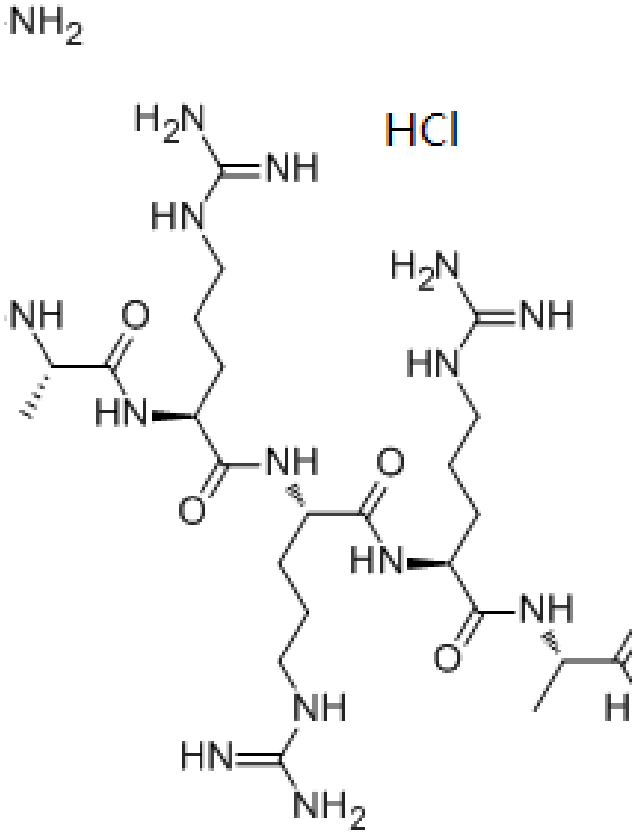
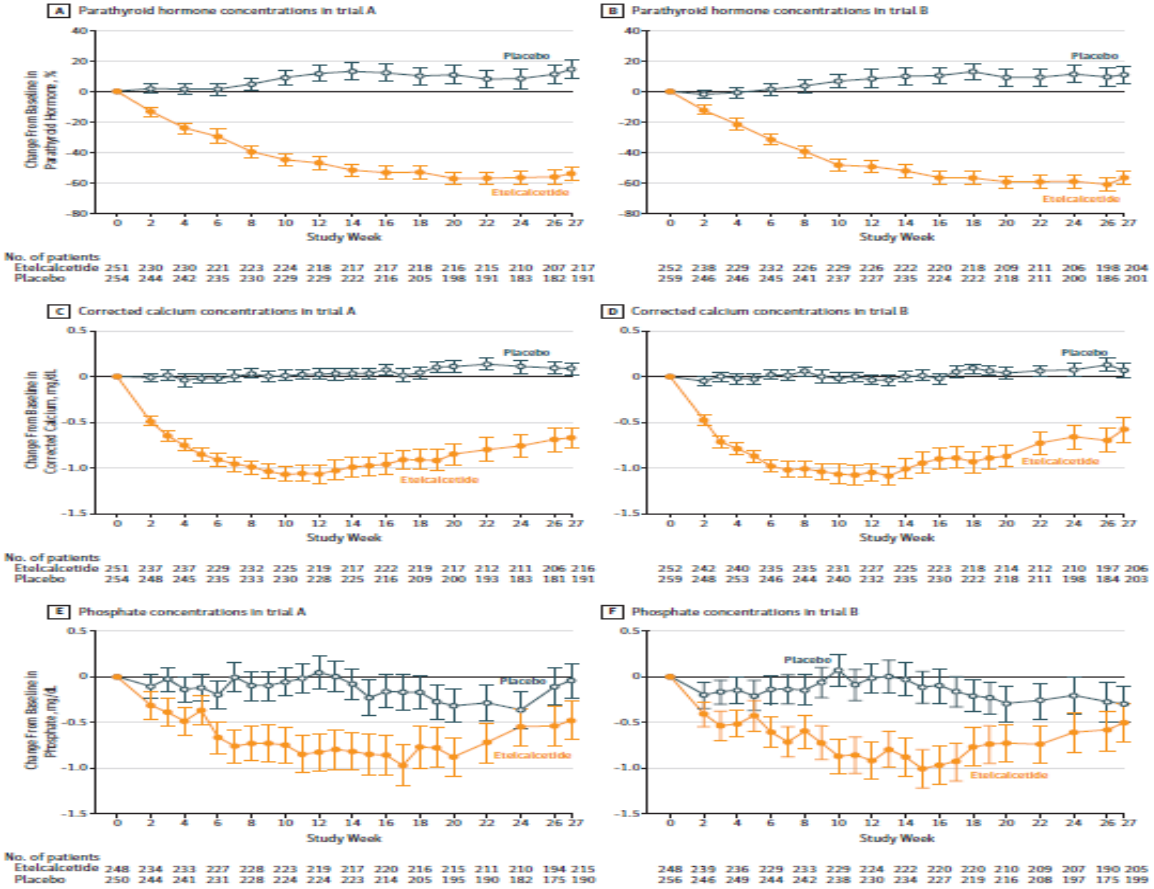


Figure 2. Mean Percentage Change From Baseline by Study Week in Parathyroid Hormone, Corrected Calcium, and Phosphate Concentrations by Randomized Group in Each Trial



Error bars indicate 95% CIs. Week 27 was a posttreatment visit.

Table 2. Treatment-Emergent Adverse Events[a]

Adverse Events	No. (%) of Participants			
	Trial A		Trial B	
	Etelcalcetide (n = 251)	Placebo (n = 254)	Etelcalcetide (n = 252)	Placebo (n = 259)
Blood calcium decrease[b]	153 (61.0)	21 (8.3)	168 (66.7)	31 (12.0)
Muscle spasms	30 (12.0)	18 (7.1)	28 (11.1)	16 (6.2)
Diarrhea	18 (7.2)	18 (7.1)	36 (14.3)	26 (10.0)
Nausea	31 (12.4)	13 (5.1)	23 (9.1)	19 (7.3)
Vomiting	26 (10.4)	18 (7.1)	19 (7.5)	8 (3.1)
Headache	18 (7.2)	20 (7.9)	20 (7.9)	11 (4.2)
Hypocalcaemia	18 (7.2)	1 (0.4)	17 (6.7)	0
Hypertension	12 (4.8)	17 (6.7)	19 (7.5)	12 (4.6)
Hypotension	16 (6.4)	10 (3.9)	14 (5.6)	16 (6.2)
Arteriovenous fistula site complication	13 (5.2)	14 (5.5)	16 (6.3)	12 (4.6)
Pain in extremity	17 (6.8)	11 (4.3)	7 (2.8)	9 (3.5)
Paresthesia	13 (5.2)	3 (1.2)	11 (4.4)	0
Back pain	8 (3.2)	8 (3.1)	14 (5.6)	11 (4.2)
Upper respiratory tract infection	8 (3.2)	10 (3.9)	13 (5.2)	16 (6.2)

Portfo

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Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
A Randomized Clinical Trial

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

You can simply impress your a

Figure 2. Parathyroid Hormone, Calcium, and Phosphate Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week

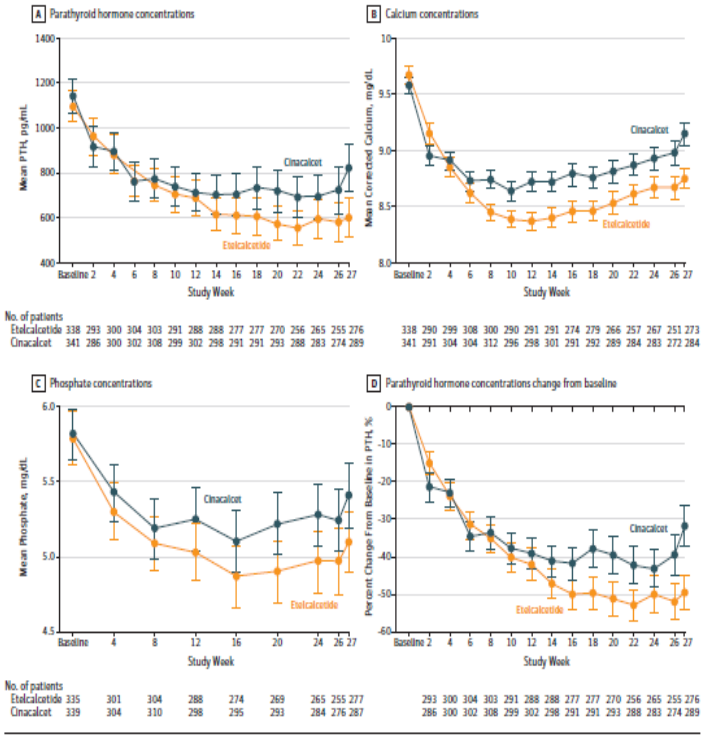

Figure 1. Flow Diagram of Patients Through the Trial

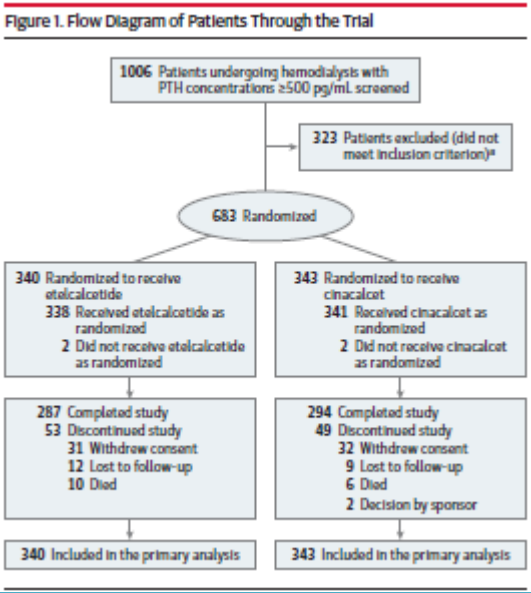

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Table 2. Treatment Emergent Adverse Events[a]

Preferred Term	Patients, No. (%) Etelcalcetide (n = 338)	Cinacalcet (n = 341)
Blood calcium decreased[b]	233 (68.9)	204 (59.8)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Hypotension	23 (6.8)	10 (2.9)
Headache	22 (6.5)	24 (7.0)
Muscle spasms	22 (6.5)	20 (5.9)
Diarrhea	21 (6.2)	35 (10.3)
Hypertension	21 (6.2)	23 (6.7)
Anemia	17 (5.0)	15 (4.4)
Hypocalcemia	17 (5.0)	8 (2.3)
Pain in extremity	17 (5.0)	14 (4.1)
Bronchitis	5 (1.5)	17 (5.0)

[a] Adverse events occurring among 5% or more patients in either group. The term *treatment emergent* refers to a condition either not present before exposure to a study drug that develops after drug exposure or a condition present before exposure that worsens in frequency or severity. Adverse events occurring after the first dose of study drug and up to 30 days after the last dose of study drug were included. Counts and proportions refer to patients rather than to adverse events. In other words, patients may have one or more adverse event.

[b] Defined as an albumin-corrected serum calcium concentrations lower than 8.3 mg/dL (to convert to mmol/L, multiply by 0.25) that resulted in a medical intervention.

Nephrol Dial Transplant (2017) 32: 1723–1730
doi: 10.1093/ndt/gfw408
Advance Access publication 4 January 2017

ndt
Nephrology Dialysis Transplantation

A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of etelcalcetide (ONO-5163/AMG 416), a novel intravenous calcimimetic, for secondary hyperparathyroidism in Japanese haemodialysis patients

Masafumi Fukagawa[1], Keitaro Yokoyama[2], Takashi Shigematsu[3], Takashi Akiba[4], Akifumi Fujii[5], Takuto Kuramoto[5], Motoi Odani[6], Tadao Akizawa[7] and the ONO-5163 Study Group

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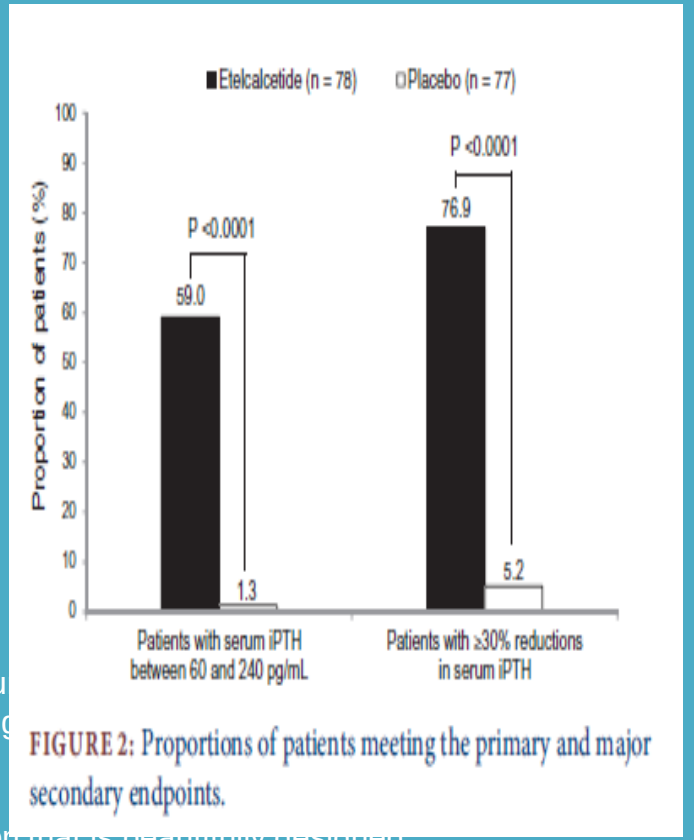

FIGURE 2: Proportions of patients meeting the primary and major secondary endpoints.

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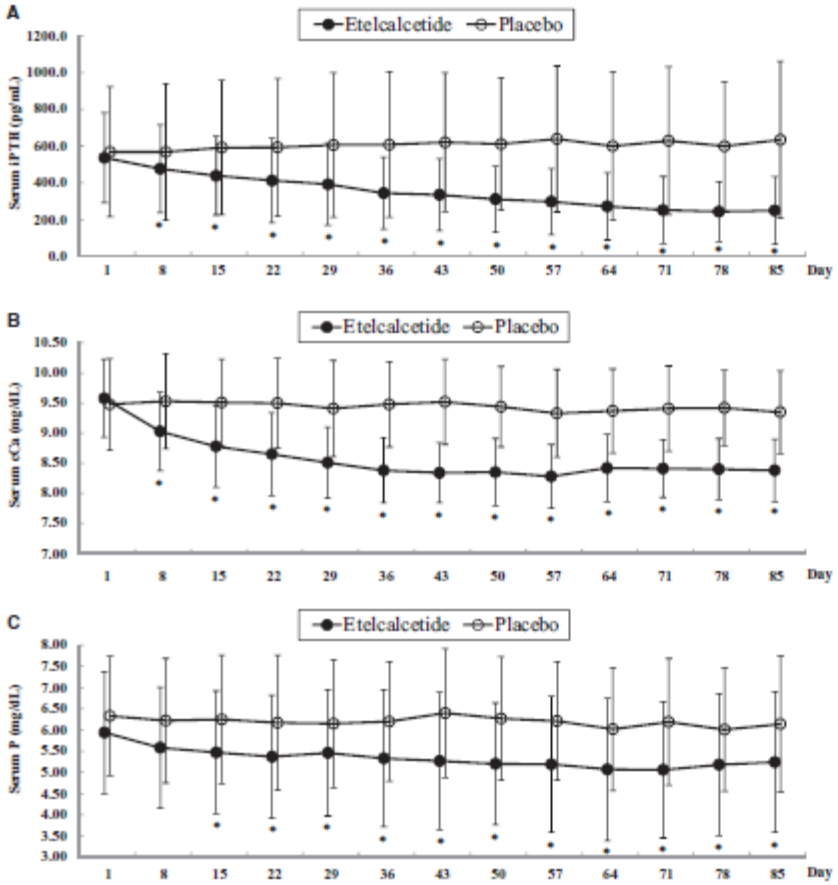

FIGURE 3: Serum iPTH (**A**), cCa (**B**) and P (**C**) levels during the study period. Data are expressed as means ± standard deviation. *$P < 0.05$ regarding per cent changes from baseline compared with placebo.

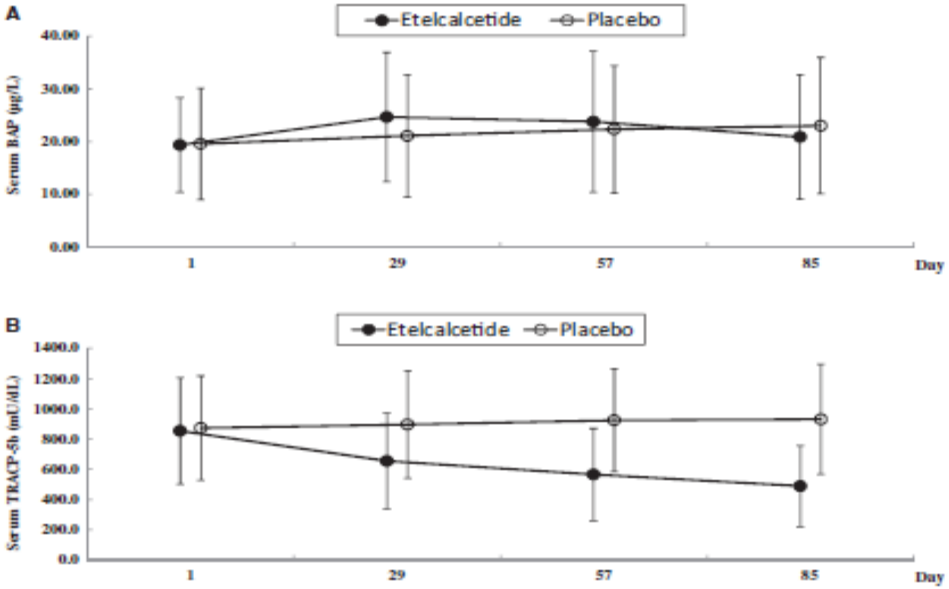

FIGURE 4: Serum BAP (**A**) and TRACP-5b (**B**) levels during the study period. Data are expressed as means ± standard deviation.

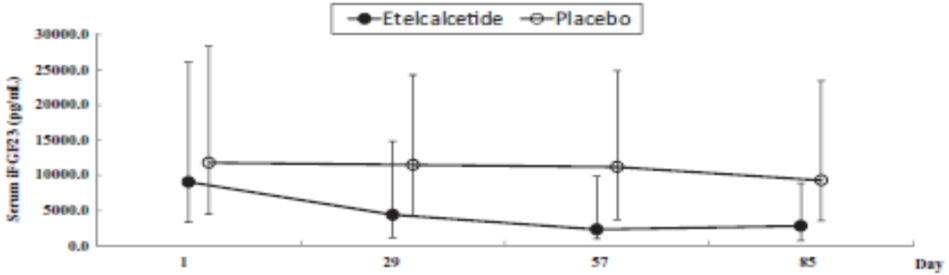

FIGURE 5: Serum iFGF23 levels during the study period. Data are expressed as median (Q1, Q3).

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In 2015, Bell et al[62] reported on results of a multicenter, double-blind, randomized, placebo-controlled, dose-escalating trial. This Phase II study included 78 hemodialysis patients with baseline PTH levels ≥350 pg/mL. Subjects were divided into three cohorts: patients in cohort 1 received either 5 mg etelcalcetide or placebo thrice weekly after each hemodialysis session for 2 weeks, and those in cohorts 2 and 3 were treated with 10 mg or 5 mg etelcalcetide or placebo at the end of each dialysis for 4 weeks. The primary end point for cohorts 2 and 3 was defined as mean percentage change in PTH levels from baseline. After 4 weeks, PTH had decreased significantly by 49.4% with 10 mg of etelcalcetide and by 33.0% with 5 mg. The proportion of patients with ≥30% PTH reduction was 76.2% in etelcalcetide-treated patients vs 9.5% in the placebo group ($P<0.0001$). Treatment with etelcalcetide was also associated with a decrease in serum-calcium and FGF23 levels. Approximately 40% of study participants reported at least one treatment-emergent adverse event (TEAE), but the incidence of TEAEs was not dose-dependent and no patient discontinued the study due to a TEAE.

Bell G, Huang S, Martin KJ, Block GA. A randomized, double-blind, phase 2 study evaluating the safety and efficacy of AMG 416 for the treatment of secondary hyperparathyroidism in hemodialysis patients. *Curr Med Res Opin*. 2015;31(5):943–952.

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Michela Mangano[1]
Luca Di Lullo[2]
Antonio Bellasi[1,3]

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REVIEW

Treatment of secondary hyperparathyroidism: the clinical utility of etelcalcetide

Therapeutics and Clinical Risk Management 2017:13 679–689

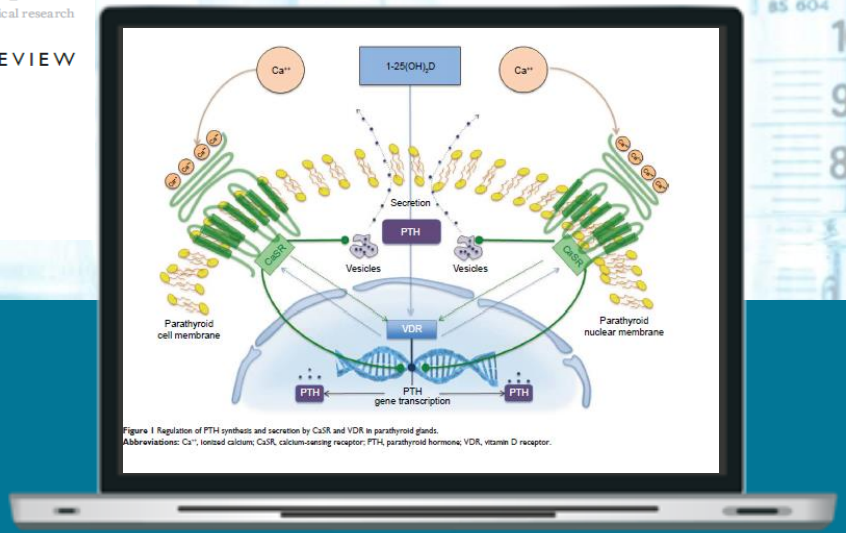
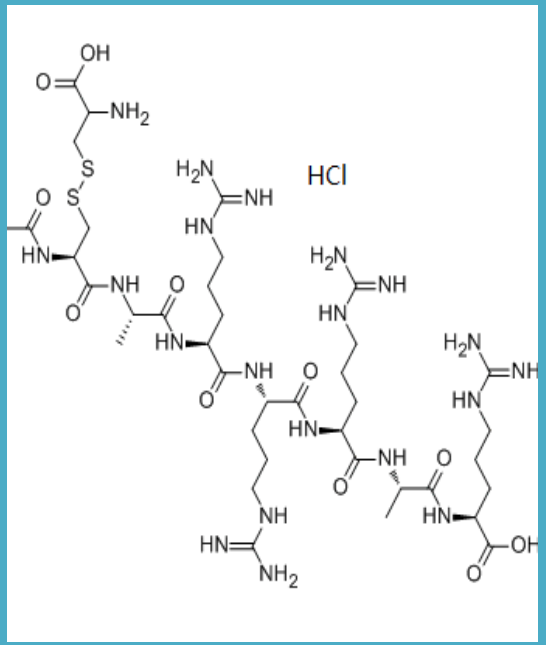


Figure 1 Regulation of PTH synthesis and secretion by CaSR and VDR in parathyroid glands.
Abbreviations: Ca^{++}, ionized calcium; CaSR, calcium-sensing receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

To date, no controlled studies directly comparing etelcalcetide with placebo, cinacalcet, or surgical parathyroidectomy with regard to hard clinical end points, such as mortality, cardiovascular events, fractures and parathyroidectomy in patients with ESKD have been conducted. The same holds true for parathyroidectomy, which has never been compared to calcimimetics in an RCT. This renders

After 2 months notification the new second-generation calcimimetic etelcalcetide effectively reduces PTH, Ph with an acceptable safety profile.

Hopefully at the end of our study protocol we will reach to more solid conclusions regarding better control of sHPT.



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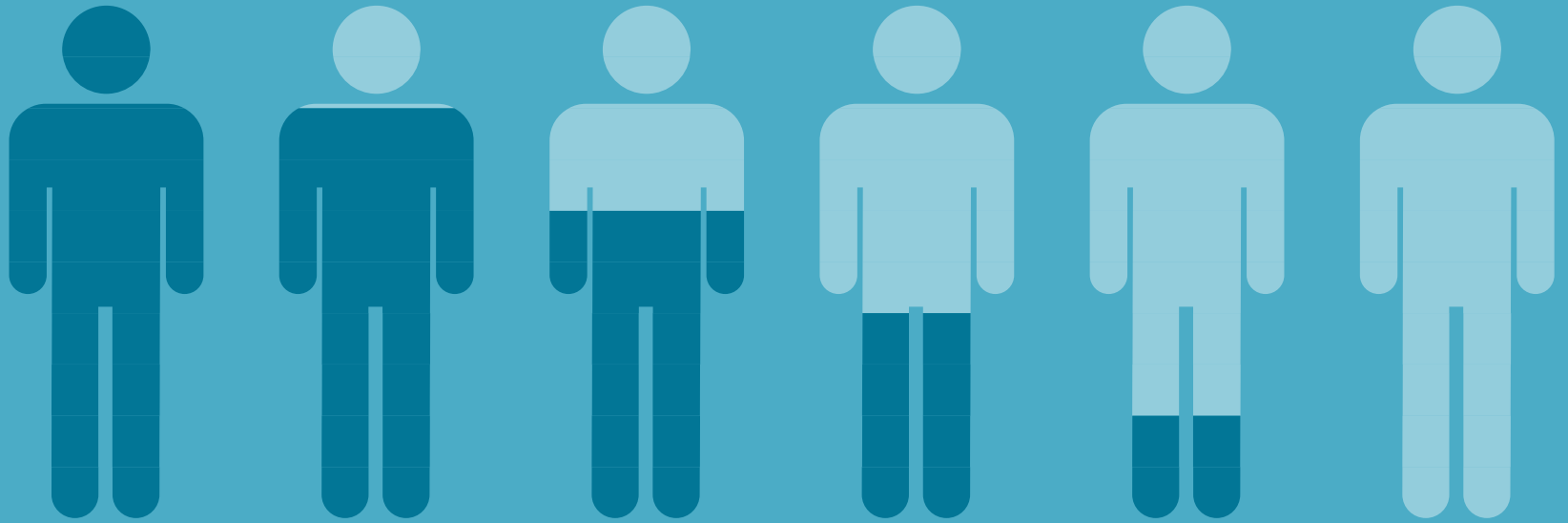

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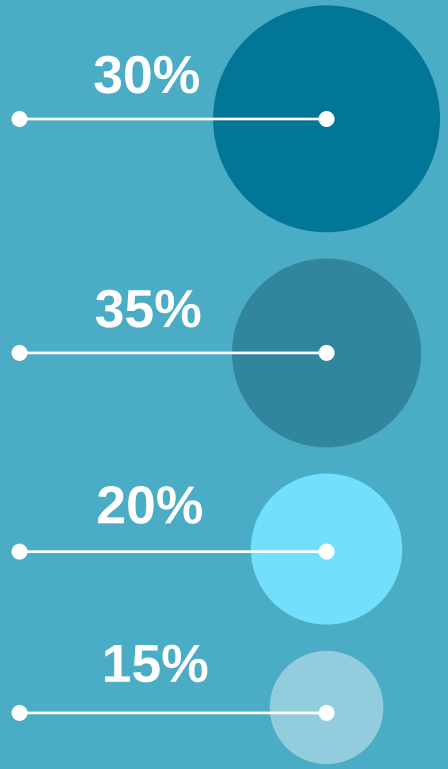

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Secondary hyperparathyroidism (sHPT)

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Day of the week	Name		Name		Name		Name		Name	
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Tuesday										
Wednesday										
Thursday										
Friday										
Saturday										
Sunday										

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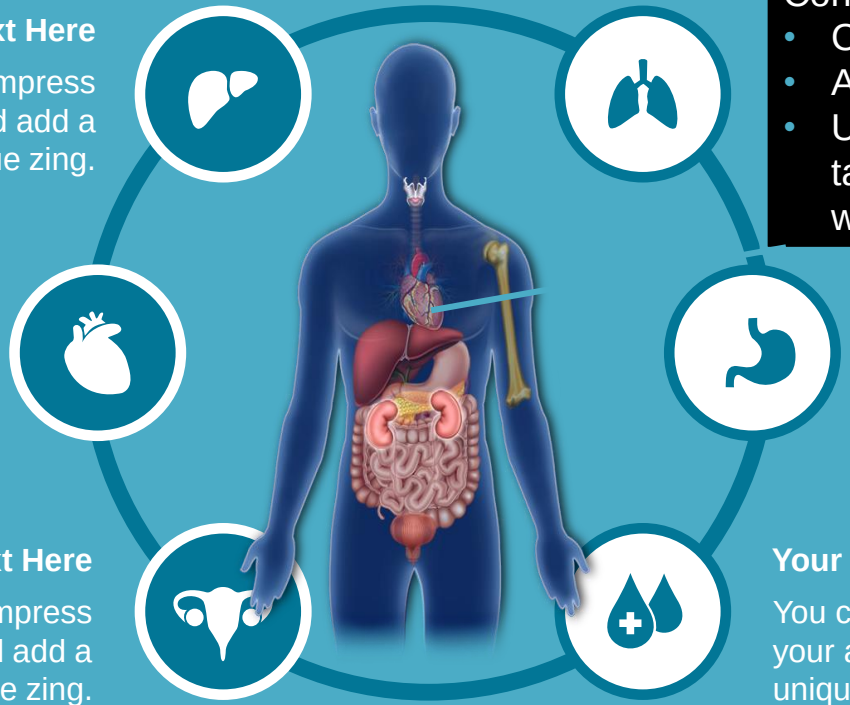

Control Ca

- Control intake
- Adjust dialysate Ca
- Use Ca supplements or vi tamin D therapy (if Ca lo w)

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REVIEW

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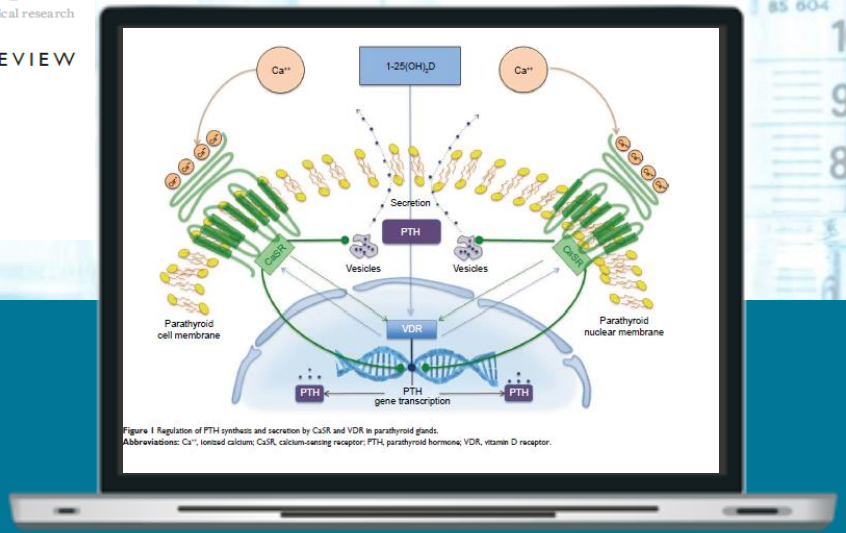

Figure 1 Regulation of PTH synthesis and secretion by CaSR and VDR in parathyroid glands.
Abbreviations: Ca^{++}, ionized calcium; CaSR, calcium-sensing receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

Under normal physiological conditions (Figure 1), the principal regulator of PTH secretion and parathyroid gland function is the calcium-sensing receptor (CaSR).[4–7] Activation of the CaSR by serum calcium rapidly inhibits PTH synthesis and secretion and parathyroid gland growth. Furthermore, the CaSR influences PTH gene expression and may also upregulate the vitamin D receptor (VDR).

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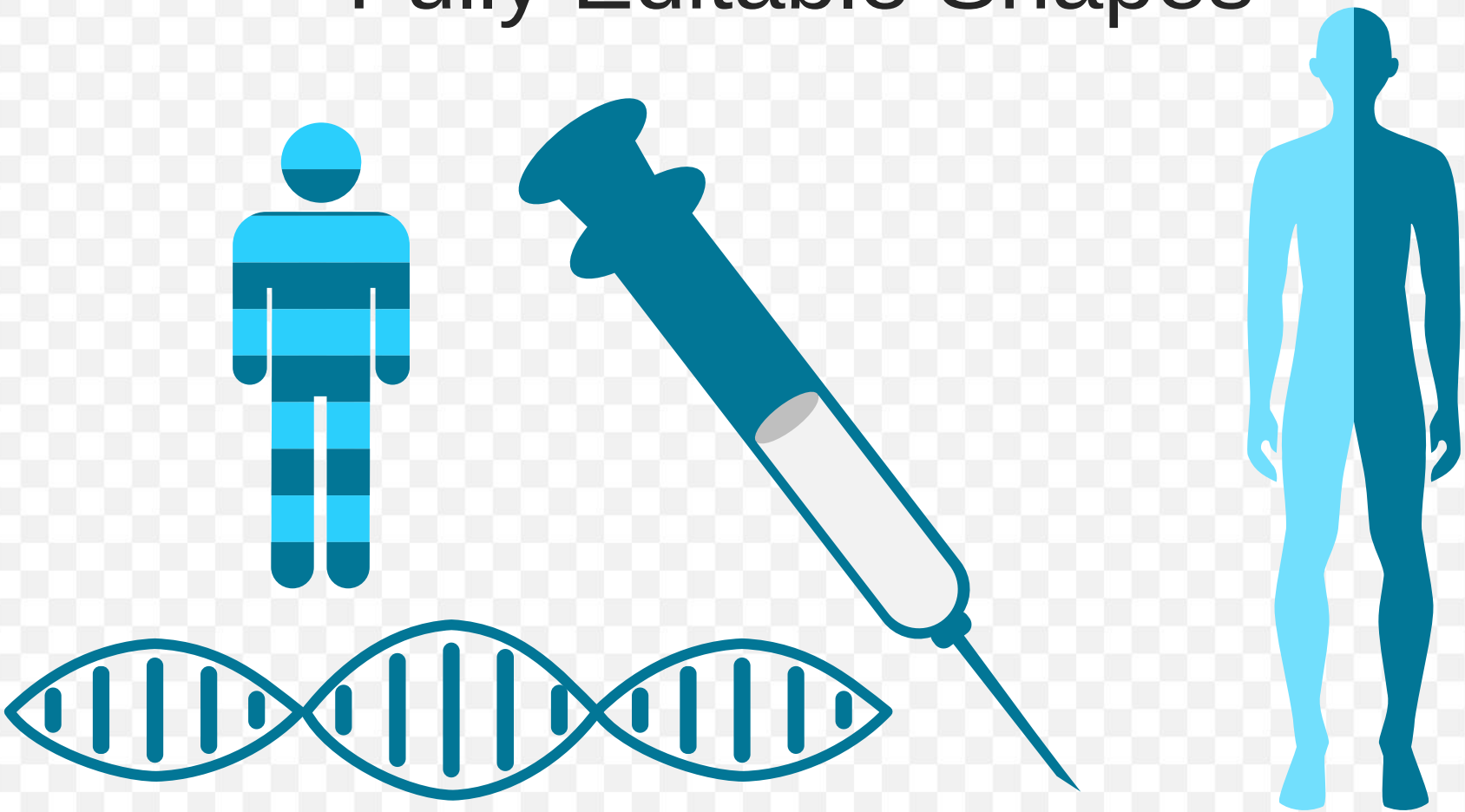

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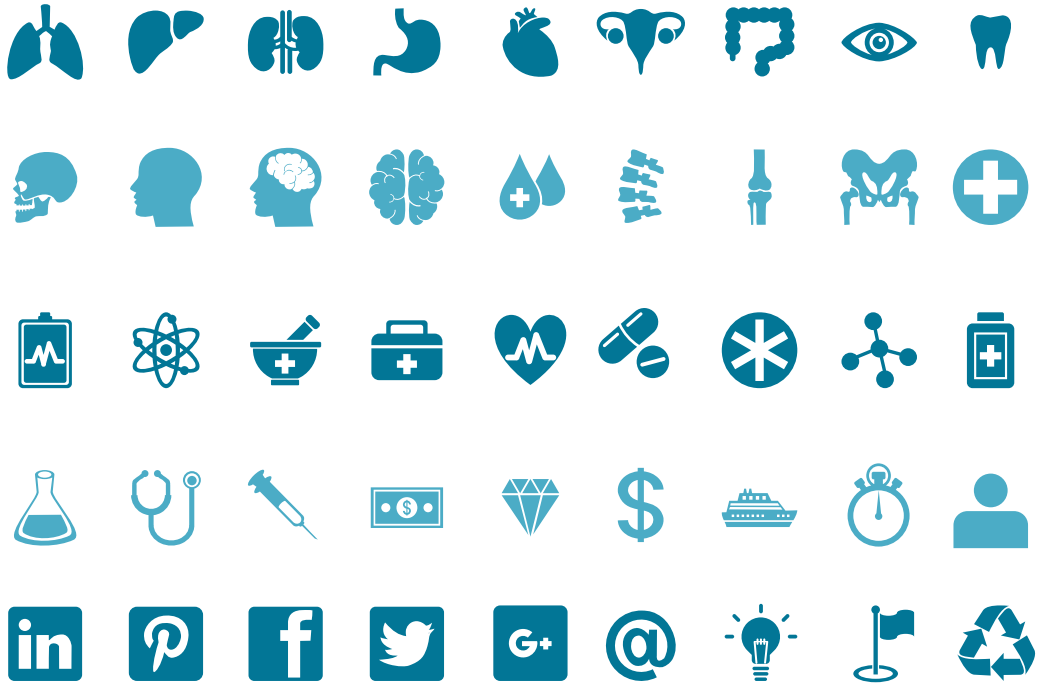

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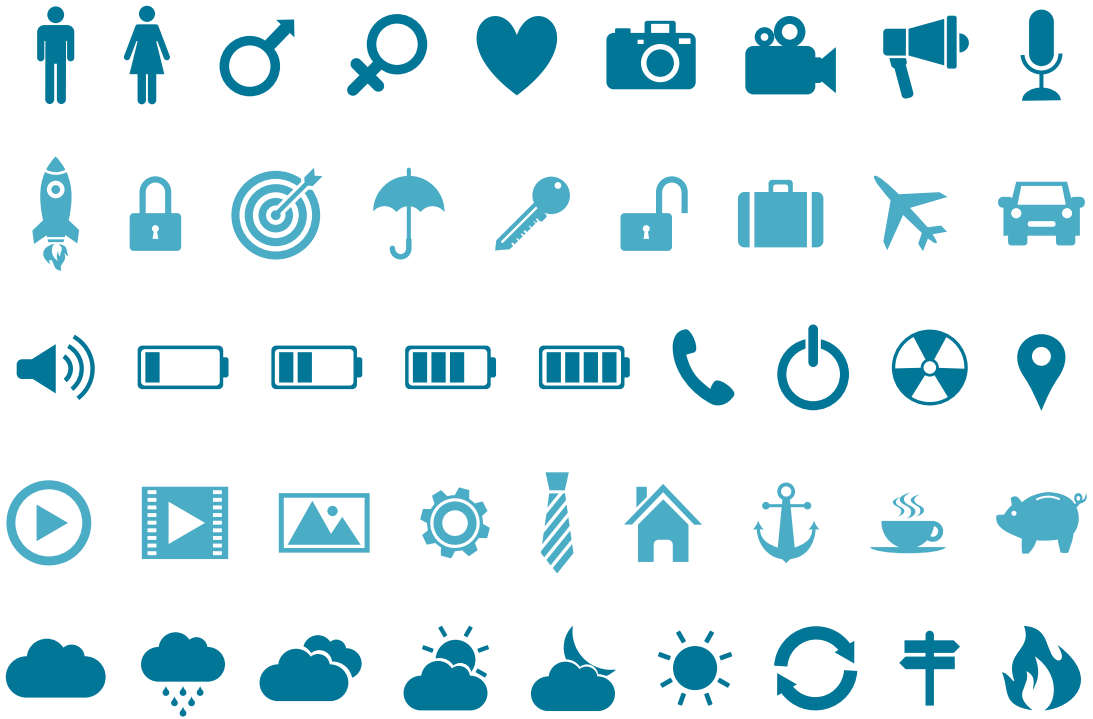

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