

Universidad de Valladolid

# PTH e hipoparatiroidismo



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***Servicio de endocrinología y nutrición.***  
***Hospital Clínico Universitario de Valladolid***

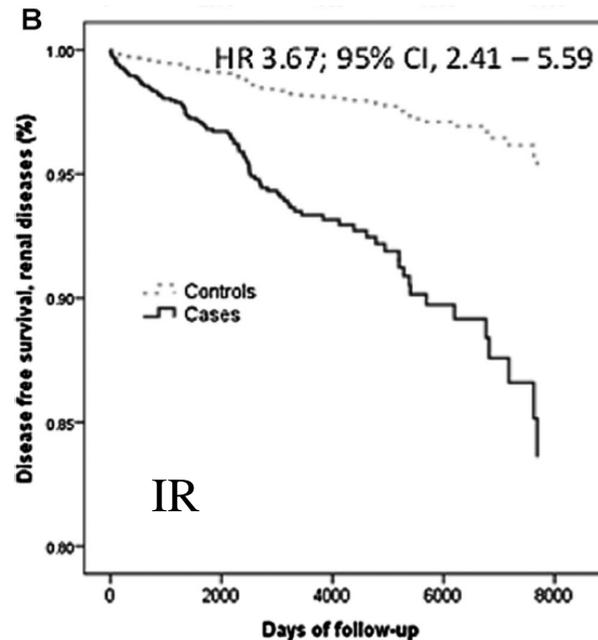
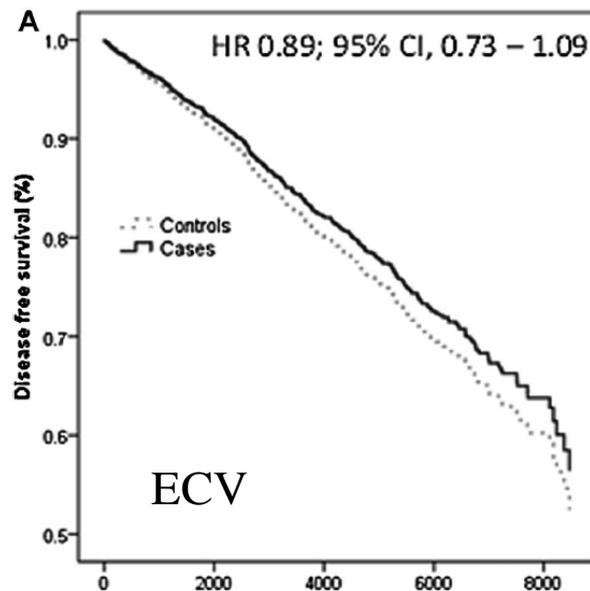
## **European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults**

- **Suplementación análogos vitamina D y calcio oral**
- **Diuréticos tiazídicos. Magnesio**

# Hipoparatiroidismo: complicaciones tratamiento

**Table 3.** Risk of Cardiovascular and Renal Diseases in Patients With Postsurgical Hypoparathyroidism

	Crude	Adjustment model 1	Adjustment model 2
Myocardial infarction, acute	1.00 (0.59–1.72)	0.86 (0.50–1.49) <sup>a</sup>	0.77 (0.44–1.34) <sup>c</sup>
Ischemic heart disease	1.40 (1.07–1.84)	1.16 (0.88–1.52) <sup>a</sup>	1.09 (0.83–1.45) <sup>c</sup>
Stroke	1.30 (0.87–1.93)	1.20 (0.81–1.80) <sup>a</sup>	1.09 (0.73–1.64) <sup>c</sup>
Arrhythmia	1.32 (0.95–1.86)	1.14 (0.83–1.60) <sup>a</sup>	1.11 (0.79–1.57) <sup>d</sup>
Cardiac arrest	0.72 (0.15–3.41)	0.75 (0.16–3.54) <sup>a</sup>	0.68 (0.15–3.23) <sup>c</sup>
Renal stones	4.82 (2.00–11.64)	4.22 (1.73–10.30) <sup>b</sup>	4.02 (1.64–9.90) <sup>d</sup>
Renal insufficiency	4.95 (2.88–8.50)	4.54 (2.63–7.84) <sup>b</sup>	3.10 (1.73–5.55) <sup>d</sup>
Renal disease	4.31 (2.84–6.52)	3.97 (2.61–6.03) <sup>b</sup>	3.67 (2.41–5.59) <sup>d</sup>
Seizures	3.77 (2.12–6.70)	3.82 (2.15–6.79) <sup>e</sup>	



# Hipoparatiroidismo: complicaciones

	<u>Postsurgical</u>	<u>Non-surgical</u>
Mortality	0.98 (0.76 - 1.26)	1.25 (0.90 - 1.73)
Renal insufficiency	3.10 (1.73 - 5.55)*	6.01 (2.45 - 14.75)*
Nephrolithiasis	4.02 (1.64 - 9.90)*	0.80 (0.17 - 3.85)
Ischemic heart disease	1.09 (0.83 - 1.45)	2.01 (1.31 - 3.09)*
Stroke	1.09 (0.73 - 1.64)	1.84 (0.95 - 3.54)
Arrhythmia	1.11 (0.79 - 1.57)	1.78 (0.96 - 3.30)
Seizures	3.82 (2.15 - 6.79)*	10.05 (5.39 - 18.72)*
Cataract	1.17 (0.66 - 2.09)	4.21 (2.13 - 8.34)*
Neuropsychiatric	2.01 (1.16 - 3.50)*	2.45 (1.78 - 3.35)*
Infections	1.42 (1.20 - 1.67)*	1.94 (1.55 - 2.44)*
Fractures	1.03 (0.83 - 1.29)	1.40 (0.93 - 2.11)
Upper extremities Fx	0.69 (0.49 - 0.97)*	1.93 (1.31 - 2.85)*
Cancer	0.83 (0.61 - 1.13)	0.44 (0.24 - 0.82)*
Gastrointestinal cancer	0.62 (0.42 - 0.92)*	0.29 (0.07 - 1.25)

# Introducción: tratamiento PTH

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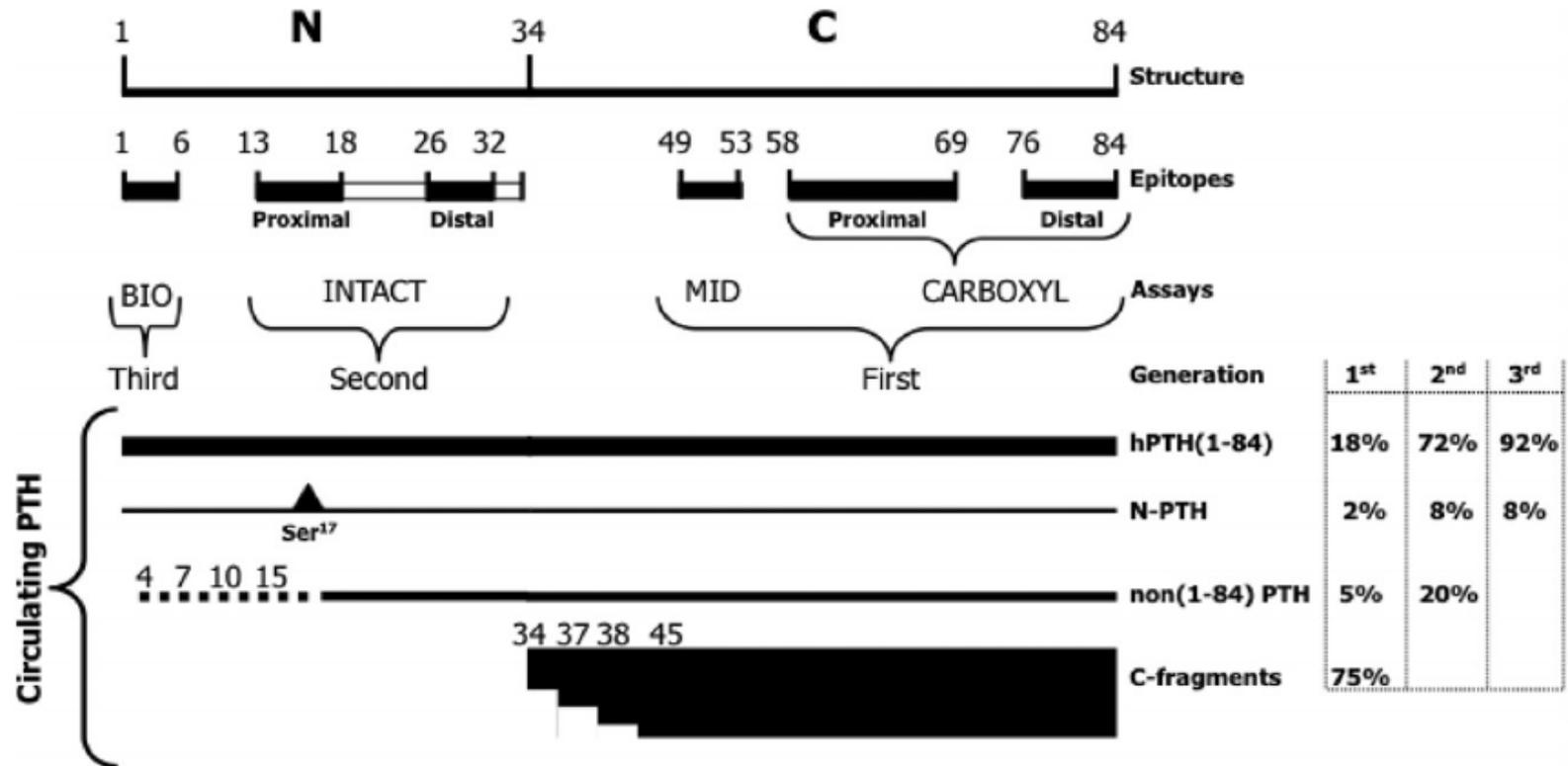
EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 June 2015  
EMA/COMP/712586/2013 Rev.1  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

Recombinant human parathyroid hormone for the treatment of  
hypoparathyroidism

# PTH circulante



**Figure 1.** Circulating PTH molecular forms. Role of three generations of PTH assays. The first-generation assays are mainly detecting C-terminal fragments. The-second generation assays are mainly detecting intact PTH and some N-PTH and some non (1–84) PTH. The third-generation assays are mainly detecting PTH and some N-PTH.

# rhPTH1–34 vs. rhPTH1–84

TABLE 1: Pharmacokinetic and -dynamic characteristics of recombinant human intact parathyroid hormone (rhPTH<sub>1-84</sub>) and teriparatide (rhPTH<sub>1-34</sub>) following a subcutaneous injection into the abdominal skin [32].

	PTH analogue	
	rhPTH <sub>1-34</sub>	rhPTH <sub>1-84</sub>
Bioavailability (%)	95%	55%
Time to peak PTH level (hours)	0.5 h	1-2 h
Plasma half-life (hours)	1.0 h	1.5 h
Time to peak plasma calcium levels (hours)	4–6 h	6–8 h

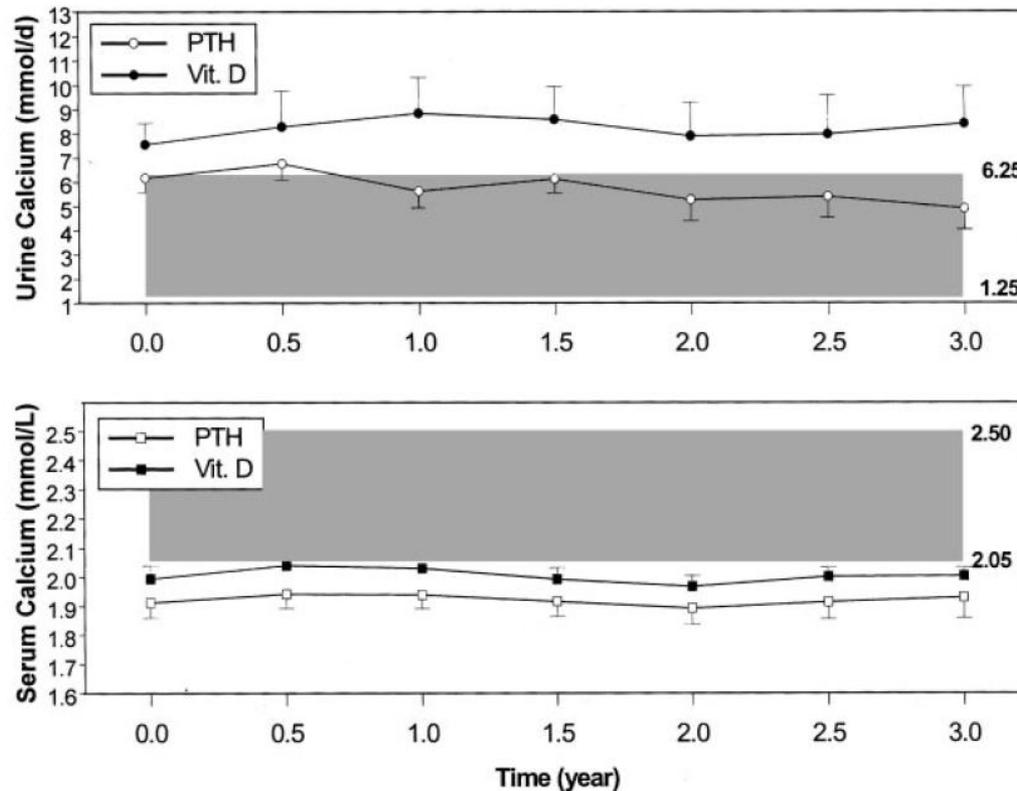
**rhPTH 1-34**

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# rhPTH 1-34

## Long-Term Treatment of Hypoparathyroidism: A Randomized Controlled Study Comparing Parathyroid Hormone-(1-34) *Versus* Calcitriol and Calcium

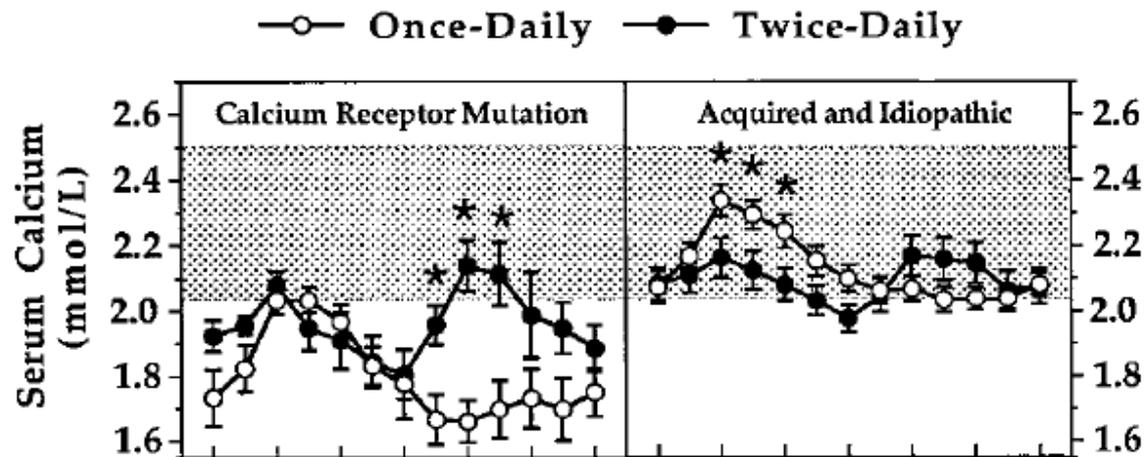
KAREN K. WINER, CHIA WEN KO, JAMES C. REYNOLDS, KAREN DOWDY, MEG KEIL, DONNA PETERSON, LYNN H. GERBER, CHARLES McGARVEY, AND GORDON B. CUTLER, JR.



## rhPTH 1-34: 1 vs 2 iny subcutánea

# A Randomized, Cross-Over Trial of Once-Daily *Versus* Twice-Daily Parathyroid Hormone 1-34 in Treatment of Hypoparathyroidism

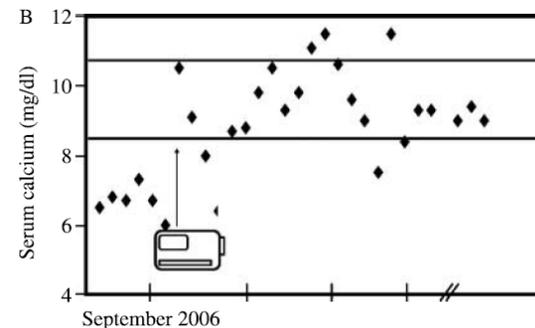
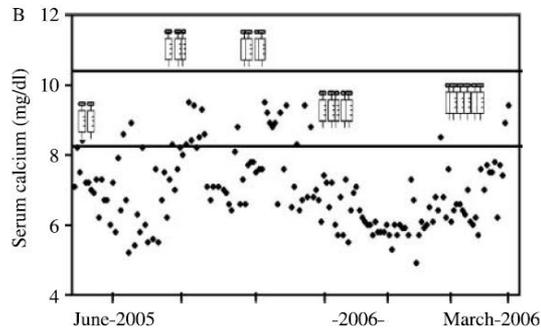
KAREN K. WINER, JACK A. YANOVSKI\*, BABAK SARANI, AND GORDON B. CUTLER, JR.



## CASE REPORT

# Successful treatment of vitamin D unresponsive hypoparathyroidism with multipulse subcutaneous infusion of teriparatide

Manel Puig-Domingo, Gonzalo Díaz, Joanna Nicolau, Cristián Fernández, Sergio Rueda and Irene Halperin



## Efficacy and Safety of Long Term Treatment of Unresponsive Hypoparathyroidism Using Multipulse Subcutaneous Infusion of Teriparatide

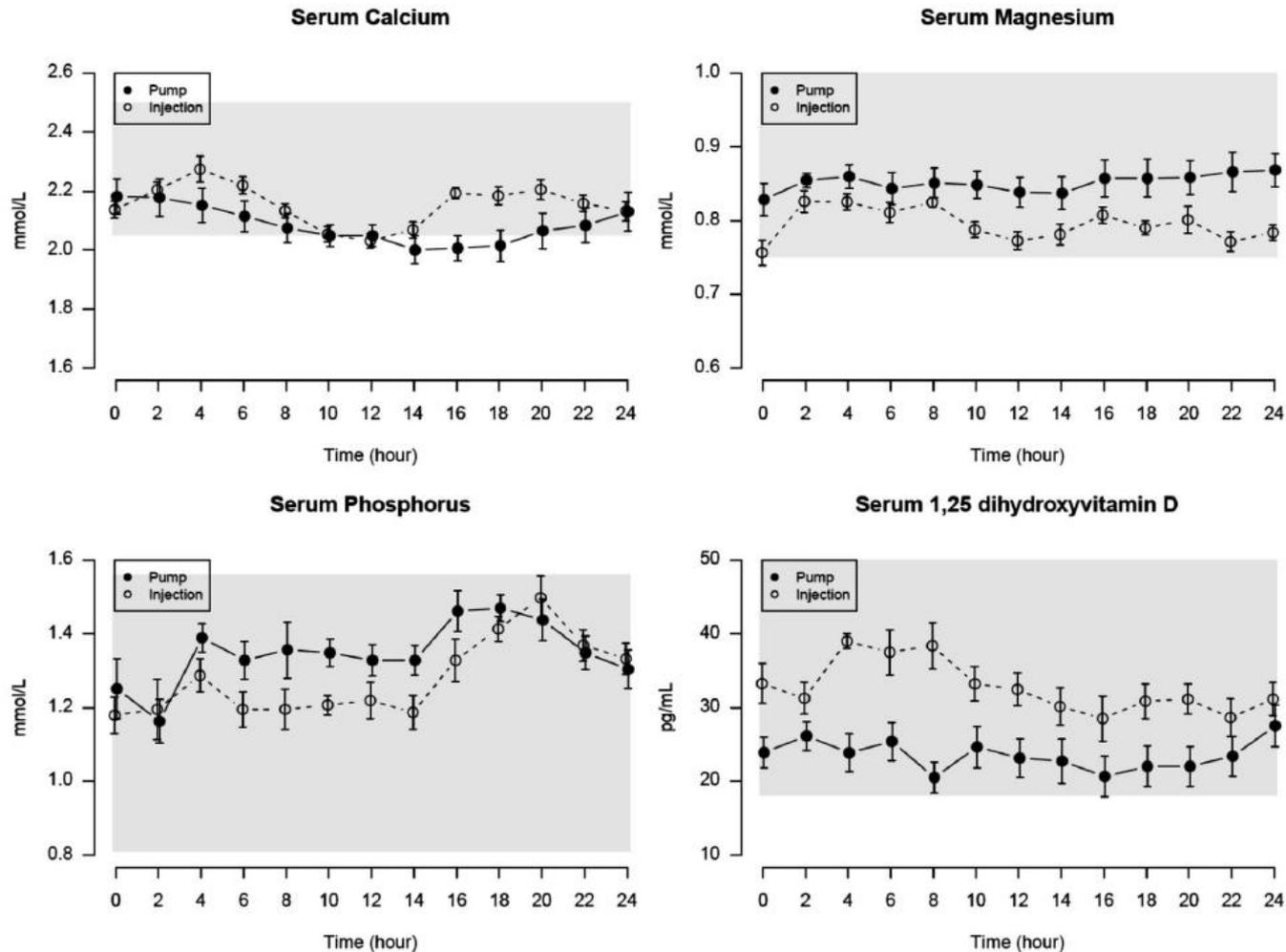
G. Díaz-Soto<sup>1,2</sup>, M. Mora-Porta<sup>3</sup>, J. Nicolau<sup>4</sup>, V. Perea<sup>3</sup>, I. Halperin<sup>3</sup>, M. Puig-Domingo<sup>5</sup>

Horm Metab Res

# rhPTH 1-34: infusión continua

## Synthetic Human Parathyroid Hormone 1-34 Replacement Therapy: A Randomized Crossover Trial Comparing Pump *Versus* Injections in the Treatment of Chronic Hypoparathyroidism

J Clin Endocrinol Metab, February 2012, 97(2):391–399

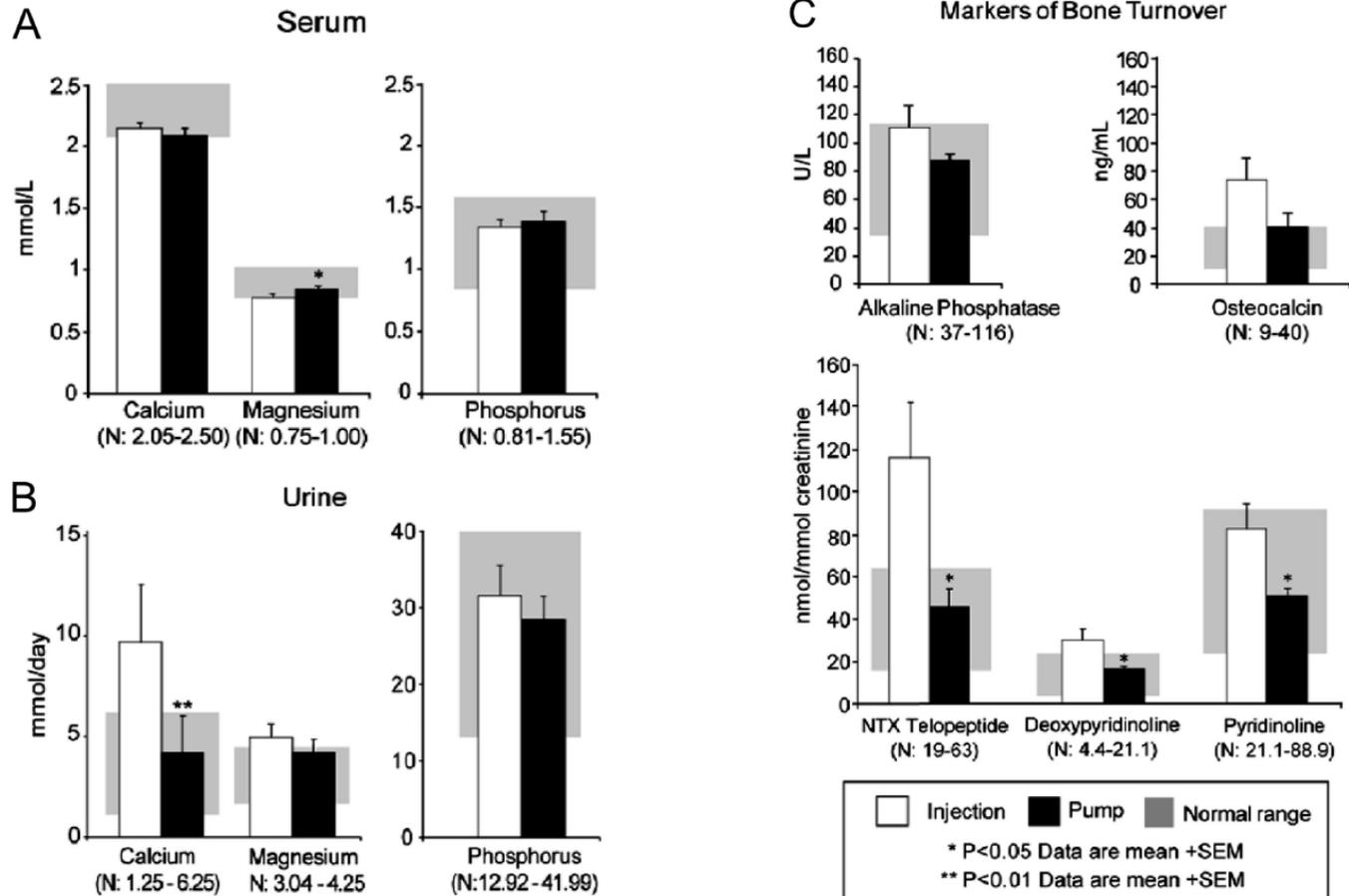


# rhPTH 1-34: infusión continua

## Synthetic Human Parathyroid Hormone 1-34 Replacement Therapy: A Randomized Crossover Trial Comparing Pump *Versus* Injections in the Treatment of Chronic Hypoparathyroidism

J Clin Endocrinol Metab, February 2012, 97(2):391–399

Karen K. Winer, Bo Zhang, Joseph A. Shrader, Donna Peterson, Michaele Smith, Paul S. Albert, and Gordon B. Cutler, Jr.



# rhPTH 1-34: calidad de vida

## PTH(1–34) for Surgical Hypoparathyroidism: A Prospective, Open-Label Investigation of Efficacy and Quality of Life

J Clin Endocrinol Metab, September 2015, 100(9):3590–3597

Assunta Santonati,\* Andrea Palermo,\* Ernesto Maddaloni, Daniela Bosco, Antonio Spada, Franco Grimaldi, Bruno Raggiunti, Raffaele Volpe, Silvia Manfrini,\* Fabio Vescini,\* and the Hypoparathyroidism AME Group

**Table 3.** Quality of Life Evaluation

	Baseline	6 Months	P Value
Physical functioning	55.5 ± 19.6	87.5 ± 10.6	<.001
Social functioning	38.4 ± 30.0	69.8 ± 17.2	<.001
Role limitation caused by physical health problems	16.3 ± 27.5	71.6 ± 20.9	<.001
Role limitations due to emotional	37.3 ± 29.8	82.0 ± 25.0	<.001
Vitality	37.4 ± 11.7	62.9 ± 16.3	<.001
Mental health	40.3 ± 11.6	72.4 ± 14.6	<.001
Bodily pain	56.5 ± 25.8	78.3 ± 18.9	<.001
Perception of general health	31.6 ± 12.3	69.8 ± 16.3	<.001
Physical component summary	159.9 ± 56.4	307.2 ± 38.1	<.001
Mental component summary	153.4 ± 63.7	287.1 ± 54.6	<.001

**Skeletal Changes in Rats Given Daily Subcutaneous Injections of Recombinant Human Parathyroid Hormone (1-34) for 2 Years and Relevance to Human Safety**

JOHN L. VAHLE,<sup>1</sup> MASAHIKO SATO,<sup>1</sup> GERALD G. LONG,<sup>1</sup> JAMIE K. YOUNG,<sup>1</sup> PAUL C. FRANCIS,<sup>1</sup> JEFFERY A. ENGELHARDT,<sup>1</sup> MICHAEL S. WESTMORE,<sup>1</sup> YANFEI LINDA MA,<sup>1</sup> AND JAMES B. NOLD<sup>2</sup>

TOXICOLOGIC PATHOLOGY, vol 30, no 3, pp 312–321, 2002

**The US Postmarketing Surveillance Study of Adult Osteosarcoma and Teriparatide: Study Design and Findings From the First 7 Years**

Elizabeth B Andrews,<sup>1</sup> Alicia W Gilseman,<sup>1</sup> Kirk Midkiff,<sup>1</sup> Beth Sherrill,<sup>1</sup> Yun Wu,<sup>1</sup> Beth H Mann,<sup>2</sup> and Daniel Masica<sup>2</sup>

Journal of Bone and Mineral Research, Vol. 27, No. 12, December 2012, pp 2429–2437

**rhPTH 1-84**

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# rhPTH1–34 vs. rhPTH1–84

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# rhPTH 1-84

## The Effect of Adding PTH(1-84) to Conventional Treatment of Hypoparathyroidism: A Randomized, Placebo-Controlled Study

Tanja Sikjaer,<sup>1</sup> Lars Rejnmark,<sup>1</sup> Lars Rolighed,<sup>2</sup> Lene Heickendorff,<sup>3</sup> Leif Mosekilde,<sup>1</sup>  
and the Hypoparathyroid Study Group

Journal of Bone and Mineral Research, Vol. 26, No. 10, October 2011, pp 2358-2370

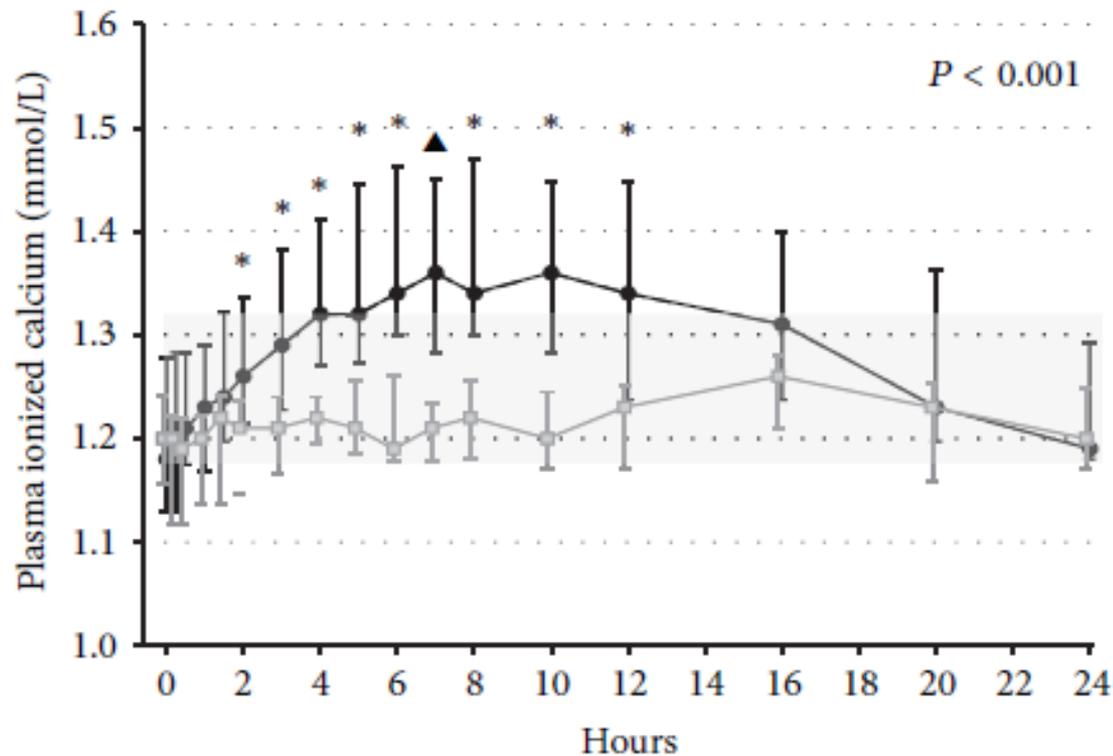


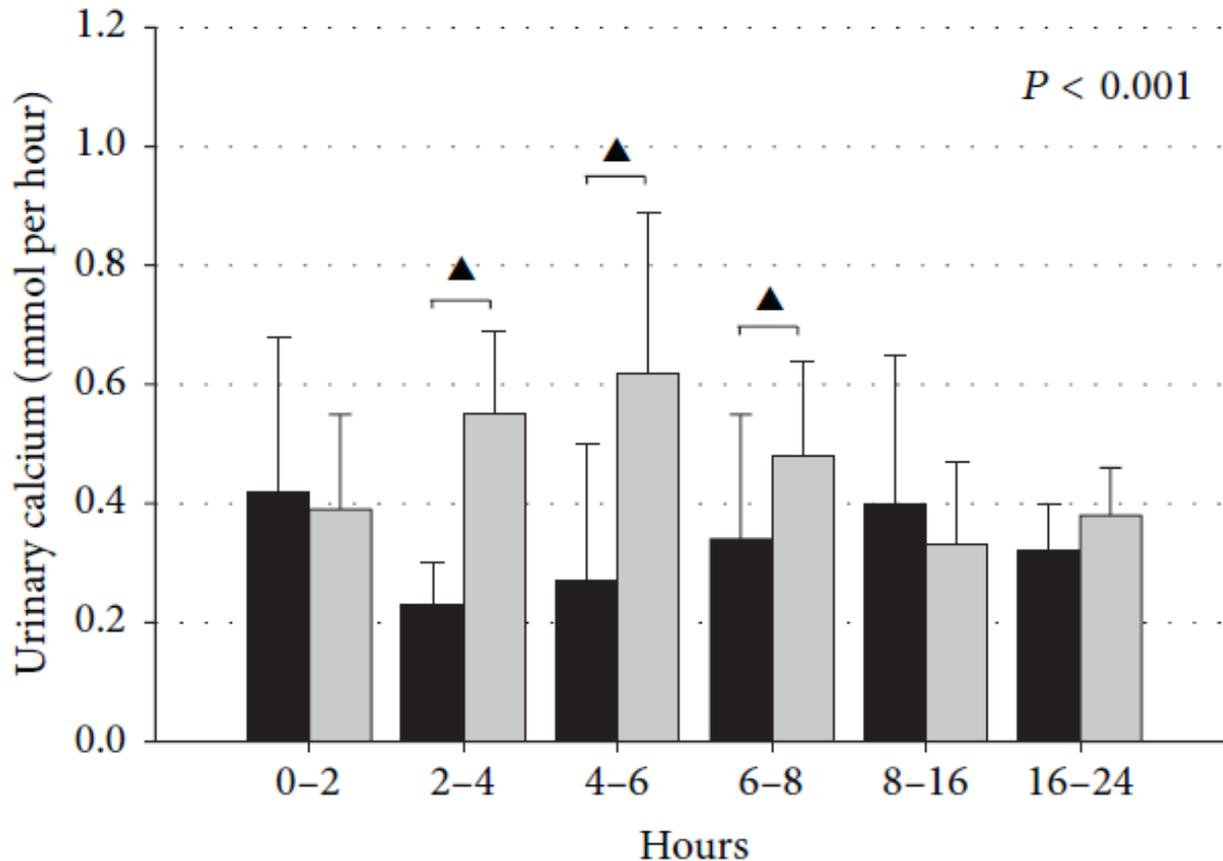
FIGURE 2: Diurnal variations in plasma ionized calcium levels in

# rhPTH 1-84

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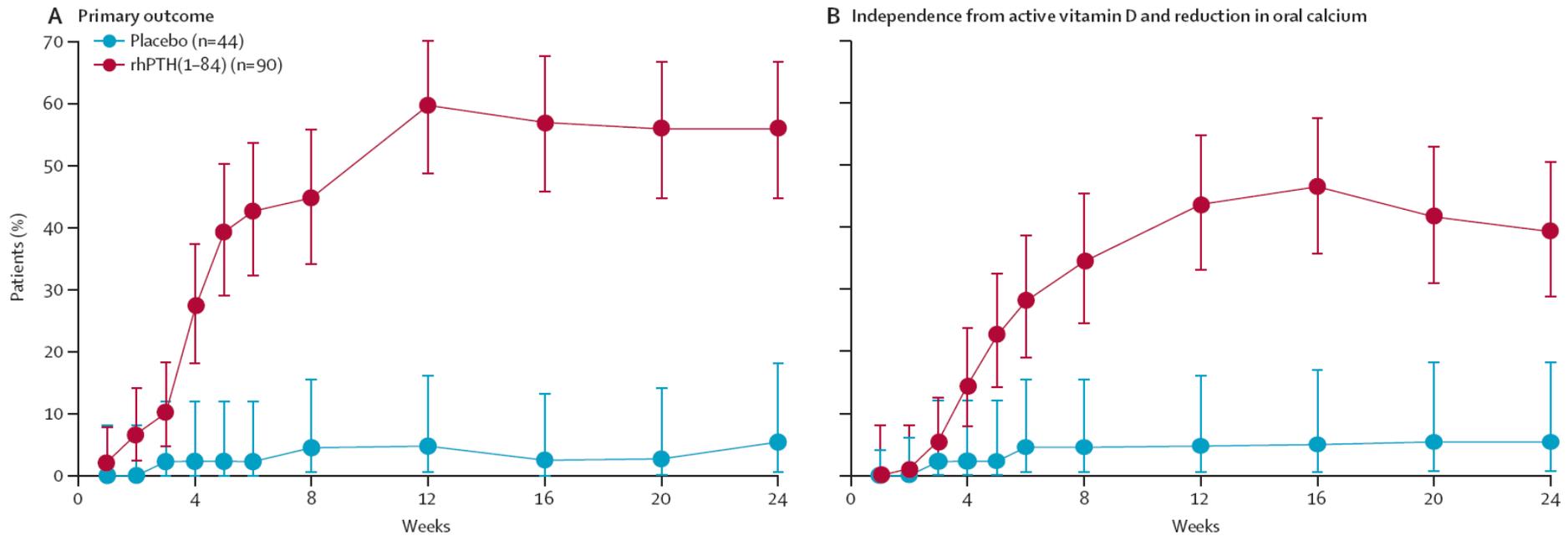
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# rhPTH 1-84 REPLACE

## Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study

[www.thelancet.com/diabetes-endocrinology](http://www.thelancet.com/diabetes-endocrinology) Published online October 7, 2013

Michael Mannstadt, Bart L Clarke, Tamara Vokes, Maria Luisa Brandi, Lakshminarayan Ranganath, William D Fraser, Peter Lakatos, Laszlo Bajnok, Roger Garceau, Leif Mosekilde, Hjalmar Lagast, Dolores Shoback, John P Bilezikian



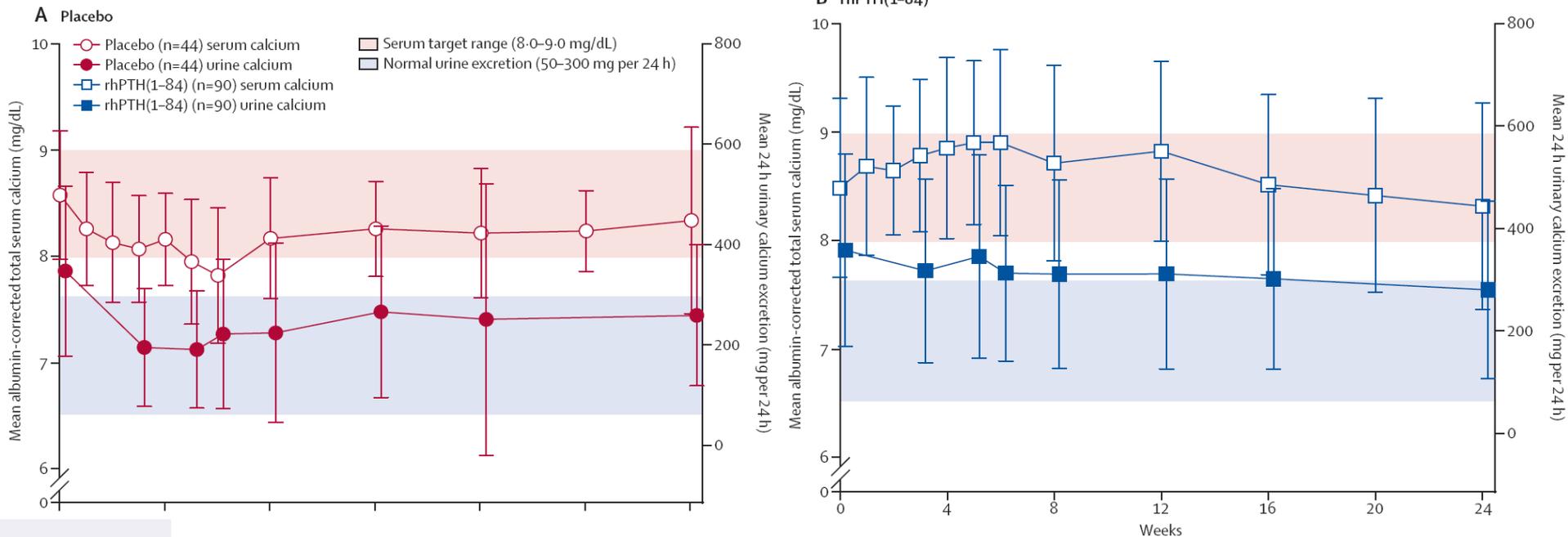
**Figure 2: Achievement of primary outcome and independence from active vitamin D and reduction in oral calcium during treatment period, according to patient diary data**  
(A) Proportion of patients achieving the criteria for the primary endpoint throughout the 24 week treatment period. (B) Proportion of patients who were able to stop taking active vitamin D and to reduce their dose of oral calcium dose to  $\leq 500$  mg per day throughout the 24 week treatment period. rhPTH(1-84)=recombinant human parathyroid hormone 1-84.

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## PTH(1–84) Is Associated With Improved Quality of Life in Hypoparathyroidism Through 5 Years of Therapy

J Clin Endocrinol Metab, October 2014, 99(10):3694–3699

Natalie E. Cusano, Mishaela R. Rubin, Donald J. McMahon, Dinaz Irani, Laura Anderson, Elizabeth Levy, and John P. Bilezikian

**Table 3.** RAND 36-Item Health Survey Total, Component, and Individual Domain Scores at Baseline and Through 5 year of PTH(1–84) Therapy

Time	n	Total	MCS	VT	SF	RE	MH	PCS	PF	RF	BP	GH
Baseline	69	386 ± 19	199 ± 11	32 ± 3	57 ± 3	51 ± 5	59 ± 2	187 ± 10	62 ± 3	40 ± 5	43 ± 2	45 ± 3
2 months	51	468 ± 21 <sup>c</sup>	248 ± 11 <sup>c</sup>	46 ± 3 <sup>c</sup>	70 ± 3 <sup>c</sup>	63 ± 5 <sup>a</sup>	69 ± 2 <sup>c</sup>	221 ± 11 <sup>c</sup>	72 ± 3 <sup>b</sup>	52 ± 5 <sup>a</sup>	46 ± 2	55 ± 3 <sup>c</sup>
6 months	57	482 ± 20 <sup>c</sup>	250 ± 11 <sup>c</sup>	45 ± 3 <sup>c</sup>	70 ± 3 <sup>c</sup>	68 ± 5 <sup>b</sup>	69 ± 2 <sup>c</sup>	233 ± 11 <sup>c</sup>	74 ± 3 <sup>c</sup>	59 ± 5 <sup>c</sup>	46 ± 2	54 ± 3 <sup>c</sup>
1 y	58	462 ± 20 <sup>c</sup>	235 ± 11 <sup>c</sup>	44 ± 3 <sup>c</sup>	67 ± 3 <sup>c</sup>	57 ± 5	69 ± 2 <sup>c</sup>	227 ± 11 <sup>c</sup>	74 ± 3 <sup>c</sup>	53 ± 5 <sup>a</sup>	47 ± 2	54 ± 3 <sup>c</sup>
2 y	42	472 ± 22 <sup>c</sup>	241 ± 12 <sup>c</sup>	45 ± 3 <sup>c</sup>	68 ± 4 <sup>b</sup>	61 ± 6	68 ± 2 <sup>c</sup>	233 ± 11 <sup>c</sup>	73 ± 3 <sup>c</sup>	57 ± 6 <sup>b</sup>	50 ± 2 <sup>a</sup>	54 ± 3 <sup>c</sup>
3 y	33	440 ± 23 <sup>b</sup>	226 ± 13 <sup>a</sup>	41 ± 3 <sup>b</sup>	63 ± 4	57 ± 6	65 ± 3 <sup>b</sup>	215 ± 12 <sup>b</sup>	68 ± 4	53 ± 6	41 ± 3	53 ± 3 <sup>b</sup>
4 y	26	448 ± 25 <sup>b</sup>	225 ± 14 <sup>a</sup>	43 ± 3 <sup>c</sup>	65 ± 4 <sup>a</sup>	55 ± 7	63 ± 3	224 ± 13 <sup>b</sup>	70 ± 4 <sup>a</sup>	61 ± 7 <sup>b</sup>	44 ± 3	51 ± 3 <sup>a</sup>
5 y	25	482 ± 25 <sup>c</sup>	246 ± 14 <sup>c</sup>	42 ± 3 <sup>b</sup>	68 ± 4 <sup>b</sup>	69 ± 7 <sup>a</sup>	68 ± 3 <sup>b</sup>	237 ± 13 <sup>c</sup>	76 ± 4 <sup>c</sup>	62 ± 7 <sup>b</sup>	45 ± 3	54 ± 3 <sup>b</sup>

Values are mean ± SE.

<sup>a</sup>  $P < .05$  compared to baseline.

<sup>b</sup>  $P < .01$  compared to baseline.

<sup>c</sup>  $P < .001$  compared to baseline.

# rhPTH 1-84



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### FDA News Release

# FDA approves Natpara to control low blood calcium levels in patients with hypoparathyroidism

**For Immediate  
Release**

January 23, 2015

 **Natpara**  
(parathyroid hormone)  
for Injection

25/50/75/100 ug

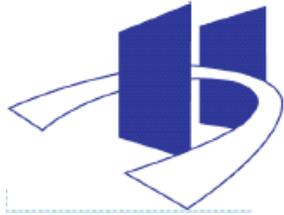
# Conclusiones

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# Conclusiones I

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1. Hipoparatiroidismo: se asocia a complicaciones metabólicas no resueltas por el tratamiento convencional.
2. Tratamiento con rhPTH está restringidos a casos excepcionales. Pediatría, cronicidad. Estudios a largo plazo, seguridad.
3. rhPTH1-34 y rhPTH1-84 presenta un perfil farmacocinético diferente. No existen estudios comparación.
4. El tratamiento con rhPTH disminuye los requerimientos de calcio y vit D, manteniendo el calcio sérico. Algunos estudios demuestran mejoría en los parámetros renales, óseos y calidad de vida.
5. La mejoría de los parámetros metabólicos se ha asociado a formas más fisiológicas de aplicación: perfusión, parches...



Universidad de Valladolid

# PTH e hipoparatiroidismo



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