PASIREOTIDE EXPERIENCE: REGISTRATION STUDY VERSUS REAL WORLD EVIDENCE

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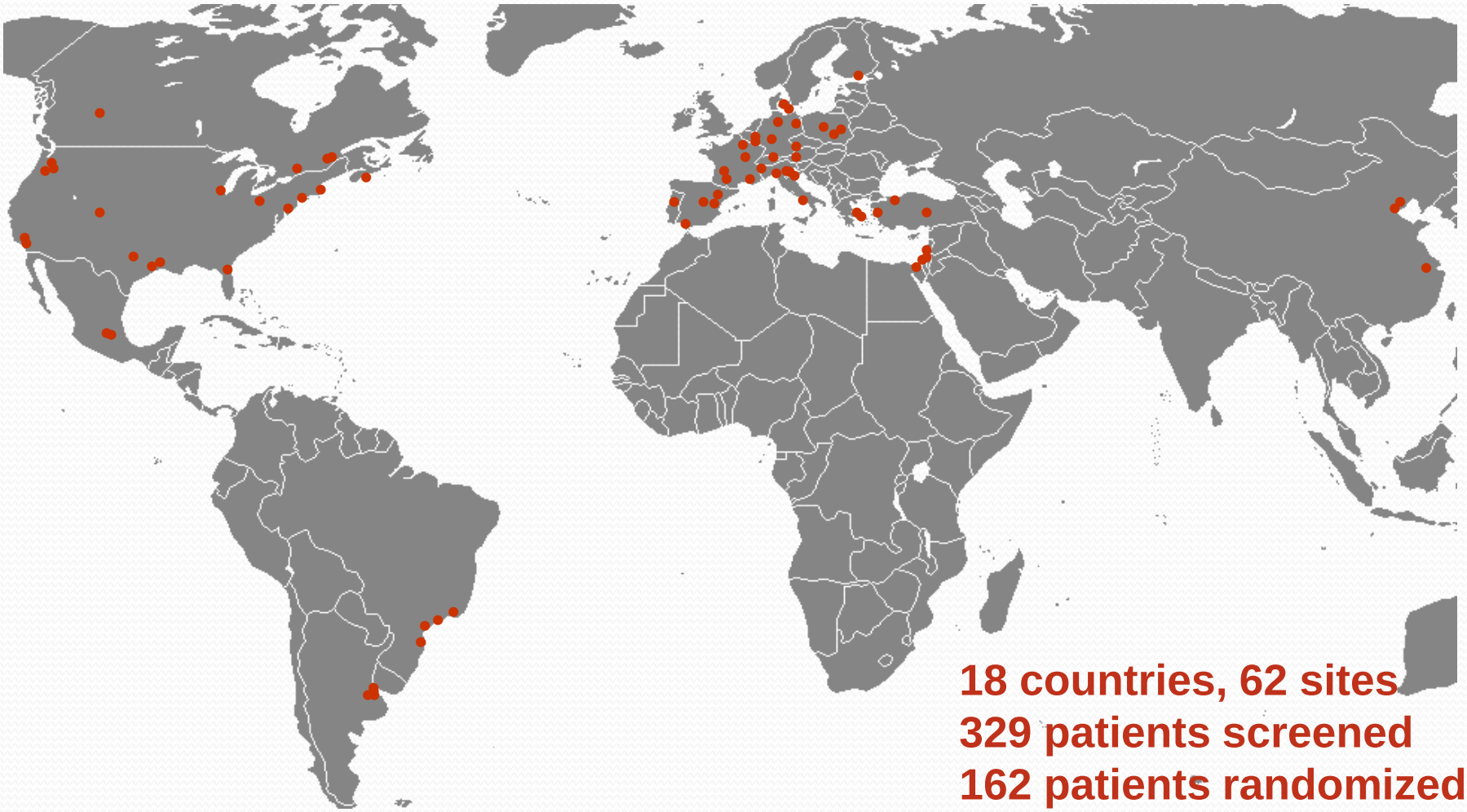
Background

- A multimodal treatment strategy, including pituitary surgery, pituitary radiotherapy, adrenal surgery and medical treatment, is often required to obtain a persistent remission or cure
- Medical treatment is based on a limited number of drugs, which are licensed for the treatment of the disease
- Pasireotide is the only authorised pituitary-directed drug with the indication for Cushing's disease, particularly for patients in whom surgery is not an option or failed to induce remission

CSOMB2305: REGISTRATIVE STUDY



18 countries, 62 sites
329 patients screened
162 patients randomized

Colao A et al. N Engl J Med 2012;366:914–924

Argentina, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Poland, Portugal, Spain, Turkey, United States

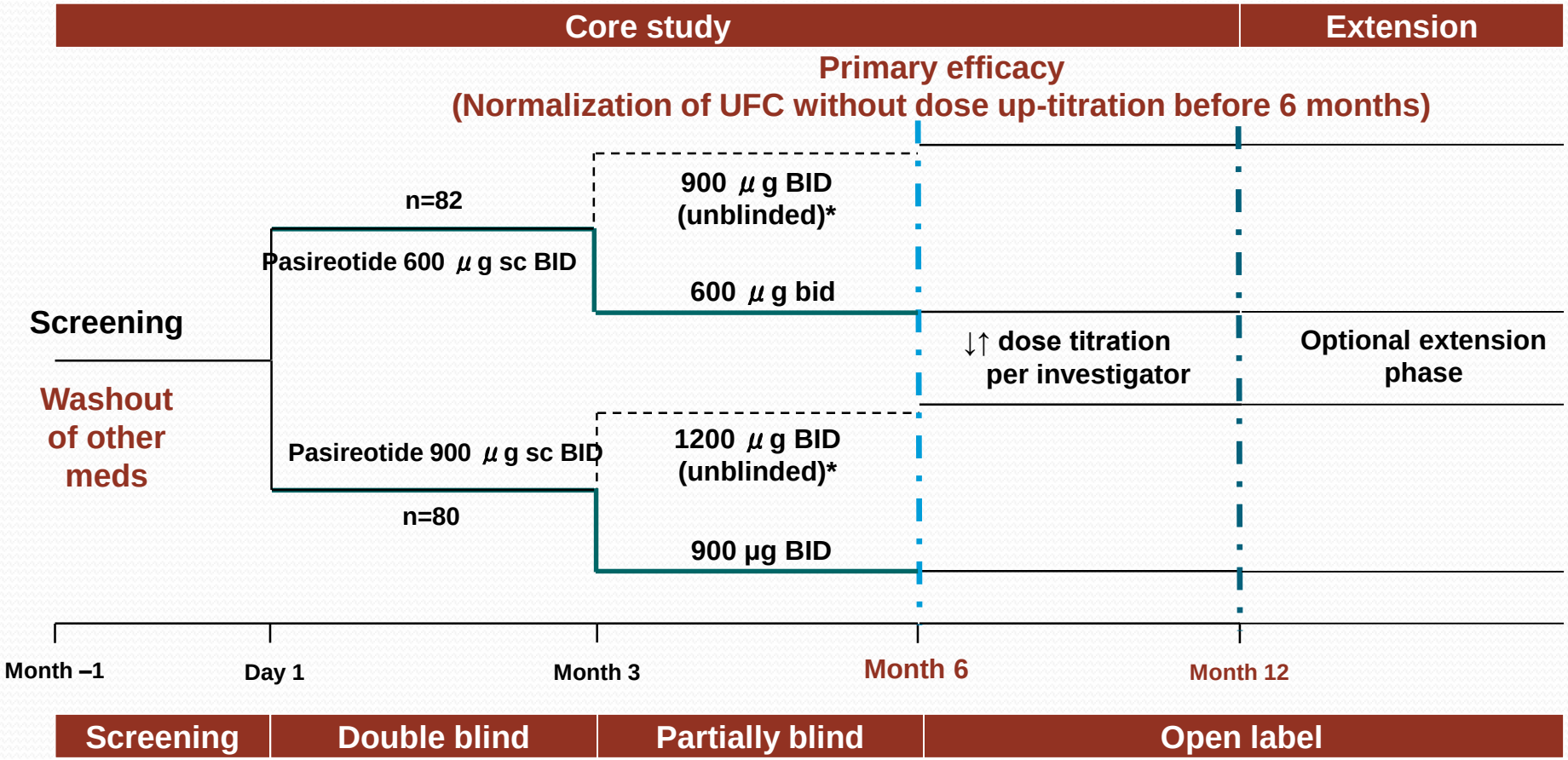
REGISTRATIVE STUDY: Key Inclusion and Exclusion Criteria

- **Key inclusion criteria**
  - Male or female patients aged ≥18 years
  - Confirmed persistent/recurrent or de novo Cushing's disease
  - **Active Cushing's disease (baseline UFC ≥1.5x ULN)**
    - **Mean UFC based on 4 collections**
  - De novo Cushing's disease if not a pituitary surgical candidate
    - Poor surgical candidates, surgically unapproachable tumors, refused surgery
- **Key exclusion criteria**
  - Pituitary irradiation within the last 10 years
  - Compression of the optic chiasm
  - Poorly controlled diabetes mellitus (HbA_{1c} >8%)
  - Risk factors for torsades de pointes
    - QTc >480 ms, hypokalaemia, family history of long QT syndrome, concomitant medications known to prolong QT interval

Colao A et al. N Engl J Med 2012;366:914–924

REGISTRATIVE STUDY

Study Design



*For patients who had a mean baseline UFC ≥2x ULN with a 3-month UFC >2x ULN OR
For patients who had a mean baseline UFC 1.5–2x ULN with a 3-month UFC above their baseline UFC

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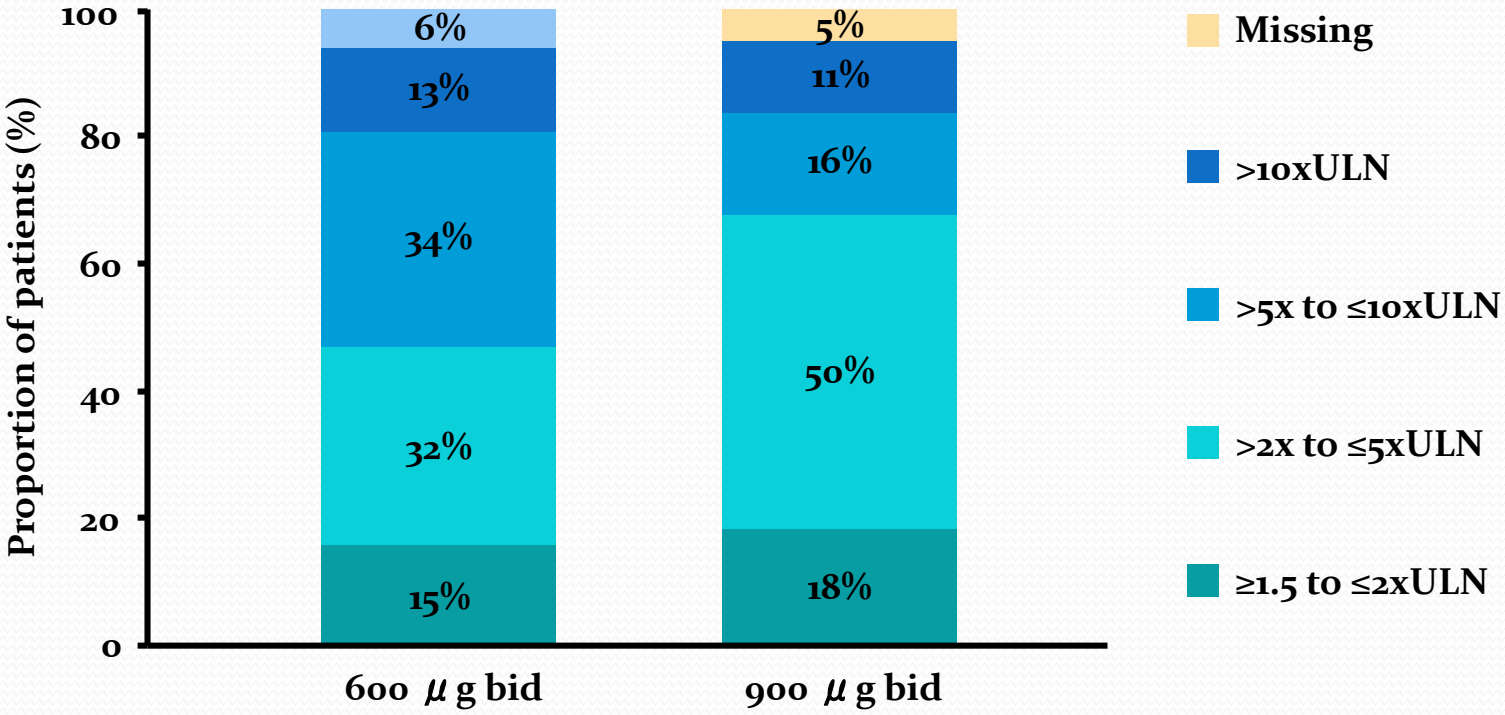
Registrative study

Distribution of disease severity

At baseline, 78% of patients had moderate to very severe hypercortisolism



Colao A *et al. N Engl J Med* 2012;366:914–924

REGISTRATIVE STUDY-EFFICACY ANALYSIS

A prospective randomized double-blind phase III study have evaluated the efficacy and safety of pasireotide in a large number of patients with Cushing's disease

	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

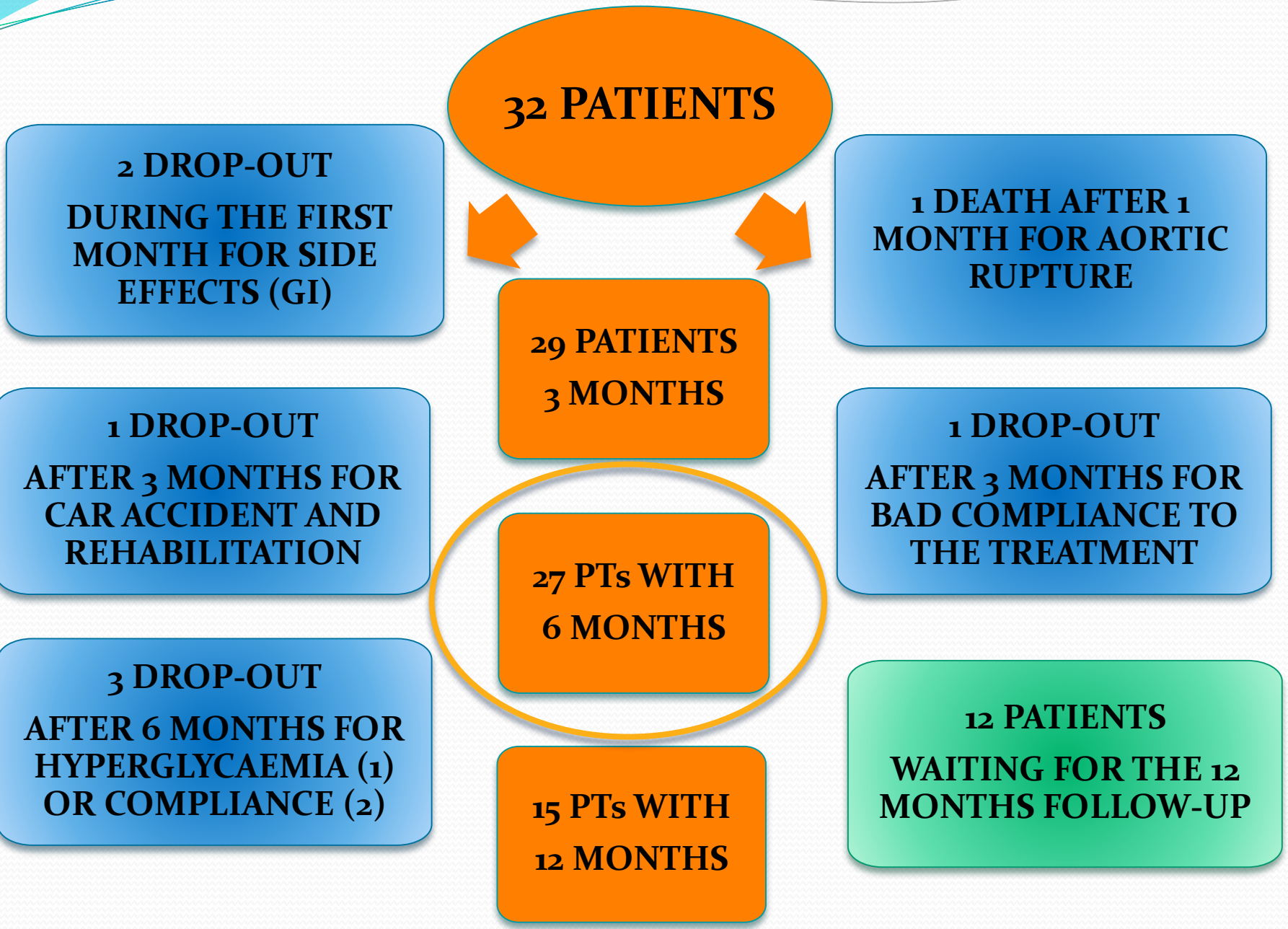
REGISTRATIVE STUDY: LIMITATIONS

- The phase III study enrolled mostly (78%) patients with moderate to very severe disease (disease was severe in 25% and very severe in 12% of patients).
- The primary efficacy endpoint was represented by the proportion of patients who normalized urinary cortisol levels at 6 months follow-up without previous up-titration of the drug dose
- The primary efficacy analysis was based on an “intention to treat” methodology where patients who discontinued treatment were considered non responsive, independently from the hormonal response

Pasireotide and Cushing in the real world evidence

Multicentre prospective open label study to evaluate the efficacy and safety of pasireotide treatment in a group of patients with Cushing's disease according with real-world evidence

Patients disposition



Patients features

27 PATIENT AT THE 6-MONTH FOLLOW-UP

DISEASE SEVERITY

VERY MILD 14

MILD 6

MODERATE 6

VERY SEVERE 1

26 PATIENTS

VERY MILD TO MODERATE

20 females

6 males

Age

47.4±13.2

median: 49

VERY MILD (1-1.5 ULN)

MILD (1.5-2 ULN)

MODERATE (2-5 ULN)

SEVERE (5-10 ULN)

VERY SEVERE (>10 ULN)

Treatment Protocol

INITIAL DOSE

600 µg bid

At 3 months, evaluation of UFC levels and clinical benefit

INCREASE OF DOSE

Not controlled after 3 months

900 µg bid

Follow-up every 3 months for monitoring of parameters

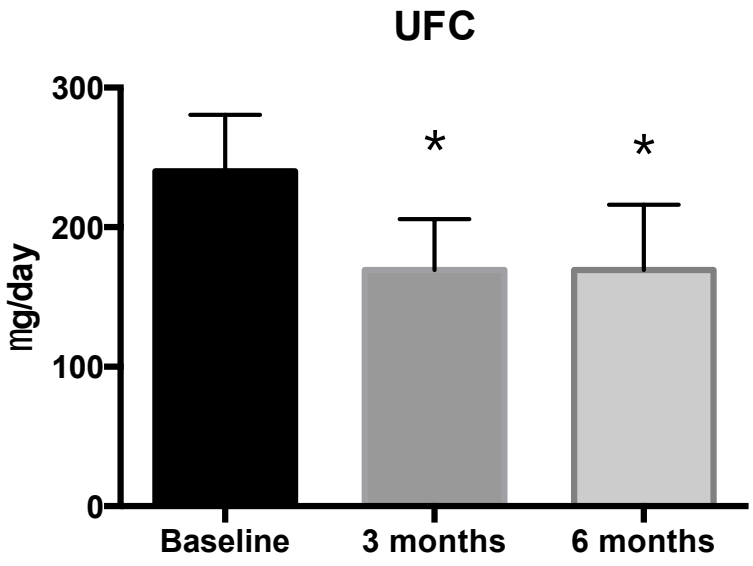
Efficacy analysis

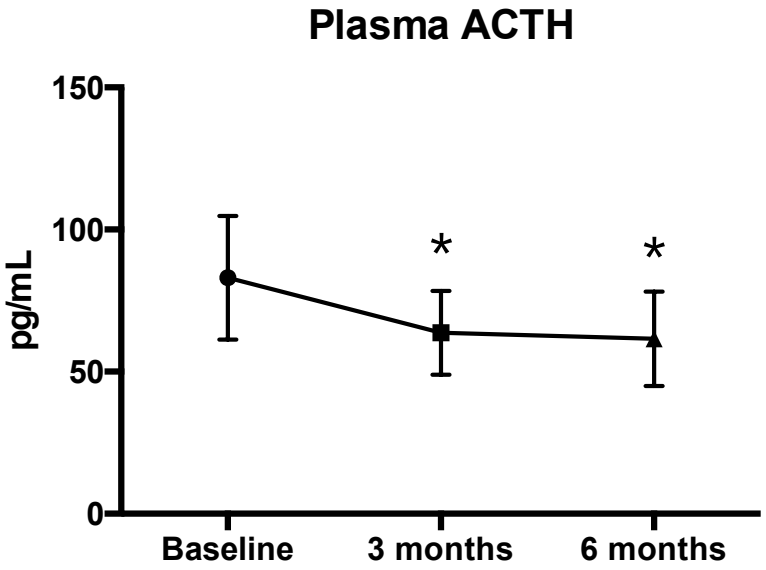
RESPONSE	6 MONTHS (n=31/26) N (%)
NORMALIZATION, n (%)	19 (61.3/ 73.1)
NEAR NORMALIZATION, n (%)	2 (6.4 / 7.7)
NO NORMALIZATION, n (%)	5 (16.1 / 19.2)
DISCONTINUATION	5/31 (16.1)
RESPONSE PP * (NORMAL + NEAR NORMAL) n (%)	**21/26 (80.8)**
RESPONSE ITT ** (NORMAL + NEAR NORMAL) n (%)	**21/31 (67.7)**

***RESPONSE PP: Percentage of responsive patients over the totality of patients, who completed the period of treatment (3 months or 6 months).**

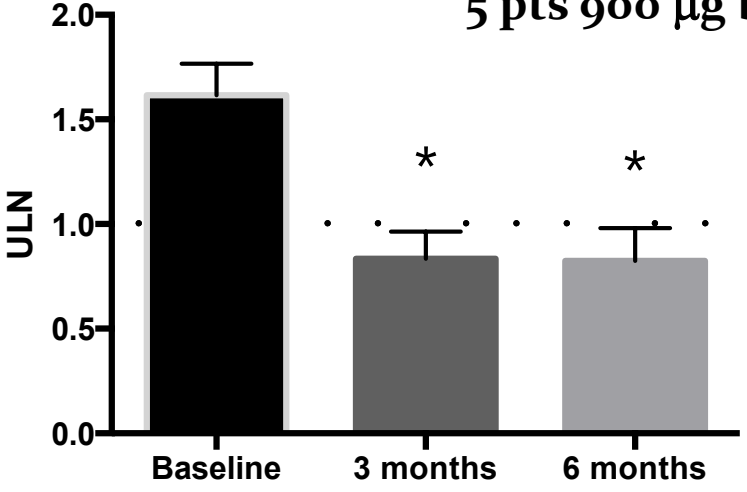
****RESPONSE ITT: Percentage of responsive patients at the evaluable period of treatment (3 months or 6 months) over the totality of patients starting treatment**

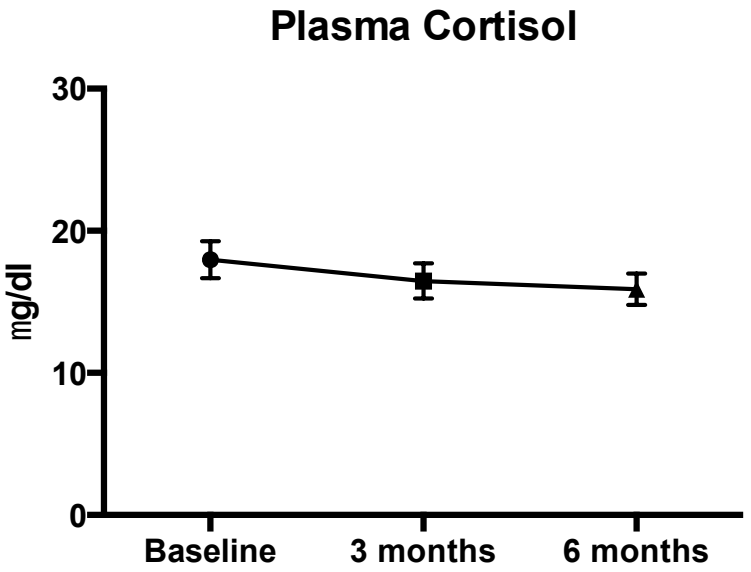
Effect on hormone levels



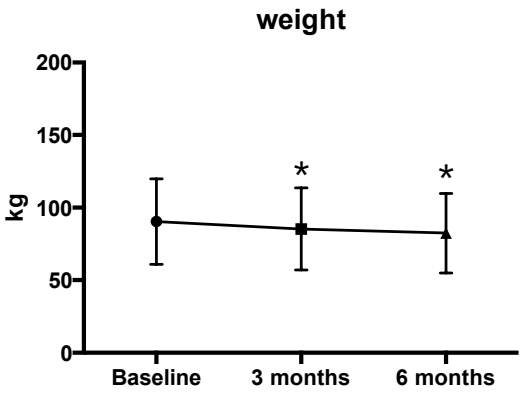


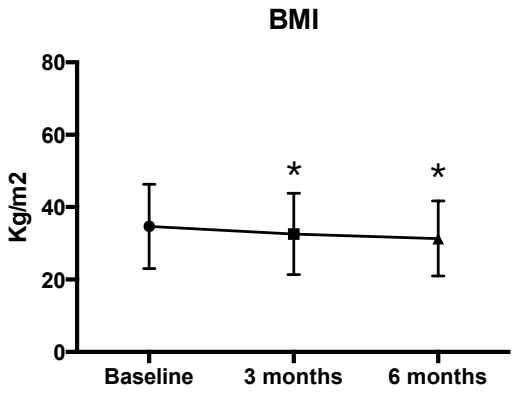
14 pts 600 µg bid
5 pts 900 µg bid

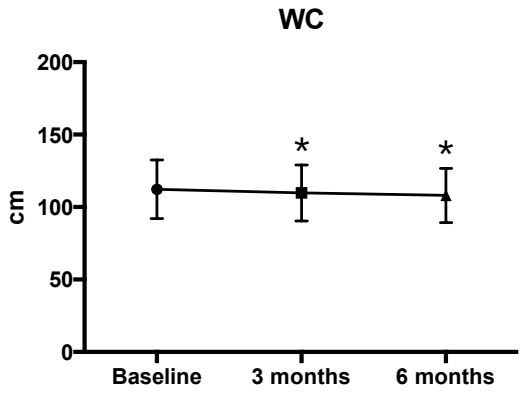


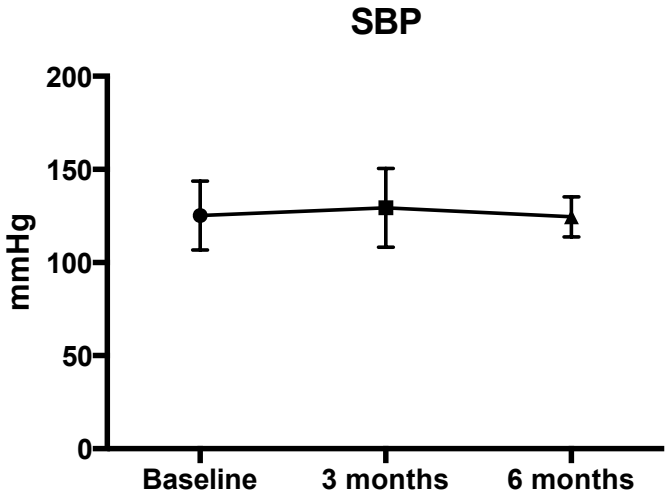


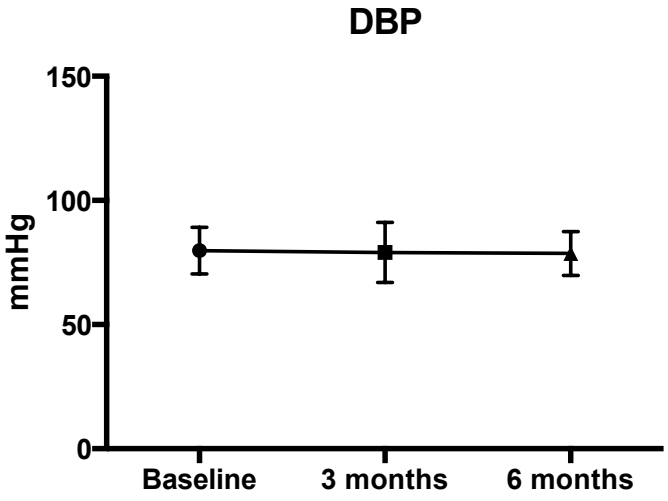
Effect on clinical parameters



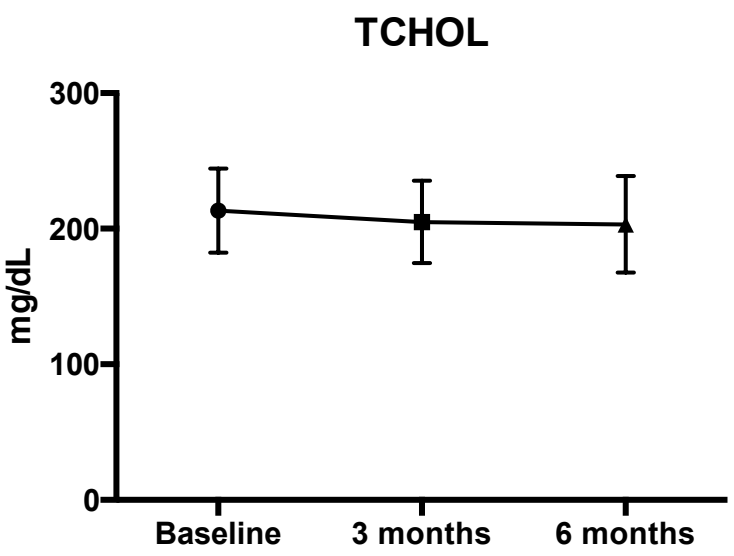


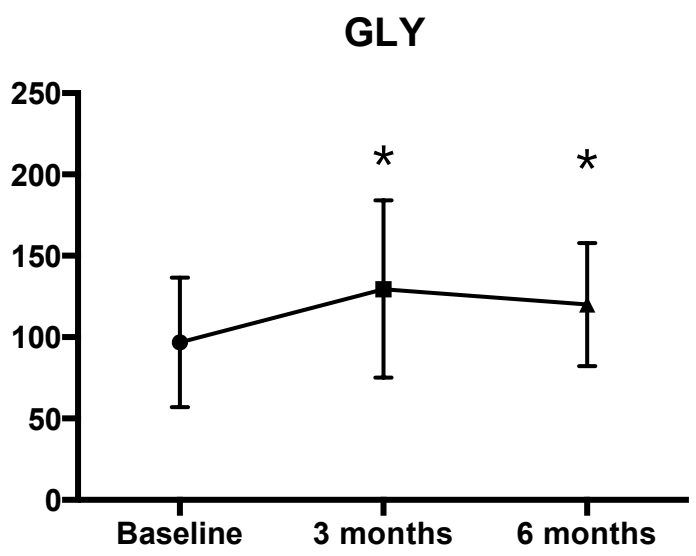


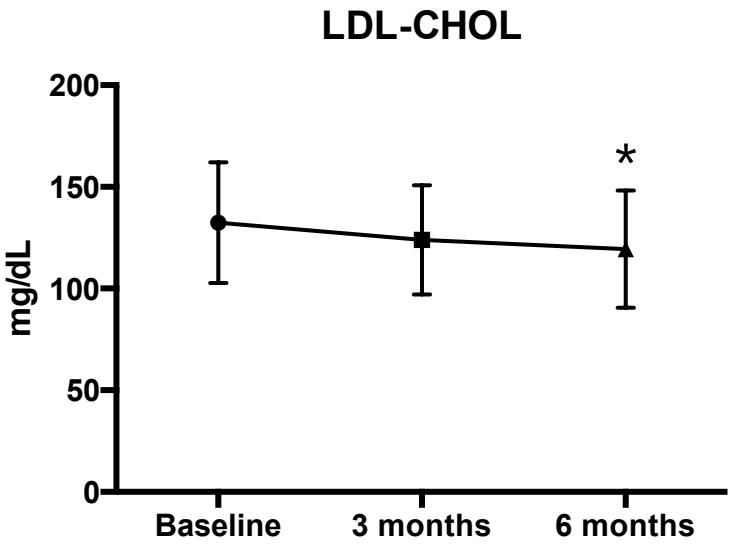


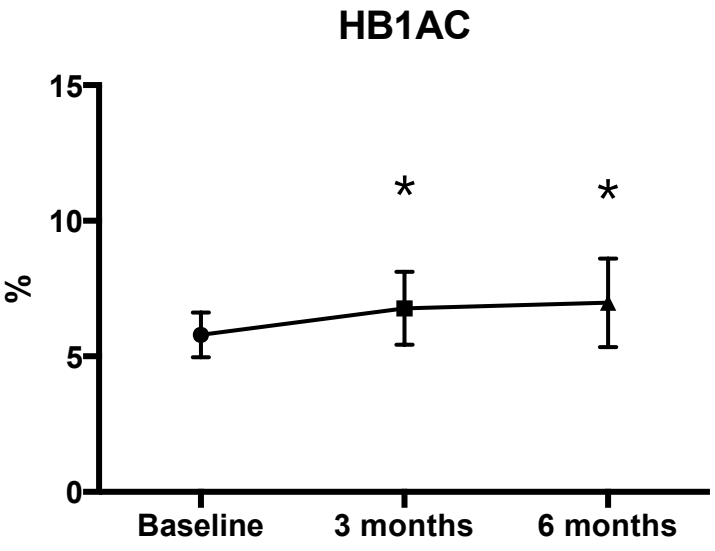


Effect on metabolic parameters









Effect on co-morbidities

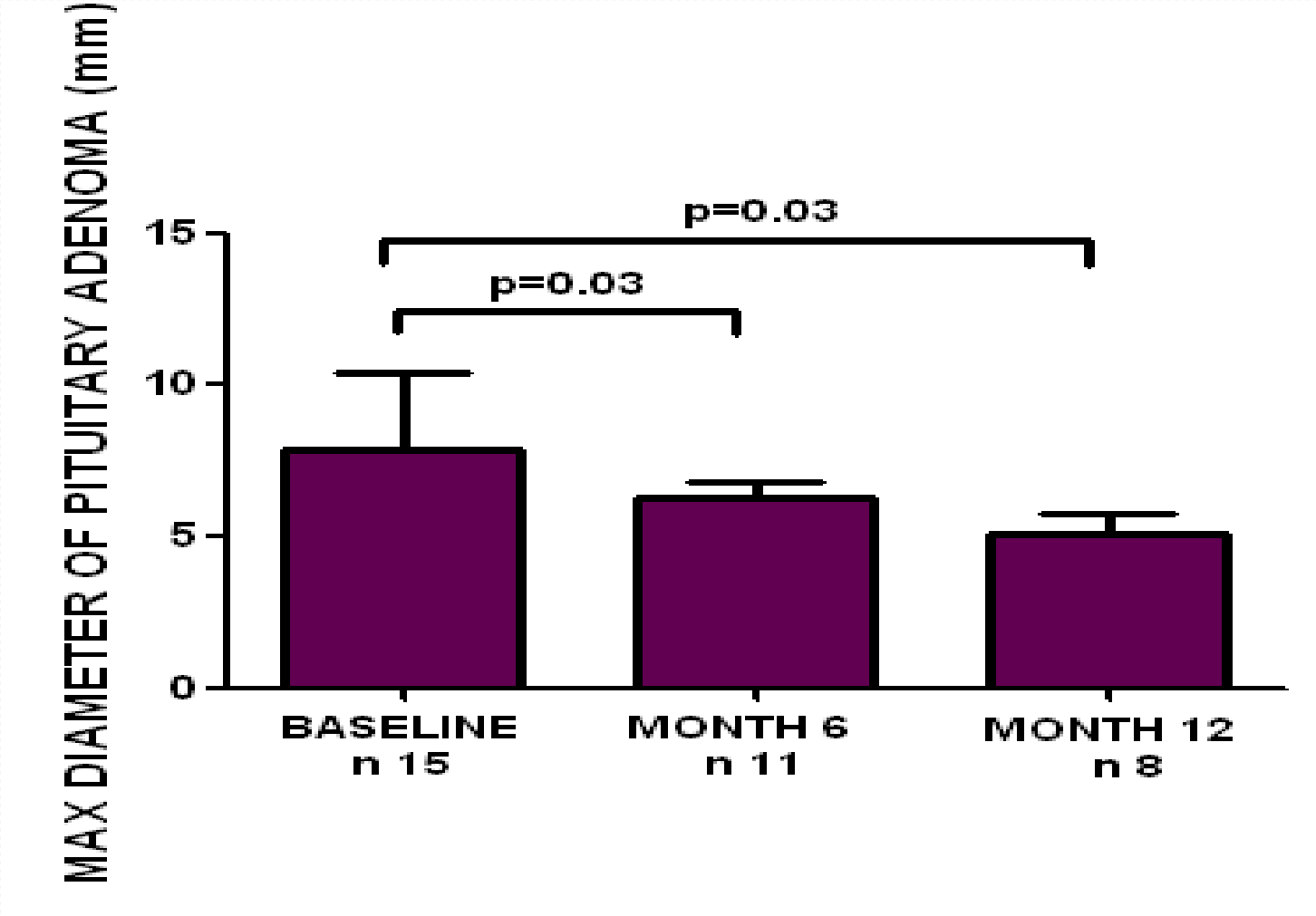
COMORBIDITY	BASELINE (N PTS)	6 MONTHS (N PTS)
OVERWEIGHT/OBESITY	8/15	10/10
HYPERTENSION	16	15 (5*)
HYPERCHOLESTEROLEMIA	12	7
HYPERTRIGLYCERIDEMIA	9	7
IFG/IGT/DIABETES	1/5/9	1/1/19**

* Patients with a reduction of drug number or dose
** Diabetes reversed completely to normal glucose profile in 1 patient

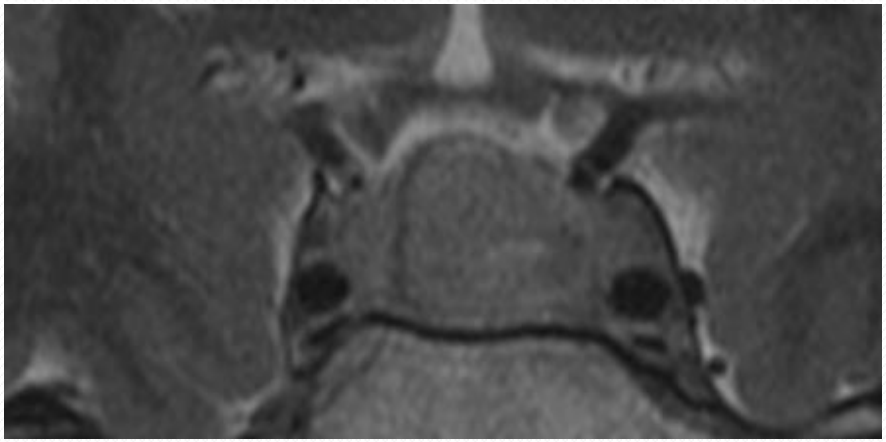
Effect on tumour mass

- At baseline, 6 patients had a macroadenoma and 10 patients had a microadenoma, whereas invisible tumour was documented in the remaining 10 patients
- After 6 months, pituitary MRI was available in 12 patients (3 with macroadenoma, 4 with microadenoma and 5 with invisible tumour)
- In these 12 patients, tumour characteristics were unchanged in 4 cases, whereas a decrease in tumor volume was documented in 5 cases, and a slight enlargement was observed in one case of macroadenoma
- In particular, tumour volume was reduced for 2 macroadenomas (one macroadenoma became a microadenoma), whereas 3 microadenomas at baseline completely disappeared after 6 months of treatment

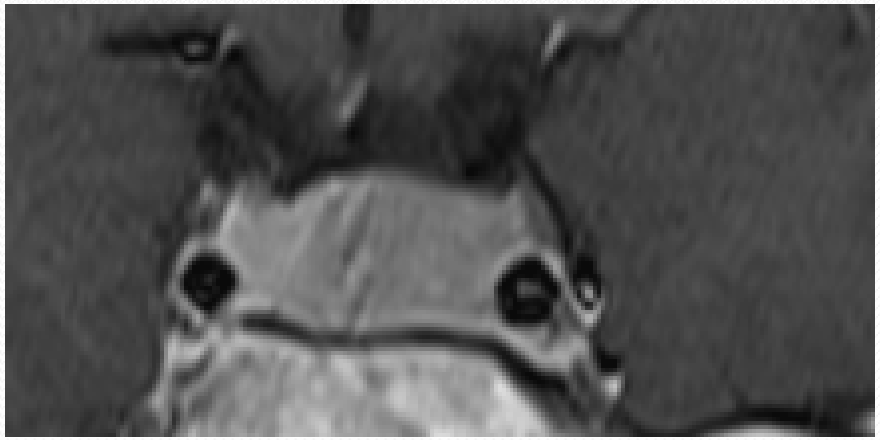
Tumor Size (Naples experience)



A Clinical Case of Shrinkage in patient with Pituitary Macroadenoma



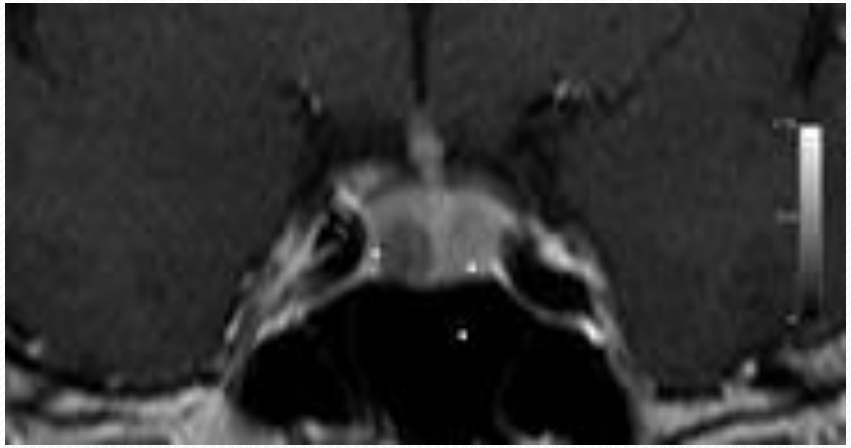
1.Baseline



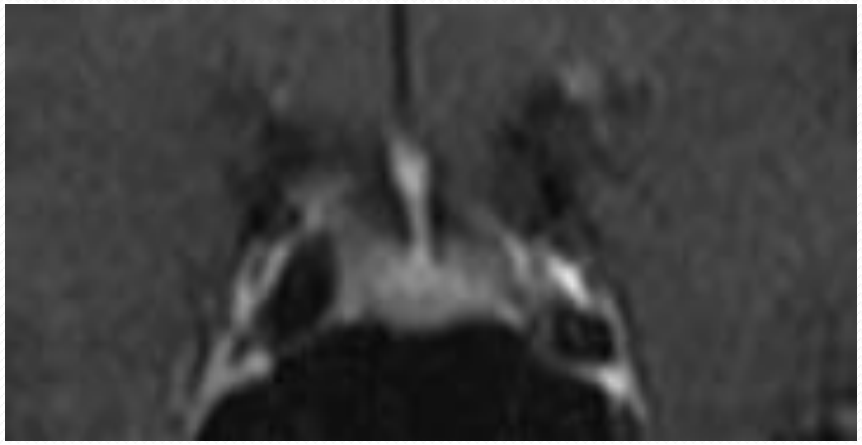
2. After 12 Months

	Baseline	Month 12
Diameters (mm)	15x21x17	10x12x8
Volume (mm3)	2.802,43	502,39

A Clinical Case of Pituitary Microadenoma Disappearance



1.Baseline



2. After 12 Months

	Baseline	Month 12
Diameters (mm)	7x5	0

Registrative study: adverse events

	Overall (N=162)	
AE	**All grades n (%)**	**Grades 3 or 4 n (%)**
Hyperglycemia related	118 (72.8)	40 (24.7)
Diarrhea related	95 (58.6)	5 (3.1)
Nausea related	85 (52.5)	4 (2.5)
Gallbladder and biliary related	54 (33.3)	4 (2.5)
Liver chemistry related	26 (16.0)	7 (4.3)
Bradycardia related	23 (14.2)	3 (1.9)
Hypocortisolism related	13 (8.0)	4 (2.5)
QT prolongation related	13 (8.0)	4 (2.5)
Hypothyroidism related	7 (4.3)	0

Grading (1–4) of AEs follows the US HHS Common Terminology Criteria for Adverse Events (CTCAE) 2009. Common AE terms were pooled, for example, all terms relating to elevations in blood glucose or terms relating to diarrhea

Colao A *et al. N Engl J Med* 2012;366:914–924

Safety

SIDE EFFECTS	32 PTS N (%)
Glucose metabolism disorders	**22 (84.4)**
Worsening of glucose control in pre-existing IGT or DM	15 (46.9)
Hyperglycaemia	12 (37.5)
Gastrointestinal disturbances	**12 (38.7)**
Diarrhea	12 (35.5)
Abdominal Pain	8 (22.6)
Nausea	5 (16.1)
Asthenia and/or Fatigue	6 (18.8)
Colelithiasis	3 (9.4)
Liver damage (increase of liver enzyme)	2 (6.2)
Arthralgias	1 (3.1)

Safety analysis has been performed on the entire cohort of patients (31) followed-up until July 2014

Safety

SIDE EFFECTS	32 PTS N (%)
Glucose metabolism disorders	**27 (84.4)**
Worsening of glucose control in pre-existing IGT or DM	15 (46.9)
Hyperglycaemia	12 (37.5)
Mild disorder	**10 (31.2)**
Worsening of glucose control in pre-existing IGT or DM	5 (15.6)
Hyperglycaemia	5 (15.6)
Starting or modification of antidiabetic treatment	**23 (71.9)**
Good control	15 (65.2*)
Partial control	5 (15.6*)
Bad control	3 (9.4*)

Safety analysis has been performed on the entire cohort of patients (31) followed-up until July 2014

Conclusions

- In a population of patients with mild to moderate Cushing's disease, pasireotide treatment at the median dose of 600 ug twice a day is able to normalize or nearly normalize cortisol secretion in more than 65% of patients
- The normalization of UFC is associated with an improvement of clinical picture especially weight, body mass index, waist circumference, and lipid profile
- Hyperglycemia represents a common side effect, but it is mild in one third, and can be controlled with glucose lowering treatment, in around 70% of cases
- Discontinuation of treatment occurred in 16% of patients for gastrointestinal disturbances (during the early period of treatment) or bad compliance or hyperglycaemia (after 6 months of treatment)

THANKS

Giorgio Arnaldi
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Palermo

Salvo Cannavò
Messina

MANAGEMENT HYPERGLYCEMIA
NAPLES EXPERIENCE

CSOMB2305

1 STEP

METFORMINA

2 STEP

METFORMINA + INSULINA BED-TIME

3 STEP

INSULINA AI PASTI + INSULINA BED-TIME

RWE

1 STEP

METFORMINA

2 STEP

METFORMINA + INCRETINE

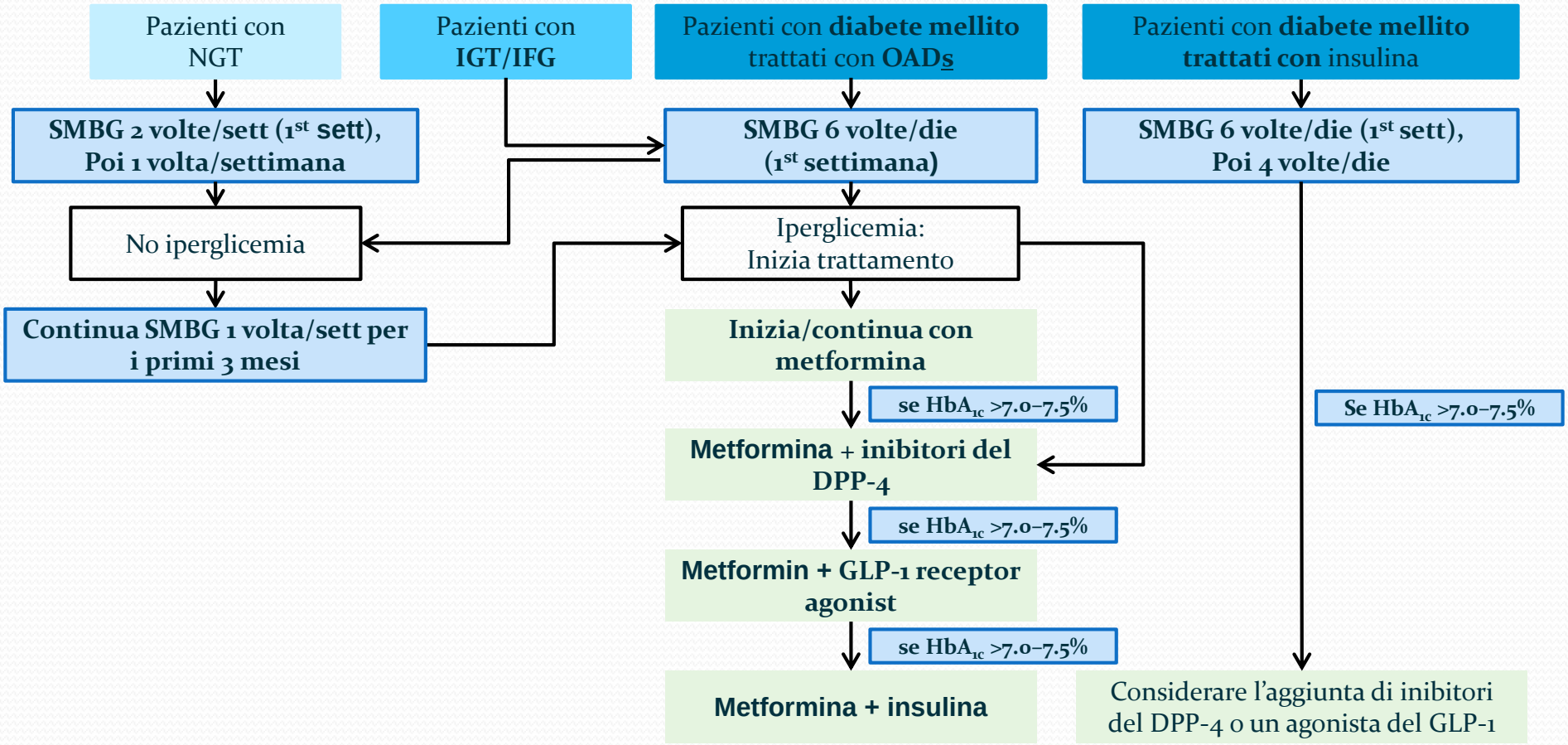
3 STEP

METFORMINA + INCRETINE + INSULINE BED-TIME

4 STEP

AGGIUNTA DI INSULINA AI PASTI

Flow chart to manage hyperglycemia Pasireotide-related in patients with Cushing's disease

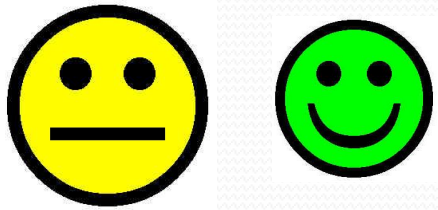


Colao A *et al. Pituitary* 2014;17:132–140

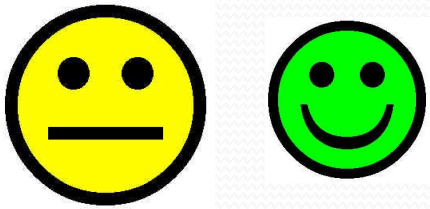
CSOM230B & RWE (NAPLES EXPERIENCE)

Metformina

Metformina +
Insulina basale

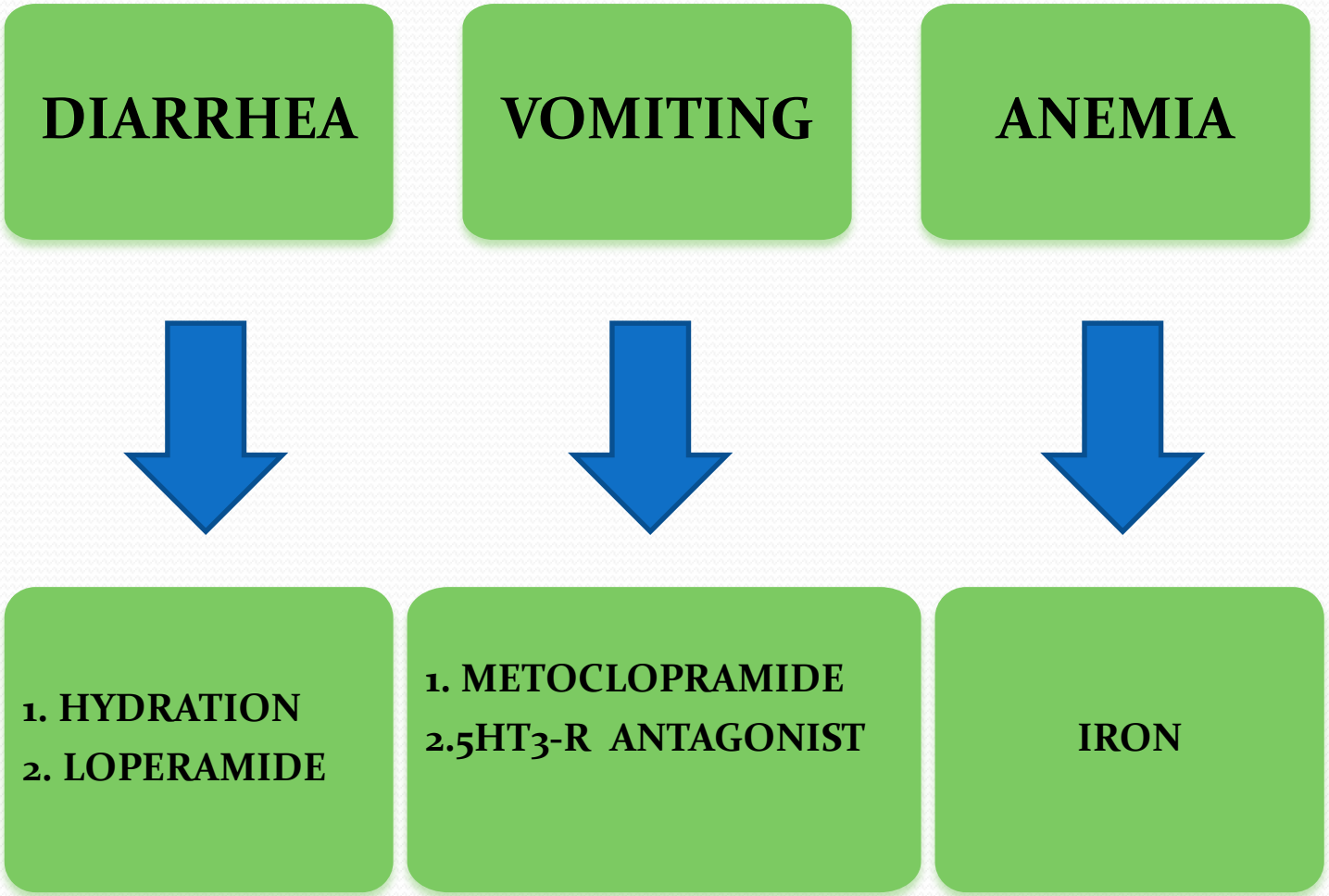


Insulina basale +
Insulina rapida



Metformina +
Liraglutide o Sitagliptin

MANAGEMENT AEs IN CSOM230B



THANKS

Sicurezza del pasireotide a 12 mesi di terapia

	600 µg bid (n=82)	900 µg bid (n=80)	Globale (n=162)
Eventi avversi (AEs), n (%)	80 (97.6)	79 (98.8)	159 (98.1)
AEs farmaco-correlati	79 (96.3)	76 (95.0)	155 (95.7)
Sospensione a causa di AEs	13 (15.9)	15 (18.8)	28 (17.3)
AEs di grado 3 o 4	39 (47.6)	40 (50.0)	79 (48.8)
AEs di particolare interesse, n (%)	79 (96.3)	77 (96.3)	156 (96.3)
Eventi avversi seri (SAEs), n (%)	19 (23.2)	21 (26.3)	40 (24.7)
SAEs farmaco-correlati	7 (8.5)	12 (15.0)	19 (11.7)
Sospensione a causa di SAEs	3 (3.7)	5 (6.3)	8 (4.9)
Morte durante trattamento, n (%)*	0	0	0

Colao A *et al. N Engl J Med* 2012;366:914–924

	Globale (N=162)	
AE	**Tutti i gradi n (%)**	**Gradi 3 o 4 n (%)**
Iperglicemia correlati	118 (72.8)	40 (24.7)
Diarrea correlati	95 (58.6)	5 (3.1)
Nausea correlati	85 (52.5)	4 (2.5)
Colecisti e vie biliari correlati	54 (33.3)	4 (2.5)
Funzione epatica correlati	26 (16.0)	7 (4.3)
Bradicardia correlati	23 (14.2)	3 (1.9)
Ipocortisolismo correlati	13 (8.0)	4 (2.5)
Prolungamento QT correlati	13 (8.0)	4 (2.5)
Ipotiroidismo correlati	7 (4.3)	0

Colao A *et al. N Engl J Med* 2012;366:914–924

Ipocortisolismo

- L'ipocortisolismo rappresenta un rischio di tutte le terapie efficaci per la malattia di Cushing
- No definizione standard di ipocortisolismo; AEs sono stati determinati dall'investigatore
- Tra i pz con UFC≤ULN, 13 hanno avuto AEs ipocortisolismo-correlati, riportati come:
  - Insufficienza surrenalica (n=9)
  - Riduzione del cortisolo ematico (n=1)
  - Riduzione UFC (n=2)
  - Insufficienza surrenalica secondaria (n=1)
- I pz hanno risposto alla riduzione di dose di pasireotide e/o alla supplementazione per breve tempo con steroidi esogeni

ULN, upper limit of normal

Gestione dell'ipocortisolismo

Prima della terapia	**Educare i pazienti sui sintomi: stanchezza, anoressia, nausea, vomito, ipotensione, iperkaliemia, iponatriemia, ipoglicemia**
Durante la terapia	**Monitorare i sintomi, istruire i pazienti a registrare i sintomi**
Gestione	**• Ridurre la dose di pasireotide a 0.3 mg bid** **• Se i sintomi persistono, interrompere o somministrare temporaneamente terapia corticosteroidea sostitutiva**
Dopo la sospensione	**I sintomi dovrebbero rapidamente ridursi dopo la sospensione**

La colecisti e la calcolosi

	Cambiamenti rispetto al baseline all'ultima valutazione, n (%)				
Baseline	**Normale**	**Fango**	**Calcoli**	**Dilatazione dotto biliare**	**No ecografia**
Normale (n=137)	83 (60.6)	9 (6.6)	27 (19.7)	0	18 (13.1)

- L'effetto del pasireotide è paragonabile agli altri analoghi della somatostatina nei soggetti Caucasici
- La maggior parte dei casi sono asintomatici
- Gestione: monitoraggio ecografico della colescisti, considerare l'uso di terapia con acido ursodesossicolico
- Raramente si rende necessaria la colecistectomia

Funzione epatica

- Come gli altri analoghi della somatostatina, c'è stato un lieve, transitorio aumento degli enzimi epatici (~30% dei pazienti)
- Nella maggior parte dei pazienti i livelli enzimatici sono ritornati ai valori di partenza durante il proseguimento della terapia con pasireotide
  - Sei pazienti hanno sopeso a causa dell'aumento degli enzimi epatici
- Non ci sono stati casi di concomitante aumento di AST/ALT >3xULN e bilirubina >2xULN (marker di danno epatico severo)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Gestione delle alterazioni della funzione epatica

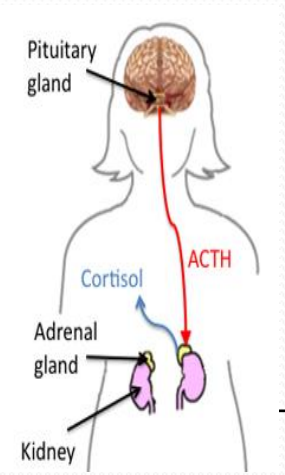
Prima della terapia	**• Monitorare la funzione epatica, valutare possibili interazioni farmacologiche** **• In pz con moderata alterazione della funzione epatica, iniziare pasireotide con 0.3 mg bid fino a un massimo di 0.6 mg bid**
Durante la terapia	**• Monitorare la funzione epatica alle settimane 1, 2, 4, 8 e 12** **• Monitorare frequentemente la funzione epatica in pz con incremento delle transaminasi fino al ritorno ai livelli pre-trattamento**
Gestione	**• Interrompere il trattamento in caso di segni clinici di disfunzione epatica insieme ad un significativo aumento di AST≥5 ULN, ALT≥5 ULN, oppure AST o ALT ≥3 ULN con bilirubina ≥2 ULN**
Dopo la sospensione	**Monitorare fino alla normalizzazione degli enzimi epatici; non riprendere il trattamento**

Ipergicemia

Il Cushing è predisposto alterazioni del metabolismo glicemico

- I livelli di cortisolo cronicamente elevati possono indurre insulino-resistenza ed intolleranza ai carboidrati [1]

Morbidity	Prevalence at diagnosis (%)[1]
Hypertension	**55–85**
Impaired glucose tolerance	**21.3–64**
Diabetes mellitus	**20–36**
Overweight (BMI 25–30)	**21–48**
Obese (BMI >30)	**32–41**
Hyperlipidaemia	**37.5–71.4**



- In B2305, 34% dei pazienti aveva diabete mellito prima del trattamento[2]
  - 24% aveva prediabete in basale

1. Feelders R et al. ENEA Cushing's Syndrome Workshop, Naples, Italy, December 2009
2. Colao A et al. N Engl J Med 2012;366:914–924

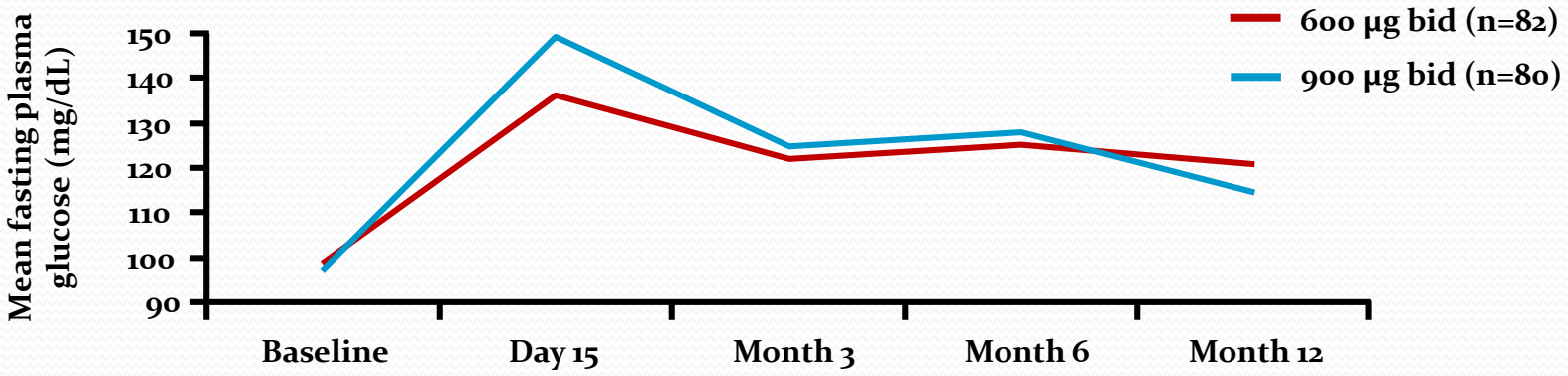
Ruolo della somatostatina nell'omeostasi glucidica

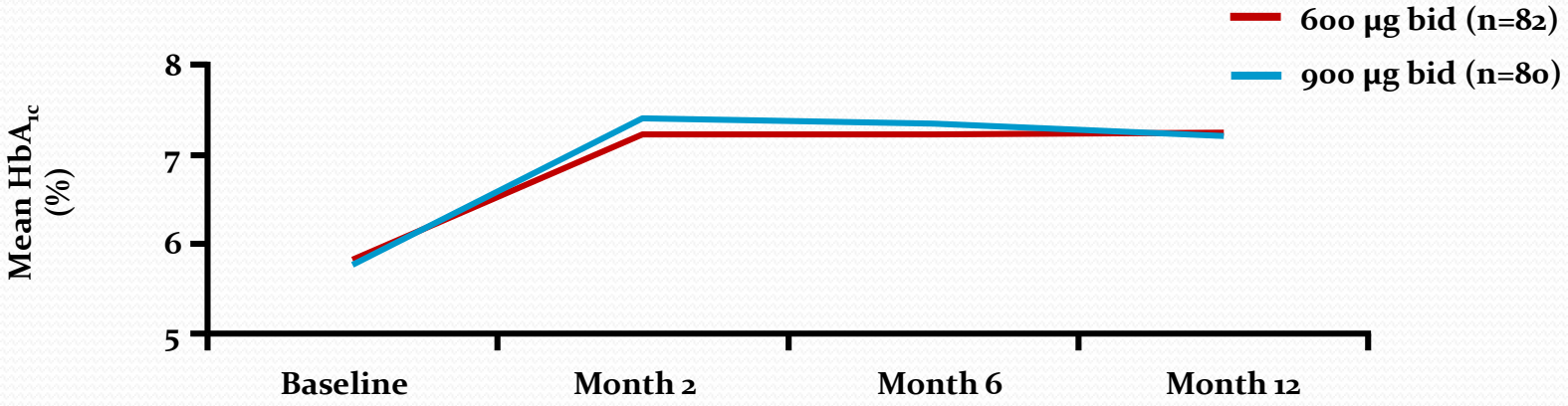
La somatostatina è un inibitore della secrezione sia di insulina che di glucagone[a]

	Somatostatin Receptors	
	sst_2	sst_5
sst expression in human pancreatic β-cells[b]	++	+++
sst expression in human pancreatic α-cells[b]	+++	+
Receptor binding affinity		
Pasireotide[c]	++	+++
Octreotide[c]	+++	+
Inhibition of insulin[d,e]	✓	✓
Inhibition of glucagon[f]	✓	

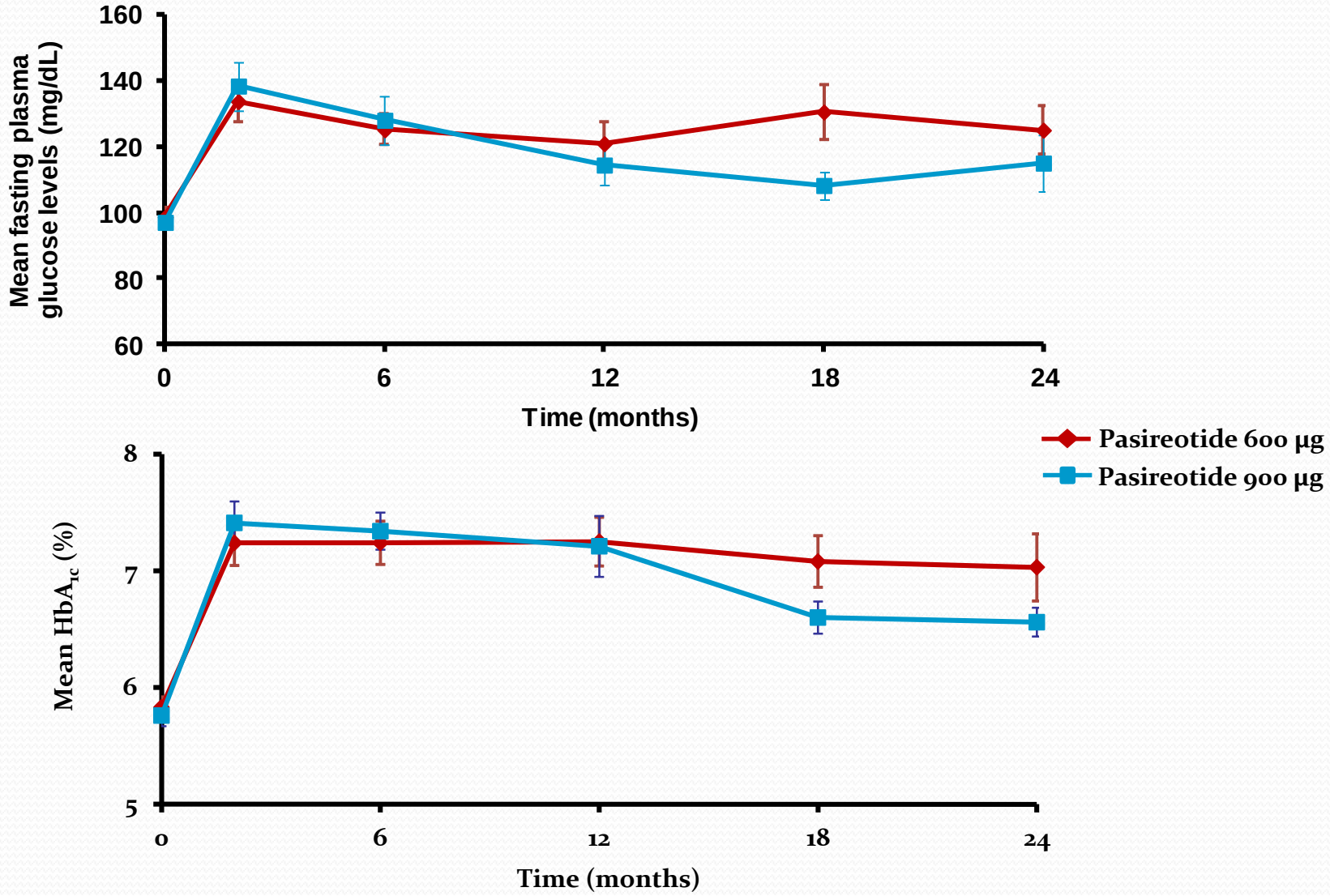
[a] Hauge-Evans AC, et al. *Diabetes.* 2009;58(2):403-411; [b] Kumar U, et al. *Diabetes*. 1999;48(1):77-85; [c] Adapted from Bruns C, et al. *Eur J Endocrinol*. 2002;146(5):707-716; [d] Zambre Y, et al. *Biochem Pharmacol.* 1999;57(10):1159-1164; [e] Singh V, et al. J *Clin Endocrinol Metab.* 2007;92(2):673-680; [f] Patel YC. *Front Neuroendocrinol.* 1999;20(3):157-198.

Cambiamenti nella glicemia

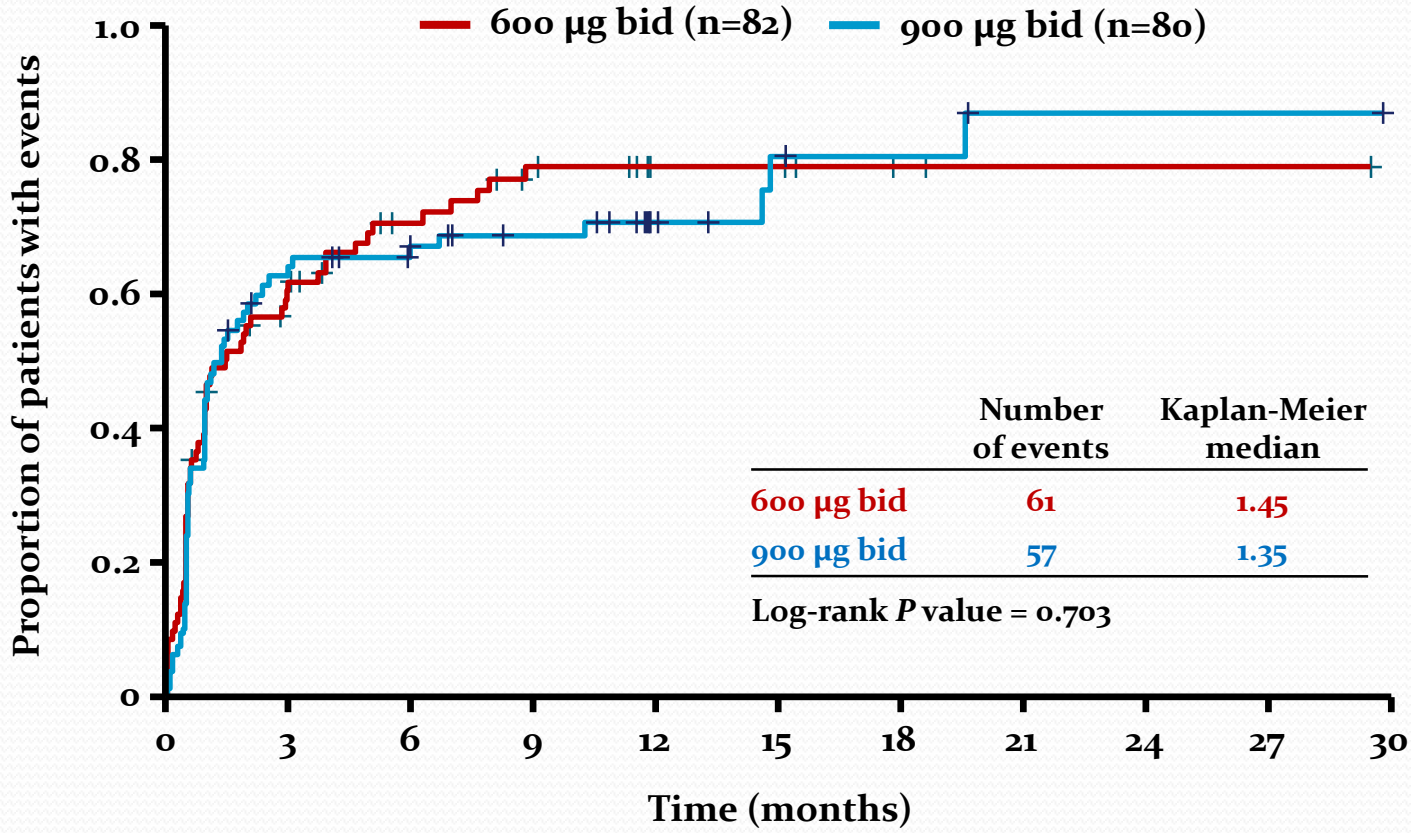




La glicemia è rimasta stabile al mese 24



Tempo al primo AE iperglicemia-correlato



Cambiamenti nella terapia antidiabetica

- Al mese 12, la terapia antidiabetica è stata iniziata in 74 su 162 pz
  - 41% di pz (53/129) che non assumeva terapia ipoglicemizzante al baseline ha iniziato ≥1 farmaco antidiabetico
  - 64% di pz (21/33) che assumeva terapia ipoglicemizzante al baseline ha assunto ≥1 terapia addizionale
- Tra i pz nei quali la terapia ipoglicemizzante è stata iniziata durante lo studio, sono state osservate riduzioni nella glicemia a digiuno media
  - 166.2 a 121.5 mg/dL (9.2 to 6.7 mmol/L) nel gruppo 600 µg
  - 159.4 a 133.8 mg/dL (8.9 to 7.4 mmol/L) nel gruppo 900 µg

Cambiamenti nello stato diabetico rispetto al baseline

	Cambiamenti rispetto al baseline all'ultima valutazione, n (%)			
Baseline	**Normali**	**Pre-diabetici**	**Diabetici**	**Mancanti**
Normali (n=67)	14 (21)	29 (43)	23 (34)	1 (1.5)
Pre-diabetici (n=39)	1 (3)	9 (23)	28 (72)	1 (3)
Diabetici (n=55)	1 (2)	6 (11)	47 (85)	1 (2)
Mancanti (n=1)	1 (100)	0	0	0

Pazienti pre-diabetici avevano un rischio maggiore di sviluppare diabete

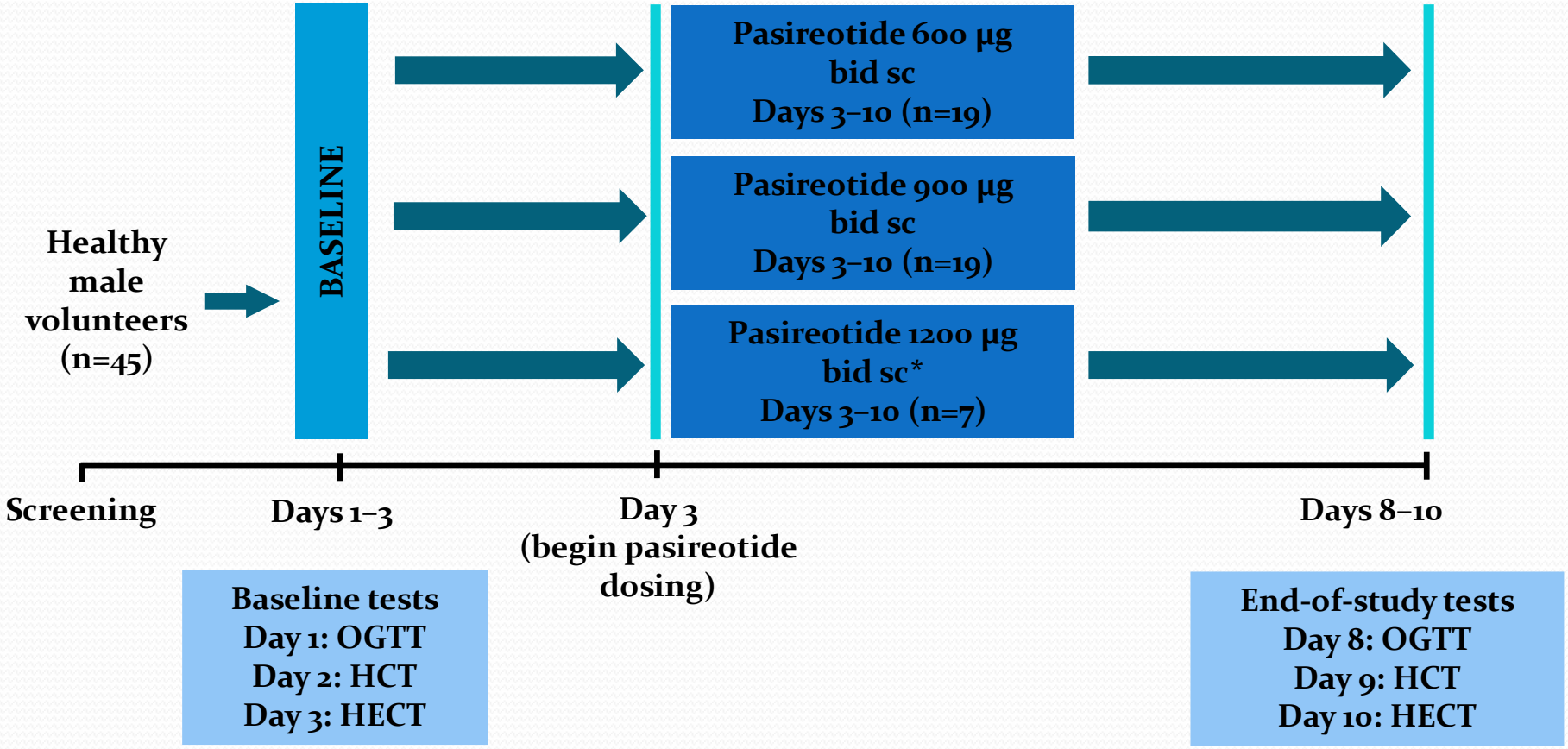
Valutazione dei meccanismi sottostanti l'iperglicemia da pasireotide

- Sono stati condotti due studi per valutare I meccanismi responsabili dell'iperglicemia da pasireotide

SOM230B2216: Studio in doppio-cieco, randomizzato, singolo-centro in volontari maschi sani per valutare il meccanismo responsabile dell'iperglicemia da pasireotide

SOM230B2124: Studio randomizzato, aperto, singolo-centro per valutare l'effetto della co-somministrazione di farmaci antidiabetici e pasireotide, rispetto al pasireotide da solo, sul metabolismo glucidico in volontari maschi sani

SOM230B2216: Disegno di studio



*1200 µg bid sc arm was closed due to AEs of nausea and vomiting
OGTT, oral glucose tolerance test; HECT, hyperinsulinemic-euglycemic clamp test; HGCT, hyperglycemic clamp test

Henry RR *et al.* ENDO 2011;abst P3-274

Analisi meccanicistica del metabolismo glucidico

Oral glucose tolerance test (OGTT)

- Test standard per confermare glicemia normale e misurare i parametri dell'assorbimento glicemico e della secrezione insulinica
- Dosaggio della glicemia per 3 ore dopo aver bevuto un liquido contenente 75 g di glucosio

Clamp iperglicemico in due tempi (HCT)

- Quantificare la secrezione insulinica
- Seguito da un test all'arginina (5 g iv) per la valutazione acuta, massimale della risposta insulinica

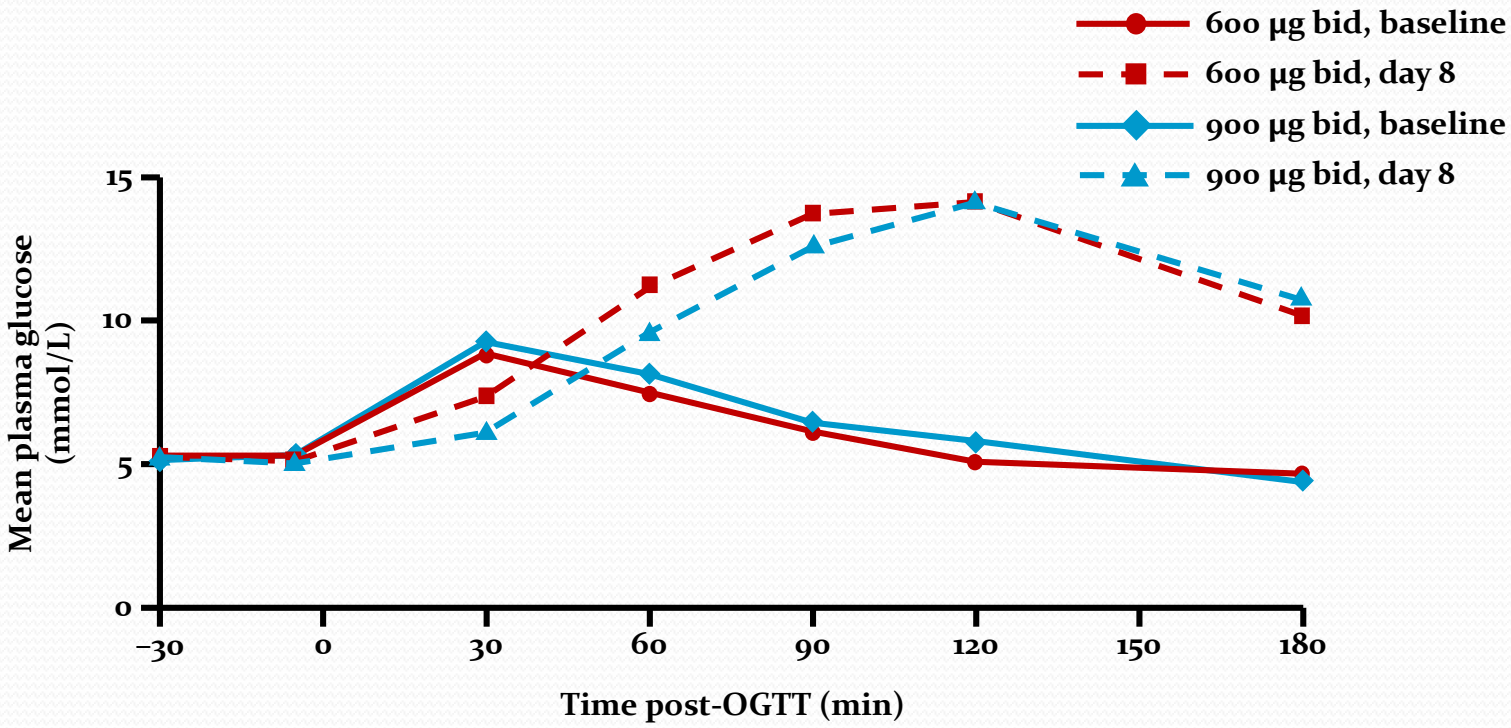
Clamp iperinsulinemico euglicemico in due tempi (HECT)

- Misura dell'insulino-sensibilità (o resistenza) dei tessuti

OGTT: Il pasireotide aumenta la glicemia plasmatica postprandiale

Glucosio

$AUC_{30–180min}$ e $AUC_{0–180min}$ significativamente più alta al giorno 8 che al baseline ($P<0.001$) in entrambi i gruppi

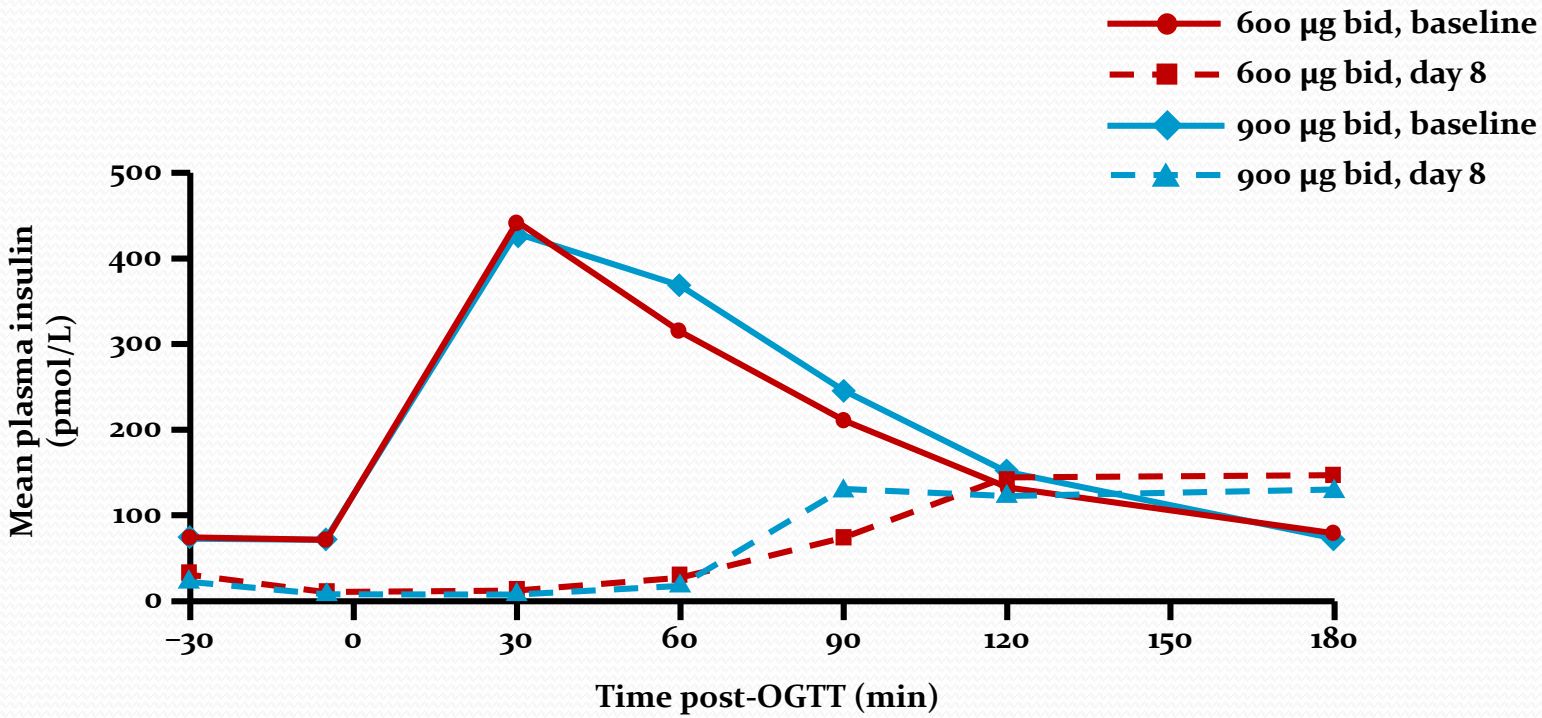


Henry RR *et al.* ENDO 2011;abst P3-274

OGTT: Il pasireotide riduce l'insulina plasmatica postprandiale

Insulin

$AUC_{0–30min}$, $AUC_{30–180min}$ e $AUC_{0–180min}$ significativamente più basse al giorno 8 che al baseline (*P*<0.001) in entrambi i gruppi



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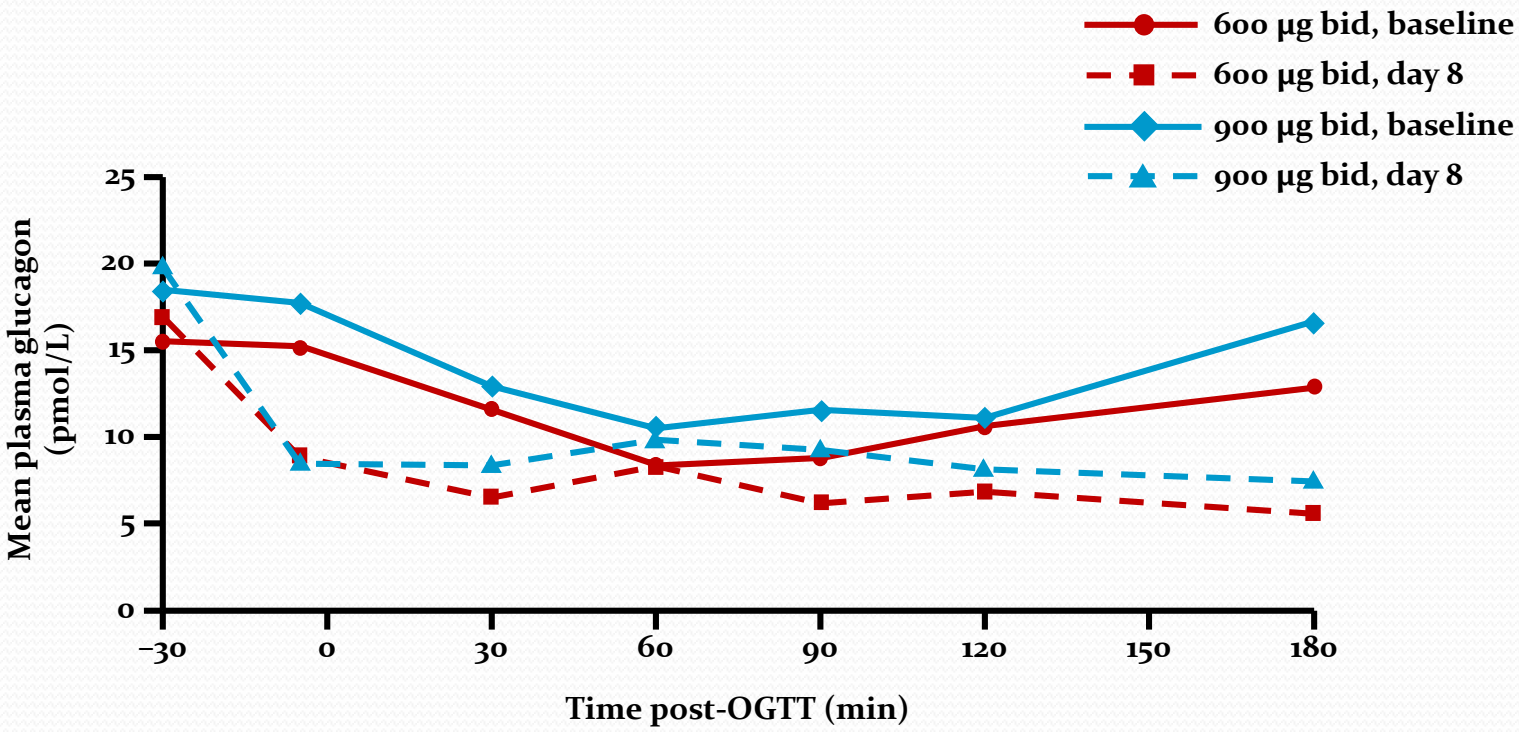
OGTT: Il pasireotide riduce il glucagone plasmatico postprandiale

Glucagone

$AUC_{0–30min}$, $AUC_{30–180min}$ e $AUC_{0–180min}$ significativamente più basse al giorno 8 che al baseline ($P<0.001$) in entrambi i gruppi



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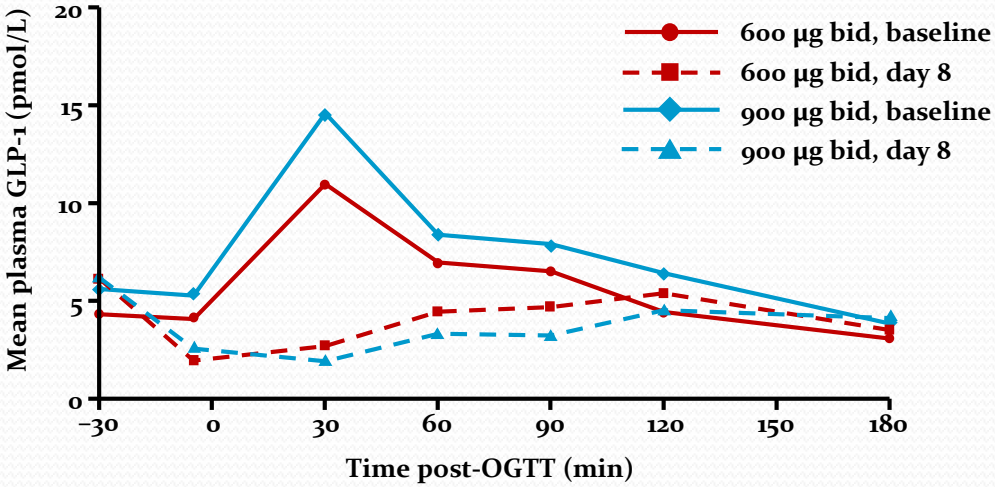
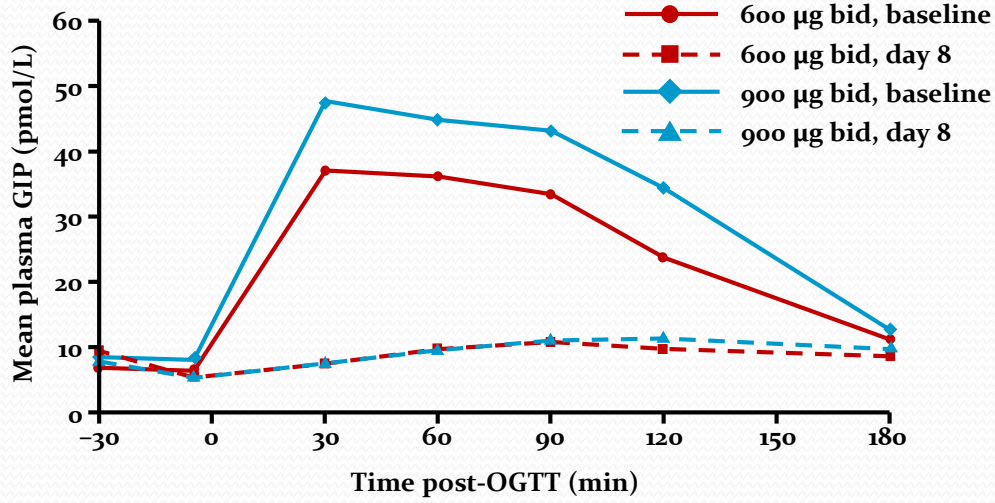
OGTT: Il pasireotide riduce GLP-1 e GIP postprandiali



GLP-1

$AUC_{0–30min}$ e $AUC_{0–180min}$ significativamente più basse al giorno 8 che al baseline nel gruppo 600 µg

$AUC_{0–30min}$, $AUC_{30–180min}$ e $AUC_{0–180min}$ significativamente più basse al giorno 8 che al baseline nel gruppo 900 µg



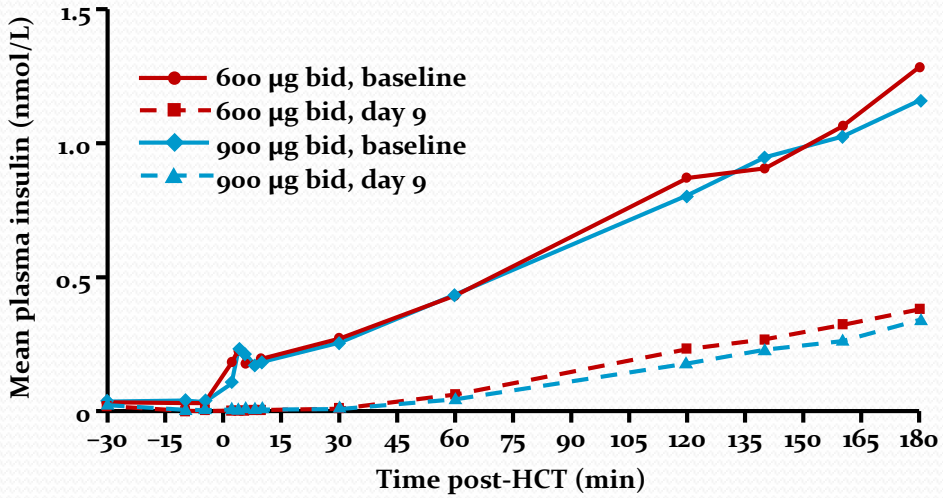
GIP

$AUC_{0–30min}$, $AUC_{30–180min}$ e $AUC_{0–180min}$ significativamente più basse al giorno 8 che al baseline in entrambi i gruppi

Henry RR *et al.* ENDO 2011;abst P3-274

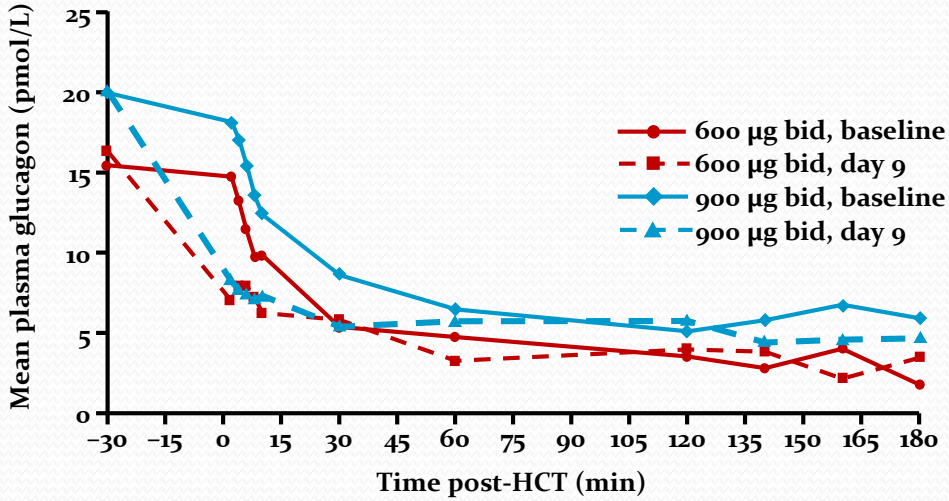
GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1

HCT: Il pasireotide riduce l'insulina plasmatica con minimi cambiamenti nel glucagone plasmatico



Insulina

Riduzione in $AUC_{0–10min}$, $AUC_{10–180min}$ e $AUC_{0–180min}$ tra baseline e il giorno 9 significative in entrambi i gruppi ($P<0.001$)

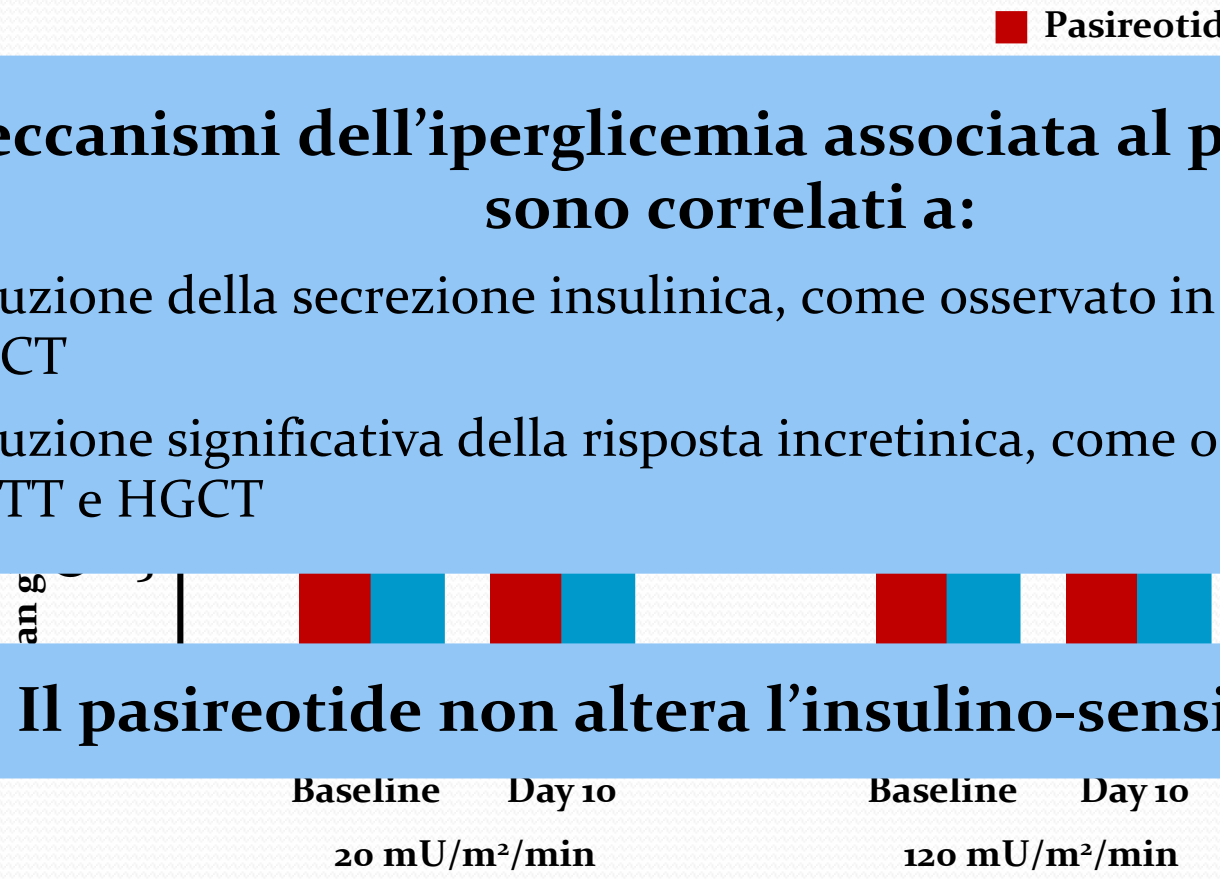


Glucagone

Minimi effetti del pasireotide sulla secrezione di glucagone

Henry RR *et al.* ENDO 2011;abst P3-274

HECT: Il pasireotide non altera l'insulino-sensibilità



I meccanismi dell'iperglicemia associata al pasireotide sono correlati a:

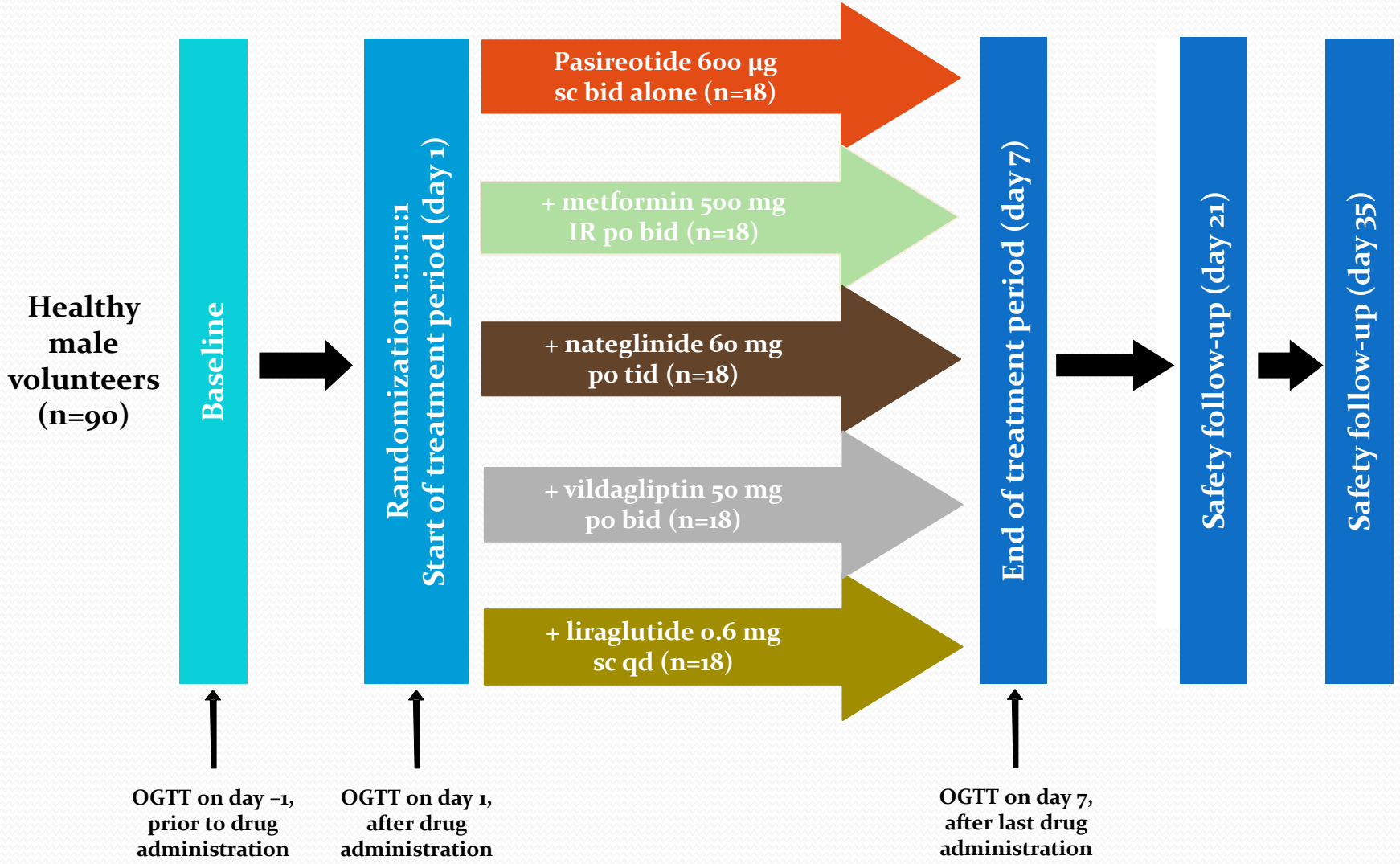
- Riduzione della secrezione insulinica, come osservato in OGTT e HCT
- Riduzione significativa della risposta incretinica, come osservato in OGTT e HGCT

Il pasireotide non altera l'insulino-sensibilità

Henry RR *et al.* ENDO 2011;abst P3-274

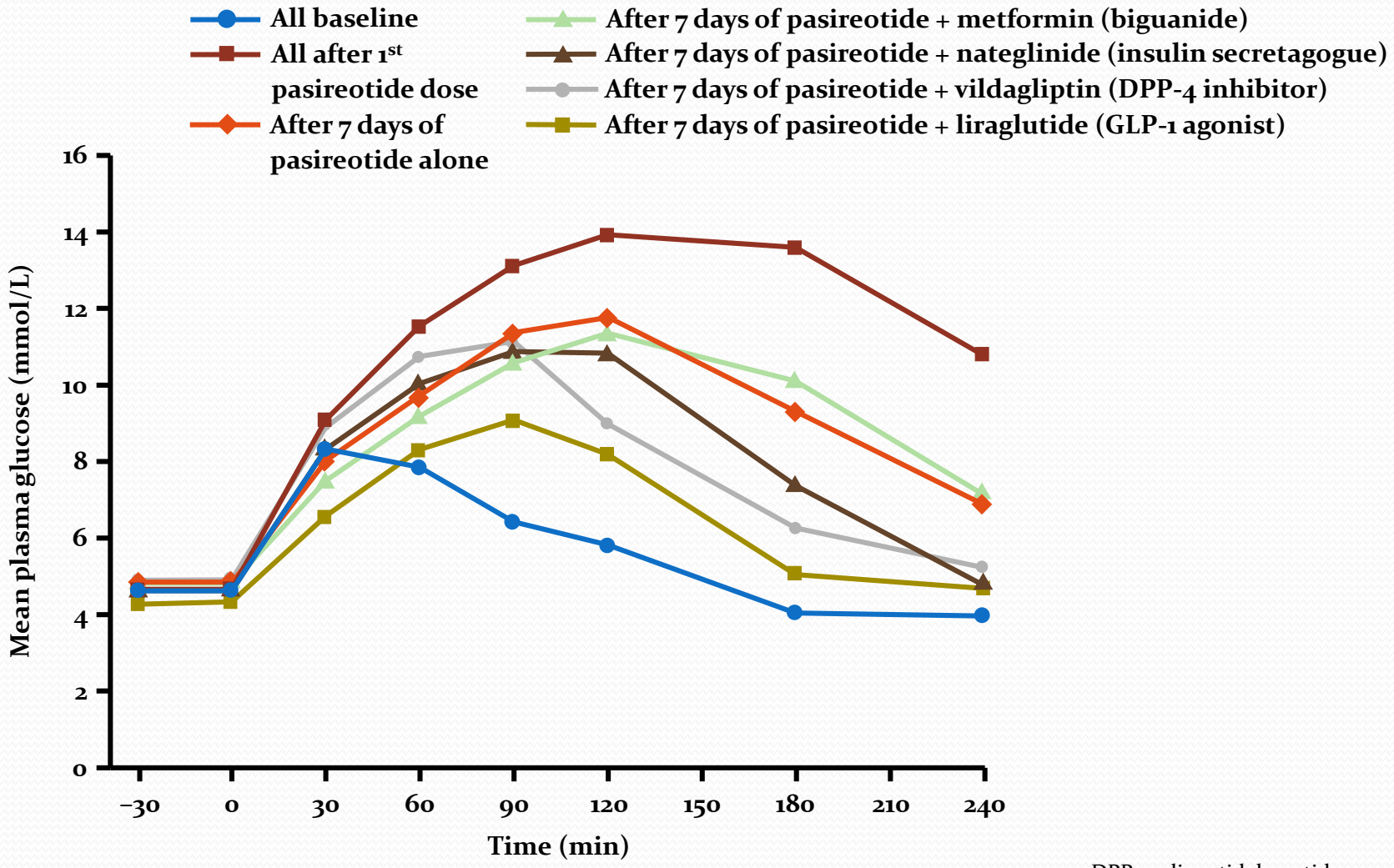
SOM230B2124: Disegno di studio

Management dell'iperglicemia



Henry RR *et al.* ENDO 2011;abst P3-274

Cambiamenti nei livelli glicemici durante OGTT



Henry RR *et al.* ENDO 2011;abst P3-274

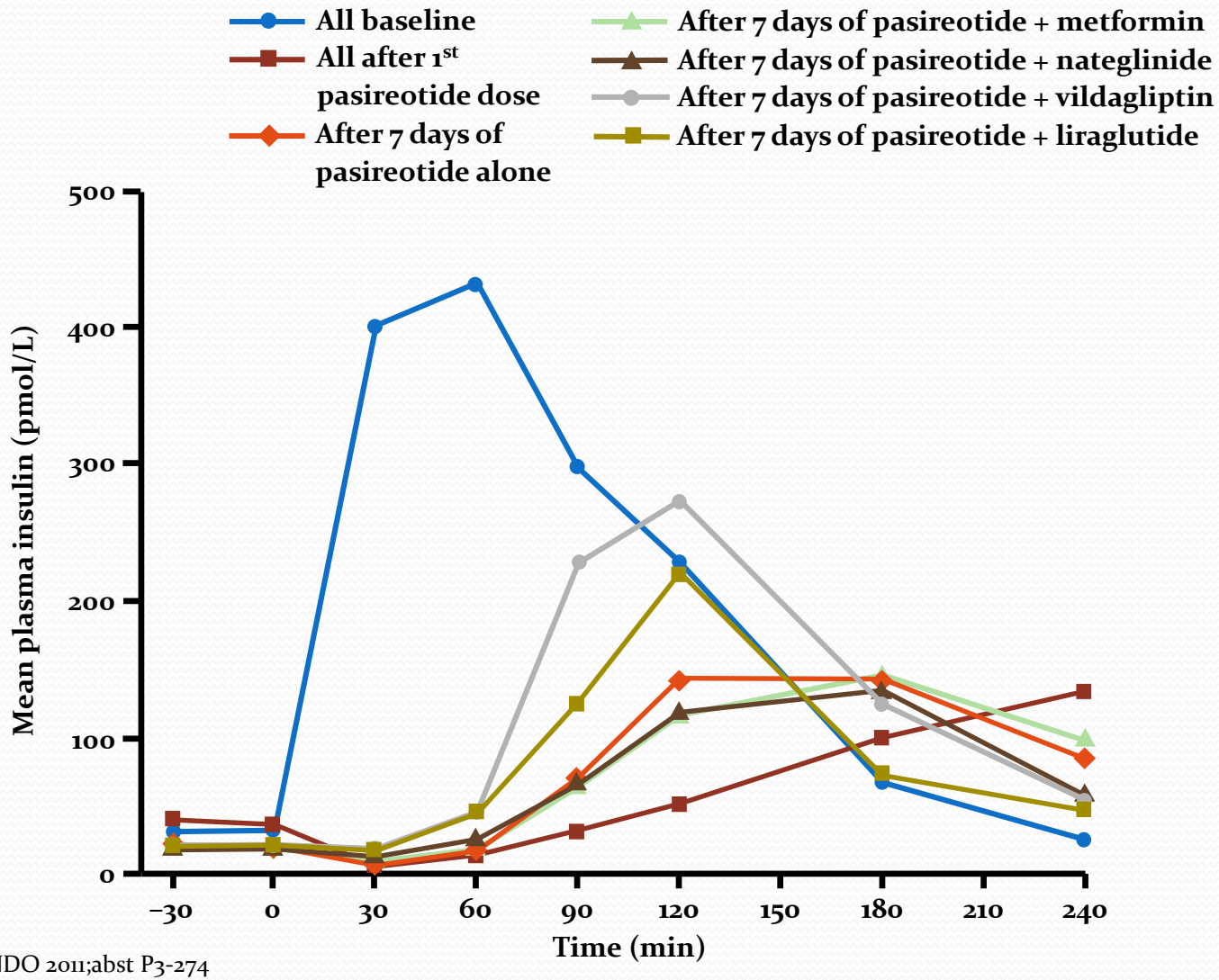
DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide-1

$AUC_{0–4h}$ della glicemia

- La glicemia si riduce dopo 7 giorni di trattamento, rispetto al pasireotide da solo:
  - 29% con liraglutide
    (geometric mean ratio 0.71; 90% CI 0.66, 0.76)
  - 15% con vildagliptin
    (geometric mean ratio 0.85; 90% CI 0.79, 0.91)
  - 10% con nateglinide
    (geometric mean ratio 0.90; 90% CI 0.83, 0.96)
  - 2% con metformina
    (geometric mean ratio 0.98; 90% CI 0.91, 1.05)

Henry RR *et al.* ENDO 2011;abst P3-274

Cambiamenti nei livelli insulinici durante OGTT



Henry RR *et al.* ENDO 2011;abst P3-274

$AUC_{0–4h}$ di insulina sierica

- L'insulina sierica dopo 7 giorni di trattamento, rispetto al pasireotide da solo:
  - 71% con vildagliptin
    (geometric mean ratio 1.71; 90% CI 1.33, 2.19)

Agonisti del GLP-1 ed inibitori del DPP-4 sembrano essere i farmaci più efficaci nel miglioramento dell'iperglicemia associata al trattamento con pasireotide

  - 6% con metformin
    (geometric mean ratio 1.06; 90% CI 0.82, 1.36)
  - 3% con nateglinide
    (geometric mean ratio 1.03; 90% CI 0.80, 1.32)

Henry RR *et al.* ENDO 2011;abst P3-274

SOM230B2124: Sicurezza/tollerabilità

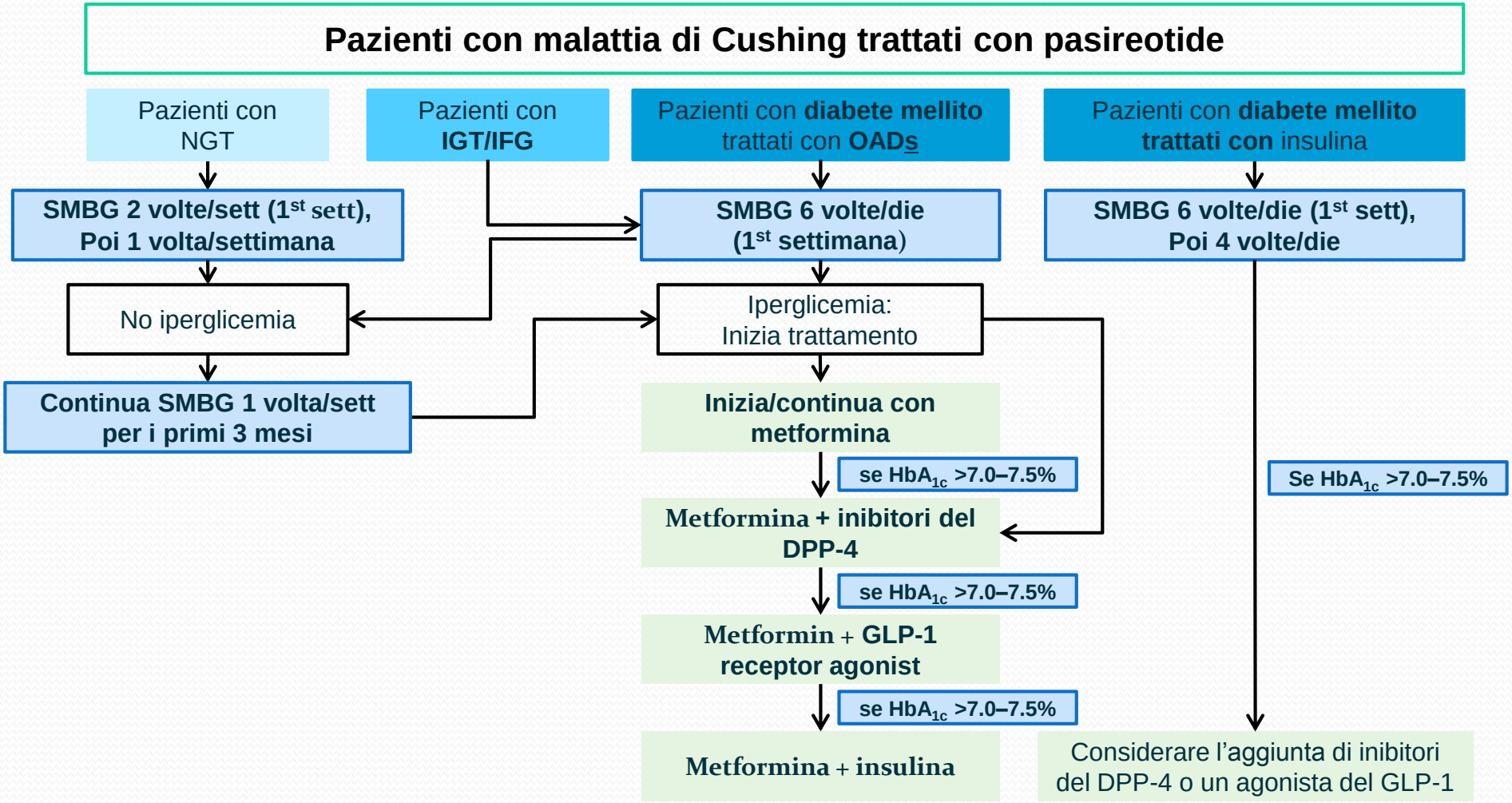
Eventi avversi si osservano più frequentemente che con il pasireotide da solo

Liraglutide	Nateglinide	Metfomina	Vildagliptin
Appetito ridotto (38.9%)	Nausea (83.3%)	Diarrea (77.8%)	Distensione addominale (22.2%)
Fatica (22.2%)	Ipoglicemia (66.7%)		
Mal di testa (27.8%)			
Colestasi SAE (5.6%)			

Globalmente, AEs sono stati coerenti con il profilo di sicurezza del pasireotide e dei farmaci antidiabetici utilizzati

Henry RR *et al.* ENDO 2011;abst P3-274

Raccomandazioni dell'advisory board europeo per la gestione dell'iperglicemia da pasireotide in pz con malattia di Cushing



Colao A *et al. Pituitary* 2014;17:132–140

Hyperglycemia Key Message Flow to Address Customer Information Need

Physicians Questions	Key Messages
Who is more likely to develop hyperglycemia?	▪ Patients with prediabetes and diabetes mellitus at baseline had a greater risk for increased glucose and HbA_{1c} levels
When is it likely to occur?	▪ Hyperglycemia may appear shortly after treatment initiation
Why does it happen?	▪ Pasireotide reduces insulin secretion without affecting insulin sensitivity
What steps do I need to take to manage it?	▪ Correct management of hyperglycemia should include:* • Regular monitoring of blood glucose levels • Proactive approach of an antidiabetic treatment initiation or adjustment ▪ Primary medical therapy might include* • DPP-IV inhibitors (eg, vildagliptin) • GLP-1 agonists (eg, liraglutide) • Insulin secretagogues (eg, nateglinide) secondary option

*Following current treatment guidelines

Summary: Pasireotide safety profile

- Safety of pasireotide was similar to that of other somatostatin analogues, except for the degree of hyperglycemia
  - Most frequently reported AEs were gastrointestinal
  - 11.7% of patients had ≥1 serious AE suspected to be study drug related
- As expected with an effective treatment for Cushing's disease, some patients (8%) experienced hypocortisolism
  - Responded to dose reduction and/or temporary corticosteroid substitution
- 72.8% of patients had at least one hyperglycemia-related AE
  - 6% of patients discontinued treatment because of a hyperglycemia-related AE during the core study
- No new safety issues were identified up to the 24-month data cut-off
  - No deaths were reported during the entire study

Colao A *et al. N Engl J Med* 2012;366:914–924

Summary: Mechanism and management of hyperglycemia

- The mechanisms of hyperglycemia seen with pasireotide sc at doses of 600 and 900 µg bid are related to:
  - Decreases in insulin secretion, as observed following OGTT and HGCT
  - Significantly decreased incretin response, as observed following OGTT and HGCT
- Pasireotide does not affect insulin sensitivity
- GLP-1 agonists and DPP-4 inhibitors appear to be the most effective drugs for ameliorating hyperglycemia associated with pasireotide treatment
- Despite a lack of efficacy in healthy volunteers, metformin may provide clinical benefit in patients with Cushing's disease who often present with underlying insulin resistance and β-cell dysfunction
- Hyperglycemia during treatment with pasireotide may be effectively managed by early intervention and regular (self-) monitoring of blood glucose levels

Henry RR *et al.* ENDO 2011;abst P3-274