Altogether to Beat Cushing's Syndrome

ABC

Viaggio alla (ri)scoperta della Sindrome di Cushing

4ª Edizione / 4th Edition

Journey to the (re)discovery of Cushing's Syndrome

Napoli, 5-7 May 2015
Hotel S. Lucia

Scientific Coordinators
Annamaria Colao, Rosario Pivonello

SESSION 3: A PECULIAR ASPECT OF TREATMENT IN CUSHING'S DISEASE: PASIREOTIDE BETWEEN PRESENT AND FUTURE

Chairs: **Marco Boscaro, Luca Persani**

THE HYSTORY OF PASIREOTIDE
Giorgio Arnaldi

PASIREOTIDE EXPERIENCE: REGISTRATION STUDY VERSUS REAL WORLD EVIDENCE
Rosario Pivonello

THE ROLE OF PASIREOTIDE ON CLINICAL PICTURE
Carla Scaroni

THE ROLE OF PASIREOTIDE ON TUMOUR MASS
Salvo Cannavò

Giorgio Arnaldi
Clinica di Endocrinologia e Malattie del Metabolismo - Ancona
gioarnaldi@gmail.com

1968

Stimulatory and Inhibitory Effects of Purified Hypothalamic Extracts on Growth Hormone Release from Rat Pituitary *in Vitro*[1]

L. KRULICH,[2] A. P. S. DHARIWAL, AND S. M. McCANN[3]
Department of Physiology, University of Texas Southern Medical School, Dallas, Texas 75235

cubated glands. The findings are consistent with the hypothesis that hypothalamic extracts of rat and sheep origin contain a GH-inhibiting factor (GIF) in addition to the GH-releasing factor (GRF). The GH-releasing activity of crude extracts is explained by assuming that the relative concentration of GRF exceeds that of GIF. (*Endocrinology* **83:** 783, 1968)

1973

The New York Times

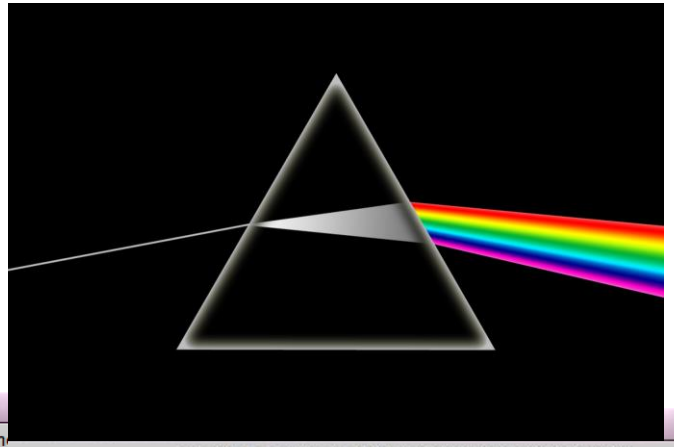
NIXON RESIGNS

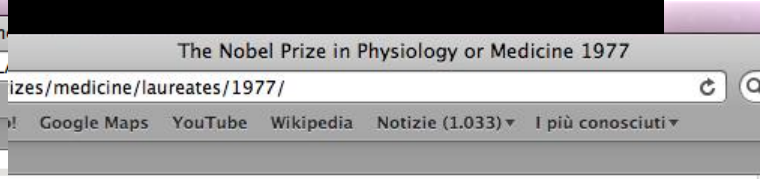
HE URGES A TIME OF 'HEALING'; FORD WILL TAKE OFFICE TODAY

'Sacrifice' Is Praised; Kissinger to Remain

The 37th President Is First to Quit Post

Rise and Fall





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Home > Science Magazine > 5 January 1973 > Brazeau et al., 179 (4068): 77–79

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Science 5 January 1973:
Vol. 179 no. 4068 pp. 77–79
DOI: 10.1126/science.179.4068.77

‹ Prev | Table of Contents | Ne

REPORTS

Hypothalamic Polypeptide That Inhibits the Secretion of Immunoreactive Pituitary Growth Hormone

Paul Brazeau[1], Wylie Vale[1], Roger Burgus[1], Nicholas Ling[1], Madalyn Butcher[1], Jean Rivier[1], Roger Guillemin[1]

± Author Affiliations

ABSTRACT

A peptide has been isolated from ovine hypothalamus which, at 1 x 10^{-9}M, inhibits secretion in vitro of immunoreactive rat or human growth hormones and is similarly active in vivo in rats. Its structure is H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH The synthetic replicate is biologically active.

Share this: 4

The Nobel Prize in Physiology or Medicine 1977

Roger Guillemin
Prize share: 1/4

Andrew V. Schally
Prize share: 1/4

Rosalyn Yalow
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1977 was divided, one half jointly to Roger Guillemin and Andrew V. Schally *"for their discoveries concerning the peptide hormone production of the brain"* and the other half to Rosalyn Yalow *"for the development of radioimmunoassays of peptide hormones"*.

Photos: Copyright © The Nobel Foundation

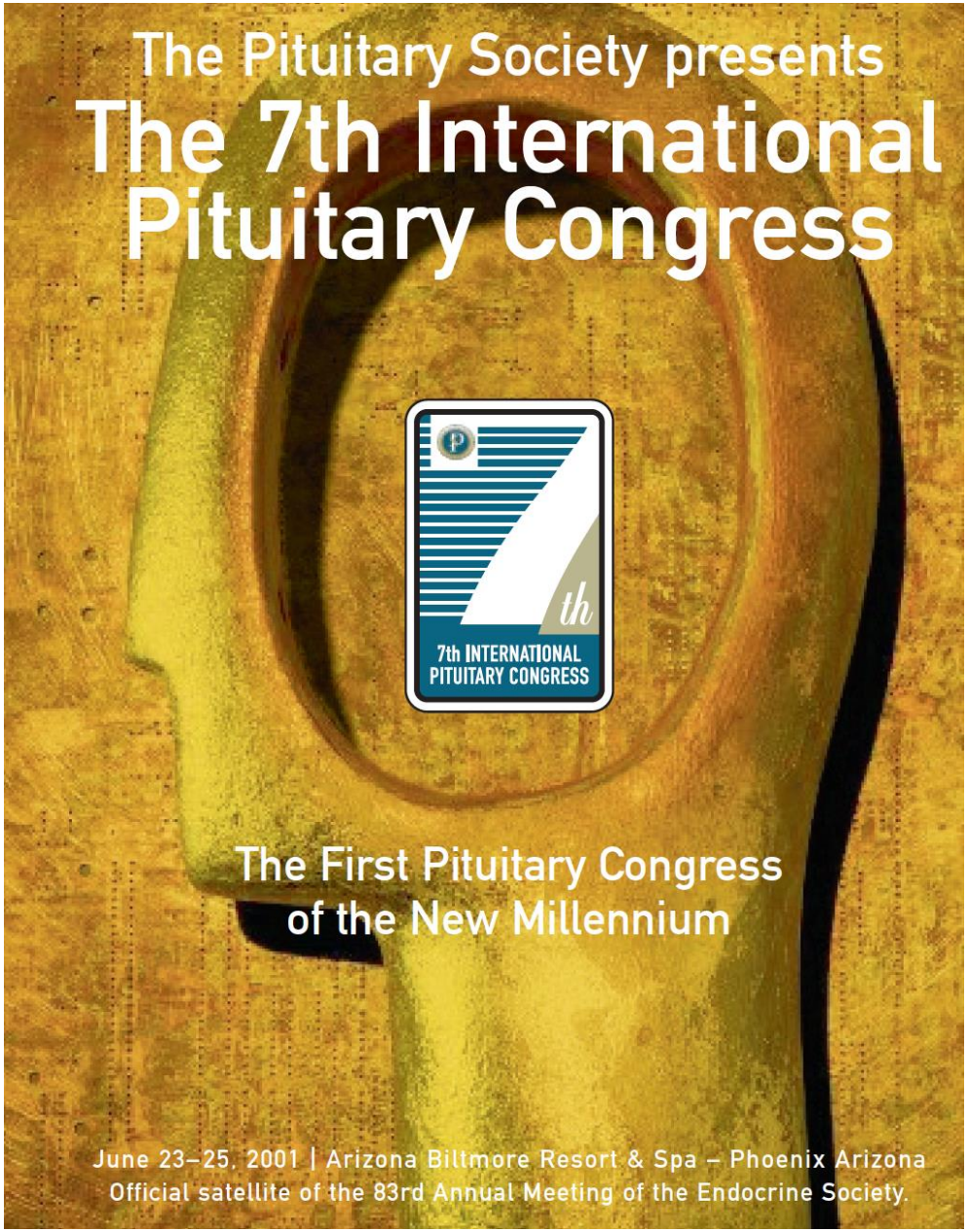
SMS and Octreotide in Cushing' s Disease

Reference	Pts n°	Drug	Effect on ACTH
Benker, 1976	1	SMS	-50%
Julesz, 1980	1	SMS	Decreased
Lamberts, 1989	3	Oct	No effect
Ambrosi, 1990	2 and 5	SMS and Oct	No effect
Stalla, 1994	5	Oct	No effect

Van der Hoek et al. 2005 modified

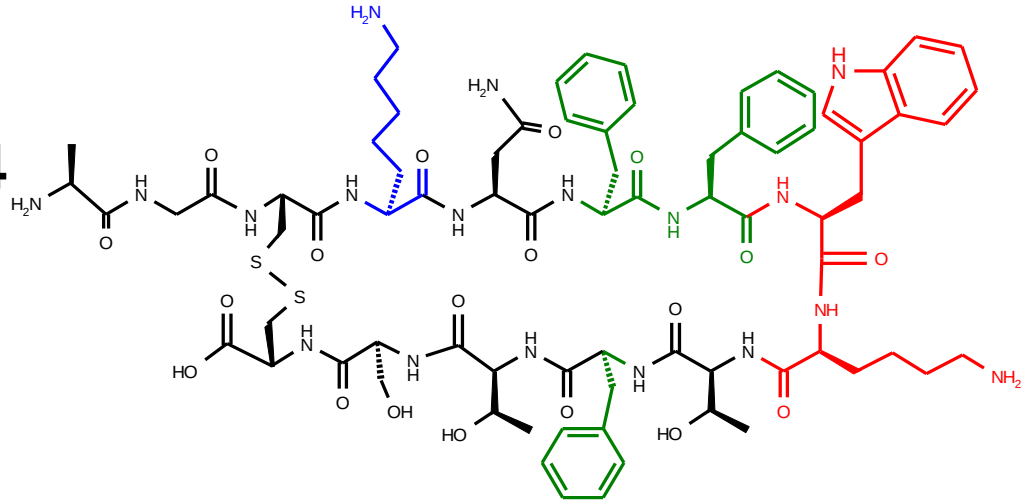
La novità

2001


The Pituitary Society presents
The 7th International Pituitary Congress
7th INTERNATIONAL PITUITARY CONGRESS
The First Pituitary Congress of the New Millennium
June 23–25, 2001 | Arizona Biltmore Resort & Spa – Phoenix Arizona
Official satellite of the 83rd Annual Meeting of the Endocrine Society.

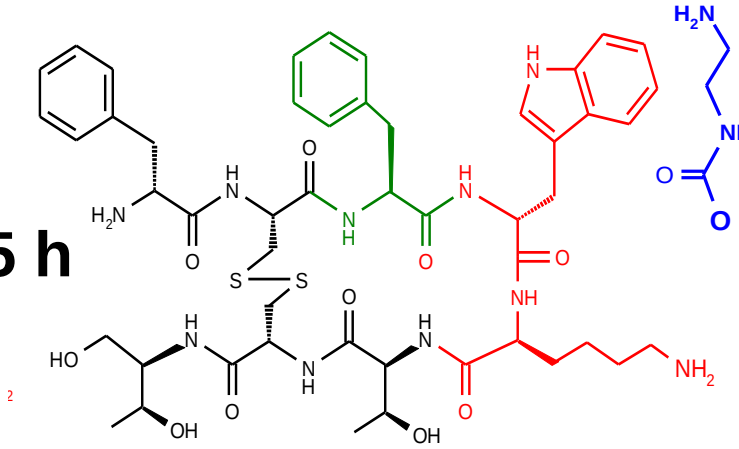
Transposition of functional groups

SRIF-14

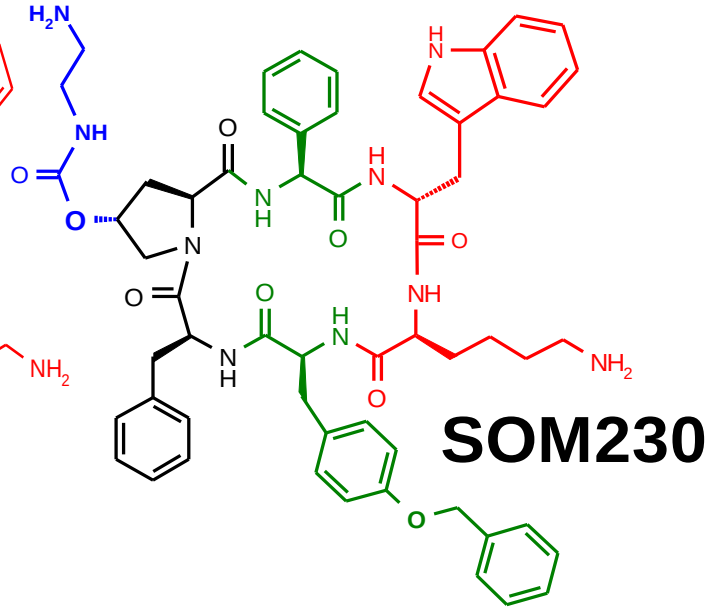


$t_{1/2}$: 90 s

$t_{1/2}$: 1.5 h



OCTREOTIDE



SOM230

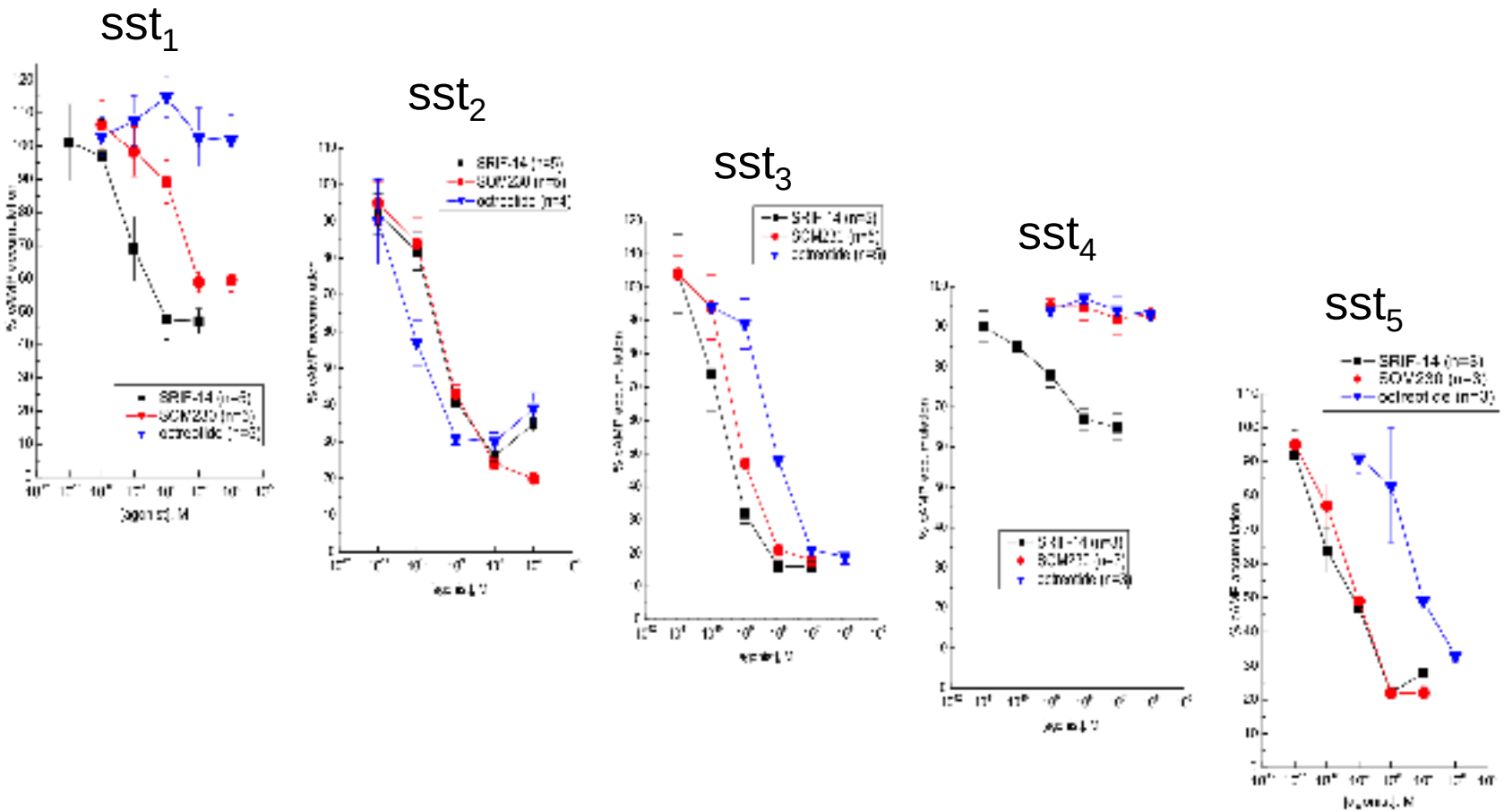
$t_{1/2}$: 11 h

Comparative in vitro binding profile of SOM230

Binding profile of somatostatin analogues to human $sst_{1–5}$
(IC50 values, nM)

Compound	sst_1	sst_2	sst_3	sst_4	sst_5
SRIF-14	0.9	0.2	0.6	1.5	0.3
Sandostatin	280.0	0.4	7.1	>1000	6.3
SOM230	9.3	1.0	1.5	>1000	0.2
Sandostatin: SOM230	30	0.4	5	-	40

SOM230 and octreotide functional activity at human sst receptors

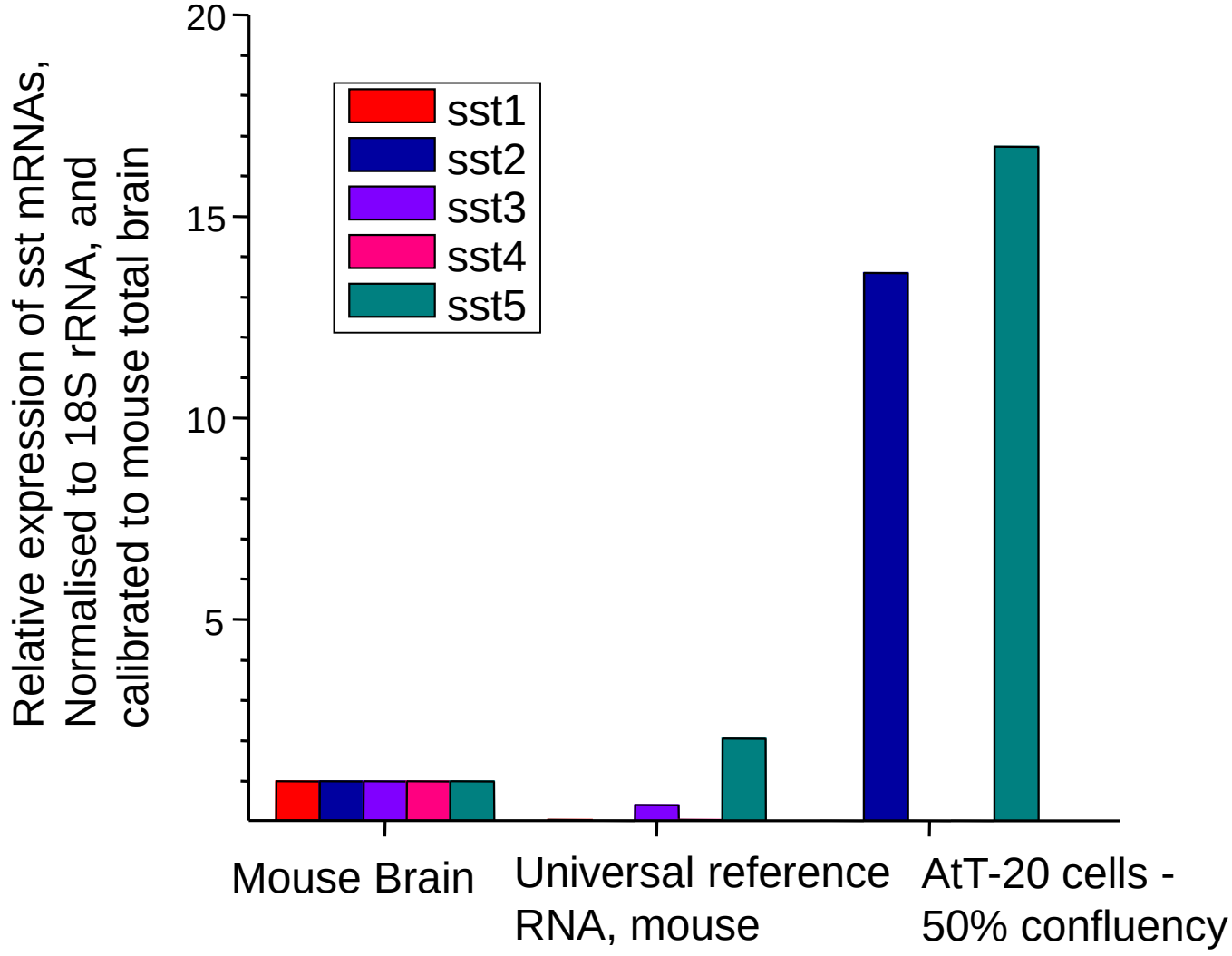


Concentration-response curves of SRIF-14, SOM230 and octreotide for inhibition of forskolin-stimulated cAMP accumulation in CHO-K1 cells expressing human recombinant $sst_{1–5}$

Schmid, Neuroendocrinology, 2004:80; 47-50

La base molecolare nei tumori corticotropi

Expression of ssts in AtT-20 cells: high sst_5 and sst_2

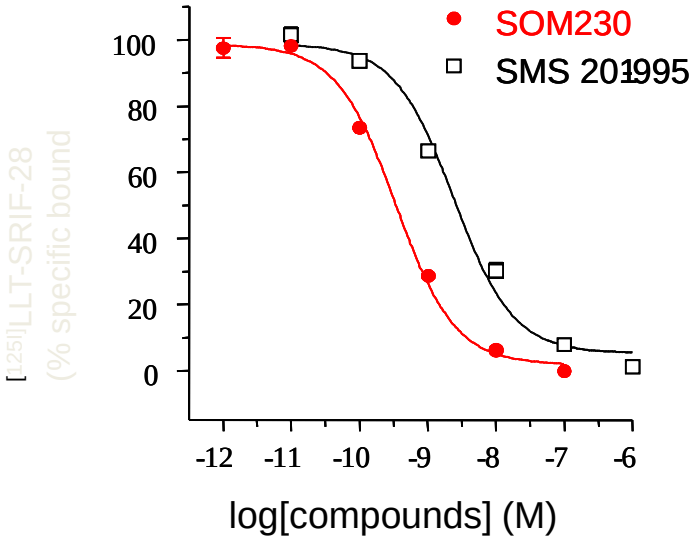


TaqMan quantitative real-time RT-PCR (mouse pituitary cell line secreting ACTH)

Hofland et al, 2005

Effect of SOM230 and SMS 201-995 on ACTH-secreting AtT20 cells

Binding affinities at different radioligand-labelled sites in AtT-20 cell membranes



Ligand	*n*	*[^{125}I]LTT-SRIF-28* pK_d (-logM) ± SEM	*IC_{50} values*
SOM230	**8**	**9.74 ± 0.08**	**0.18 x 10^{-9}**
octreotide	**3**	**8.92 ± 0.03**	**1.2 x 10^{-9}**

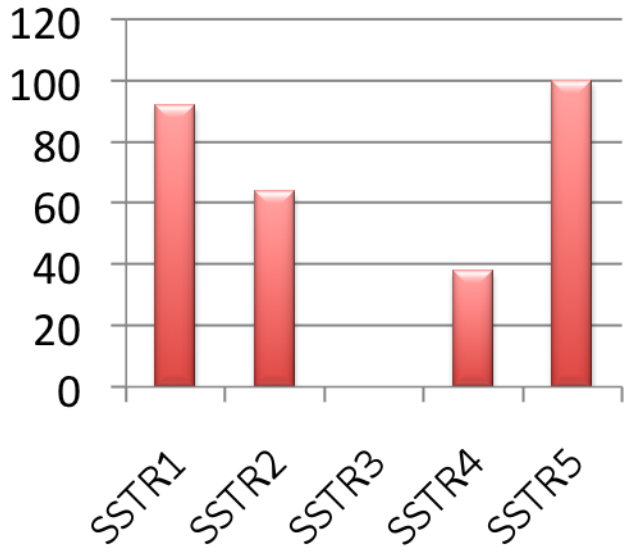
Hofland et al, 2005

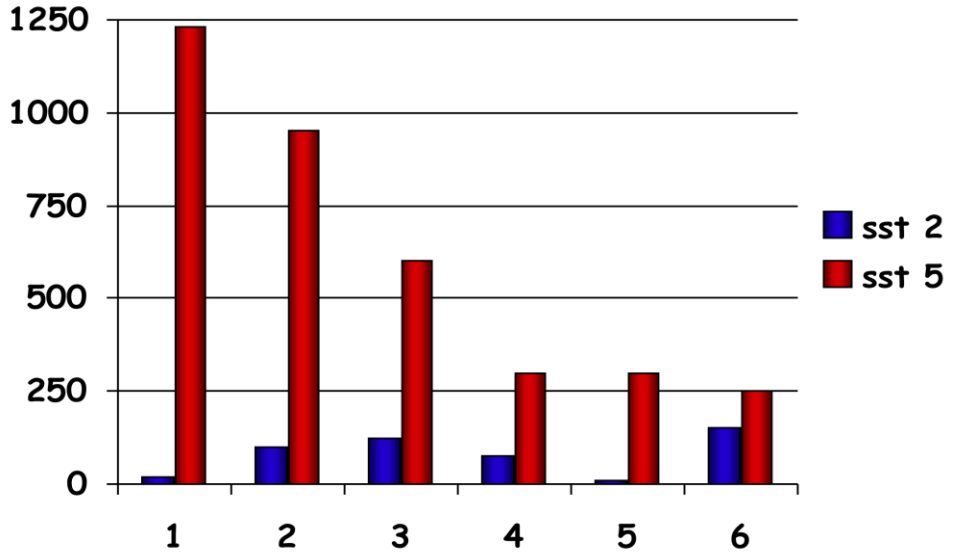
Tumor-directed Drugs

New Somatostatin analogs

Pasireotide (SOM 230)

Somatostatin receptors (SSTR) mRNA expression in human corticotroph adenomas

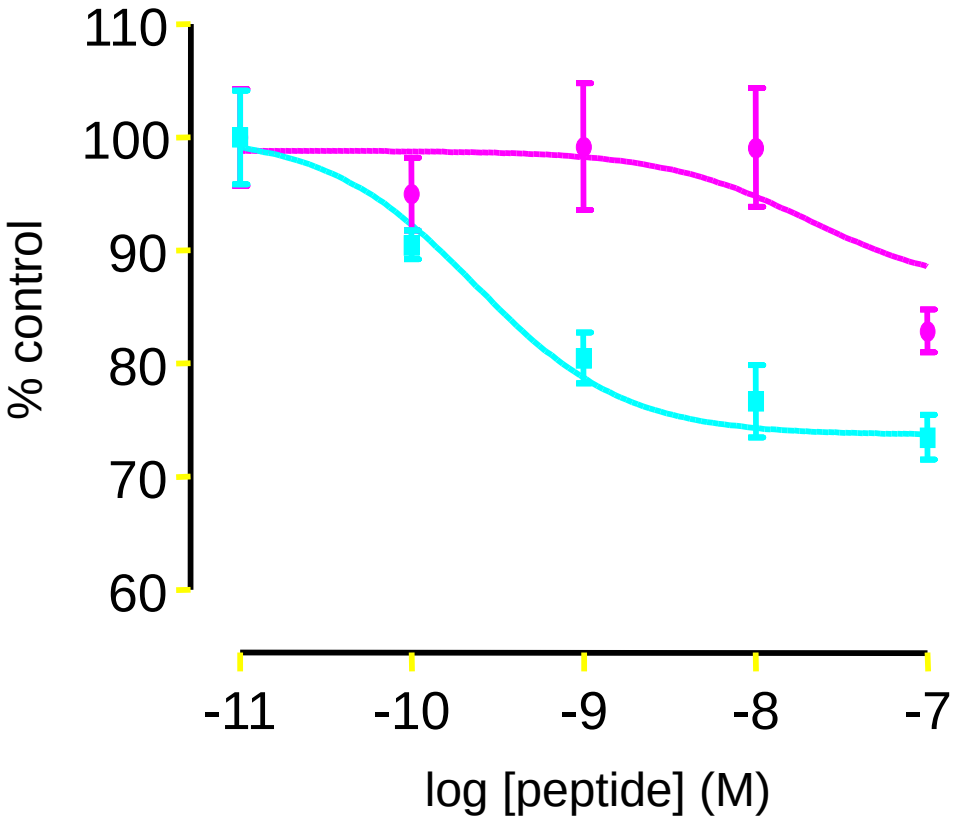




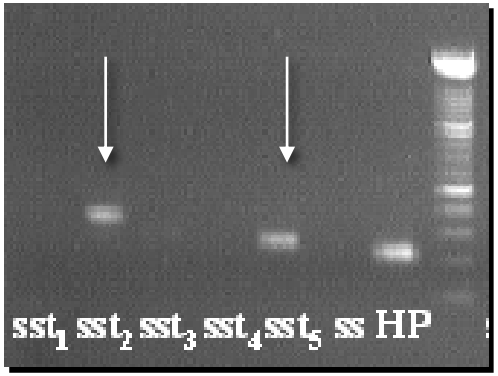
Data from Batista et al.
J Clin Endocrinol Metab 2006;91:4482-4488

Hofland et al.
Eur. J Endocrinol. 2005; 152: 645-654

Inhibitory effect of SOM230 and octreotide on *basal* ACTH release



sst mRNA



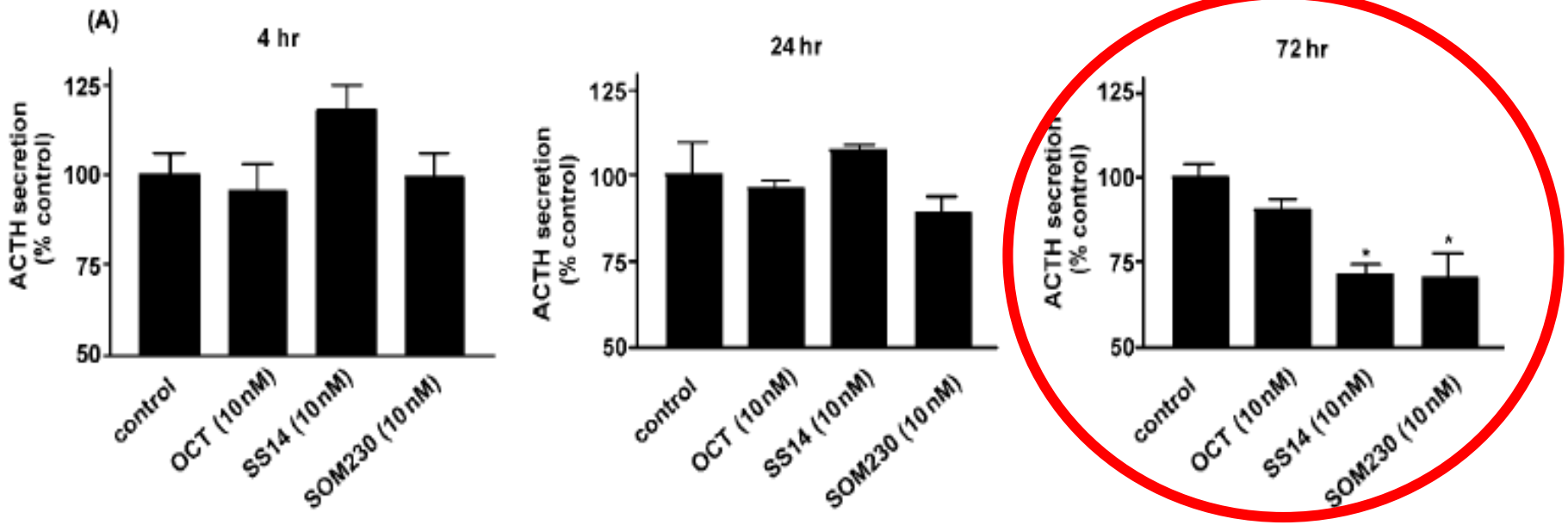
SOM230: IC_{50} 0.2 nM

OCT : IC_{50} 20 nM

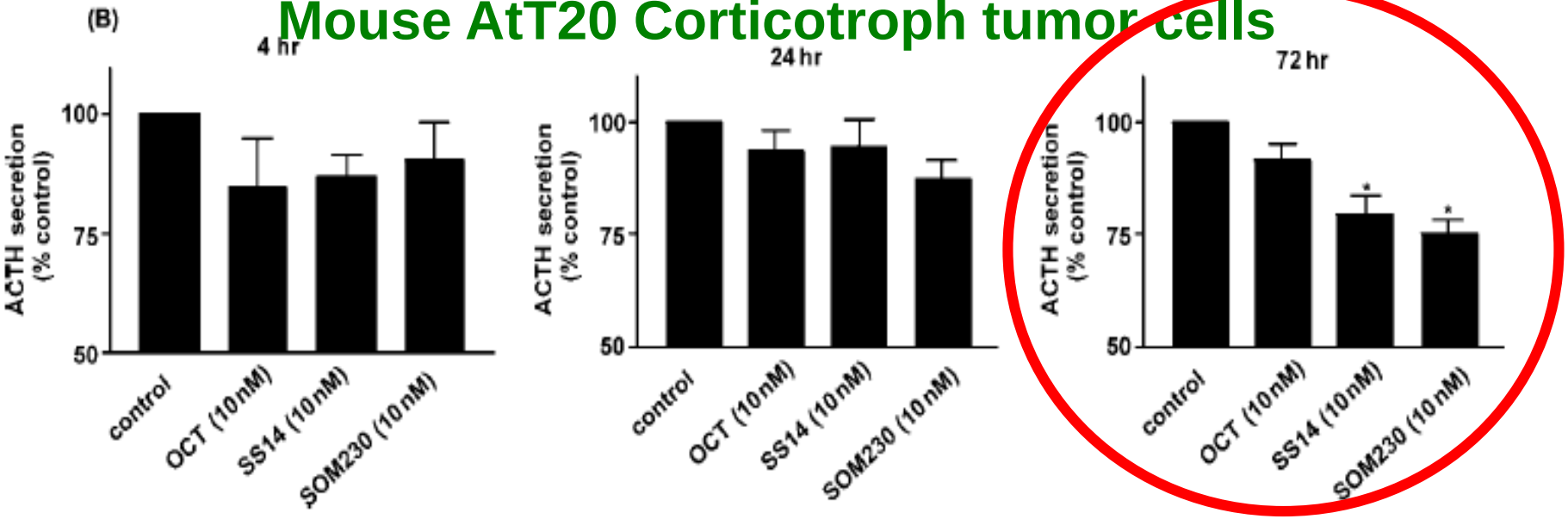
} sst5-like response!

Hofland et al, 2005

Cultured human Corticotroph adenoma n°8

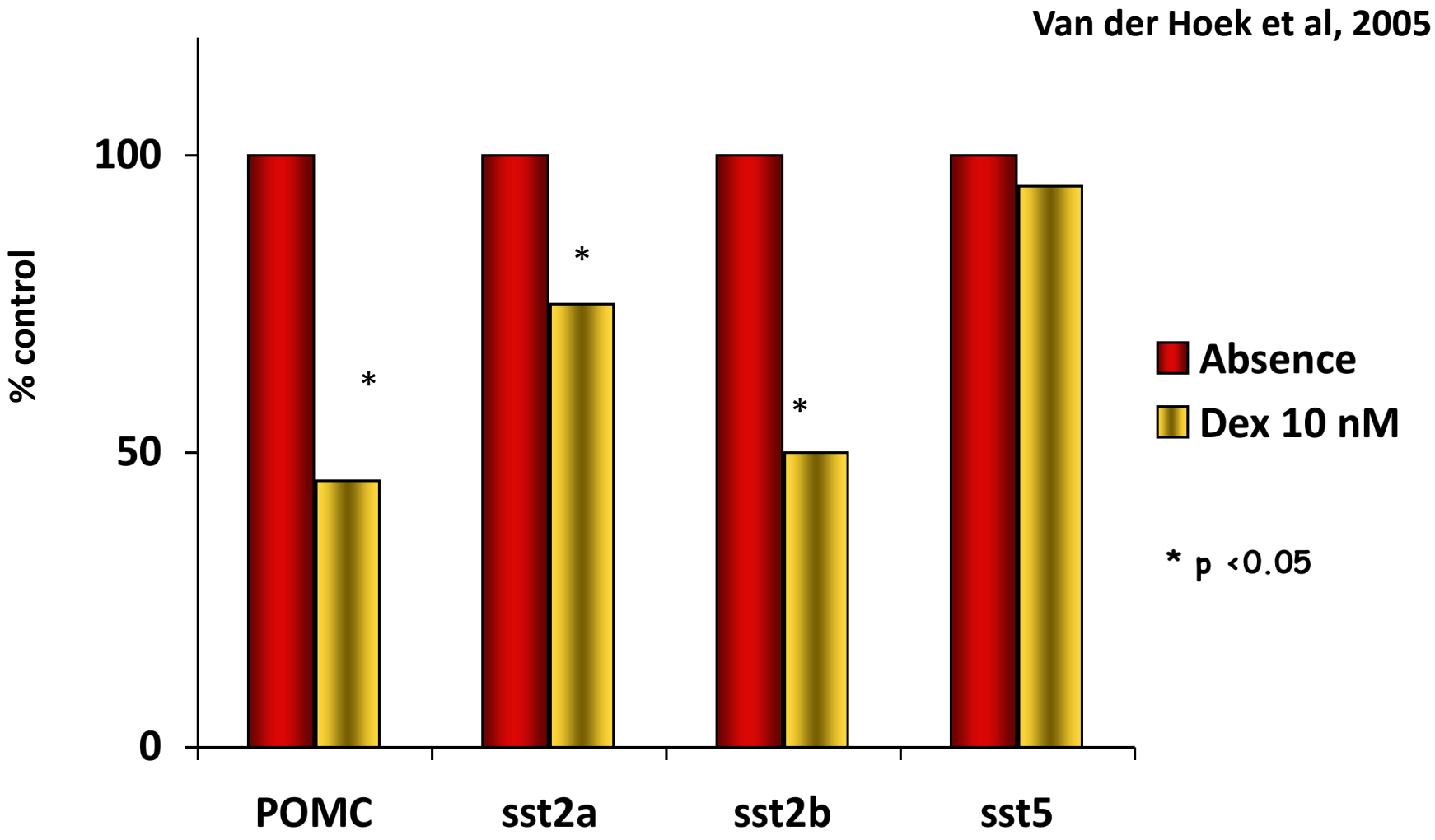


Mouse AtT20 Corticotroph tumor cells



Hofland et al, 2005

Effect of glucocorticoids on POMC and sst mRNA expression levels in AtT20 cells (24 h)



Malattia di Cushing: il primo trial clinico B2208

Maggio 2004 - Primo paziente al mondo arruolato: Ernesta 25 anni

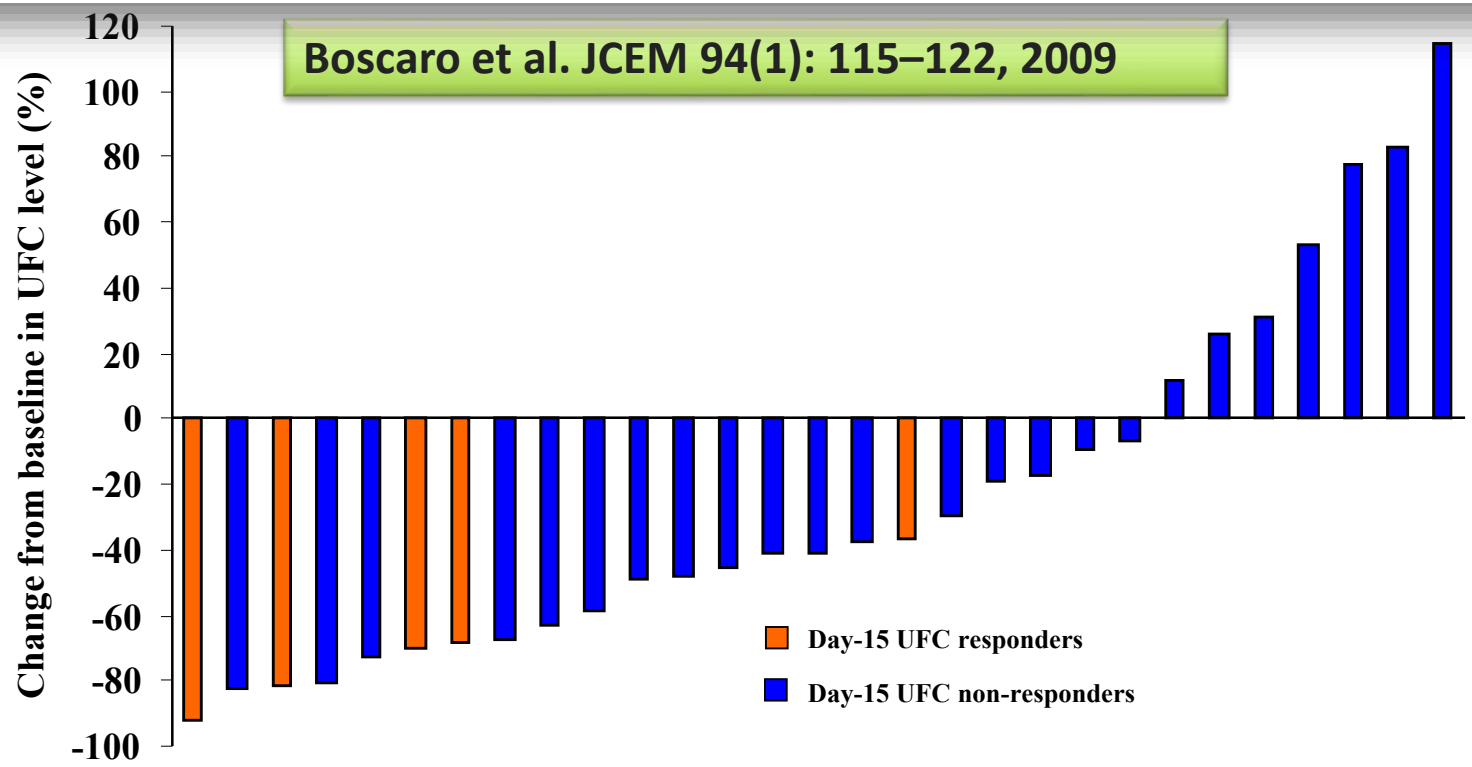
- Microadenoma ipofisario ACTH-secernente
- Recidiva dopo un anno dalla chirurgia (2001)
- Ipercortisolismo severo
  - Cortisolo h8 27,5 mcg/dl ed h23 24,5 mcg/dl
  - CLU-HPLC 350 mcg/dl (vn <50 mcg/24h)
  - ACTH 125 pg/ml
  - Dex 1mg: cortisolo 23,5 mcg/dl
  - Dex 8mg: cortisolo 5,3 mcg/dl
  - CRH test: ACTH + 700% ; cortisolo + 50%
- Ipertensione ed osteoporosi

Primary efficacy data

Patient	Status	Mean UFC baseline (nmol/24 hours)*	Mean UFC endpoint (nmol/24 hours)*	Change (%)
1	Recurrent	2546.5	207	↓ 91.9
2	*De novo*	5949.5	1138.5	↓ 80.9
3	Recurrent	978.5	575.5	↓ 41.2
4	*De novo*	495	291	↓ 41.2
5	Recurrent	1601	1133	↓ 29.2
6	*De novo*	582.5	483	↓ 17.1

**Normal range: 55–276 nmol/24 hours*

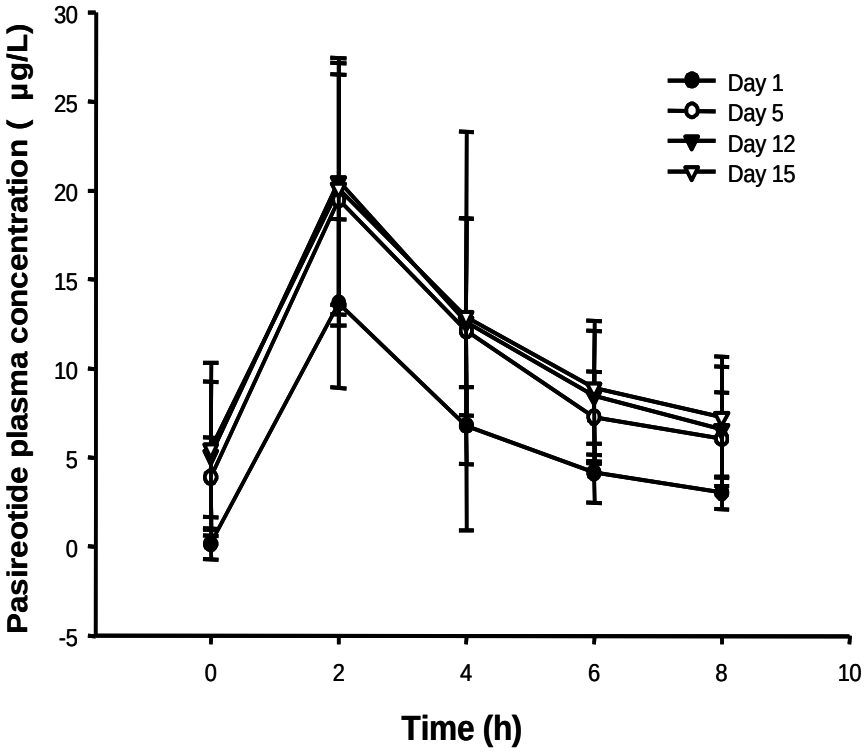
Treatment of Pituitary-Dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial

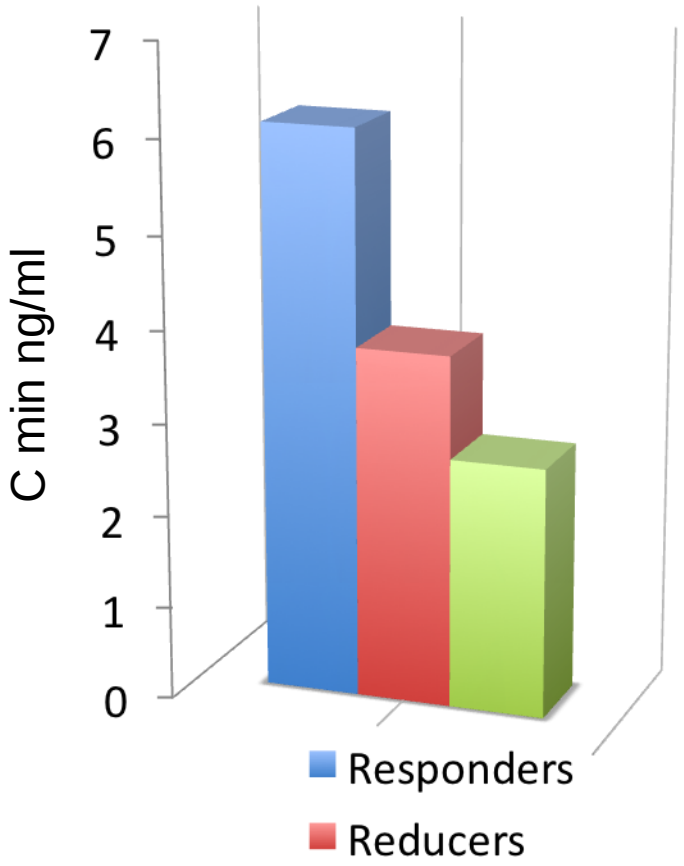


After 15 days of treatment with pasireotide 600 mcg bid sc (n=29)

- 17% of patients with Cushing's disease normalized UFC levels
- 76% of patients exhibited reduced UFC levels
- The mean UFC level decreased from baseline by 44.5% (p = 0.021)

Multicenter, Phase II trial of Pasireotide 600 mcg sc in patients with Cushing's disease





Boscaro et al. JCEM 2009

Data from Boscaro et al. ICE Kyoto, 2010

Malattia di Cushing: Il trial registrativo B2305

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D. for the Pasireotide B2305 Study Group

N Engl J Med 2012; 366:914-924 | March 8, 2012

	600 µg bid (n=82)	900 µg bid (n=80)	Overall (n=162)
6 months			
Response,* n (%) [95% CI]	12 (14.6) [7.0, 22.3]	**21 (26.3) [16.6, 35.9]**	33 (20.4) [14.2, 26.6]
Fully controlled, n (%)	13 (15.9)	23 (28.8)	36 (22.2)
Partially controlled, n (%)	15 (18.3)	10 (12.5)	25 (15.4)
Uncontrolled, n (%)	54 (65.9)	47 (58.8)	101 (62.3)
Fully and partialy controlled, n (%)	**28 (34.2)**	**33 (41.3)**	**61 (37.6)**

Hyperglycaemia represents a frequent adverse event, being documented in 78% of patients, followed by gastrointestinal disturbances

Clinical Endocrinology (2014)

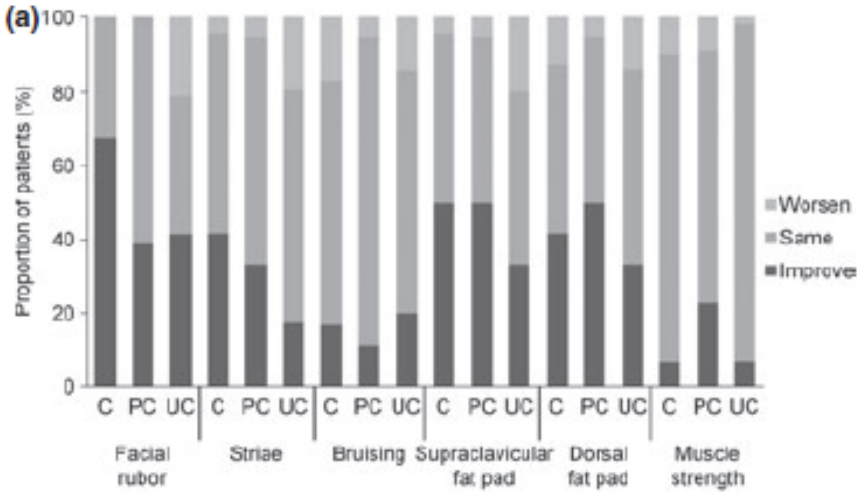
doi: 10.1111/cen.12431

ORIGINAL ARTICLE

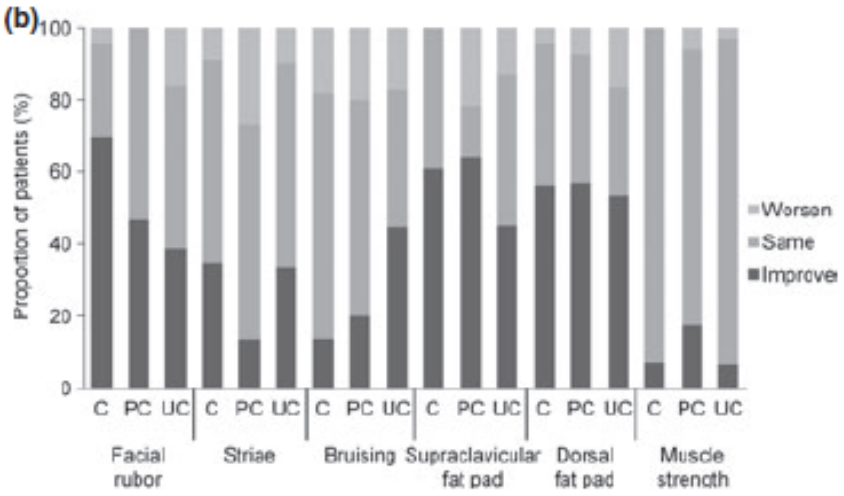
Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study

Rosario Pivonello*, Stephan Petersennt, John Newell-Price‡, James W. Findling§, Feng Gu¶, Mario Maldonado**, Andrew Trovato**, Gareth Hughest†, Luiz R. Salgado‡‡, André Lacroix§§, Jochen Schopohl¶¶ and Beverly M.K. Biller*** on behalf of the Pasireotide B2305 Study Group[1]

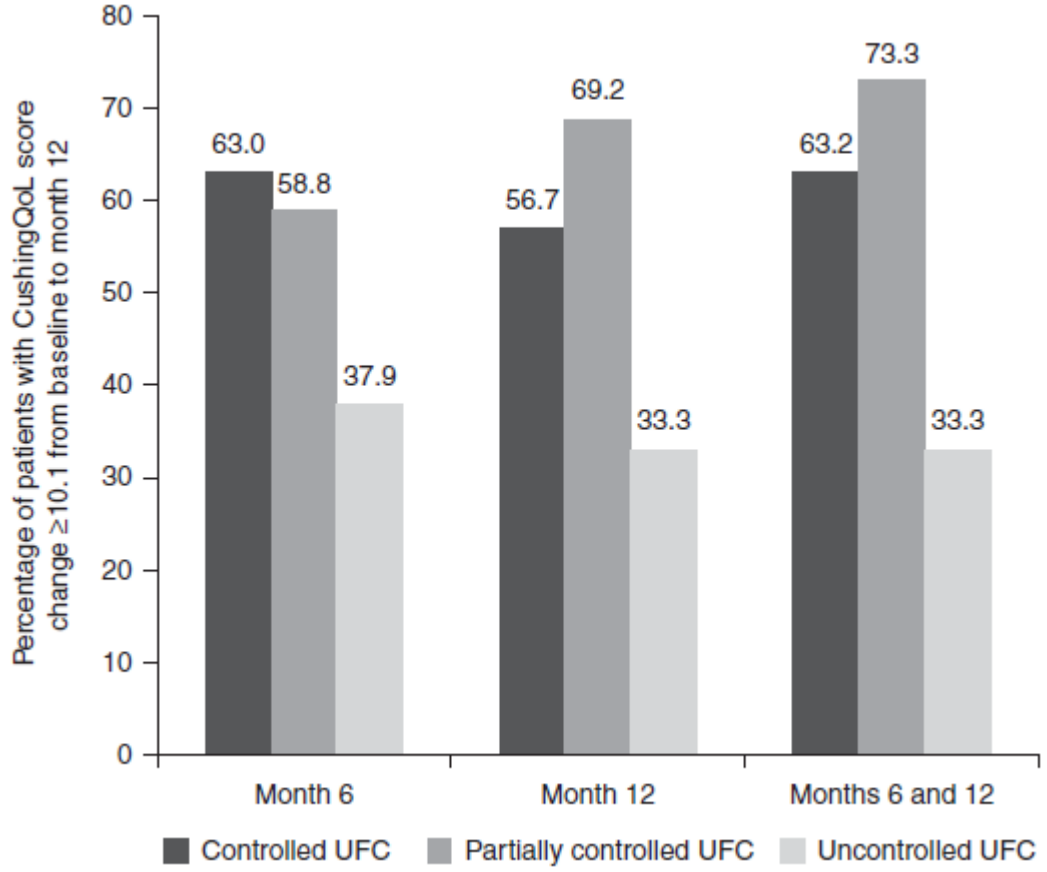
Month 6



Month 12

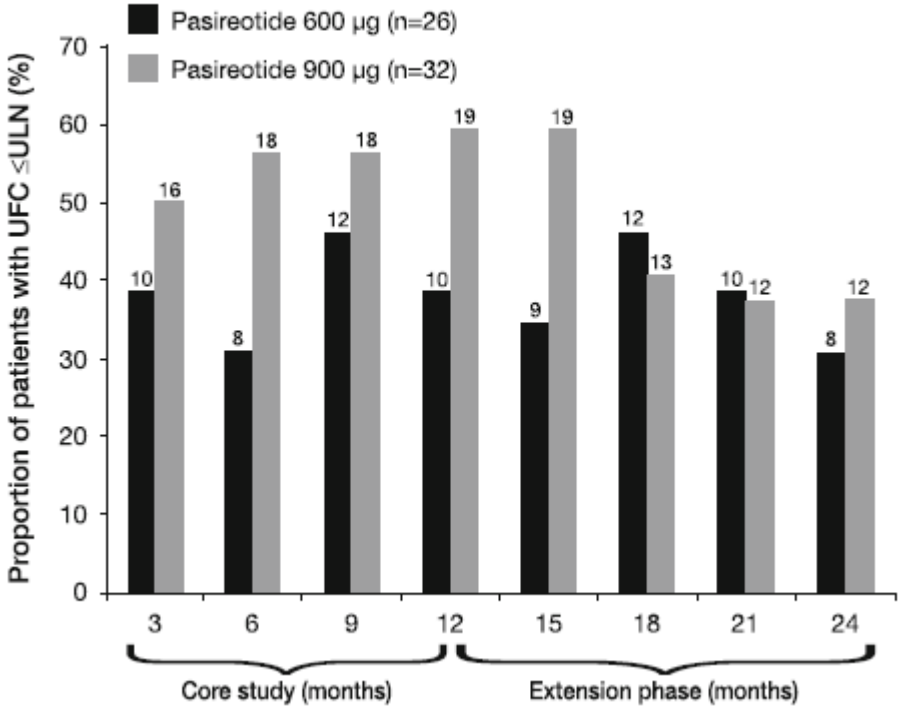


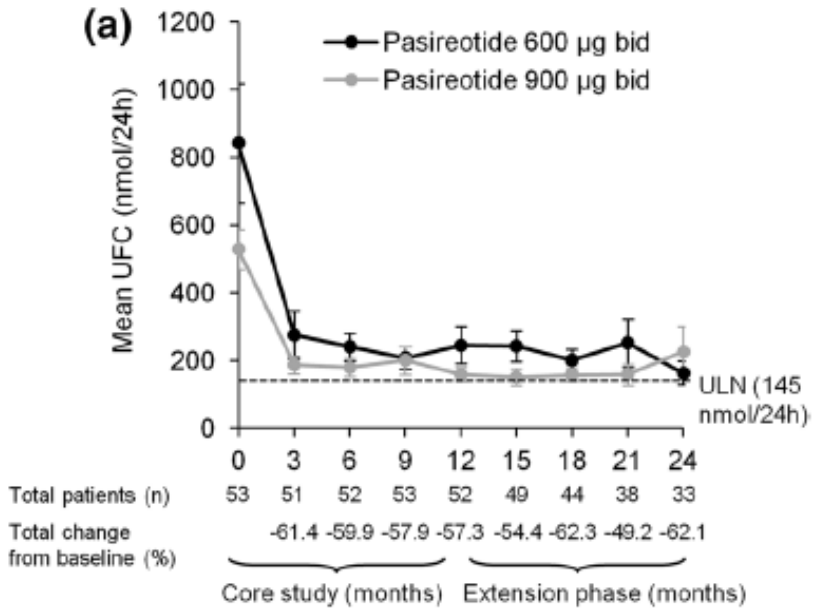
Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease



Webb S et al., EJE 2014

Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial





Reduction in mean UFC and improvements in clinical signs of Cushing's disease were manteined over 24 month

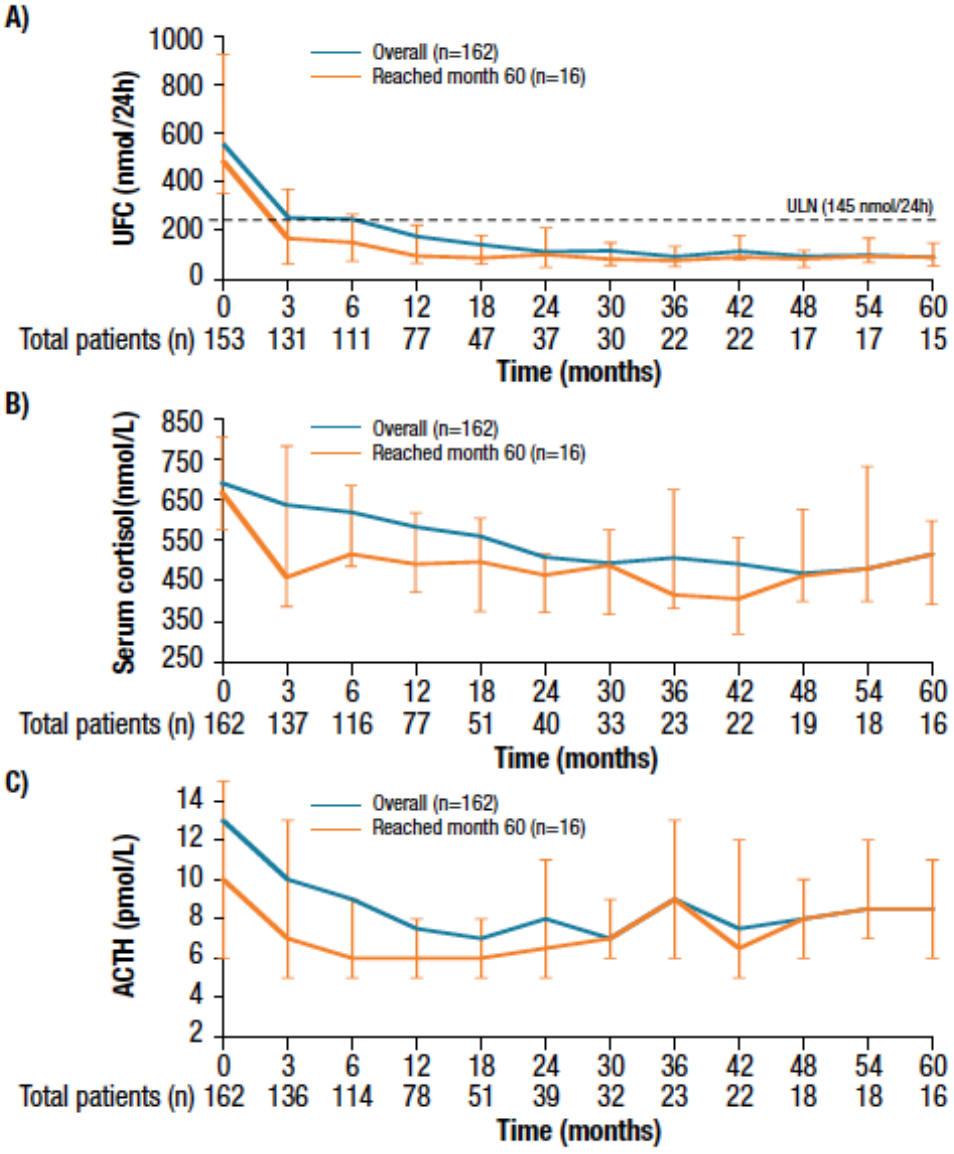
of pasireotide treatment

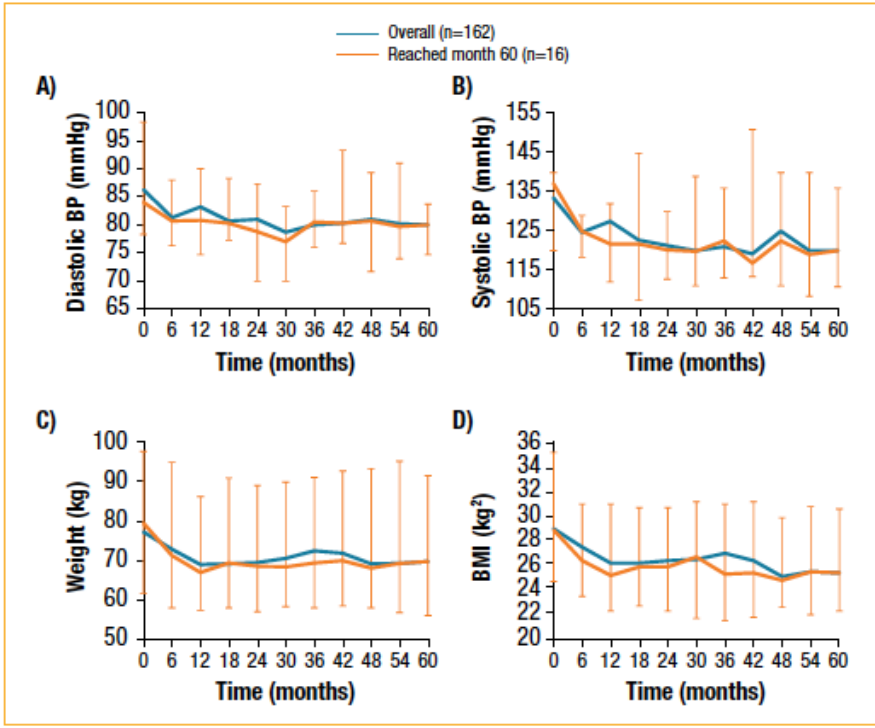
Schopohl J et al., Pituitary 2014

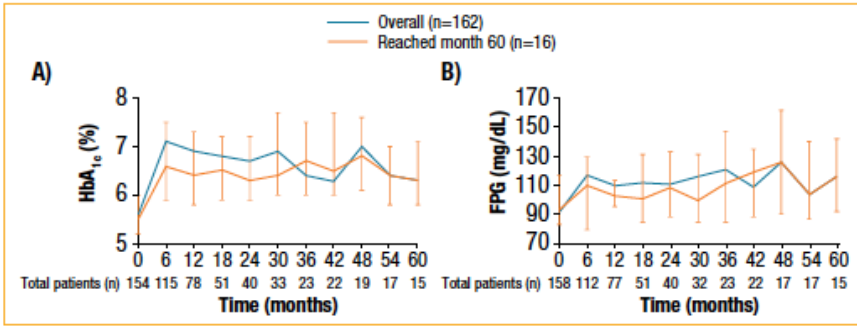
GP-22-04

Long-Term (5 Years) Treatment of Cushing's Disease with Pasireotide

S Petersenn,[1] LR Salgado,[2] J Schopohl,[3] L Portocarrero-Ortiz,[4] G Arnaldi,[5] A Lacroix,[6] S Ravichandran,[7] A Kandra,[8] BMK Biller[9]







Poster ECE – Dublin ECE 2015

Malattia di Cushing: La pratica clinica

Pasireotide in Clinical Practice

~68% UFC normalization
(median FU 6 months)

Table 3 Follow-up data of the study population ($n = 16$)

Patient	Duration of FU (months)	Baseline			LNSC change (%) during acute PST	Follow-up		
		CD severity	BMI (Kg/m^2)	Hypertension		24-h UFC	BMI [change] (Kg/m^2)	Hypertension
1	6	Mild	39.6	Yes	−30	Normalized	35.3 [−4.3]	Improved
2	2	Mild	27	Yes	+19	No response	27	Unchanged
4	8	Mild	33.3	Yes	−46	Normalized	29.6 [−3.7]	Improved
5	3	Severe	36.7	Yes	−45	>40 % reduction	33.9 [−2.8]	Improved
6	9	Mild	34.5	Yes	−41	Normalized	32.4 [−2.1]	Improved
8	9	Mild	31.4	Yes	−70	Normalized	30.4 [−1.0]	Normalized
9	1	Moderate	23	Yes	−26	>40 % reduction	22.7 [−0.3]	Unchanged
10	6	Severe	32.3	Yes	−42	>40 % reduction	29 [−3.3]	Improved
11	6	Mild	36.9	Yes	−59	Normalized	32.6 [−4.3]	Improved
12	1	Mild	33	Yes	NA	Normalized	33	Unchanged
13	6	Mild	29.4	Yes	NA	Normalized	28.4 [−1.0]	Unchanged
14	6	Moderate	27.7	No	−75	Normalized	26.5 [−1.2]	Unchanged
15	3	Mild	28.7	Yes	−53	Normalized	27.8 [−0.9]	Unchanged
16	1	Mild	41.3	Yes	+17	No response	41.3	Unchanged
17	3	Mild[a]	41.5	Yes	−26	Normalized	41.5	Unchanged
18	6	Mild	30	Yes	−28	Normalized	26 [−4.0]	Improved

FU follow-up, *CD* Cushing's disease, *BMI* body mass index, *LNSC* late-night salivary cortisol, *PST* pasireotide suppression test, *NA* not available, *UFC* urinary-free cortisol

[a] Patient with near normal UFC levels at baseline (<1.2 × ULN)

Trementino et al., Endocrine 2014

An Italian Experience

Annamaria Colao
Marco Boscaro

Padova: Carla Scaroni

Ancona: Giorgio Arnaldi

2014-2015

Napoli: Rosario Pivonello

Palermo: Carla Giordano

Messina: Salvo Cannavò

Pasireotide
nella terapia della malattia di Cushing

Con quale dose iniziare ?

300/600/900 mcg bid

Dopo quanto tempo
e come valutare l'efficacia ?

Effetti sulla massa tumorale ?

Pasireotide e metabolismo glucidico

Pasireotide
nella terapia della malattia di Cushing

Elementi predittivi di risposta ?

Trattamento pre-operatorio ?

Terapia primaria ?

Terapia combinata ?

Pasireotide & Malattia di Cushing:
Casi clinici e studi spontanei

Effetti sulla massa tumorale ?

Shimon I, L. Rot, E. Inbar
Pituitary-directed medical therapy with pasireotide for a corticotroph macroadenoma: pituitary volume reduction and literature review.
Pituitary 15, 608–613 (2012)

Endocrine
DOI 10.1007/s12020-015-0557-2

2015

ORIGINAL ARTICLE

The treatment with pasireotide in Cushing's disease: effects of long-term treatment on tumor mass in the experience of a single center

Chiara Simeoli · Renata Simona Auriemma · Fabio Tortora · Monica De Leo · Davide Iacuaniello · Alessia Cozzolino · Maria Cristina De Martino · Claudia Pivonello · Ciro Gabriele Mainolfi · Riccardo Rossi · Sossio Cirillo · Annamaria Colao · Rosario Pivonello

Trattamento pre-operatorio ?

Endocrine
DOI 10.1007/s12020-015-0601-2

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CLINICAL MANAGEMENT OF ENDOCRINE DISEASES

Clinical management of critically ill patients with Cushing's disease due to ACTH-secreting pituitary macroadenomas: effectiveness of presurgical treatment with pasireotide

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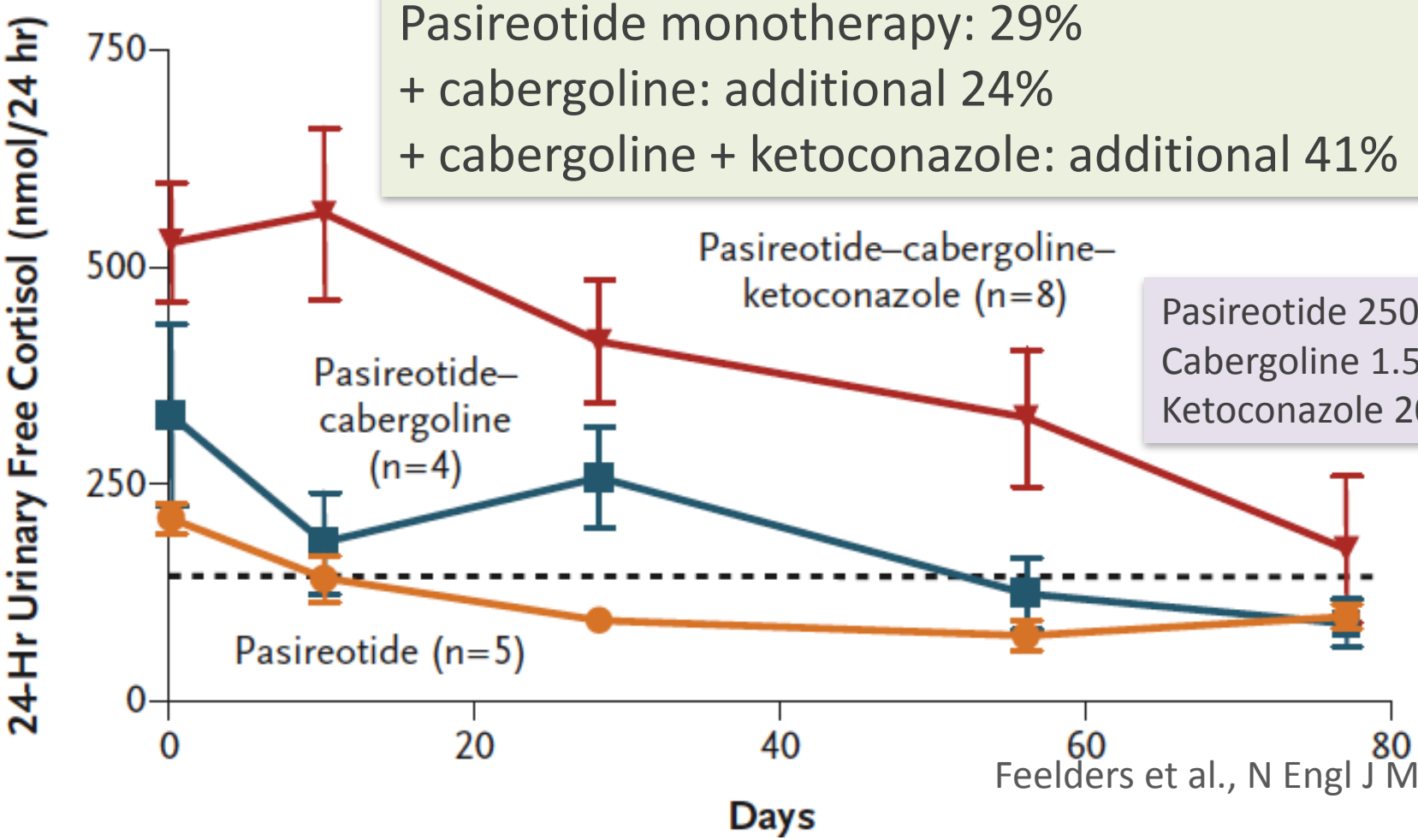
Terapia combinata ?

Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease

Biochemical control in almost 90% of patients
Pasireotide monotherapy: 29%
+ cabergoline: additional 24%
+ cabergoline + ketoconazole: additional 41%



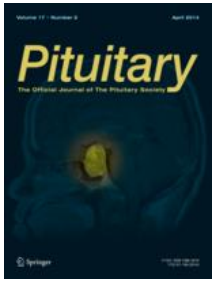
Pasireotide 250 mcg tid
Cabergoline 1.5 mg qod
Ketoconazole 200 mg tid

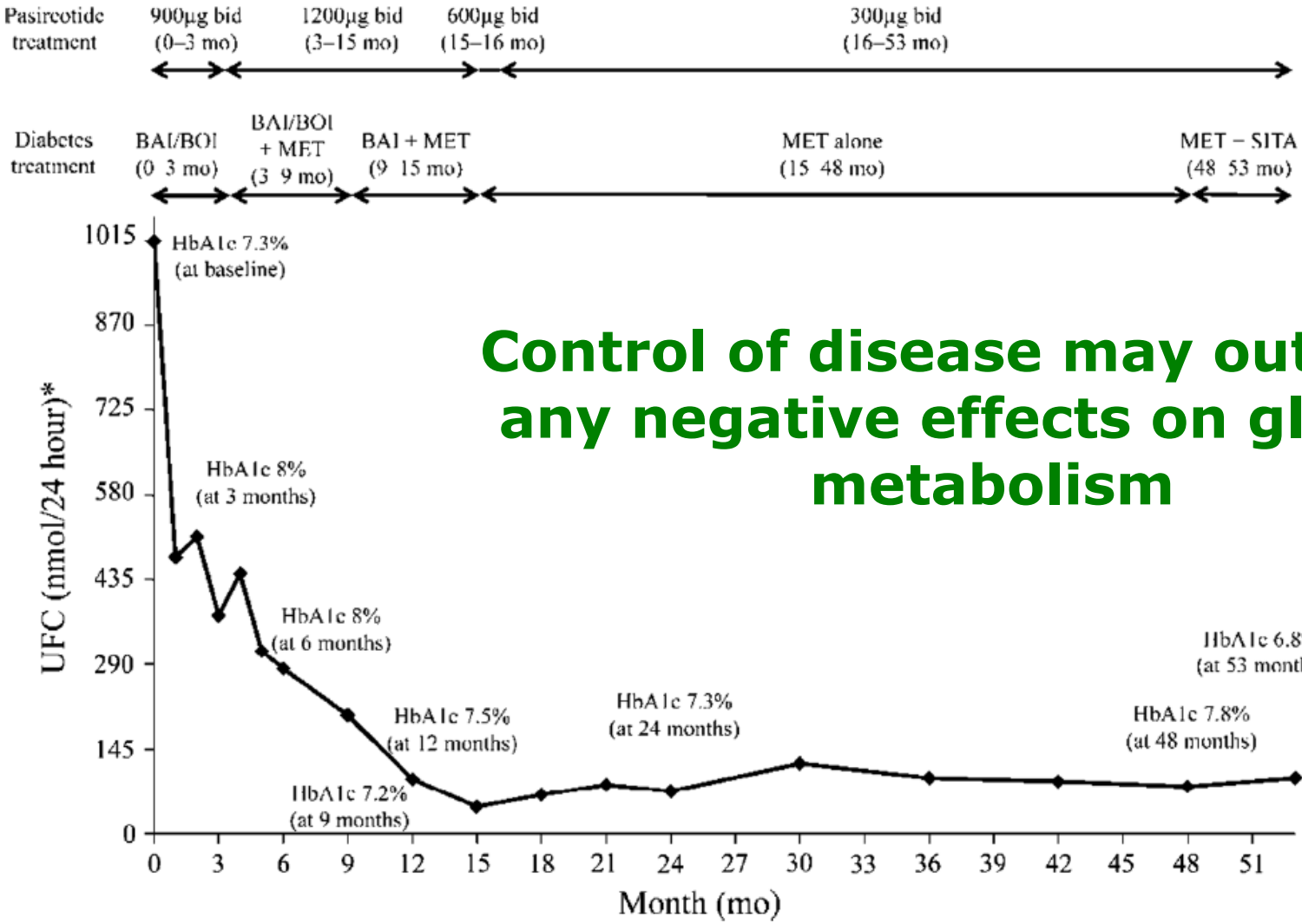
Feelders et al., N Engl J Med 2010

Pasireotide e metabolismo glucidico

Up-to 5-year efficacy of pasireotide in a patient with Cushing's disease and pre-existing diabetes: literature review and clinical practice considerations

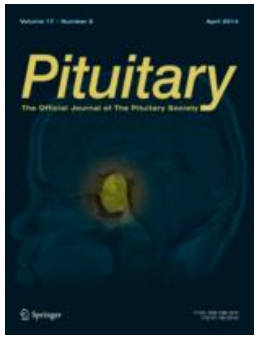
Trementino et al Pituitary 2014





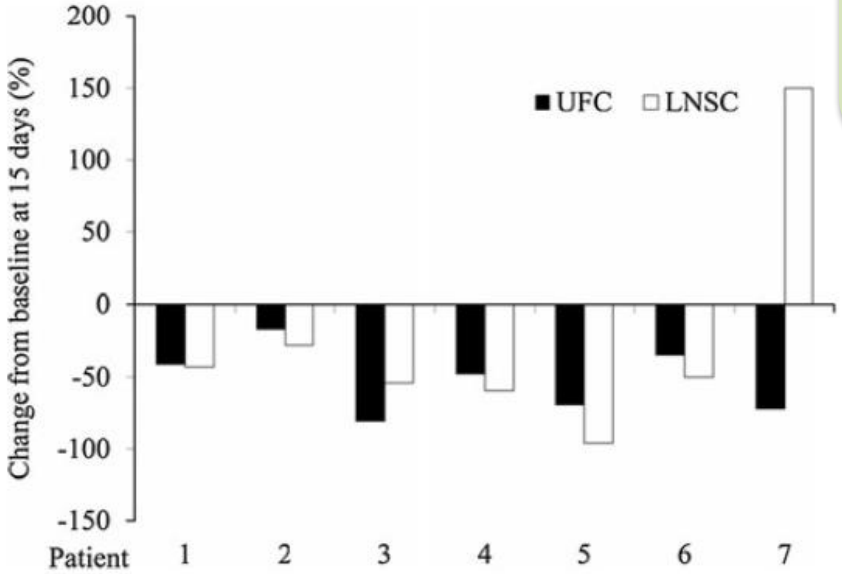
Control of disease may outweigh any negative effects on glucose metabolism

Come e quando valutare l'efficacia ?

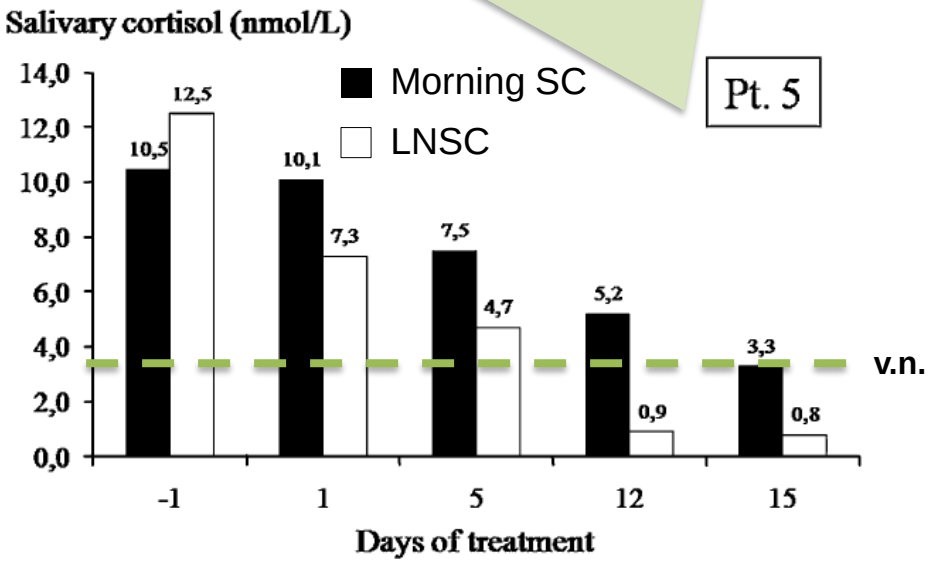


Salivary cortisol is a useful tool to assess the early response to pasireotide in patients with Cushing's disease

Pituitary
DOI 10.1007/s11102-014-0557-x



The patient who normalized LNSC with restoration of circadian cortisol rhythm at day 15 also showed normalization of UFC



After 15 days of treatment, pasireotide reduced both UFC and salivary

cortisol to a similar degree.

Trementino at al., Pituitary 2014

Elementi predittivi di risposta ?

ORIGINAL ARTICLE

Trementino et al. Endocrine 2014 online December

The role of an acute pasireotide suppression test in predicting response to treatment in patients with Cushing's disease: findings from a pilot study

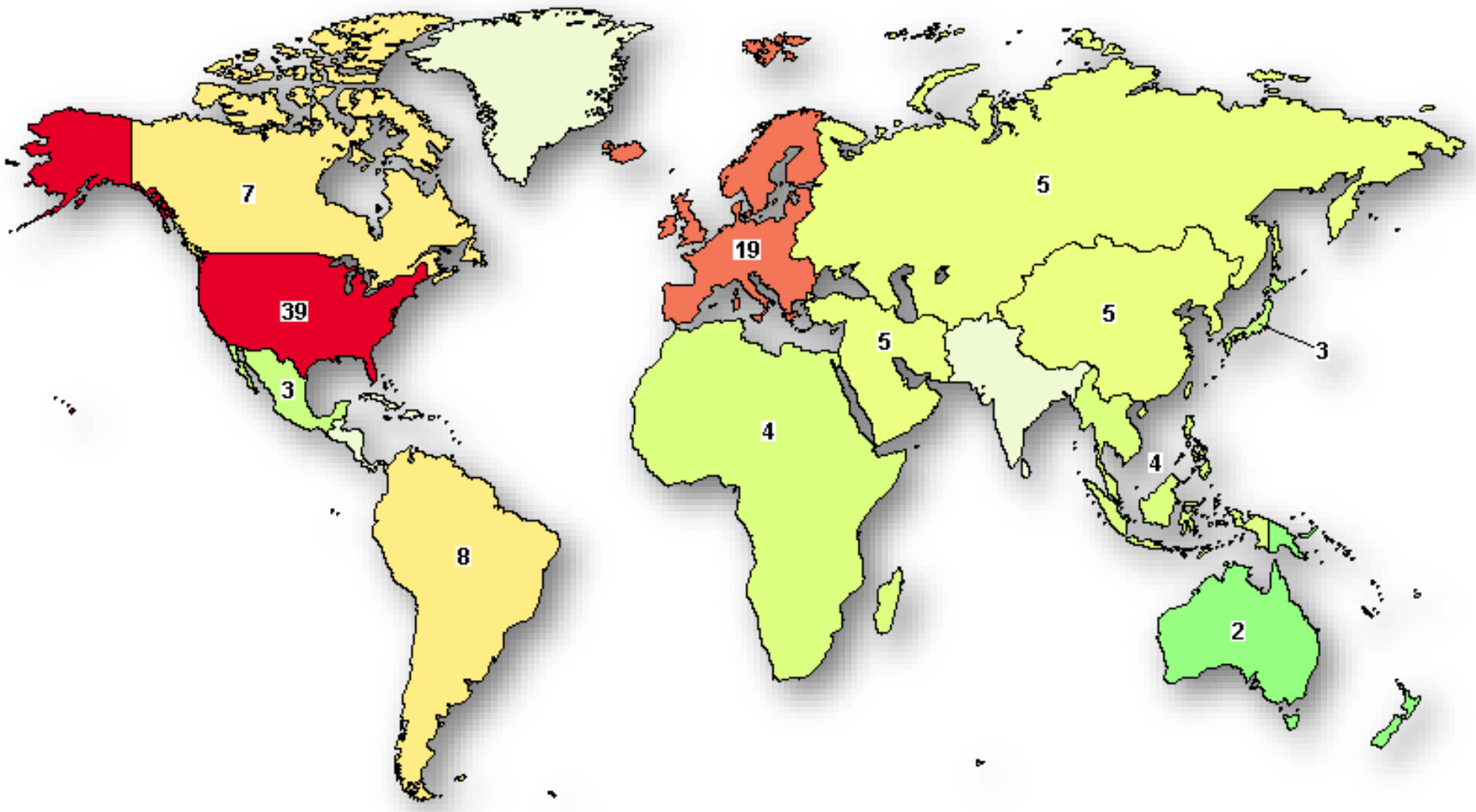
Follow-up :
Median 6 months

Pasireotide normalized 24-h UFC at last follow-up in about 68 % of patients.

Table 2 Prognostic profiles (%) of various suppression values during acute PST in predicting medium/long-term response to treatment with pasireotide in patients with CD ($n = 16$)

	Serum cortisol fall >28 %	Serum cortisol fall >57 %	Plasma ACTH fall >35 %	Plasma ACTH fall >48 %	LNSC fall >27 %
SE	92	46	69	61	91
SP	75	100	75	100	100
PPV	92	100	100	100	100
NPV	66	30	42	37	75

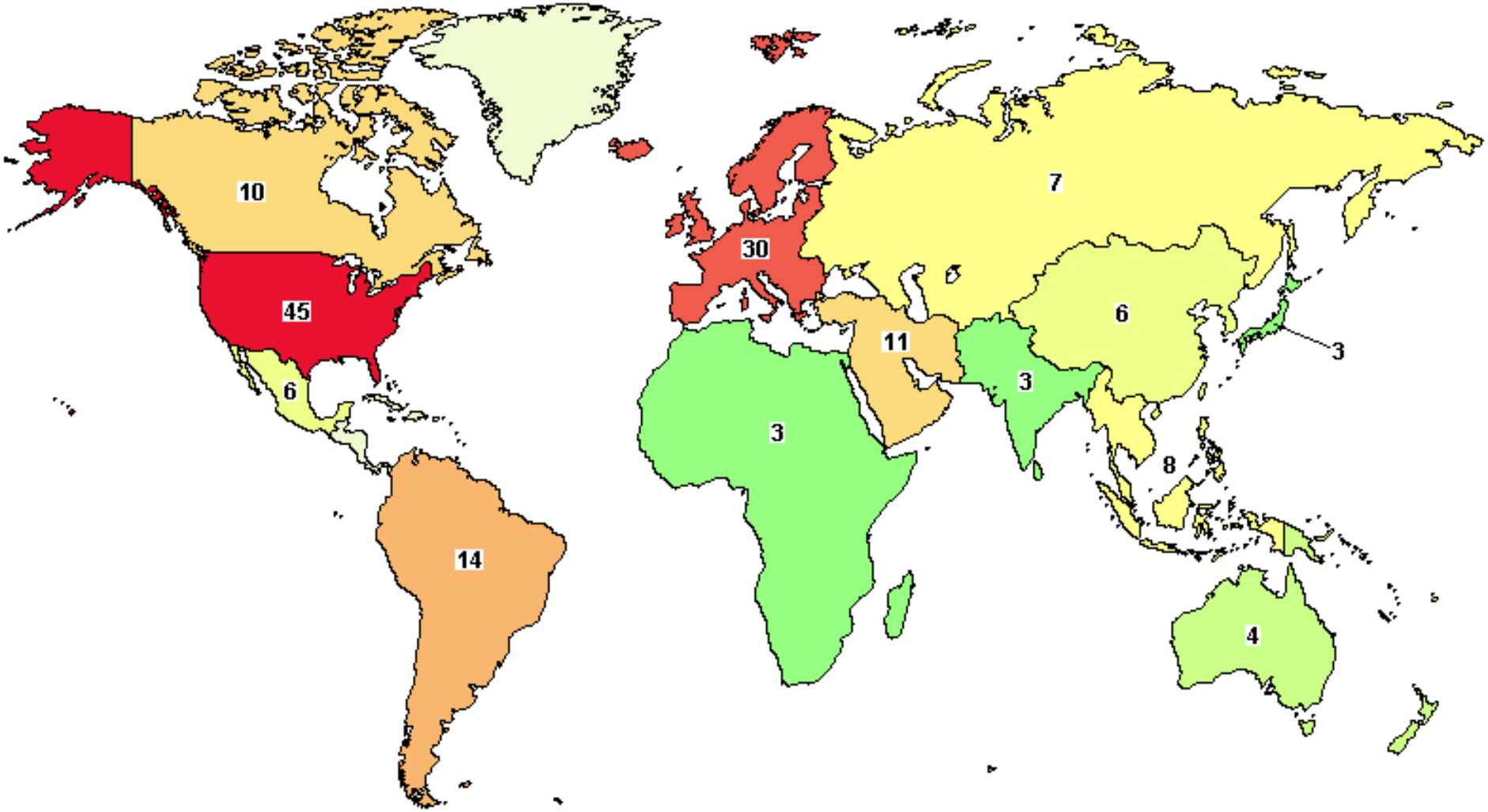
PASIREOTIDE: 51 studi *ongoing*



Dicembre 2012

data from Clinicaltrials.gov

PASIREOTIDE: 66 studi *ongoing*

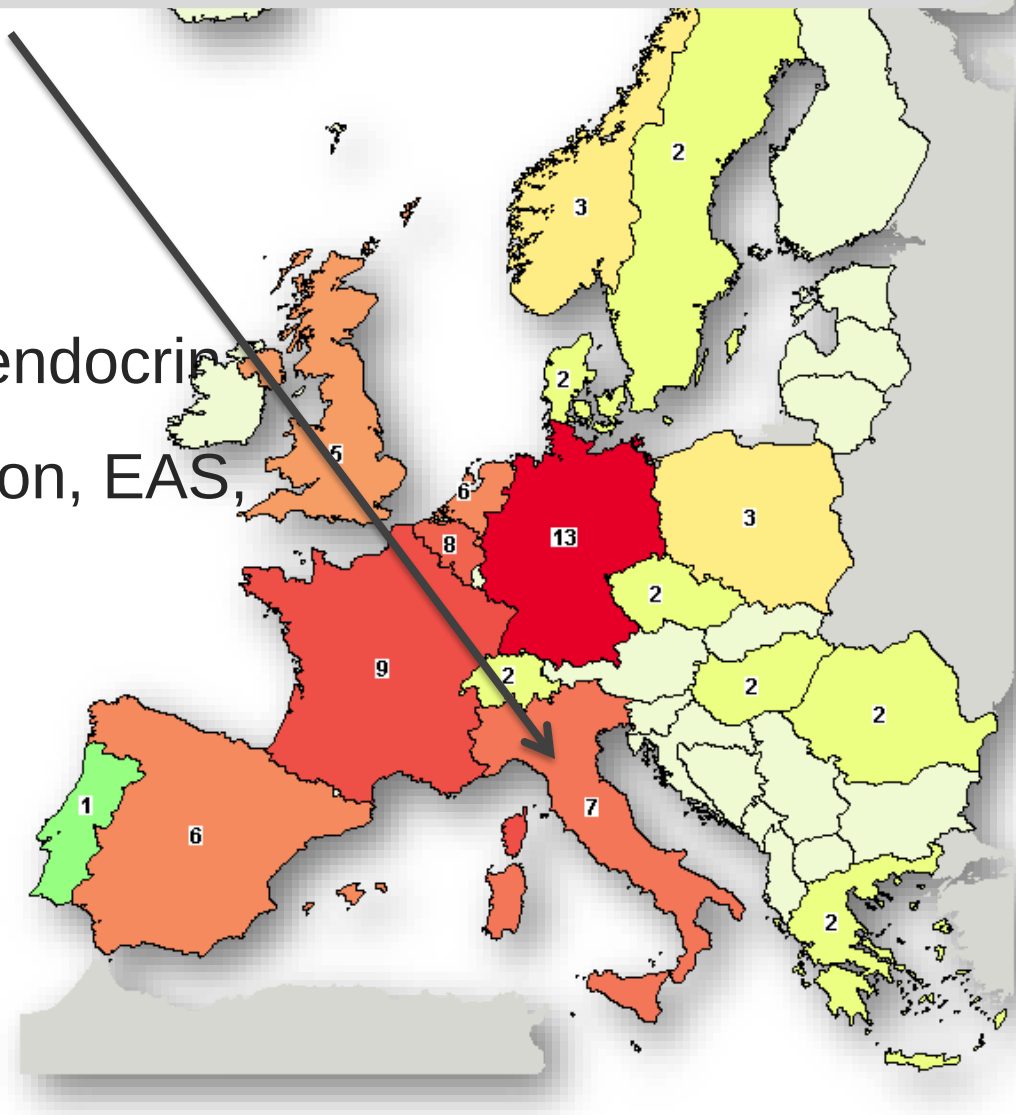


Oggi 5 Maggio 2015

data from Clinicaltrials.gov

Italia: 7 studi *ongoing*

- **Malattia di Cushing**
- **Acromegalia**
- Tumori rari di origine neuroendocrina (tumori ipofisari secernenti e non, EAS, Sdr Nelson, ..)
- pNET
- NET polmone/timo
- K midollare tiroide

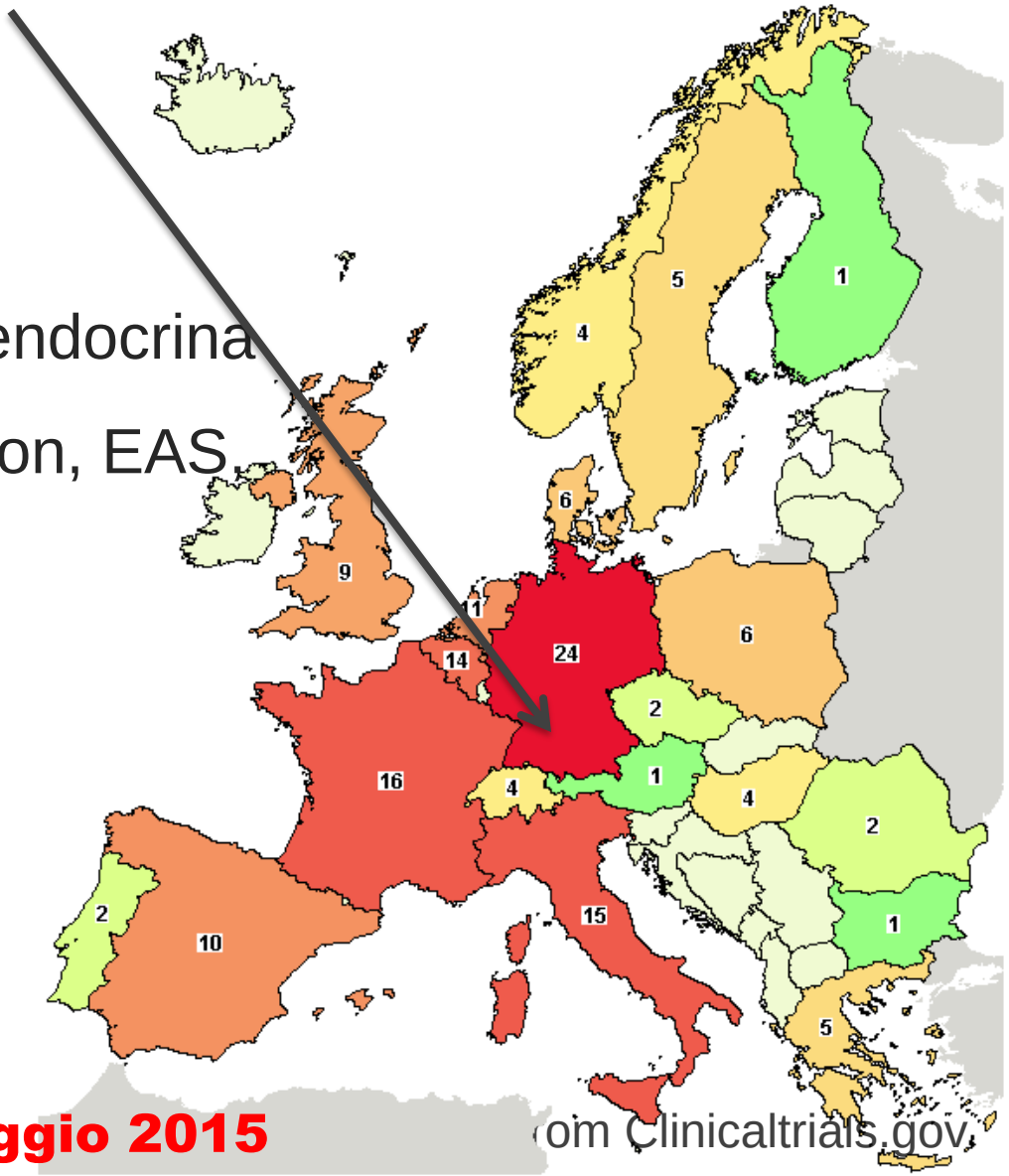


Dicembre 2012

data from Clinicaltrials.gov

Italia: 15 studi *ongoing*

- **Malattia di Cushing**
- **Acromegalia**
- Tumori rari di origine neuroendocrina (tumori ipofisari secernenti e non, EAS, Sdr Nelson, ..)
- pNET
- NET polmone/timo
- K midollare tiroide



Oggi 5 Maggio 2015

om Clinicaltrials.gov

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