Altogether
to Beat
Cushing's
Syndrome

ABC

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING

seconda edizione

Capri \ 15-18 maggio 2013
Certosa di San Giacomo
Hotel della Piccola Marina

LA TERAPIA

moderatore **Marco Boscaro**

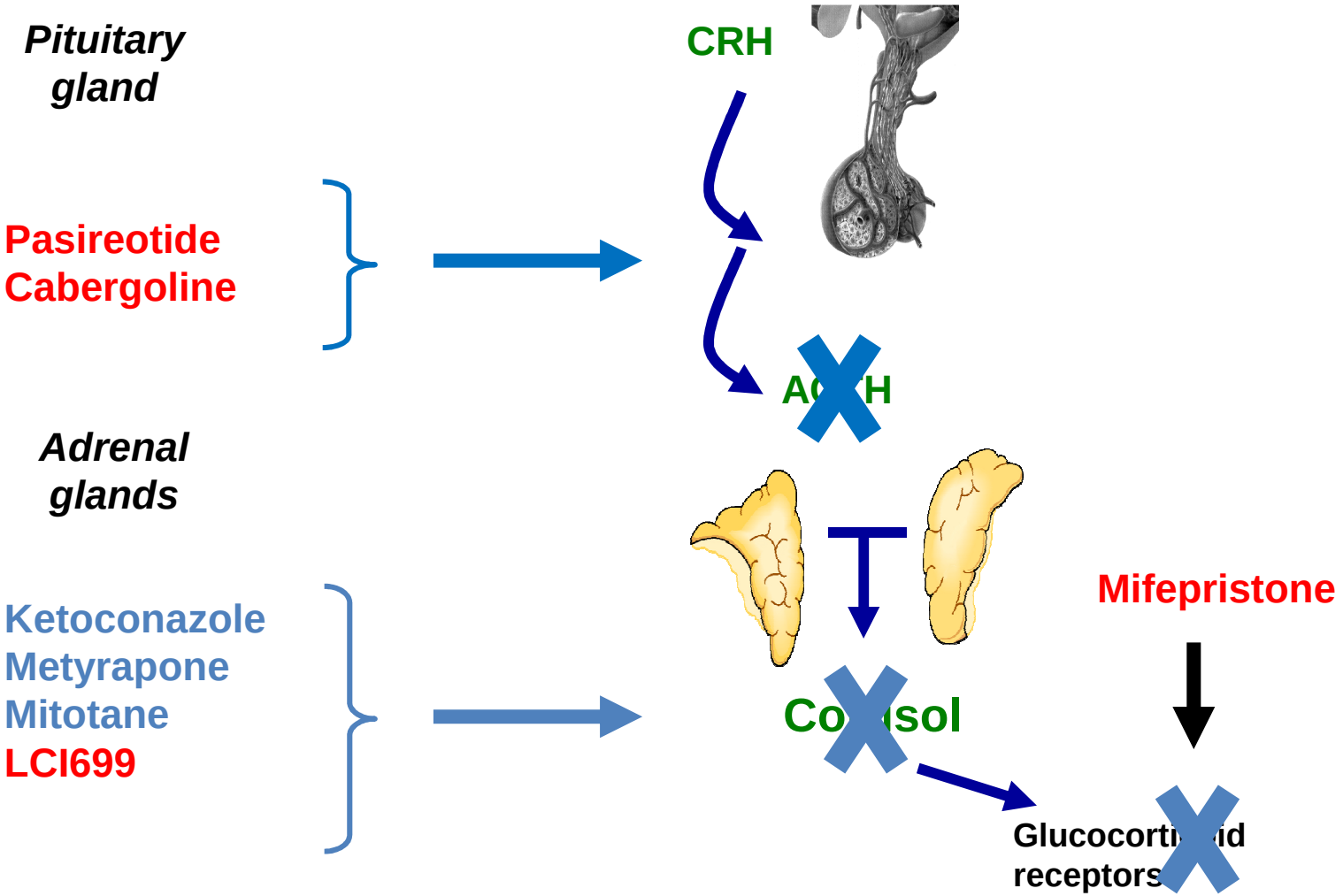
IL PASIREOTIDE: PROSPETTIVE FUTURE

Rosario Pivonello

Medical Therapy: Indications

- Severe complications of hypercortisolism
- Pre-treatment before pituitary surgery
- Post-treatment after unsuccessful surgery
- Bridging therapy before, during and after pituitary radiation
- Primary medical therapy (contraindications for surgery or refusal of surgery)

Potential Targets for Medical Therapy in Cushing's Disease

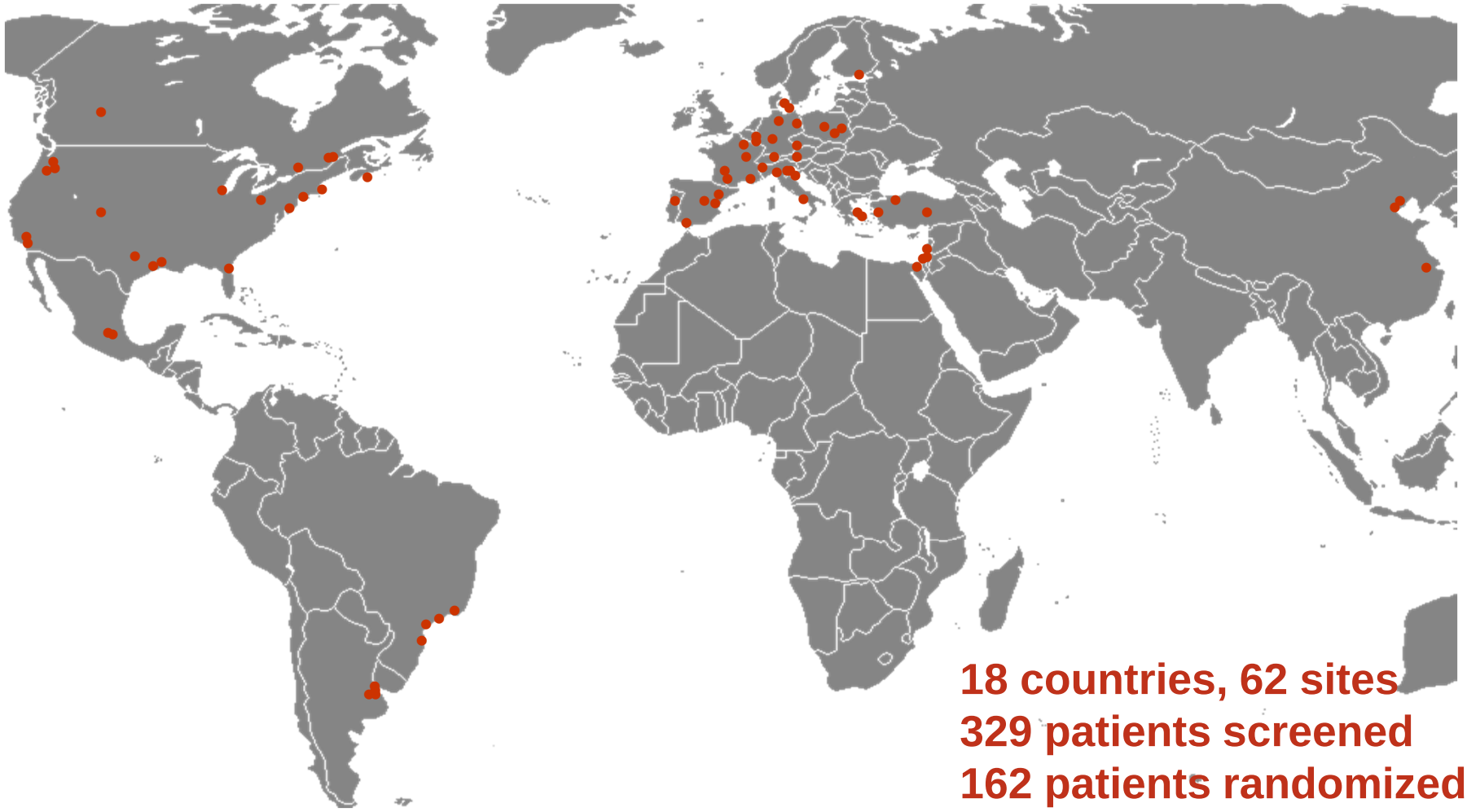


The use of pasireotide: rationale

- Limited number of effective medical therapies available and none licenced for CD
- Pasireotide
  - Somatostatin analogue targeting multiple somatostatin receptor subtypes[1]
  - Highest affinity for sst_5, the most prevalent somatostatin receptor subtype on ACTH-secreting pituitary adenomas[2]
  - Inhibits ACTH production in corticotroph adenomas in vitro[3]
  - Phase 2, 15-day study demonstrated promising clinical efficacy[4]

1. Bruns C et al. Eur J Endocrinol 2002;146:707–716
2. Hofland LJ et al. Endocr Rev 2003;24:28–47
3. Hofland LJ et al. Eur J Endocrinol 2005;152:645–654
4. Boscaro M et al. J Clin Endocrinol Metab 2009;94:115–122

B2305: Largest Cushing's Disease Trial

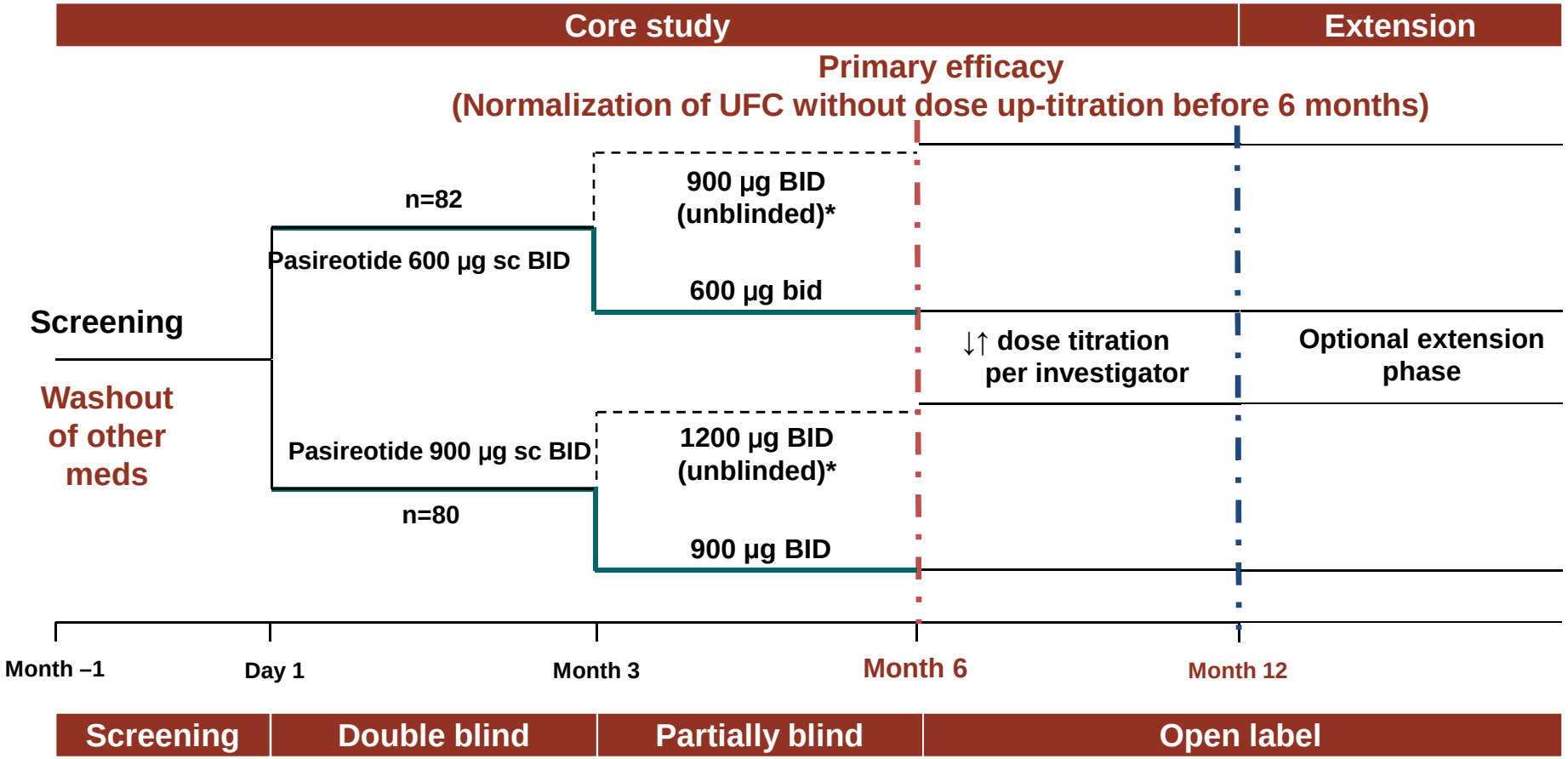


18 countries, 62 sites
329 patients screened
162 patients randomized

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

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

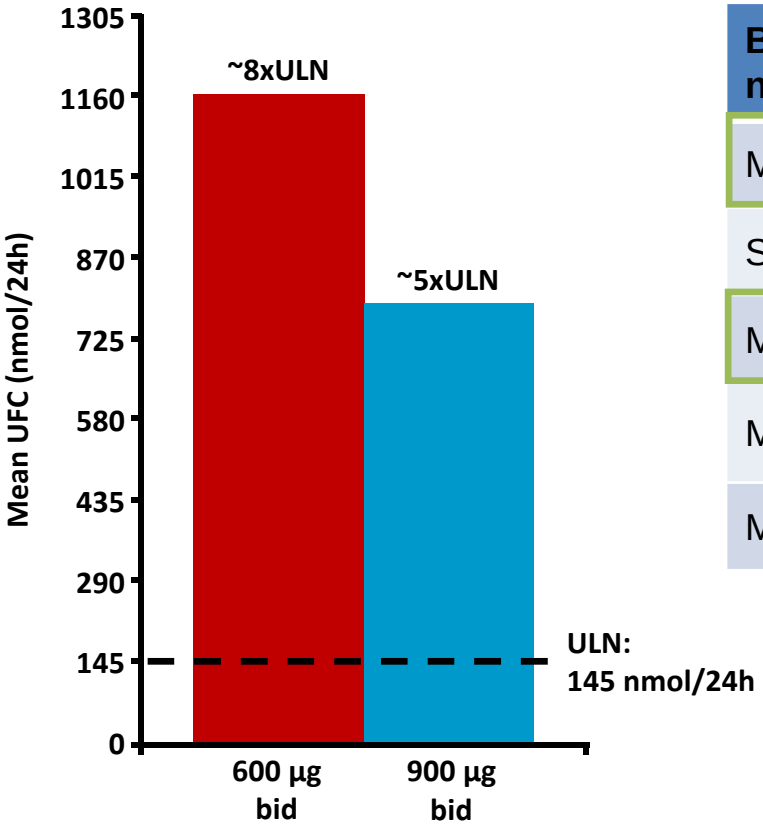
Colao A et al. N Engl J Med 2012;366:914–924

Baseline Demographics by Randomized Dose

	Overall n=162	600 µg BID n=82	900 µg BID n=80
Mean age, (years)	40.2	40.5	39.9
Female, n (%)	126 (77.8)	62 (75.6)	64 (80.0)
Time since diagnosis (months)	54.0	53.4	54.5
Cushing's disease status			
Persistent/recurrent, n (%)	135 (83.3)	67 (81.7)	68 (85.0)
De novo, n (%)	27 (16.7)	15 (18.3)	12 (15.0)
Previous surgery, n (%)	128 (79.0)	64 (78.0)	64 (80.0)
Previous medication, n (%)	78 (48.1)	36 (43.9)	42 (52.5)
Previous pituitary irradiation, n (%)	7 (4.3)	3 (3.7)	4 (5.0)

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

Baseline UFC by randomized dose

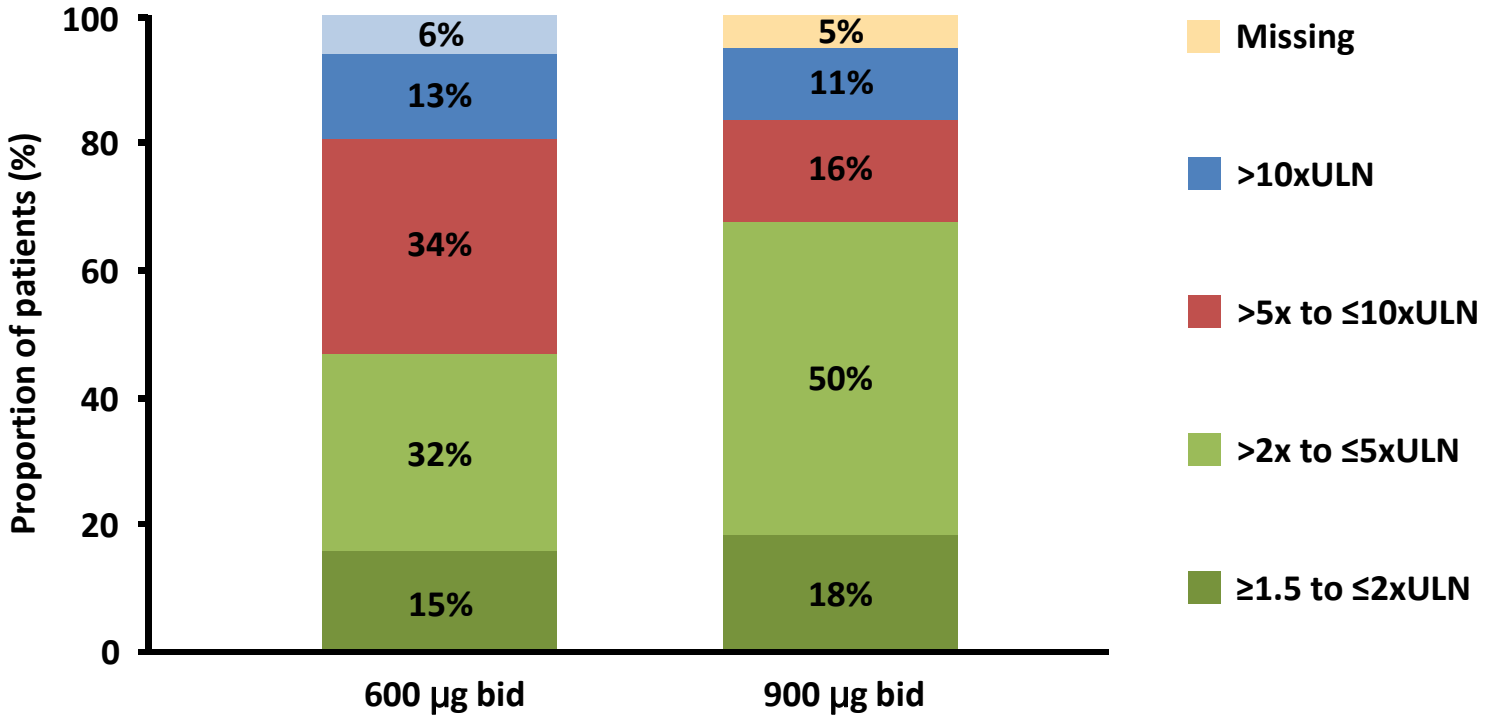


Baseline UFC, nmol/24h	600 µg bid (n=77)	900 µg bid (n=76)	Overall (n=153)
Mean	1156	781	970
SD	2630	927	1979
Median	730	487	565
Min	220	195	195
Max	22944	6123	22944

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

Distribution of baseline UFC

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



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

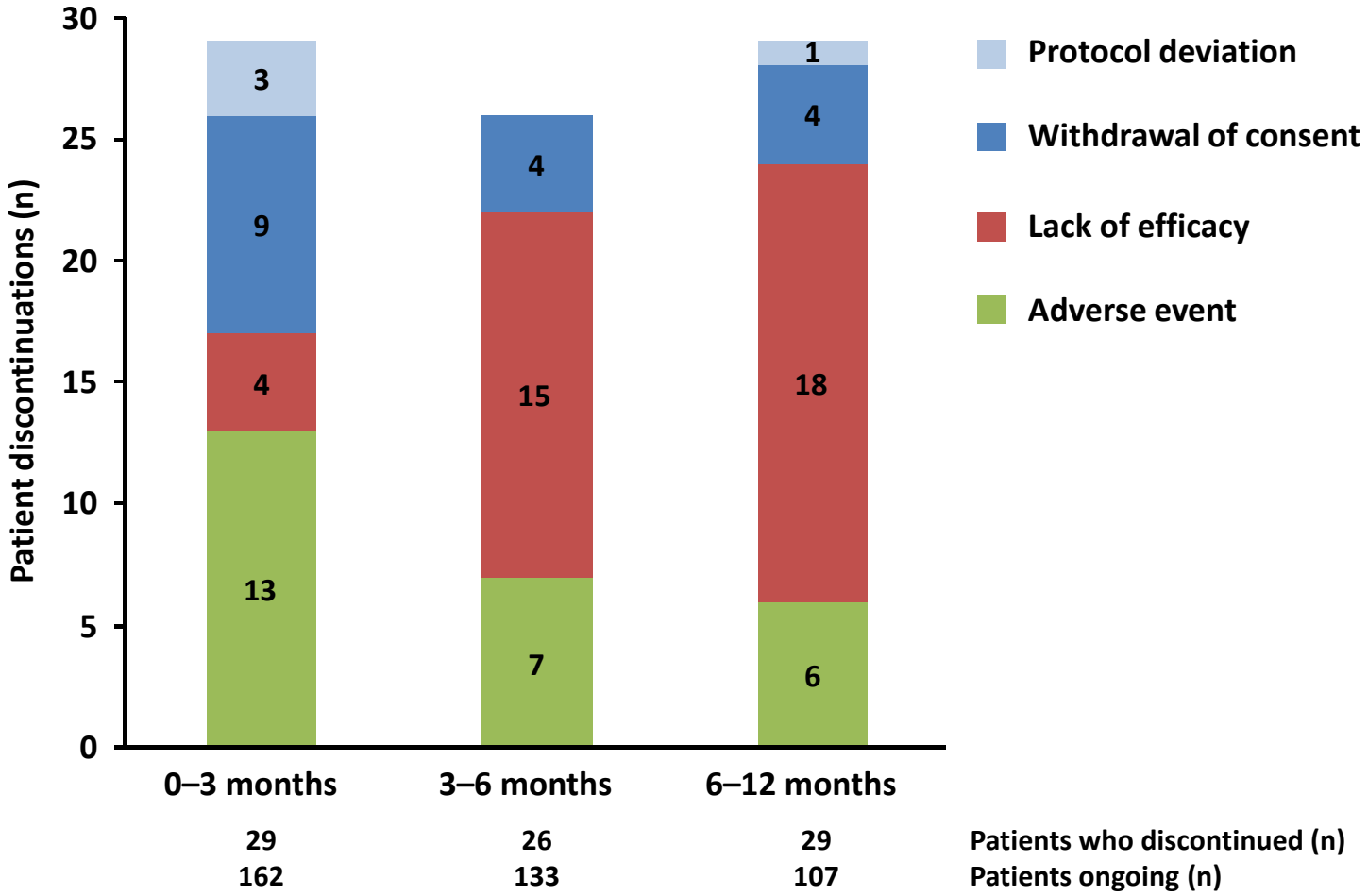
Patient disposition

329 patients screened

	Overall, n (%) N=162	600 µg bid, n (%) N=82	900 µg bid, n (%) N=80
Disposition			
Completed month 6	107 (66.0)	54 (65.9)	53 (66.3)
Completed month 12	78 (48.1)	39 (47.6)	39 (48.8)
Reason for discontinuation			
Unsatisfactory therapeutic effect	41 (25.3)	19 (23.2)	22 (27.5)
Adverse event(s)	28 (17.3)	13 (15.9)	15 (18.8)
Subject withdrew consent	24 (14.8)	13 (15.9)	11 (13.8)
Protocol deviation	4 (2.5)	4 (4.9)	0

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

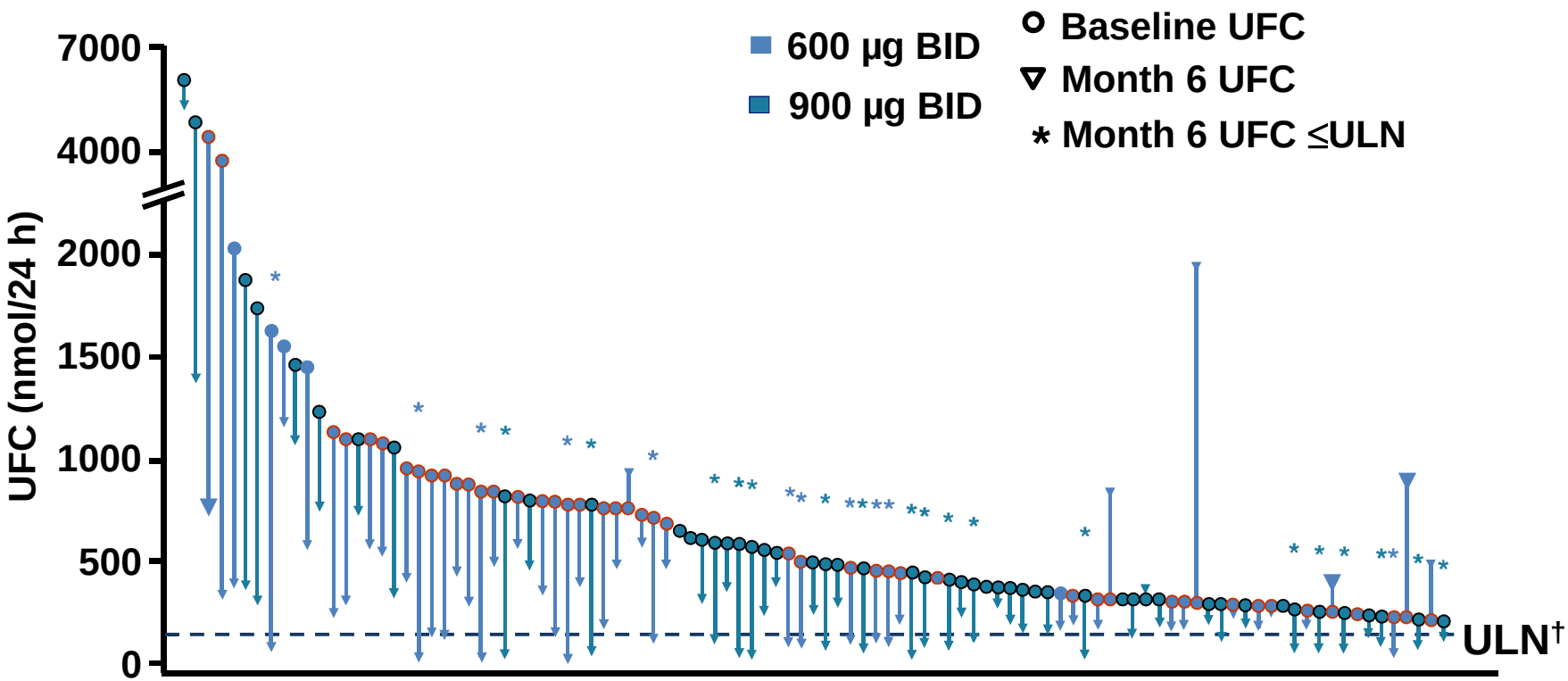
Reasons for patient discontinuation



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

Change in UFC from Baseline to Month 6

in the 103 patients with baseline and month-6 UFC measurements



Median percentage UFC change from baseline was –47.9% in both groups

†Reference line is the upper limit of normal UFC, which is 145 nmol/24 h (52.5 µg/24 h)

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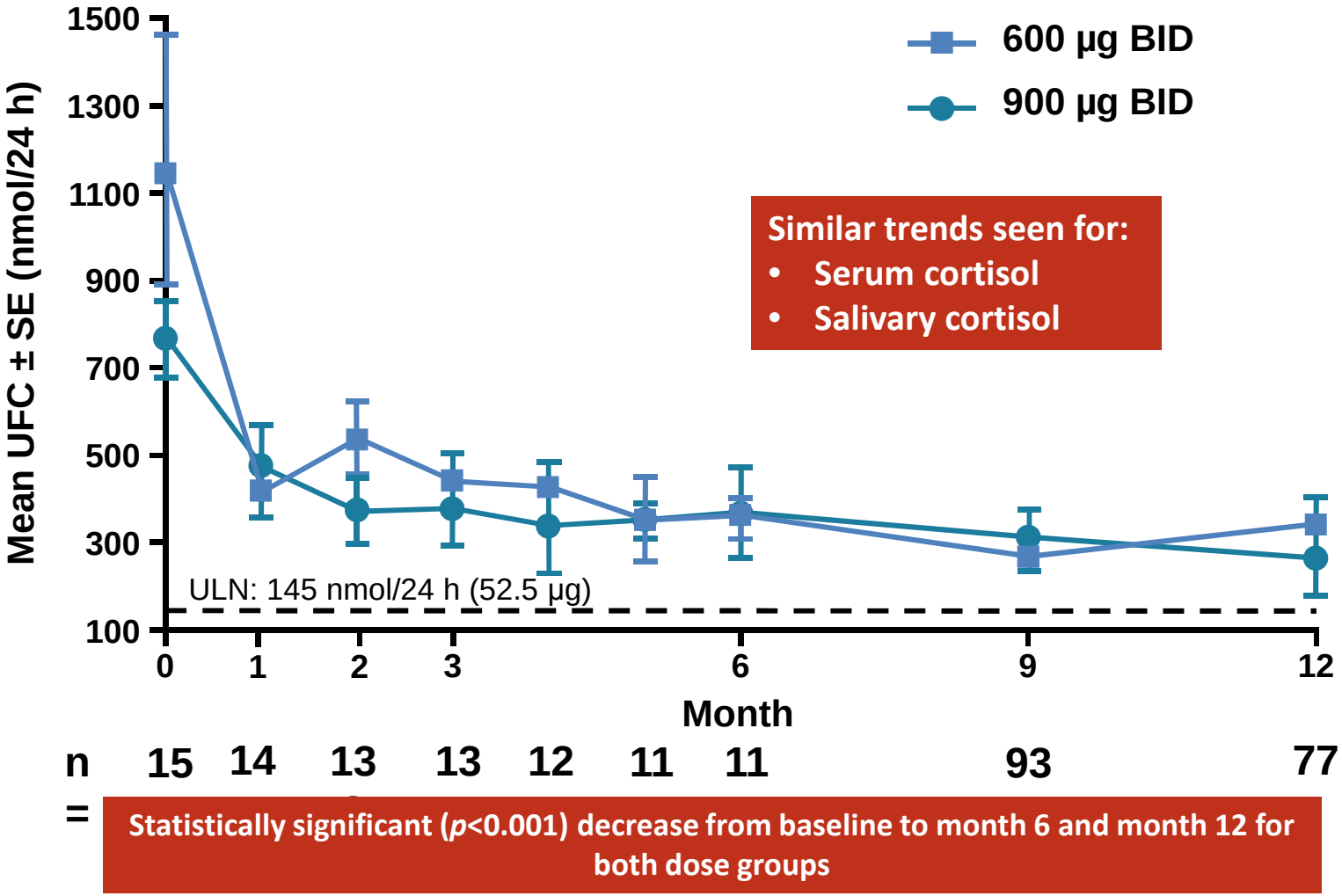
Mean UFC Levels Showed a Rapid and Robust Reduction That Was Maintained Over Time



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Primary Efficacy Results

	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]

*Note: Responder was a patient with UFC ≤ULN who did not require uptitration
Fully controlled: UFC ≤ULN

The predetermined criterion for the primary efficacy endpoint was that the lower bound of the 95% CI had to be >15% for at least one of the dose groups; this was met for the 900 µg group

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Response Rates at Month 6

	600 µg BID (n=82)	900 µg BID (n=80)
Fully controlled	13 (15.9%)	23 (28.8%)
Partially controlled	15 (18.3%)	10 (12.5%)
Uncontrolled	54 (65.9%)	47 (58.8%)
	34%	41%

Fully controlled: UFC ≤ULN; partially controlled:
UFC >ULN, but had ≥50% reduction from baseline;
Uncontrolled: UFC >ULN and <50% reduction from baseline

At month 6, 41.3% of patients treated with 900 µg BID were controlled or partially controlled

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Which is the real potential of disease control of pasireotide?

Is the dose of 900 μg more efficacious than the dose of 600 μg twice a day in term of chance of hormone control?

Early prediction of uncontrolled patients at months 6 and 12

Within 1–2 months, patients who will remain uncontrolled can be identified

	Early non-responders	Month 6 response			Month 12 response		
	UC	FC	PC	UC	FC	PC	UC
Months 1 + 2, n (%)	72 (100.0)	4 (5.6)	2 (2.8)	66 (91.7)	6 (8.3)	2 (2.8)	64 (88.9)
Months 1 + 2 + 3, n (%)	63 (100.0)	2 (3.2)	1 (1.6)	60 (95.2)	5 (7.9)	1 (1.6)	57 (90.5)

Fully controlled (FC): UFC ≤ULN
Partially controlled (PC): UFC >ULN but had ≥50% reduction from baseline
Uncontrolled (UC): UFC >ULN and <50% reduction from baseline, or missing values

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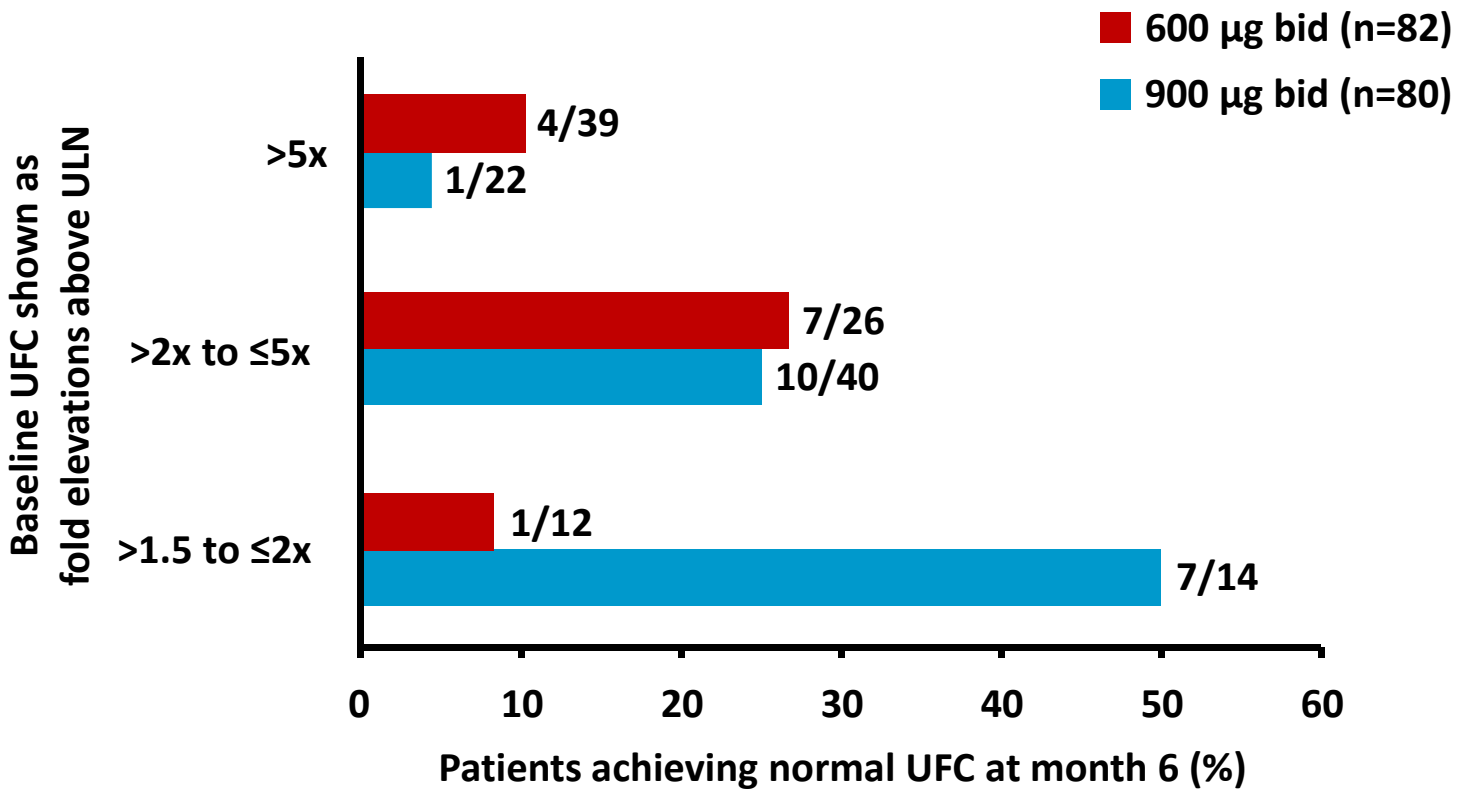
Baseline UFC level and response at month 6

Higher rate of UFC normalization with lower baseline UFC



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

What to do with patients partially controlled by pasireotide?

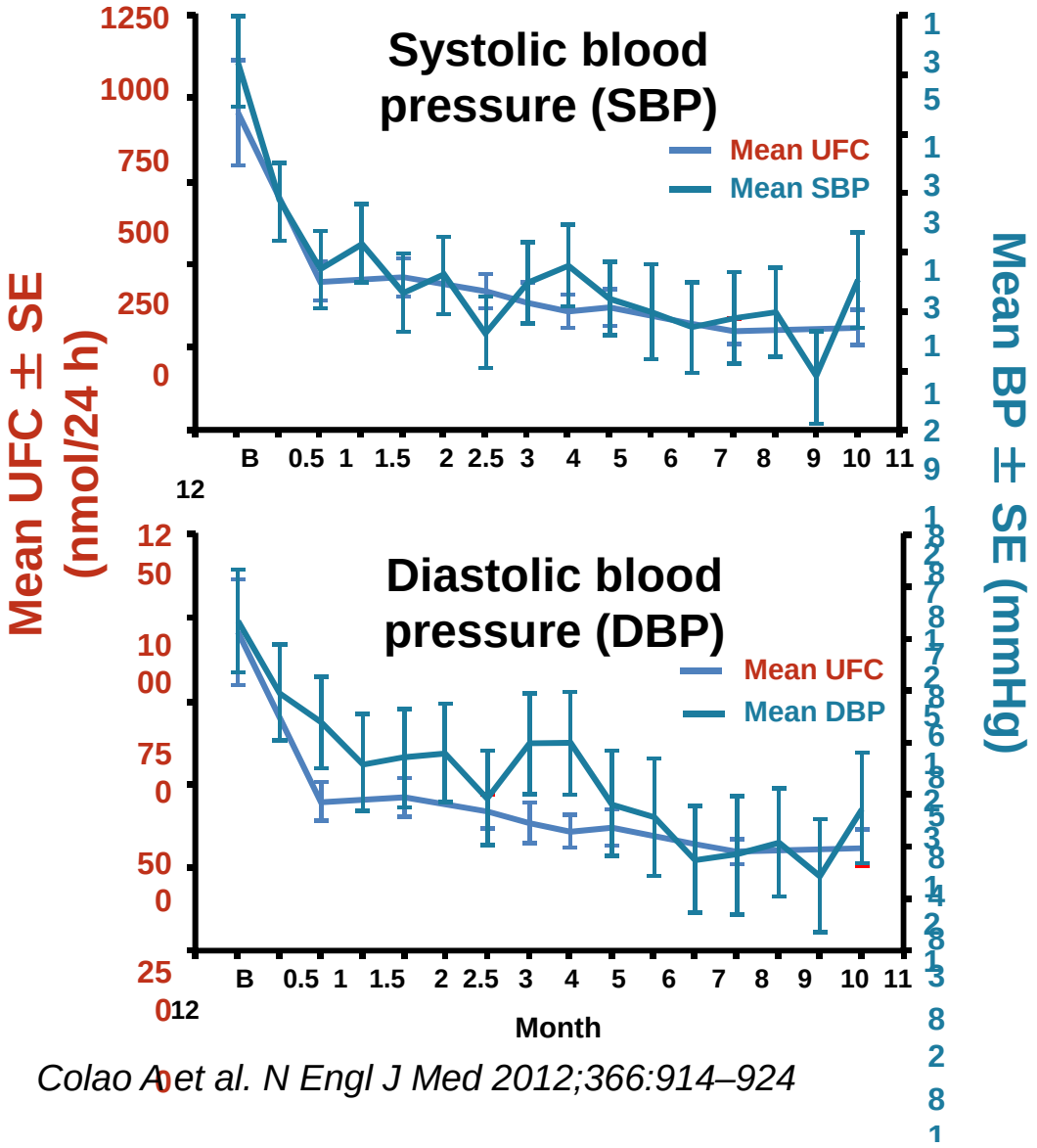
Withdrawal?

Criteria?

Combination with another drug?

Which drug?

Significant Decrease in Blood Pressure and UFC



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

Significant (p=0.03) change from baseline to month 12 was observed for:

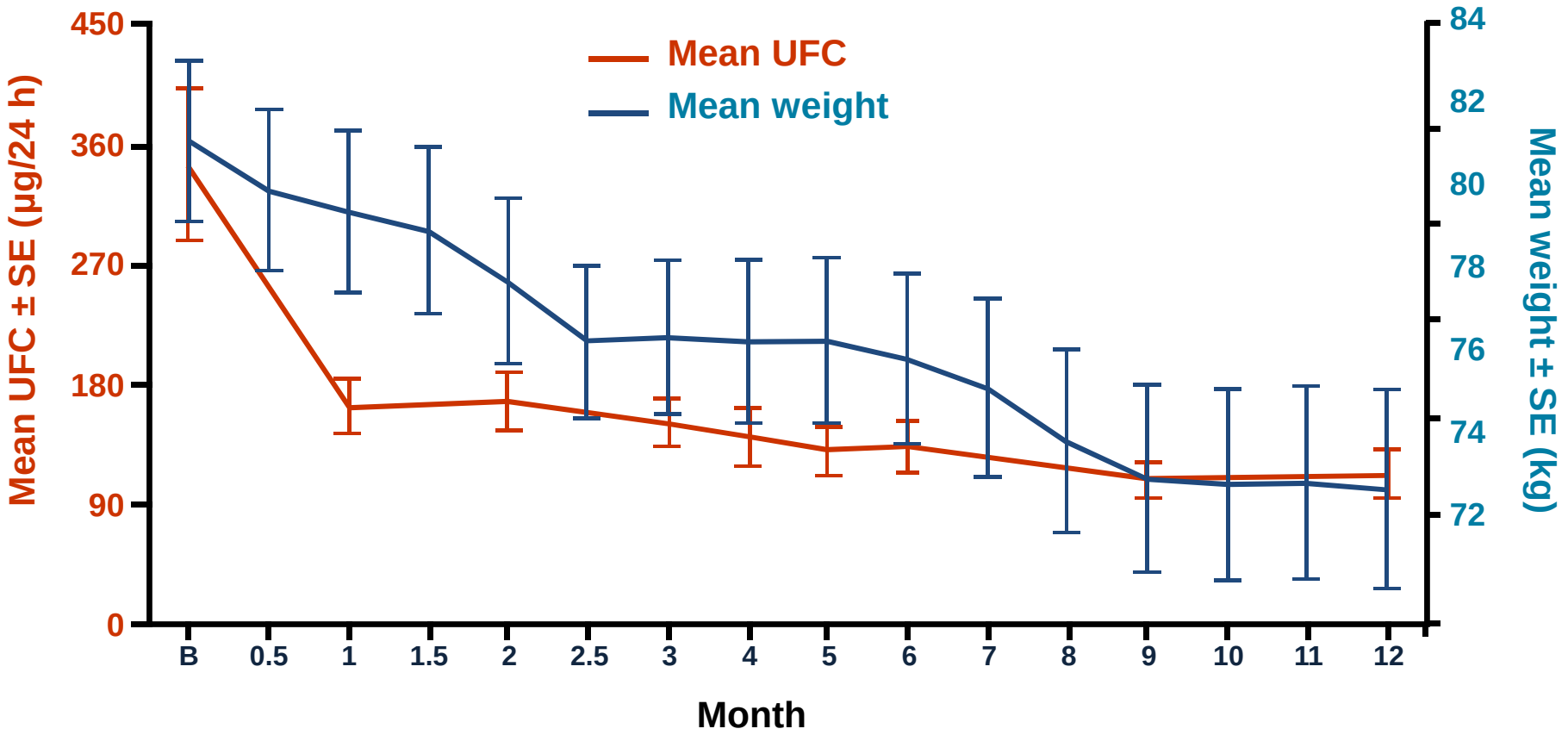
SBP –6.1 mmHg (95% CI: –9.8, –2.4)

DBP –3.7 mmHg (95% CI: –6.2, –1.2)

Note: Changes in anti-hypertensive medicines were allowed

Significant Decrease in Weight and UFC

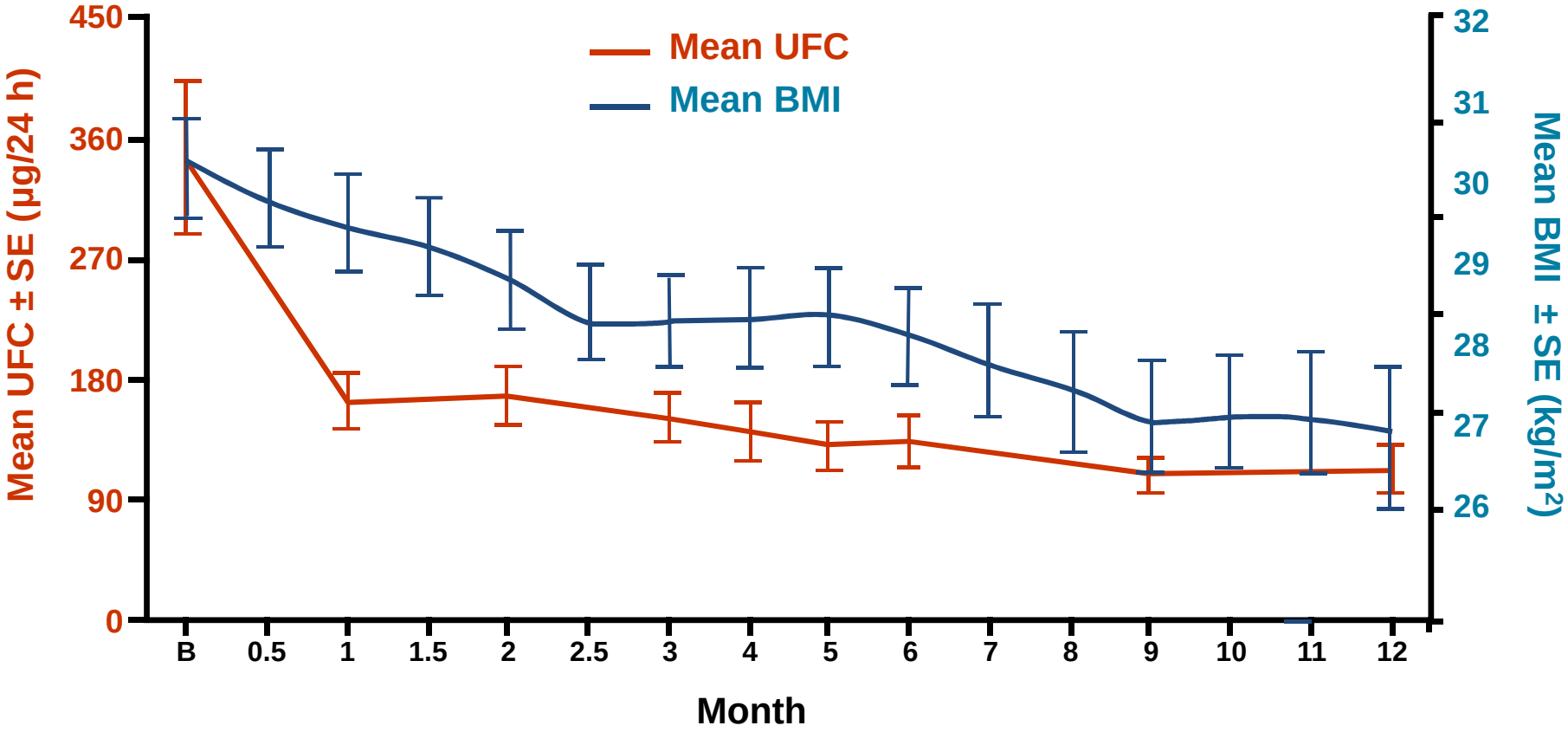
Significant ($p<0.0001$) decrease in weight of 6.7 kg from baseline to month 12 (95% CI: –8.0, –5.4)



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

Significant Decrease in BMI and UFC

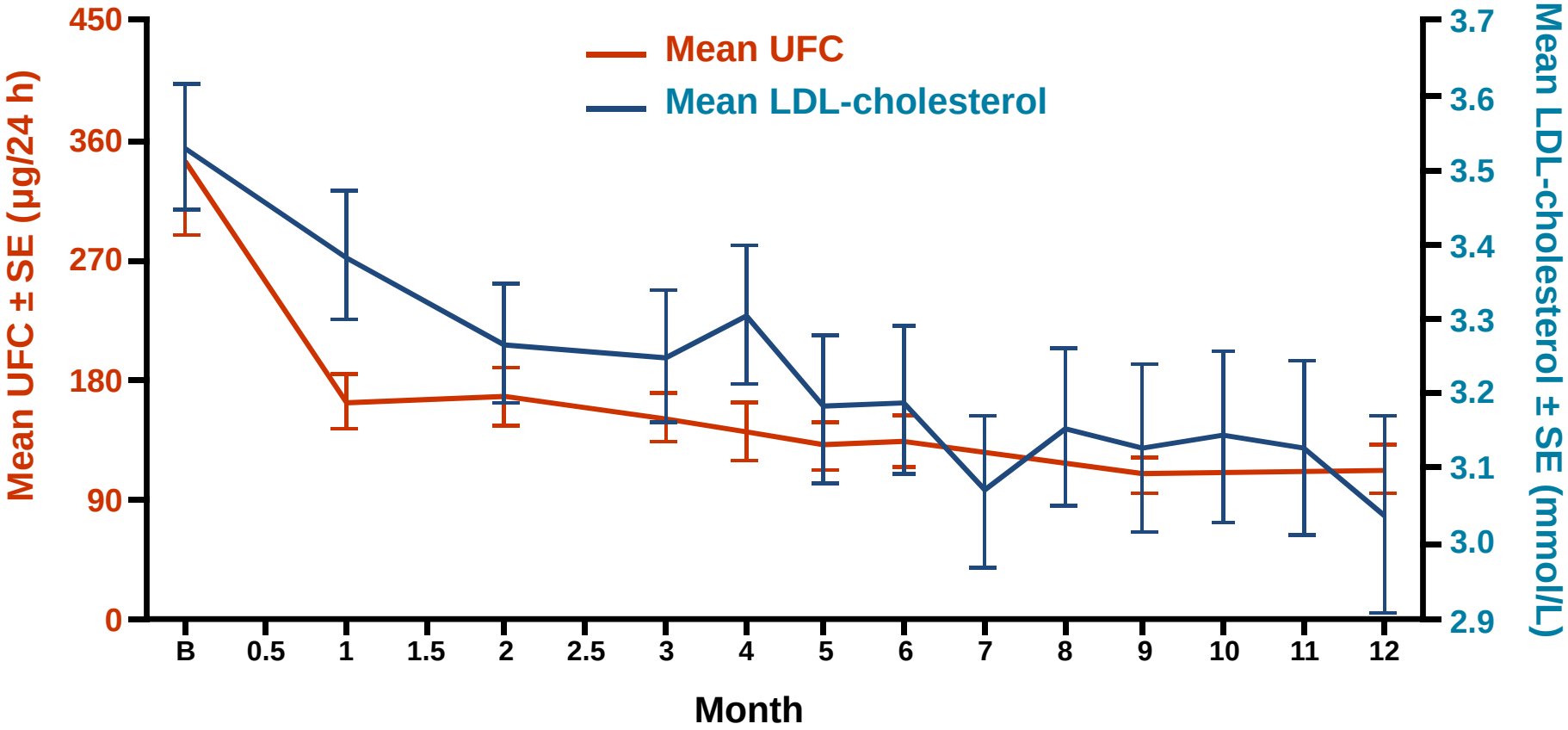
Significant decrease in BMI of 2.5 kg/m^2 from baseline to month 12 (95%CI: –3.0, –2.0)



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

Significant Decrease in LDL-cholesterol and UFC

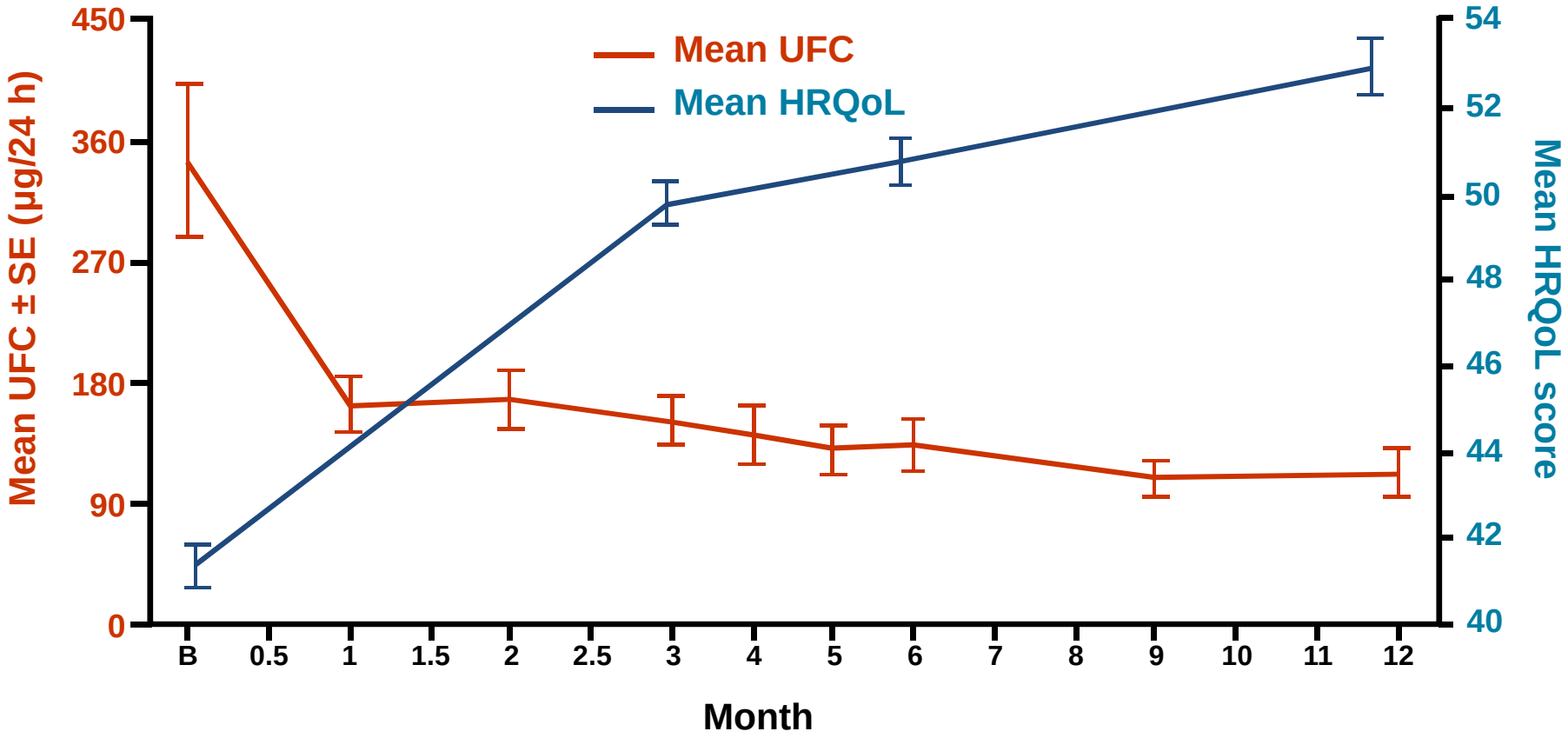
Significant (p<0.001) decrease in LDL-cholesterol of 0.4 mmol/L from baseline to month 12 (95% CI: –0.6, –0.2)



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

Significant Improvement in HRQoL and UFC

Measured via Cushing QoL
Significant (11.1 points) improvement from baseline to month 12 (95% CI: 6.8, 15.5)



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Improvements in Signs of Cushing's Disease

After 12 months of treatment, a high proportion of patients still enrolled also had improvements in the signs of Cushing's disease

	Proportion of patients with improvement (%)	
	600 µg BID	900 µg BID
Facial rubor	40.0	61.8
Striae	25.7	33.3
Bruising	29.4	28.1
Supraclavicular fat pads	51.4	57.6
Dorsal fat pads	52.9	57.6
Muscle strength	8.1	10.5

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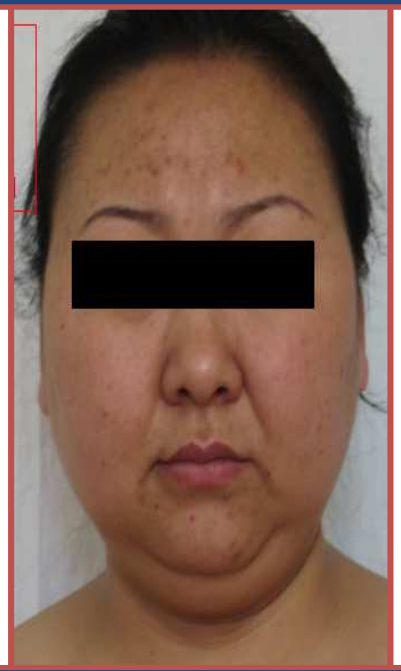
Improvements in Signs and Symptoms as Mean UFC Decreased: Clinical Case

Baseline, 900 µg BID



UFC: 417 nmol/24 h
Weight: 76 kg
SBP: 122 mmHg

Month 15,* 900 µg BID

UFC: 54.5 nmol/24 h
Weight : 55 kg
SBP: 110 mmHg

* Photograph taken at month 12; Courtesy of Dr Feng Gu, China

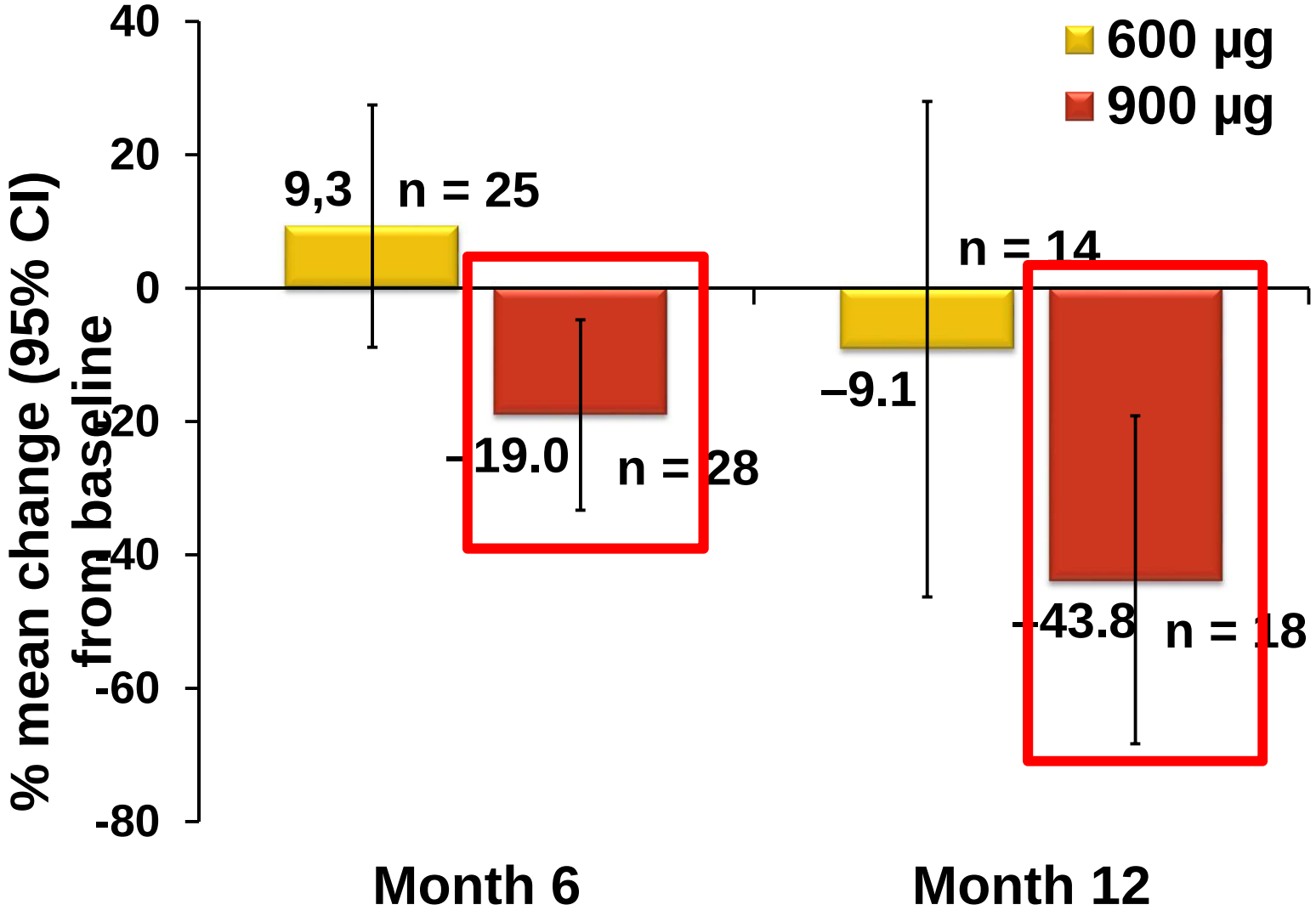
Improvement in Tumor Volume Following Treatment With Pasireotide sc BID

- Tumor volume was assessed by MRI at baseline, month 6 and 12
- At baseline 75 patients (46%) had a measureable pituitary tumor
- Median tumor volume was 0.24 cm^3 in the 600 µg group (n=36) and 0.20 cm^3 in the 900 µg group (n=39)

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

Change in Tumor Volume From Baseline

Study B2305



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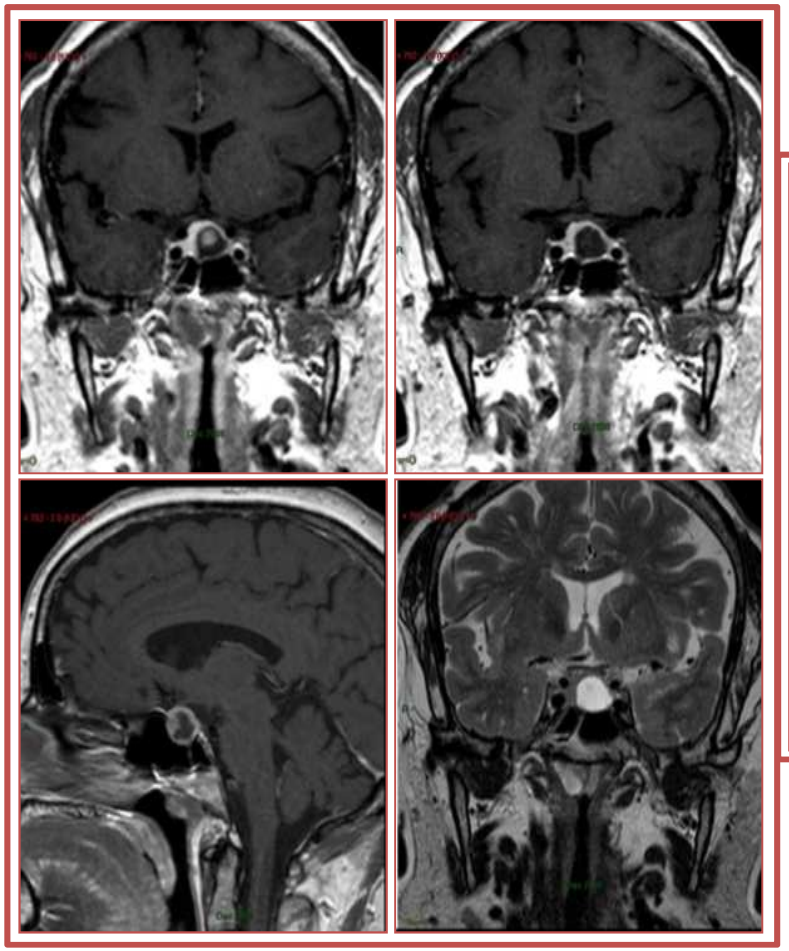
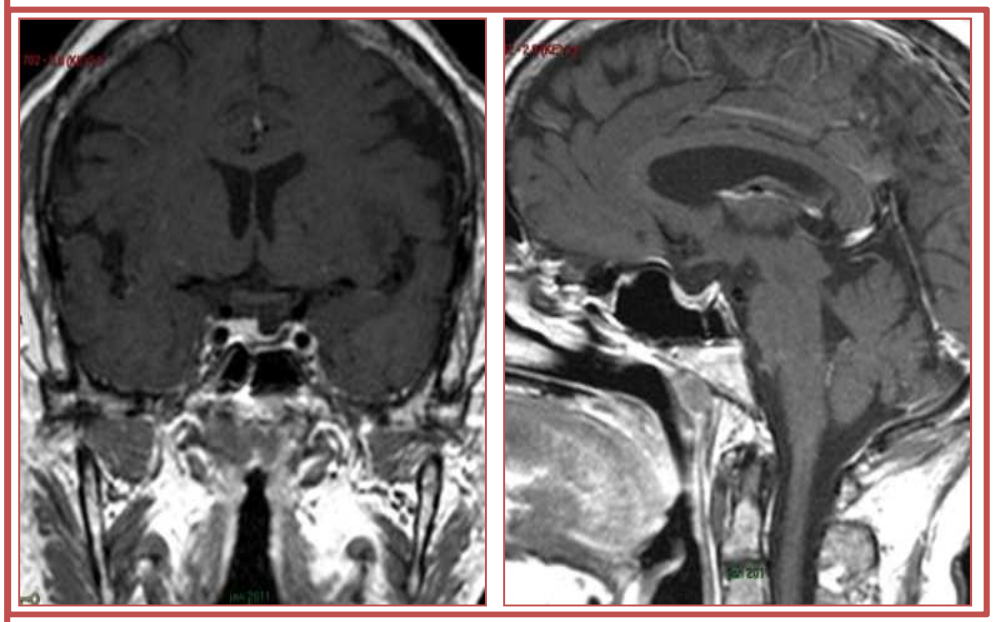
Significant Decrease in Tumor Volume

Baseline



24 months pasireotide

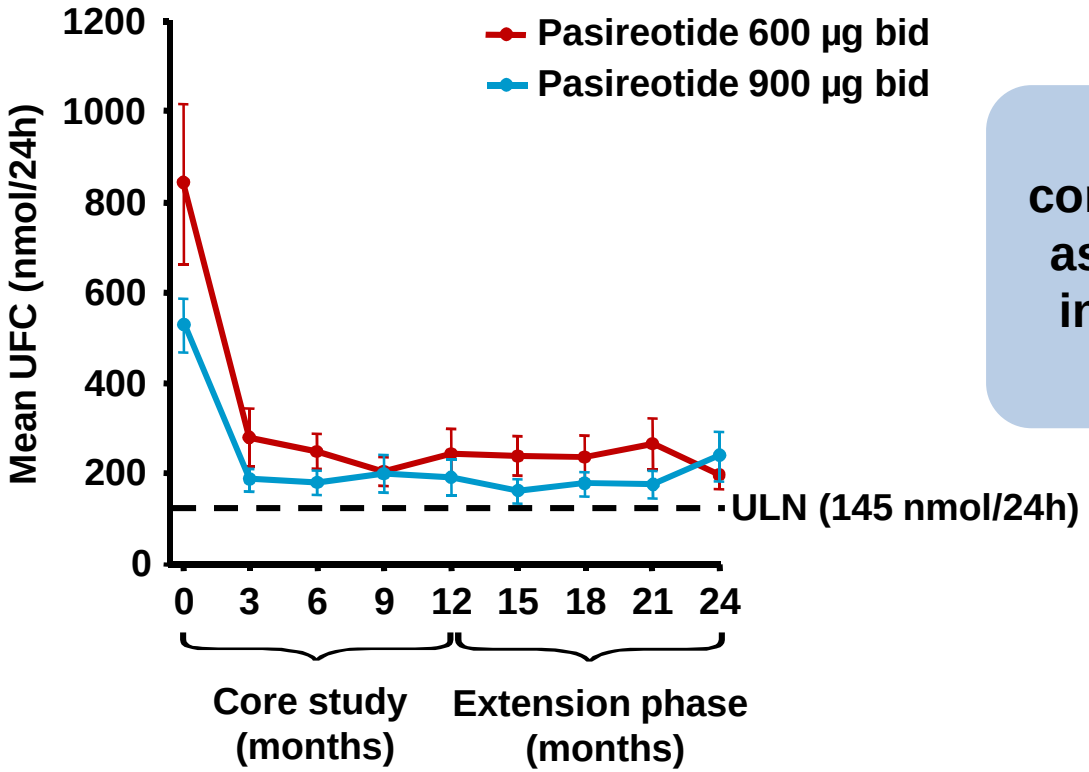


Shimon. *Pituitary*. 2012 Dec;15(4):608-13

Why this difference in tumor shrinkage with the two different dose of pasireotide?

Sustained reductions in UFC were observed through to month 24

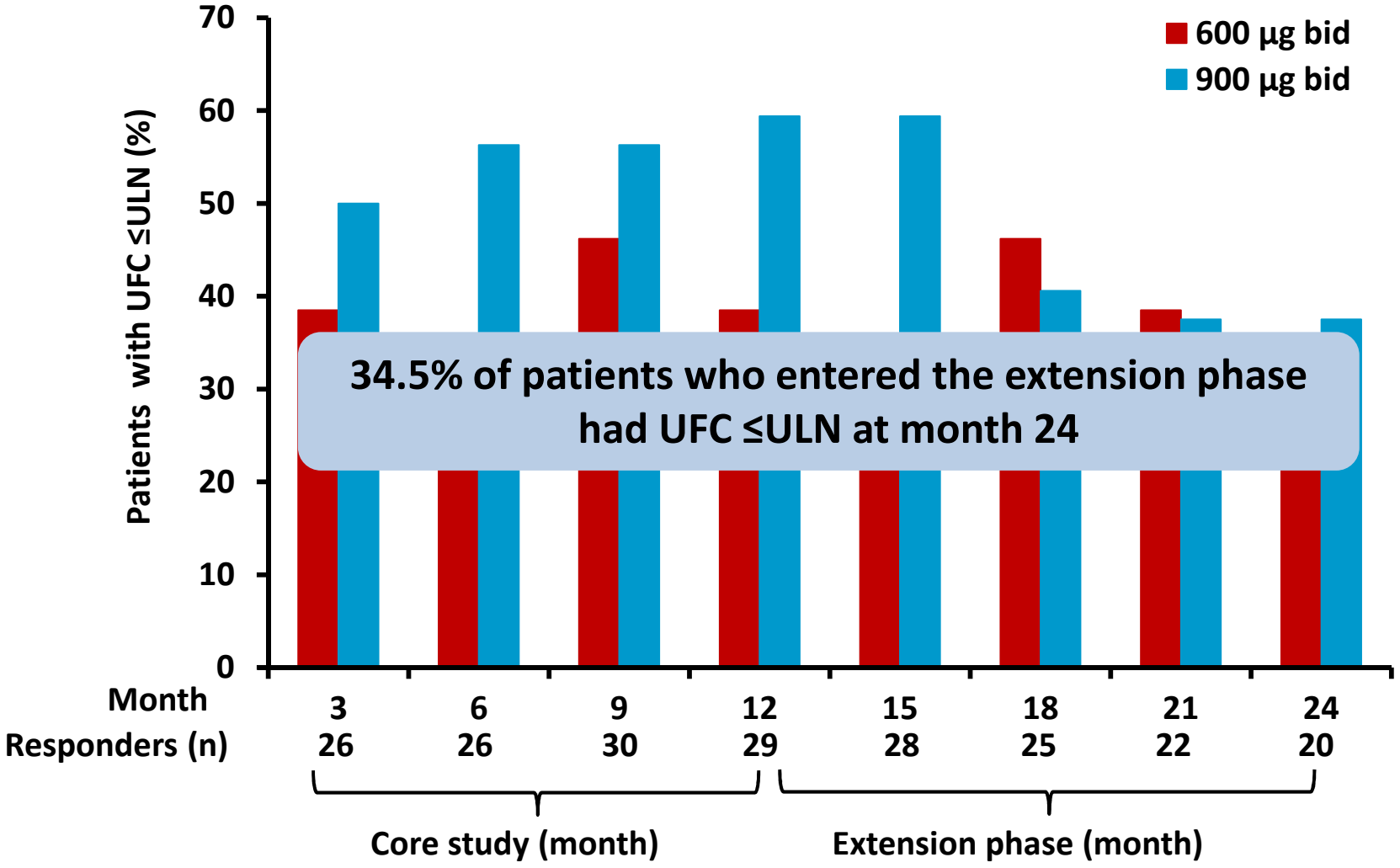
- 58 patients entered a 12-month extension phase[1,2]
- Mean decreases in UFC were maintained up to 24 months[1]



Reductions in serum cortisol and plasma ACTH, as well as improvements in signs and symptoms, were sustained[1]

[1]Bertherat J *et al*. *Endocr Rev* 2012;33:abst SUN-734;
[2]Bertherat J *et al*. *Endocr Rev* 2012;33:abst SUN-735

Control of UFC was observed up to month 24



Safety summary at the month-12 cut-off

Treatment duration was up to 38 months (mean 10.8)

	600 µg bid (n=82)	900 µg bid (n=80)	Overall (n=162)
Adverse events (AEs), n (%)	80 (97.6)	79 (98.8)	159 (98.1)
Drug-related AEs	79 (96.3)	76 (95.0)	155 (95.7)
Discontinued due to AEs	13 (15.9)	15 (18.8)	28 (17.3)
Grade 3 or 4 AEs	39 (47.6)	40 (50.0)	79 (48.8)
AEs of special interest, n (%)	79 (96.3)	77 (96.3)	156 (96.3)
Serious adverse events (SAEs), n (%)	19 (23.2)	21 (26.3)	40 (24.7)
Drug-related SAEs	7 (8.5)	12 (15.0)	19 (11.7)
Discontinued due to SAEs	3 (3.7)	5 (6.3)	8 (4.9)
Deaths during treatment, n (%)*	0	0	0

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

Most common AEs at 12 months

AE	Overall (N=162)	
	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

Hypocortisolism

- Hypocortisolism is a risk of any effective treatment for Cushing's disease
- No standard definition of hypocortisolism; AEs were determined by the investigator
- Among the patients with UFC≤ULN, 13 patients had hypocortisolism-related AEs, reported as:
  - Adrenal insufficiency (n=9)
  - Blood cortisol decreased (n=1)
  - UFC decreased (n=2)
  - Secondary adrenocortical insufficiency (n=1)
- Patients responded to a reduction in pasireotide dose and/or short-term exogenous steroid treatment

ULN, upper limit of normal

Gallbladder changes from baseline

	Changes from baseline to last assessment, n (%)				
Baseline	**Normal**	**Sludge**	**Gallstones**	**Biliary duct dilatation**	**Missing ultrasound**
Normal (n=137)	83 (60.6)	9 (6.6)	27 (19.7)	0	18 (13.1)

- Most cases were asymptomatic
- Six patients underwent cholecystectomy
- Comparable to other somatostatin analogues in Caucasians

Liver biochemistry

- As with other somatostatin analogues, there was a mild, transient elevation in liver enzyme levels (~30% of patients)
- In most patients, enzyme levels decreased to baseline during continued pasireotide treatment
  - Six patients discontinued because of elevated liver enzymes
- There were no cases of concomitant elevations of AST/ALT >3xULN and bilirubin >ULN (accepted regulatory marker for severe liver injury)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Adverse events suspected to be study drug related at month 24

Treatment duration was up to 42 months (mean 27.1)

	Overall (n=162)	
	CTCAE grades 3 & 4	All grades
Diarrhea	4 (2.5)	90 (55.6)
Nausea	4 (2.5)	78 (48.1)
Hyperglycemia	19 (11.7)	63 (38.9)
Cholelit		
Abdom		
Diabet		
Fatigue		
HbA_{1c} e		
Type 2 diabetes mellitus	7 (4.3)	15 (9.3)
GGT elevation	5 (3.1)	15 (9.3)
ALT elevation	3 (1.9)	15 (9.3)
Headache	1 (0.6)	14 (8.6)
Influenza	0	14 (8.6)

Safety profile at month 24 was similar to that at month 12

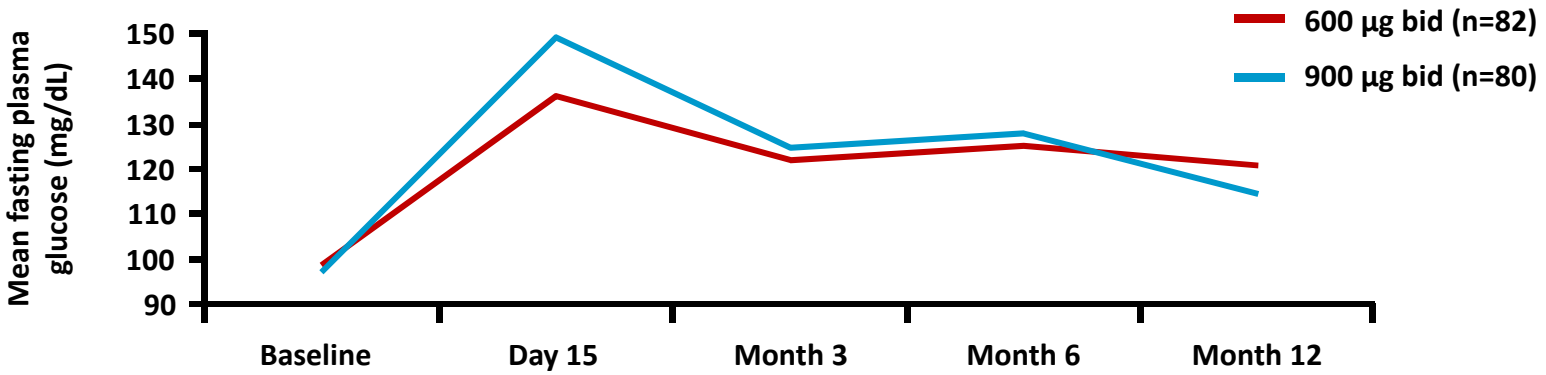
No new safety issues observed

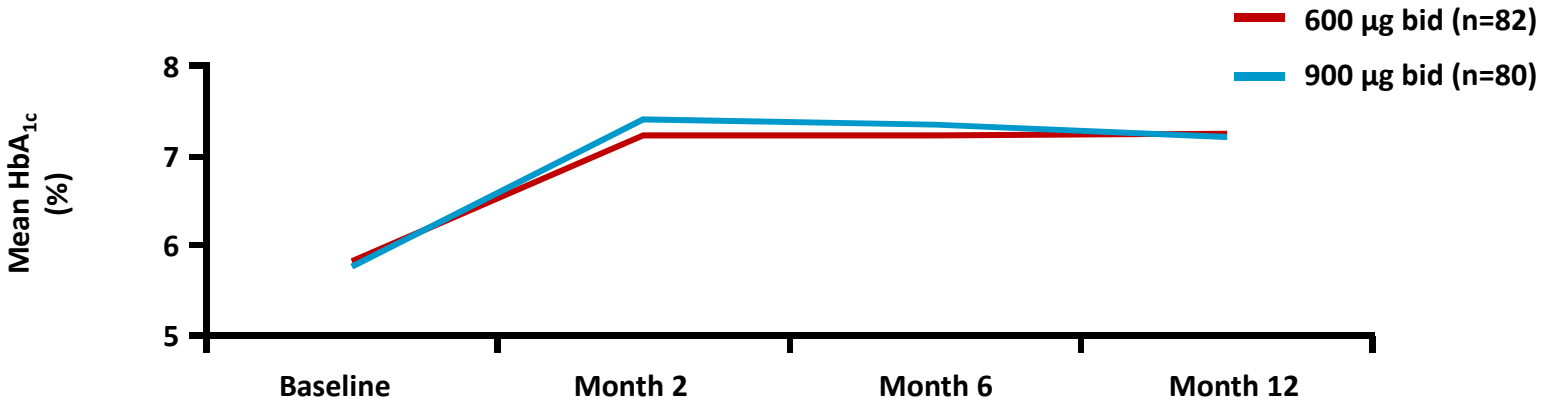
Grading (1–4) of AEs follows the US HHS Common Terminology Criteria for Adverse Events (CTCAE) 2009: Grade 3 = severe AE; grade 4 = life-threatening or disabling AE

GGT, γ-glutamyltransferase; HbA_{1c}, glycosylated hemoglobin

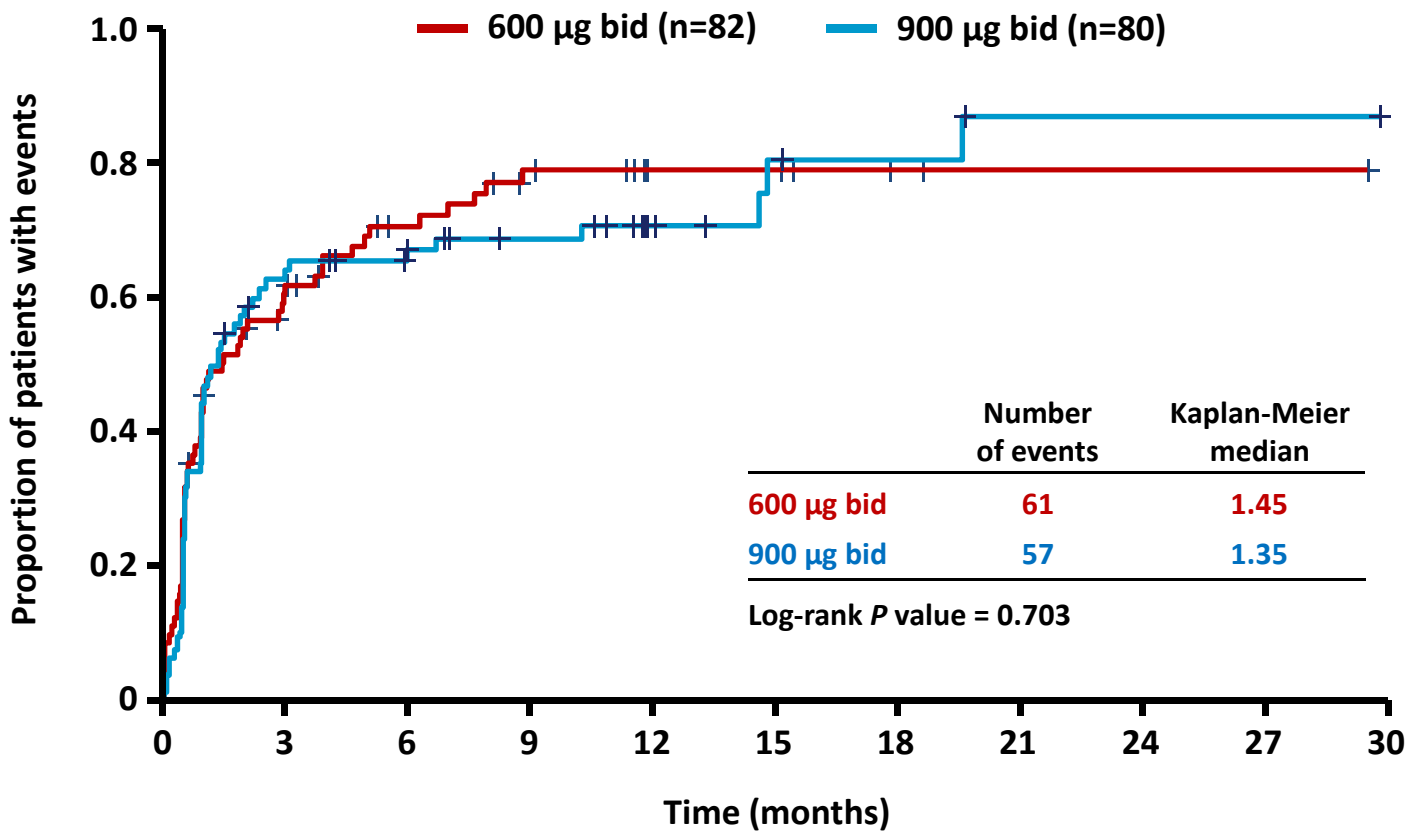
Bertherat J *et al*. *Endocr Rev* 2012;33:abst SUN-735

Changes in glycemia





Time to first hyperglycemia-related AE



Changes in antidiabetic medication

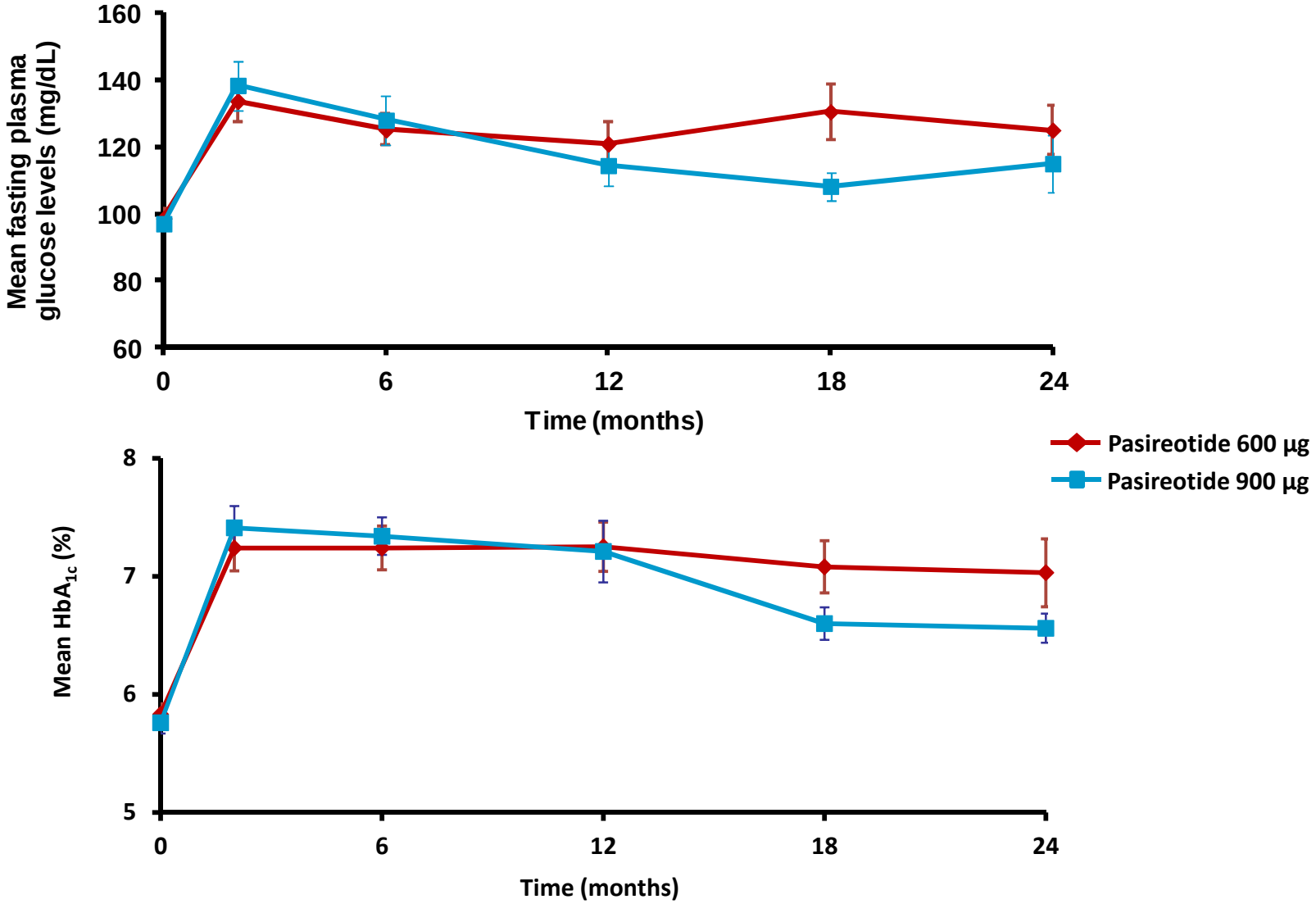
- At the month-12 cut-off, antidiabetic medication was initiated in 74 of 162 patients
  - 41% of patients (53/129) not receiving glucose-lowering medication at baseline initiated ≥1 antidiabetic medication
  - 64% of patients (21/33) receiving antidiabetic medication at baseline received ≥1 additional agent
- Among patients in whom glucose-lowering therapy was initiated during the study, reductions in mean fasting plasma glucose were observed
  - 166.2 to 121.5 mg/dL (9.2 to 6.7 mmol/L) in the 600 µg group
  - 159.4 to 133.8 mg/dL (8.9 to 7.4 mmol/L) in the 900 µg group

Changes from baseline in diabetes status

	Changes from baseline to last assessment, n (%)			
Baseline	**Normal**	**Pre-diabetic**	**Diabetic**	**Missing**
Normal (n=67)	14 (21)	29 (43)	23 (34)	1 (1.5)
Pre-diabetic (n=39)	1 (3)	9 (23)	28 (72)	1 (3)
Diabetic (n=55)	1 (2)	6 (11)	47 (85)	1 (2)
Missing (n=1)	1 (100)	0	0	0

Patients with pre-diabetes had a higher risk of developing diabetes

Glycemia remained stable to month 24



Role of somatostatin in glucose metabolism

- Somatostatin is an inhibitor of both insulin and glucagon secretion[1]
  - Binds with high affinity to the five somatostatin receptor subtypes[2]
  - sst_2 and sst_5 are the predominantly expressed subtypes in human pancreatic islet cells[3]
- Inhibition of insulin is mediated mainly by sst_2 and sst_5 in humans[4,5]
- Inhibition of glucagon is mediated almost entirely by sst_2[6,7]
- Pasireotide is a multireceptor-targeted somatostatin analogue with high binding affinity for $sst_{1–3}$ and sst_5

[1]Hauge-Evans AC *et al*. *Diabetes* 2009;58:403–411;
[2]Patel YC. *Front Neuroendocrinol* 1999;20:157–198; [3]Kumar U *et al. Diabetes* 1999;48:77–85;
[4]Fagan SP *et al*. *Surgery* 1998;124:254–258; [5]Zambre Y *et al*. *Biochem Pharmacol* 1999;57:1159–1164;
[6]Singh V *et al*. *J Clin Endocrinol Metab* 2007;92:673–680; [7]Singh V *et al*. *Endocrinology* 2007;148:3887–3899

Role of somatostatin in glucose homeostasis

Somatostatin is an inhibitor of both insulin and glucagon secretion[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.

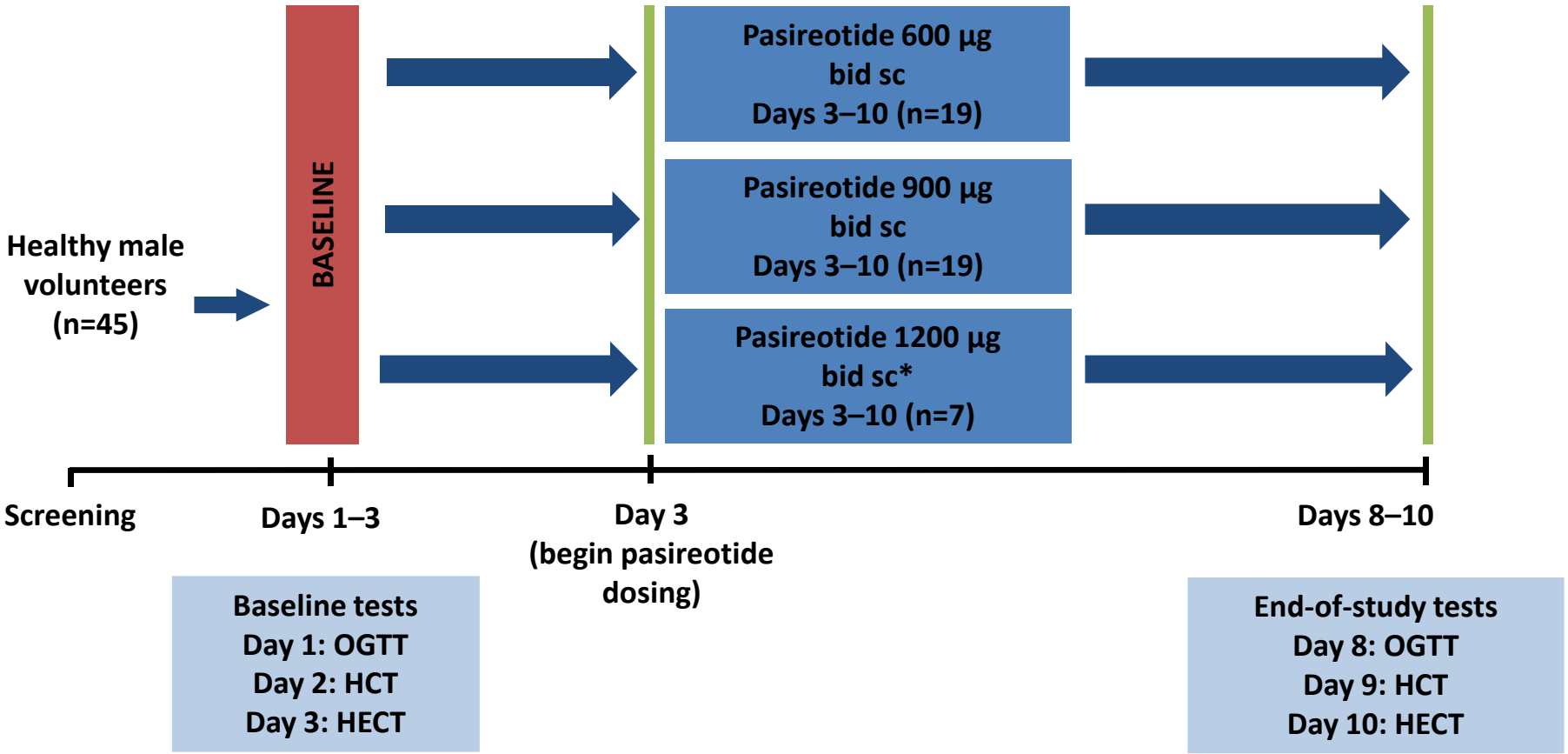
Evaluating the underlying mechanism of pasireotide-related hyperglycemia

- Two studies have been conducted to assess the mechanism(s) responsible for pasireotide-related hyperglycemia

SOM230B2216: Double-blind, randomized, single-center trial in healthy male volunteers evaluating the mechanism responsible for pasireotide-related hyperglycemia

SOM230B2124: Randomized, open-label, single-center study evaluating the effects of the co-administration of antihyperglycemic agents and pasireotide, compared with pasireotide alone, on glucose metabolism in healthy male volunteers

SOM230B2216: Study design
Mechanistic study



*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

Mechanistic investigations of glucose metabolism

Oral glucose tolerance test (OGTT)

- Standard test to confirm normal glycemia and measure parameters of glucose absorption and insulin secretion
- Measures blood glucose for 3 hours after a drink of a liquid containing 75 g of glucose

Two-step hyperglycemic clamp test (HCT)

- Quantifies insulin secretion
- Followed by an arginine (5 g iv) test for assessing acute, maximal insulin response

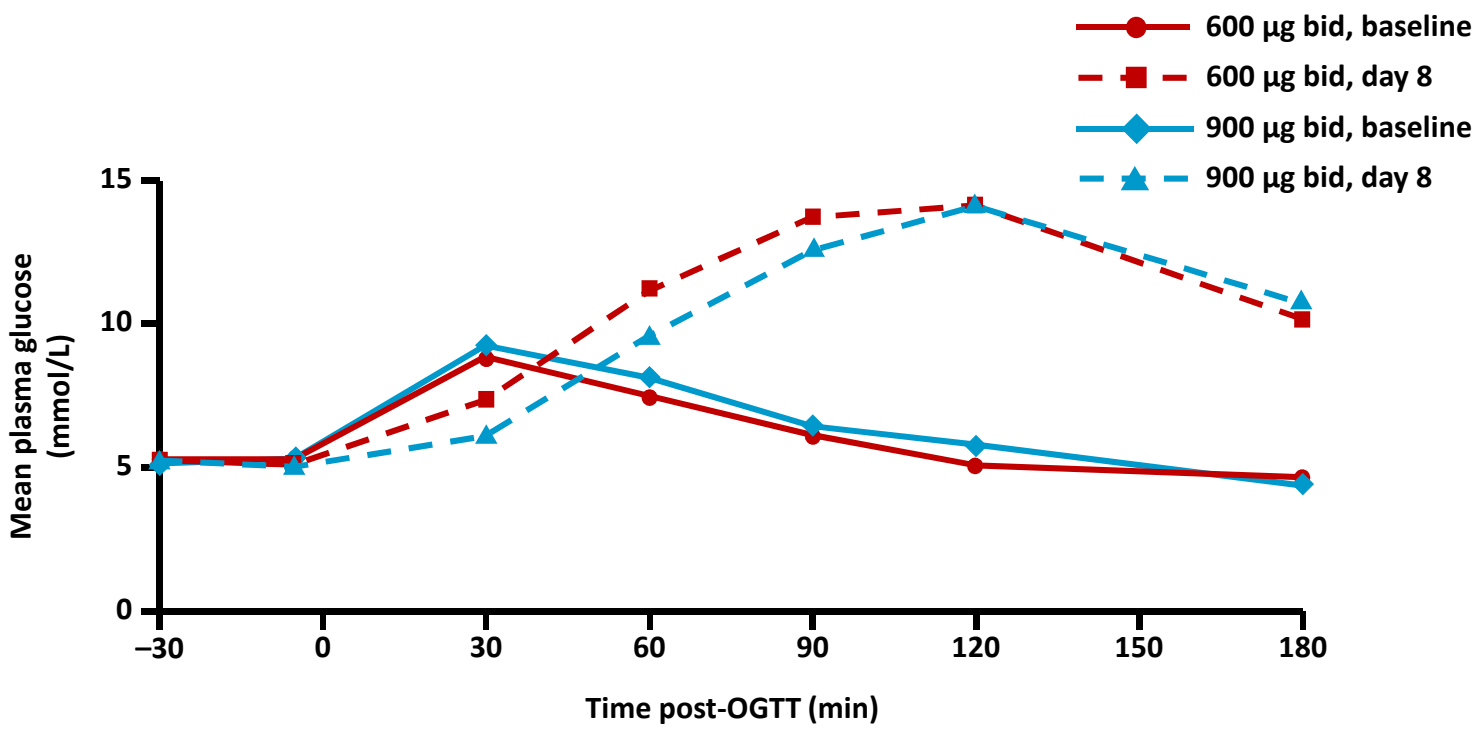
Two-step hyperinsulinemic euglycemic clamp test (HECT)

- Measures tissue insulin sensitivity (or resistance)

OGTT: Pasireotide increases postprandial plasma glucose

Glucose

$AUC_{30–180min}$ and $AUC_{0–180min}$ significantly higher at day 8 than at baseline ($P<0.001$) in both dose groups

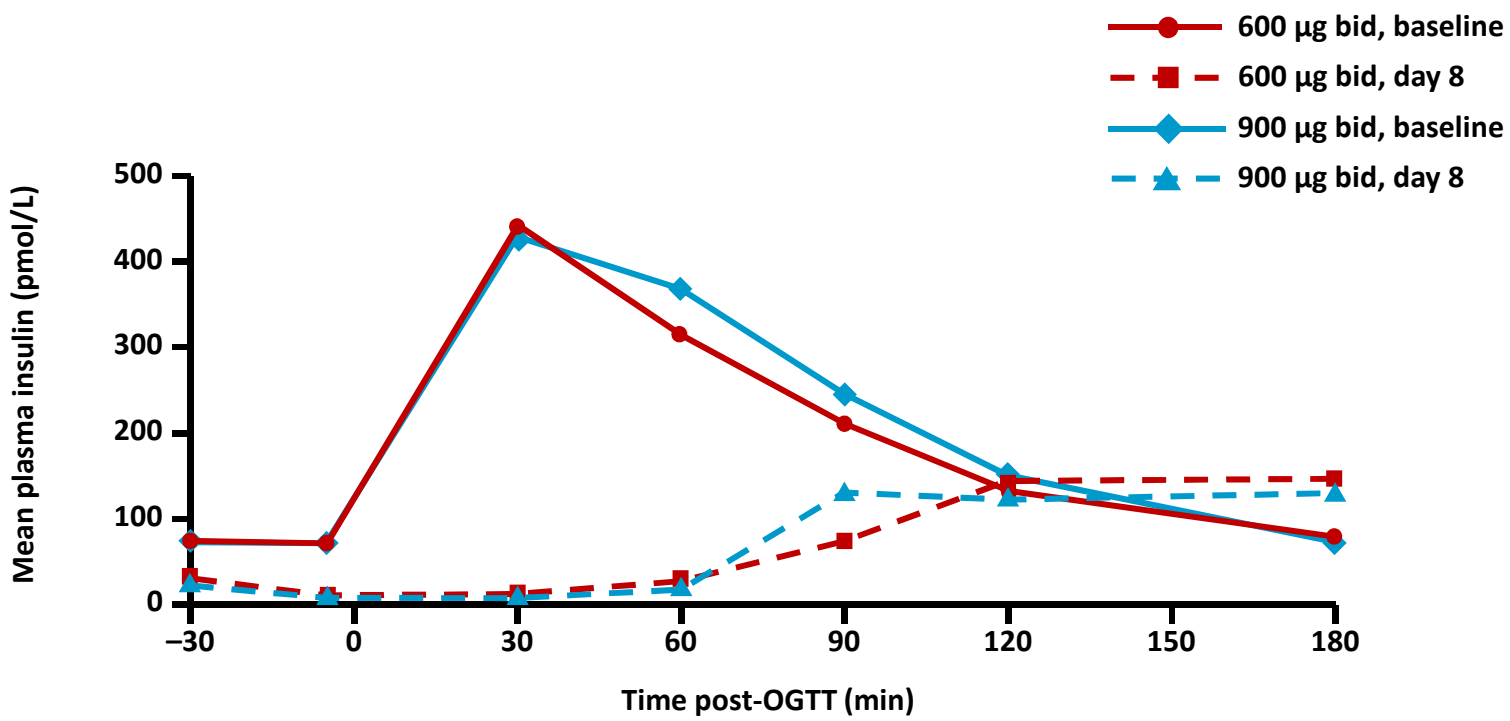


Henry RR *et al.* ENDO 2011;abst P3-274

OGTT: Pasireotide decreases postprandial plasma insulin

Insulin

$AUC_{0–30min}$, $AUC_{30–180min}$ and $AUC_{0–180min}$ significantly lower at day 8 than at baseline ($P<0.001$) in both dose groups

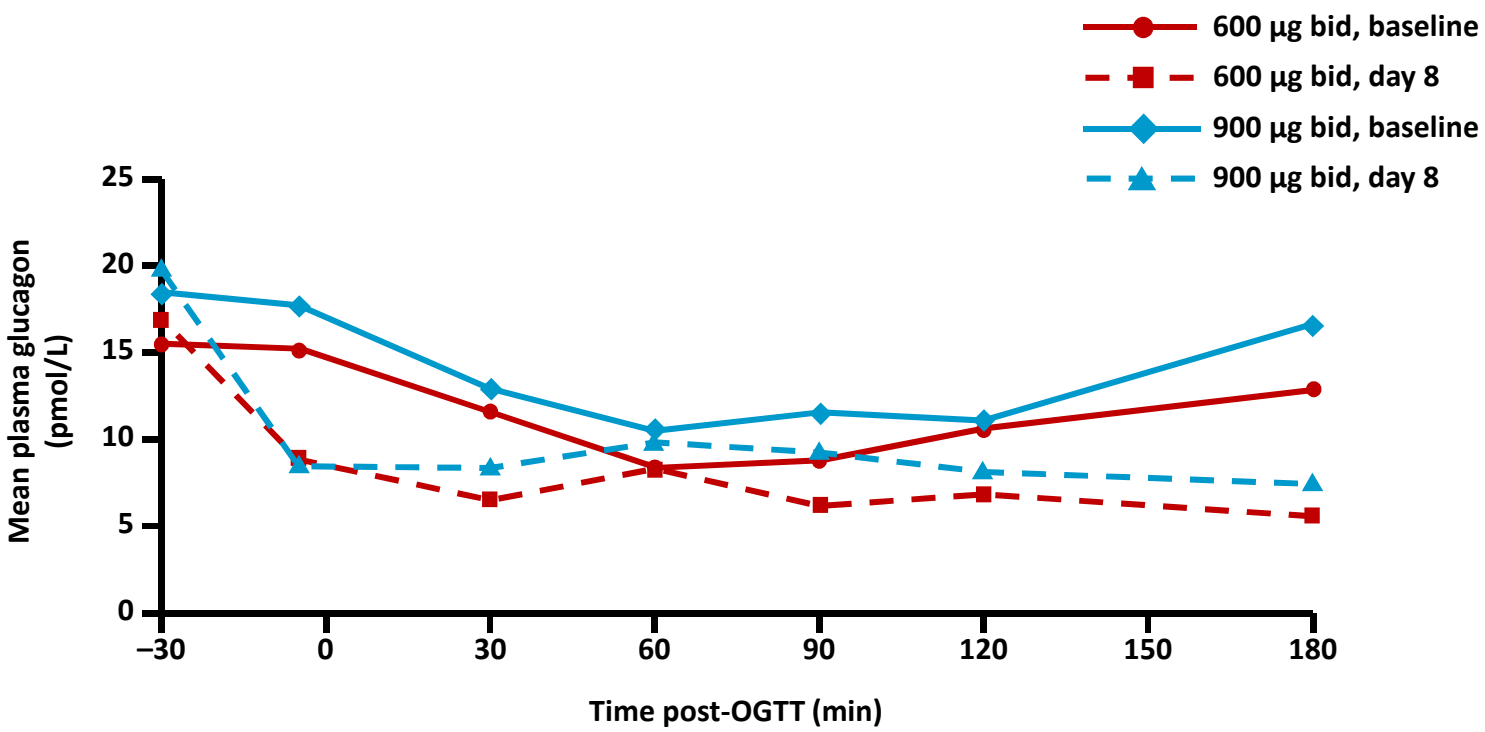


Henry RR *et al.* ENDO 2011;abst P3-274

OGTT: Pasireotide decreases postprandial plasma glucagon

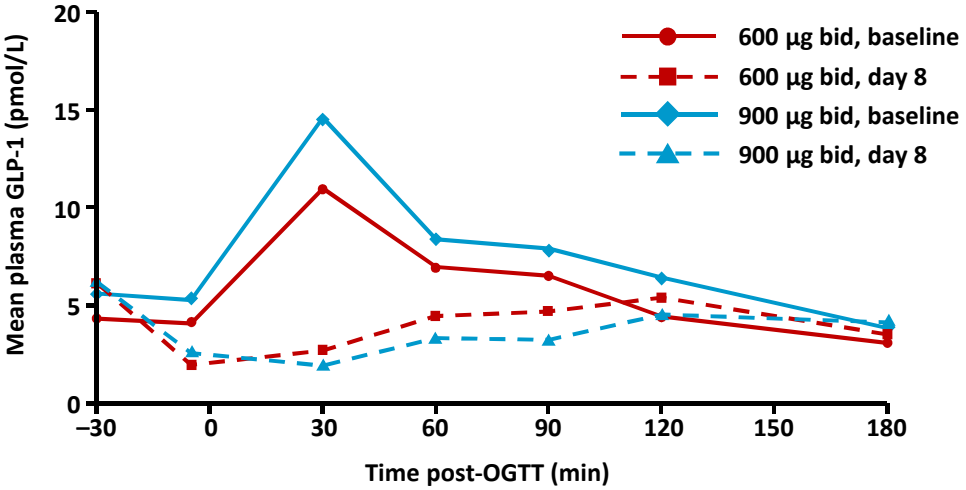
Glucagon

$AUC_{0–30min}$, $AUC_{30–180min}$ and $AUC_{0–180min}$ significantly lower at day 8 than at baseline ($P \leq 0.01$) in both dose groups



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

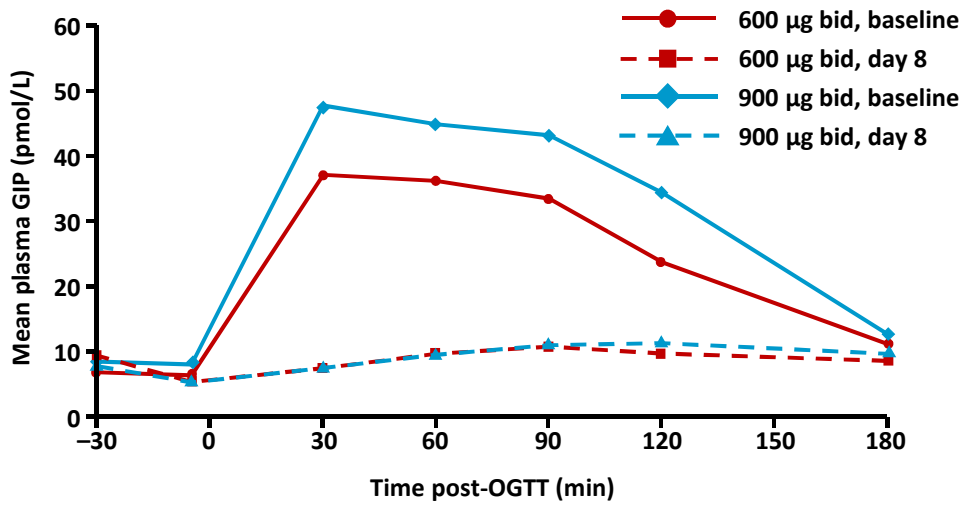
OGTT: Pasireotide decreases postprandial GLP-1 and GIP



GLP-1

$AUC_{0–30min}$ and $AUC_{0–180min}$ significantly lower at day 8 than at baseline in the 600 µg group

$AUC_{0–30min}$, $AUC_{30–180min}$ and $AUC_{0–180min}$ significantly lower at day 8 than at baseline in the 900 µg group



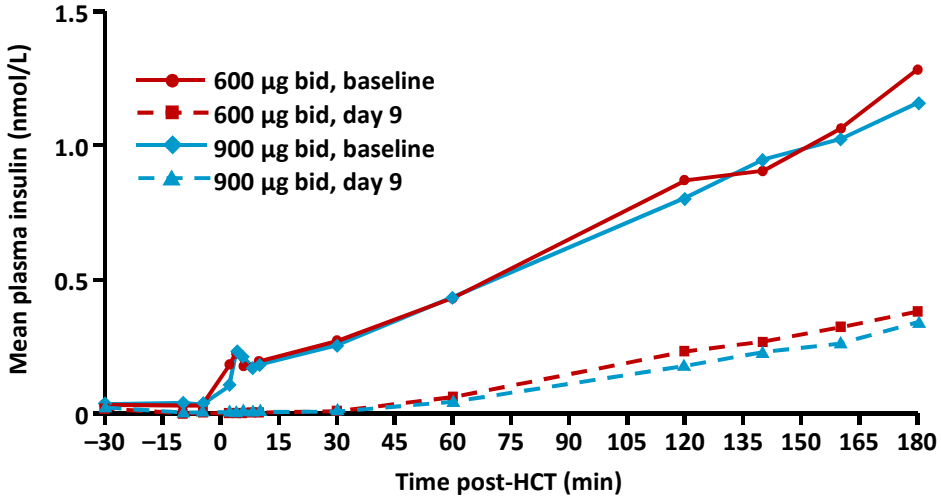
GIP

$AUC_{0–30min}$, $AUC_{30–180min}$ and $AUC_{0–180min}$ significantly lower at day 8 than at baseline in both dose groups

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

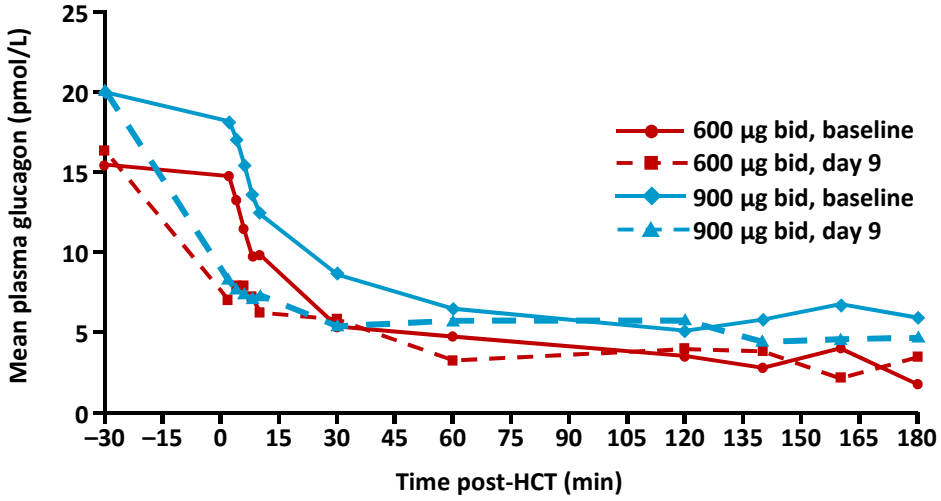
GIP, glucose-dependent insulinotropic polypeptide;
GLP-1, glucagon-like peptide-1

HCT: Pasireotide decreases plasma insulin with minimal changes in plasma glucagon



Insulin

Decreases in $AUC_{0–10min}$, $AUC_{10–180min}$ and $AUC_{0–180min}$ between baseline and day 9 were significant in both dose groups ($P<0.001$)

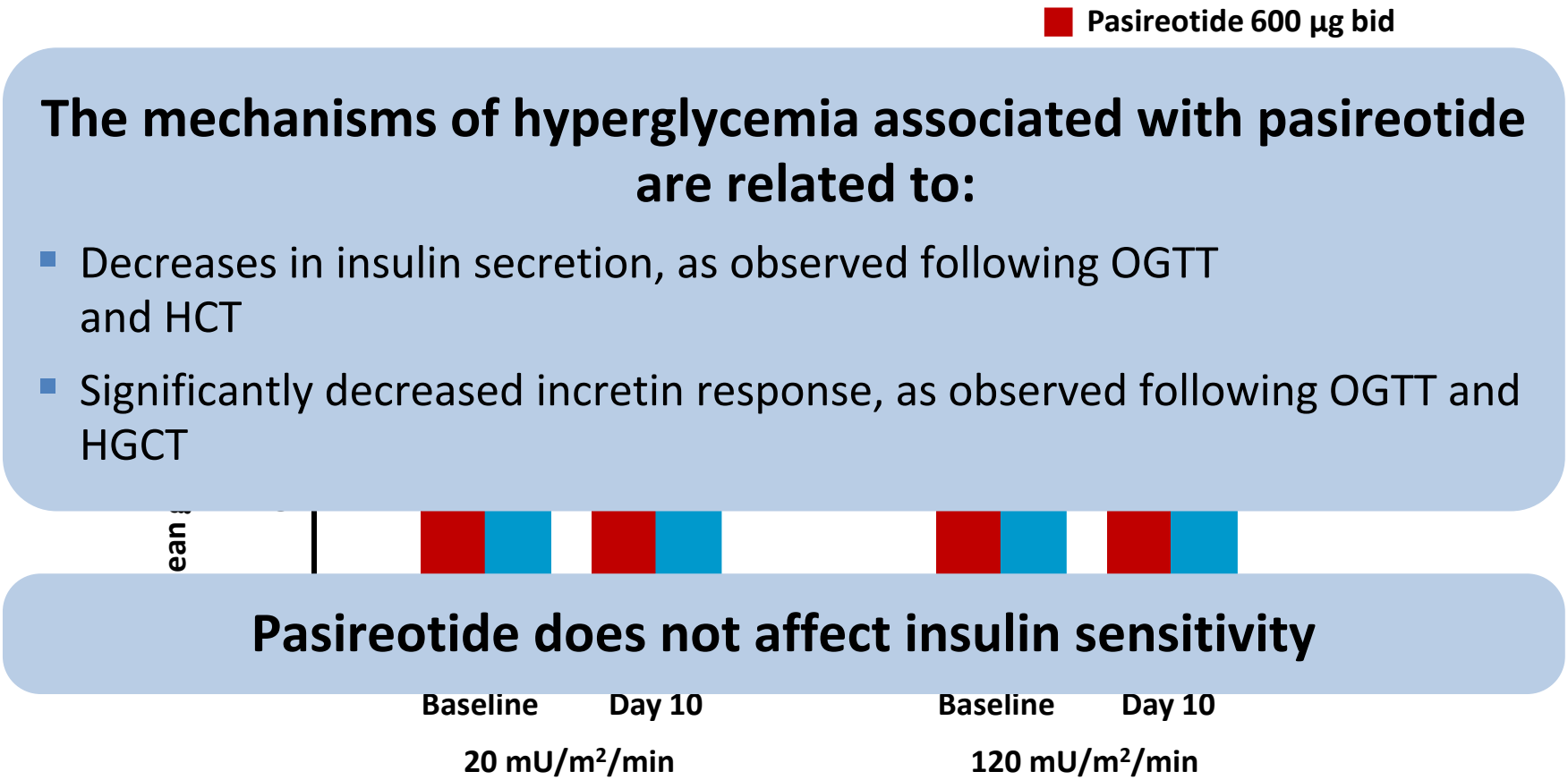


Glucagon

Minimal effect of pasireotide on glucagon secretion

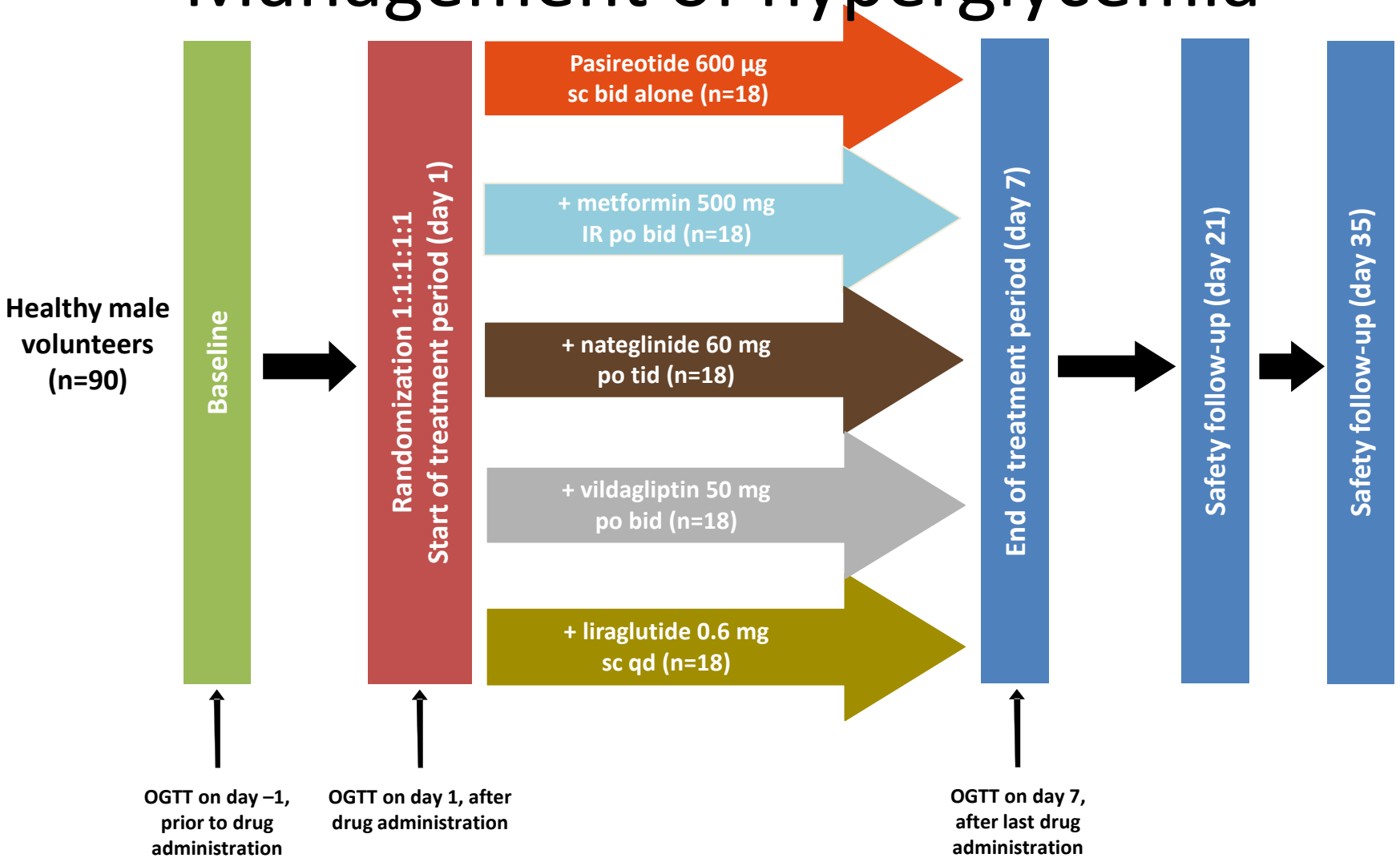
Henry RR *et al.* ENDO 2011;abst P3-274

HECT: Pasireotide does not affect insulin sensitivity



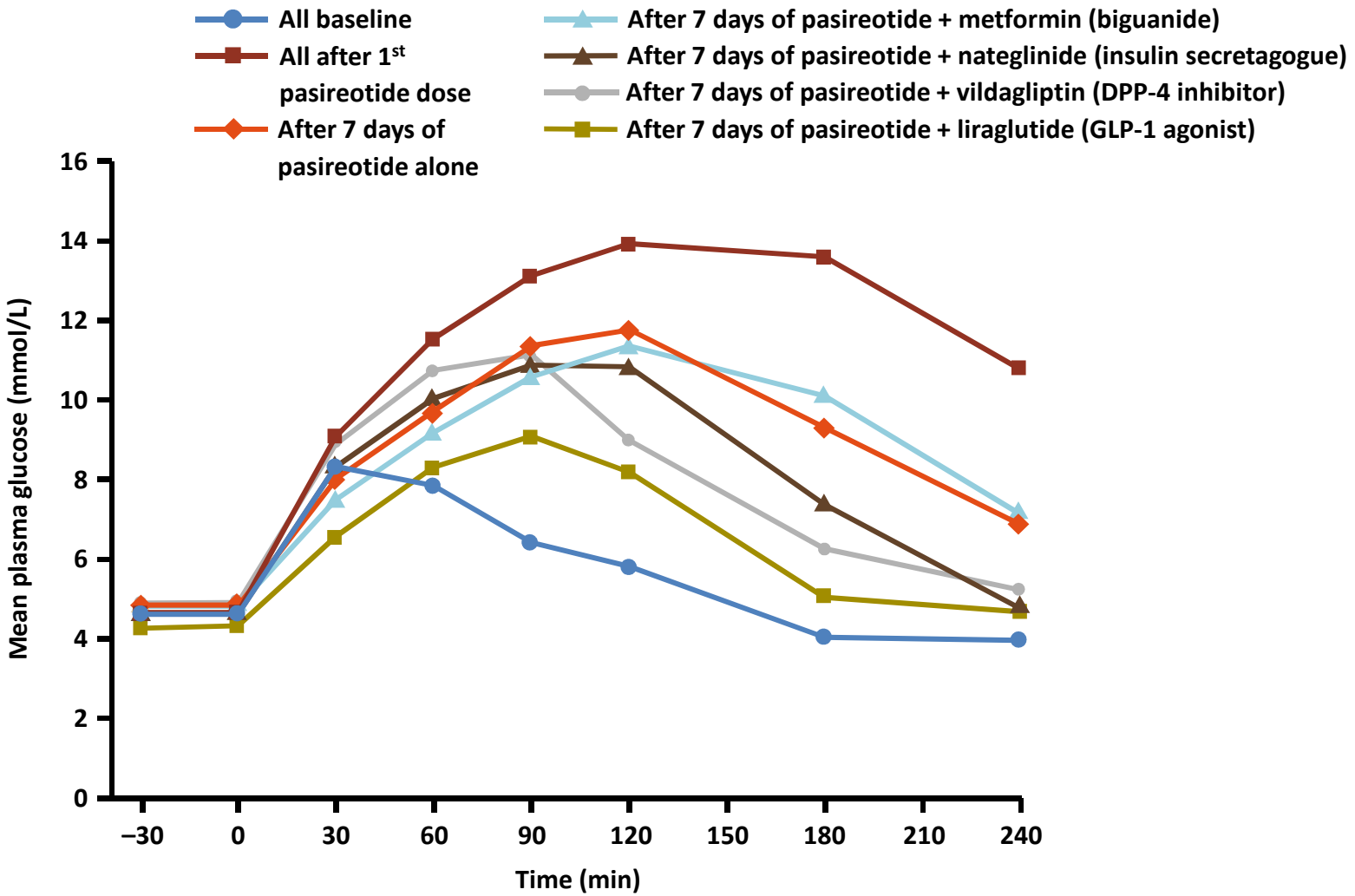
Henry RR *et al.* ENDO 2011;abst P3-274

SOM230B2124: Study design
Management of hyperglycemia



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

Changes in glucose levels during OGTT



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

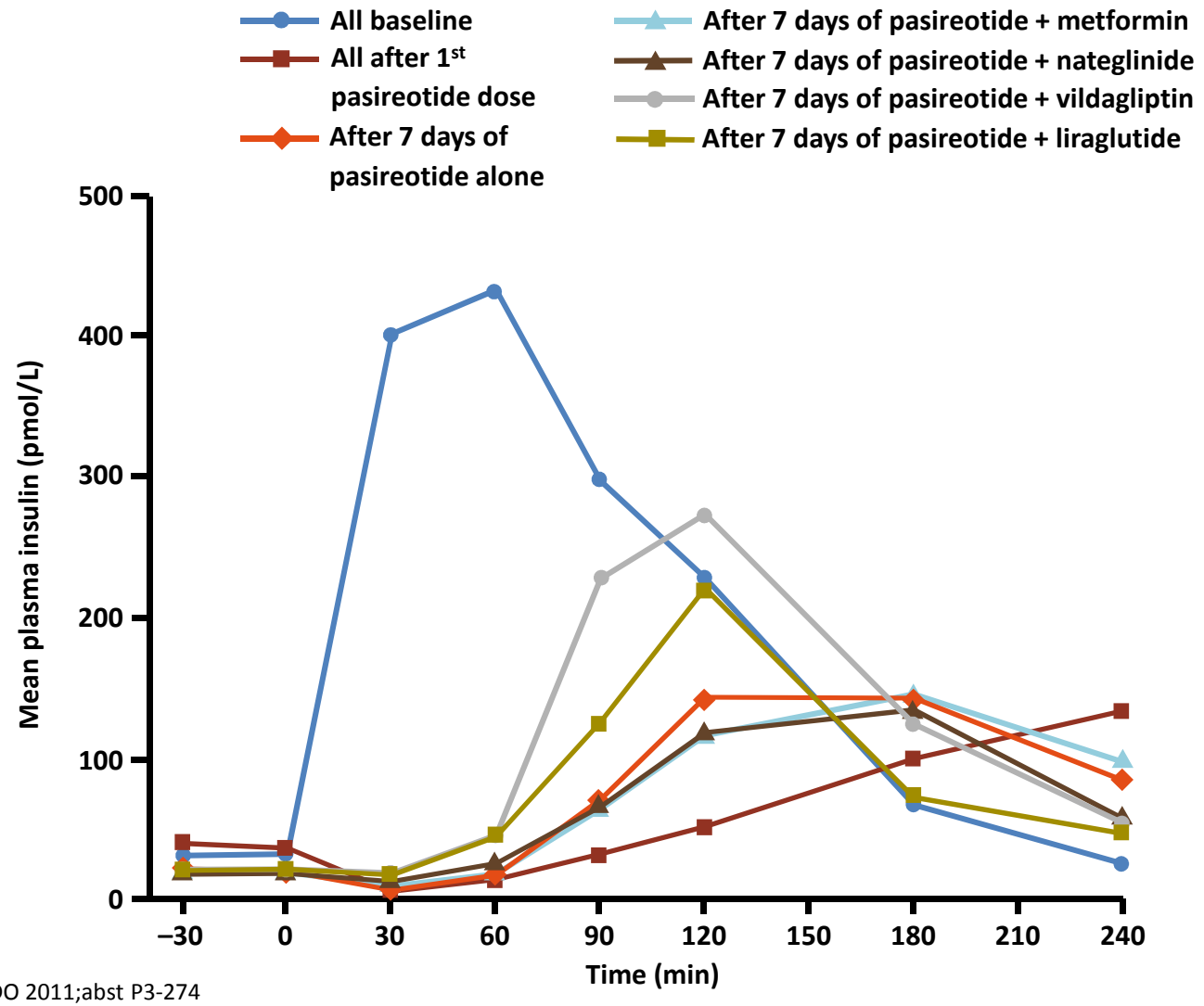
DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide-1

$AUC_{0–4h}$ of plasma glucose

- Plasma glucose decreased after 7 days of treatment, compared with pasireotide alone:
  - 29% with liraglutide
    (geometric mean ratio 0.71; 90% CI 0.66, 0.76)
  - 15% with vildagliptin
    (geometric mean ratio 0.85; 90% CI 0.79, 0.91)
  - 10% with nateglinide
    (geometric mean ratio 0.90; 90% CI 0.83, 0.96)
  - 2% with metformin
    (geometric mean ratio 0.98; 90% CI 0.91, 1.05)

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

Changes in insulin levels during OGTT



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

$AUC_{0–4h}$ of serum insulin

- Serum insulin increases after 7 days of treatment, compared with pasireotide alone:
  - 71% with vildagliptin

GLP-1 agonists and DPP-4 inhibitors appear to be the most effective drugs for ameliorating hyperglycemia associated with pasireotide treatment

  - 6% with metformin

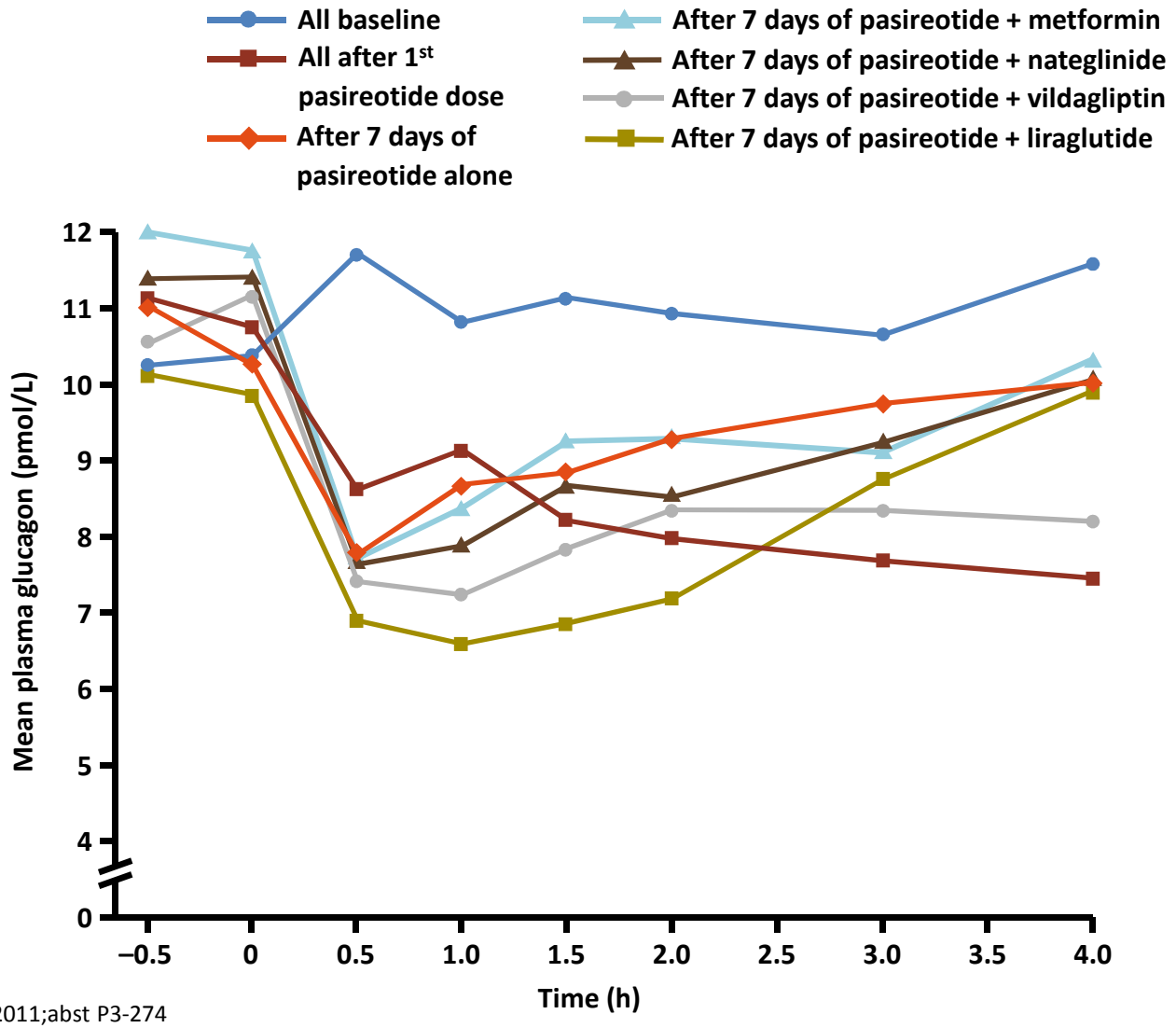
    (geometric mean ratio 1.06; 90% CI 0.82, 1.36)

  - 3% with nateglinide

    (geometric mean ratio 1.03; 90% CI 0.80, 1.32)

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

Changes in glucagon levels during OGTT



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

SOM230B2124: Safety/tolerability

Adverse events occurring more frequently than with pasireotide alone

Liraglutide	Nateglinide	Metfomin	Vildagliptin
Decreased appetite (38.9%)	Nausea (83.3%)	Diarrhea (77.8%)	Abdominal distension (22.2%)
Fatigue (22.2%)	Hypoglycemia (66.7%)		
Headache (27.8%)			
Cholestasis SAE (5.6%)			

Overall, AEs were consistent with the safety profile of pasireotide and the antidiabetic drugs used

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

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

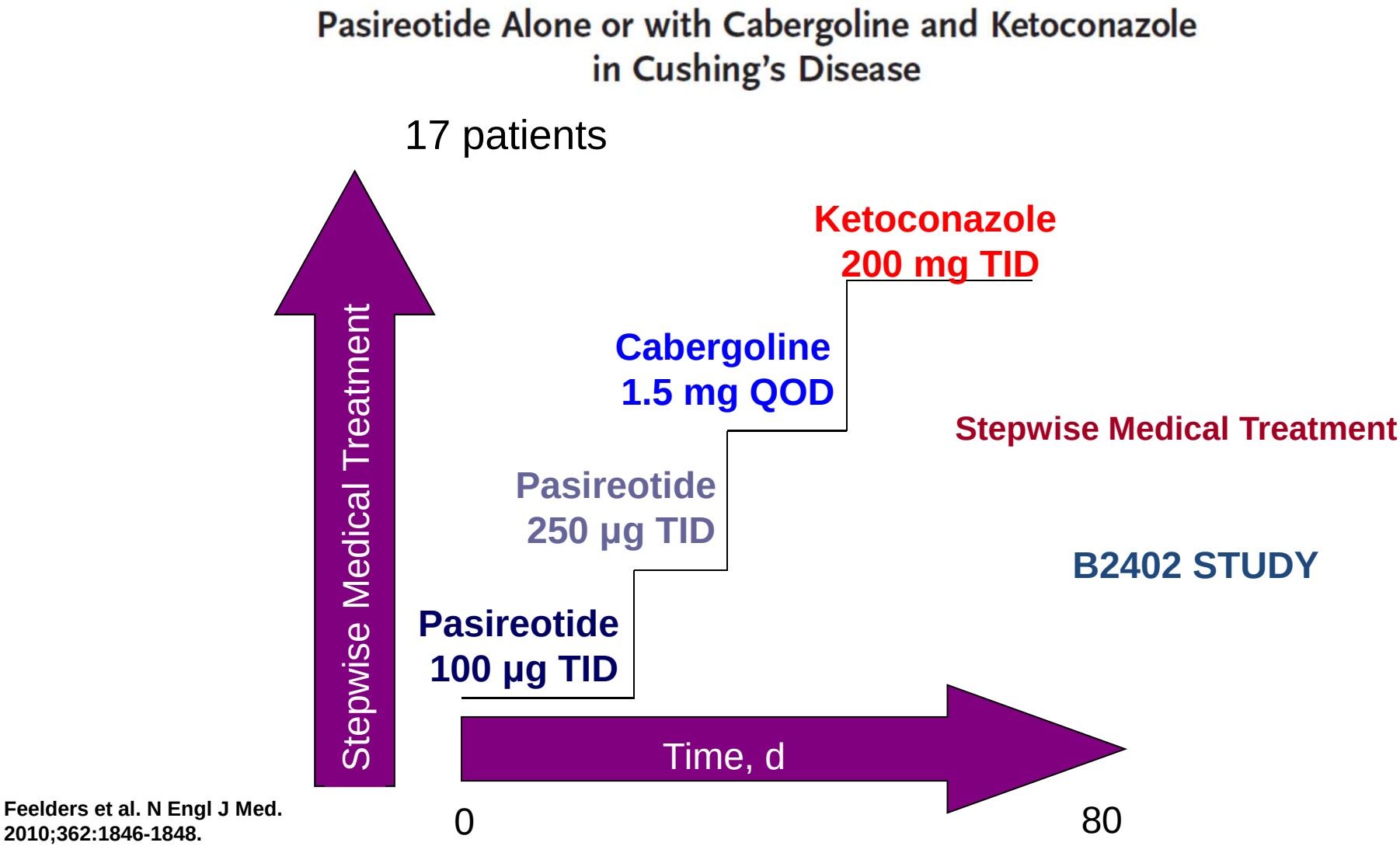
Henry RR *et al.* ENDO 2011;abst P3-274

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

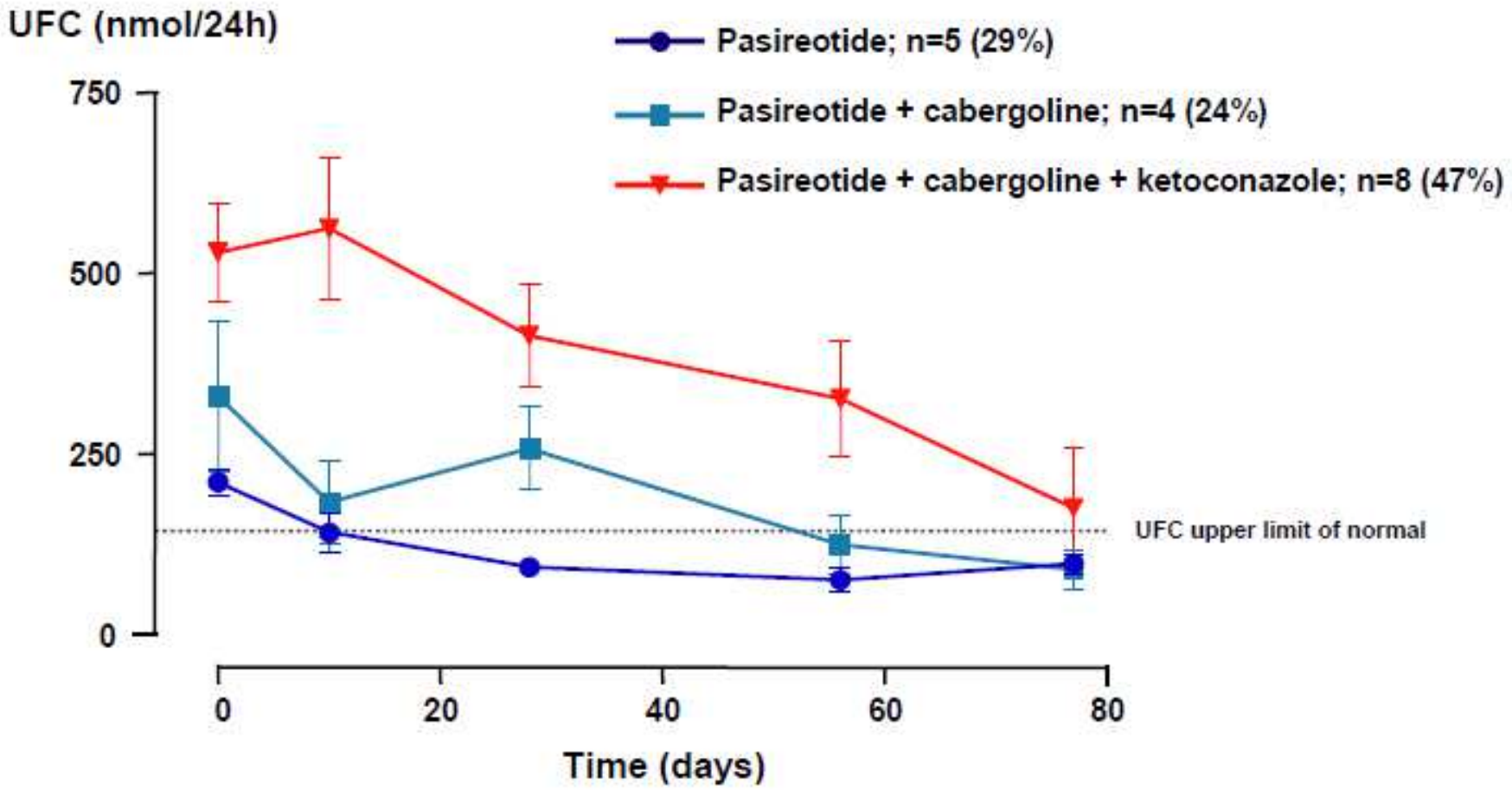
*Following current treatment guidelines

Combination Therapy



Feelders et al. N Engl J Med. 2010;362:1846-1848.

Combination Therapy



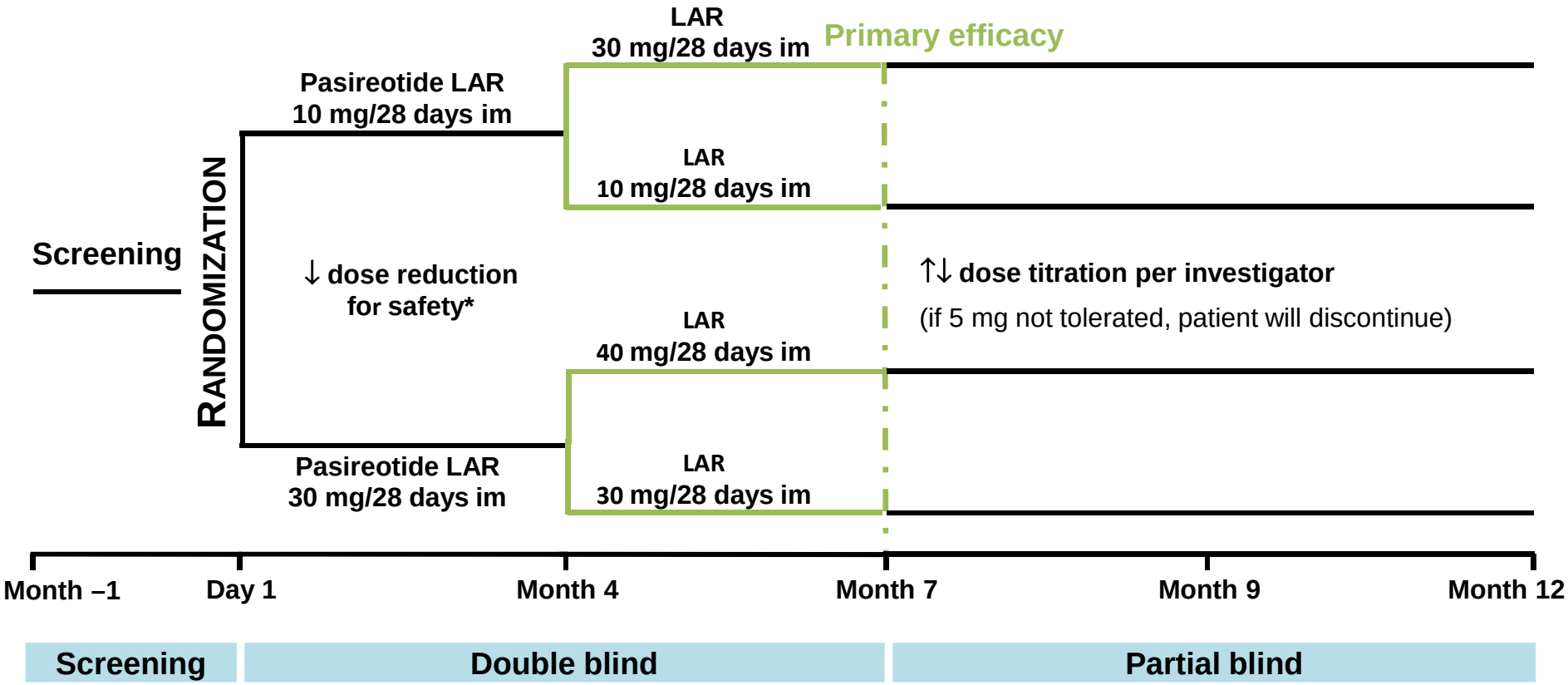
Disease control with pasireotide alone or in combination in 88% of patients with Cushing's disease

Feelders et al. N Engl J Med. 2010;362:1846-1848.

Future?

SOM230G2304: Evaluating the efficacy and safety of pasireotide LAR in patients with Cushing's disease

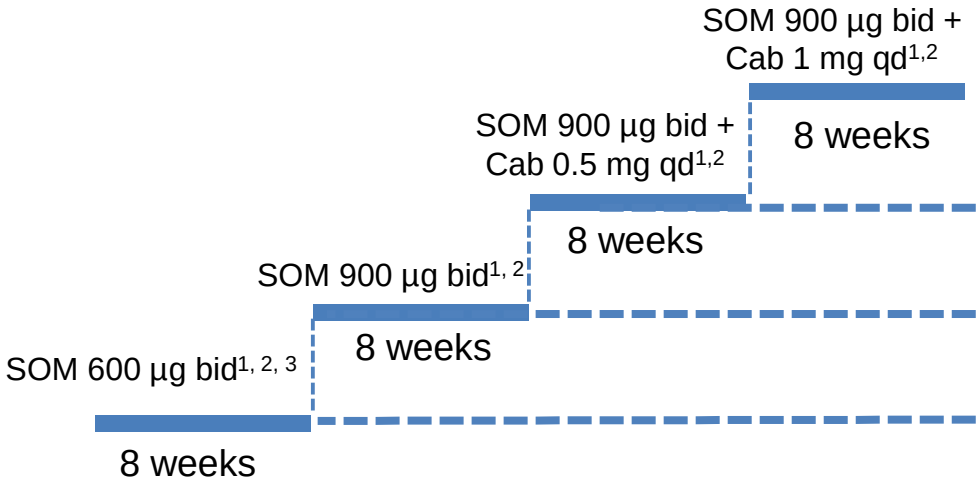
- Global, multicenter, randomized, double-blind, Phase III study
- Target enrollment is ~148 patients; recruitment is under way



*One dose level reduction permitted during the first 7 months (30 to 10 or 10 to 5 mg)
im, intramuscular injection

Ligueros-Saylan M *et al. Endocr Abstr* 2012;29:abst P1542.1

CSOM230B2410 - Pasireotide in combination with cabergoline



1. Patients not achieving normal UFC at the end of each treatment period will have the dose of the medication up-titrated to the next level
2. Patients losing biochemical control at any time point will have the dose of the study medication up-titrated to the next level
3. Patients that cannot have the dose up-titrated to 900 µg because of safety reasons, e.g. increased blood glucose levels, will be treated with the combination SOM 600 µg and cabergoline at increasing doses. Patients who cannot tolerate 600 µg bid will have the dose down-titrated to 300 µg bid

Thanks