Associazione per l'aiuto ai soggetti con Sindrome di Prader-Willi e alle loro famiglie

2° Forum di discussione e approfondimento per le famiglie e gli operatori in Campania

A che punto è la ricerca sulla Sindrome di Prader-Willi

Antonino Crinò

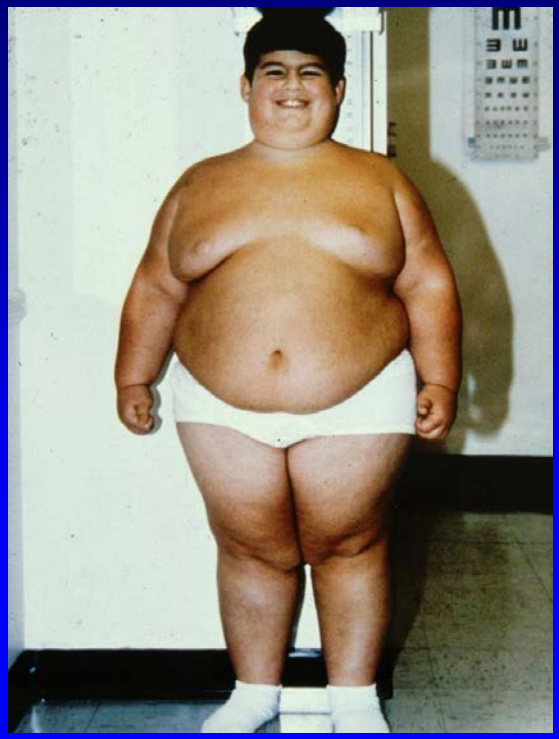
Struttura Semplice di Patologia Endocrina Autoimmune
Dipartimento Pediatrico Universitario Ospedaliero
Ospedale Bambino Gesù - IRCCS - Palidoro (Roma)

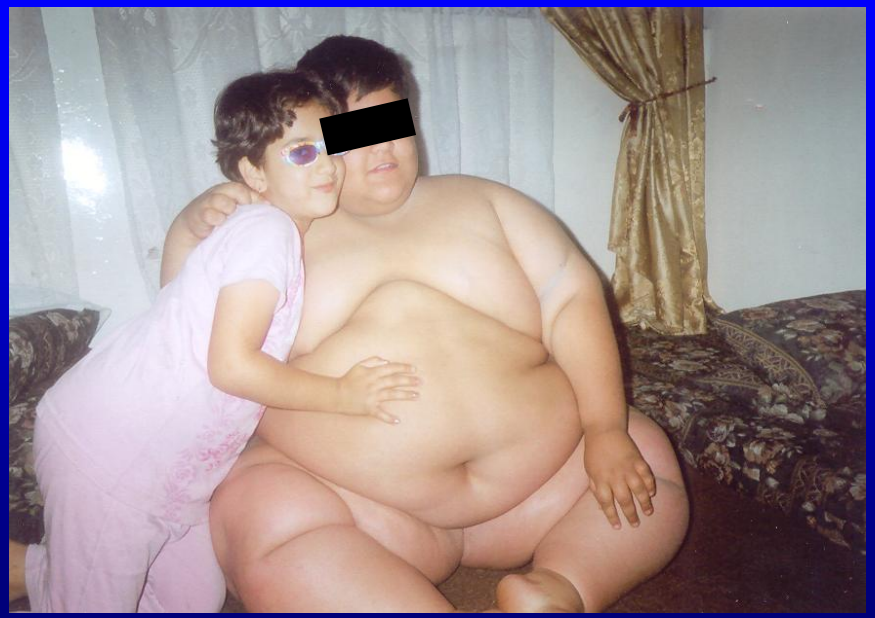
Bambino Gesù
OSPEDALE PEDIATRICO

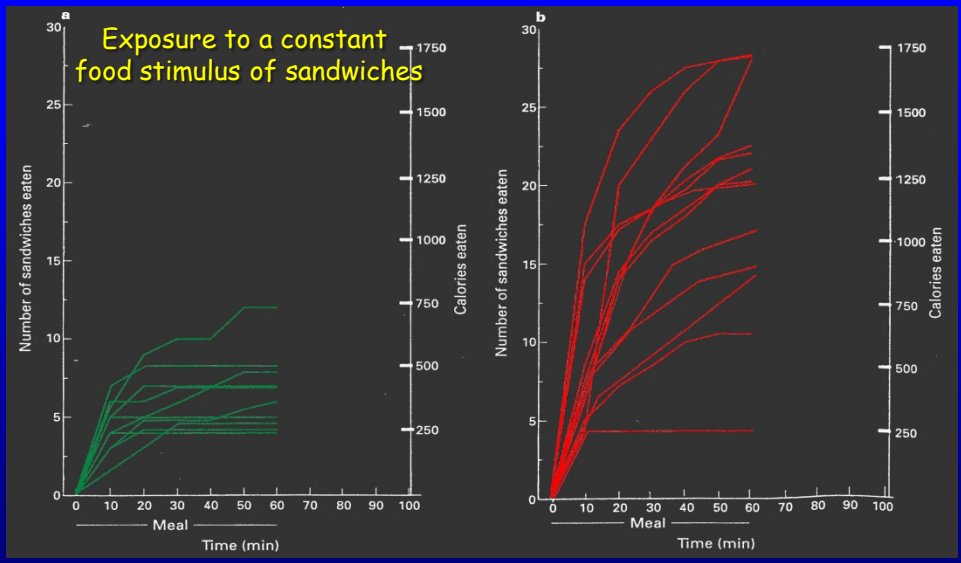
Napoli, *17 Ottobre 2015*

Obesità nella PWS

- Di tipo centrale – compare dopo i 2-4 aa
- Il grasso è per lo più localizzato all'addome, natiche, cosce (*risparmiate le mani e i piedi*)
- Massa grassa aumentata rispetto agli obesi semplici di pari peso - Ridotto grasso viscerale *(FFM)*
- Ridotta massa magra *(LBM)*
- Più frequente causa di morbilità e mortalità







adapted from Holland et al., Int J Obes 1993;17:527-32

Table 1 Nutritional phases in Prader-Willi syndrome

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Decreased fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite
1b	9–25 months	Improved feeding and appetite and growing appropriately
2a	2.1–4.5 years	Weight increasing without appetite increase or excess calories
2b	4.5–8 years	Increased appetite and calories, but can feel full
3	8 years to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

Modified from *Am J Med Genet A.*[3] 2011 Miller JL et al

COMPORTAMENTO ANORMALE VERSO IL CIBO
nella sindrome di PRADER-WILLI

IPERFAGIA

AUMENTO DELLA FAME

DIMINUITO SENSO DI SAZIETA'

- Ossessione morbosa verso il cibo
- Appetito insaziabile
- Rubare il cibo
- Rubare soldi per comprare il cibo
- Fame anche dopo aver mangiato
- Ridotta sazietà
- Abbuffarsi
- Ingestione di materiale non edibile

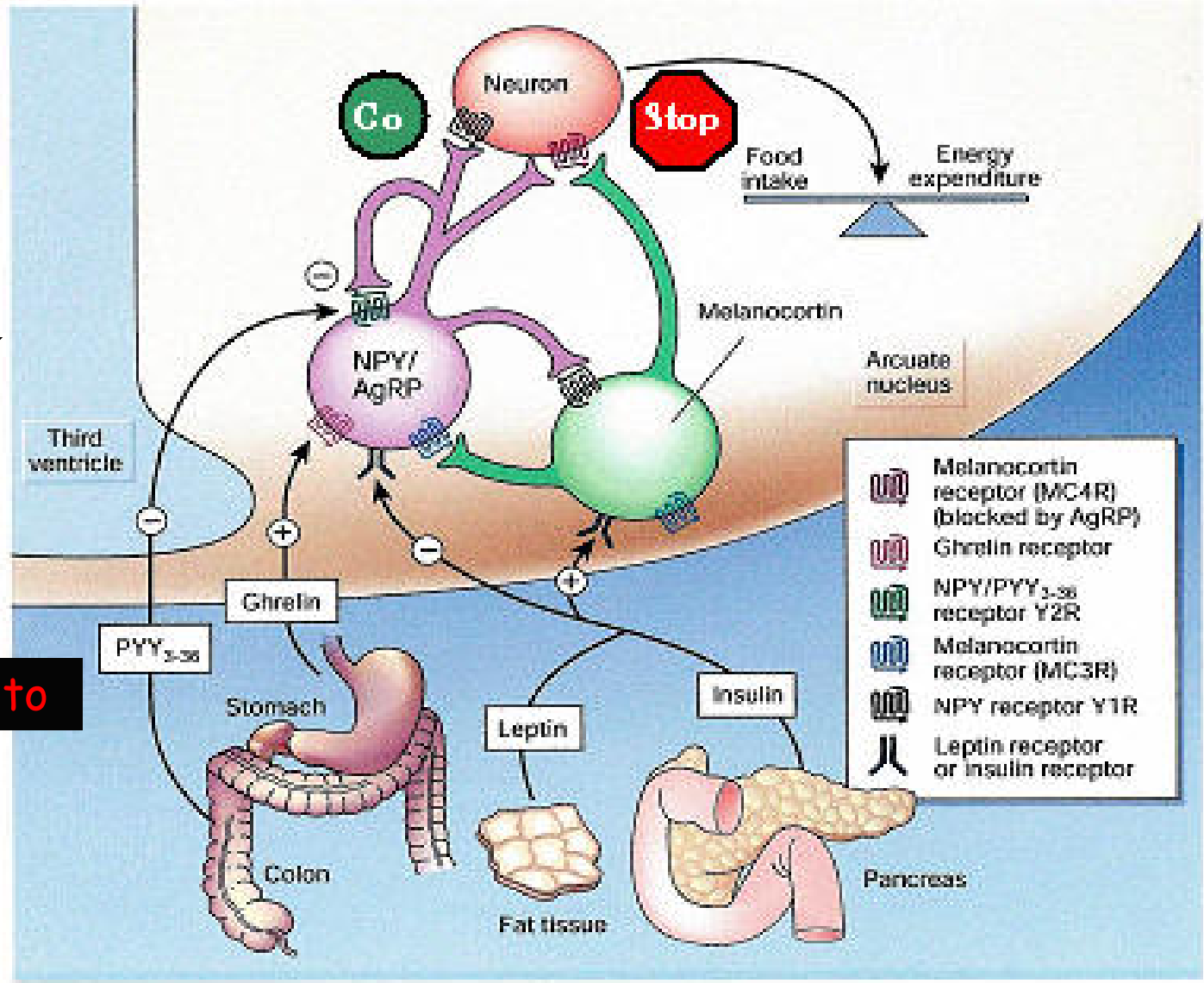
Hormones that Control Eating

Anoressizzanti

- Leptina ↑
- Peptide YY (PYY) ↓
- Ossitocina ↓
- Pancreatic polypeptide (PP) ↓
- GLP-1 N

Stimolano l'appetito

- Ghrelina ↑
- NPY N
- AGRP neurons N
- Insulin ↓ N



Modified from Nature 418 595 (2002)

Sindrome di Prader-Willi

Protocolli di ricerca internazionali

in via di attuazione

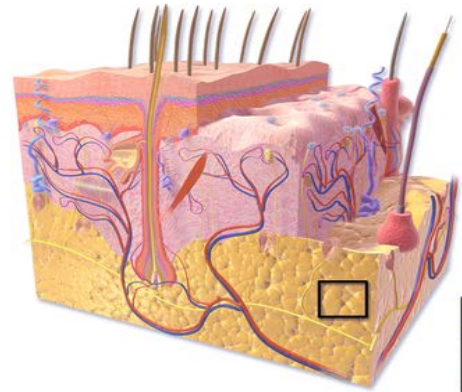
Current Medication Trials in Prader-Willi syndrome (PWS).

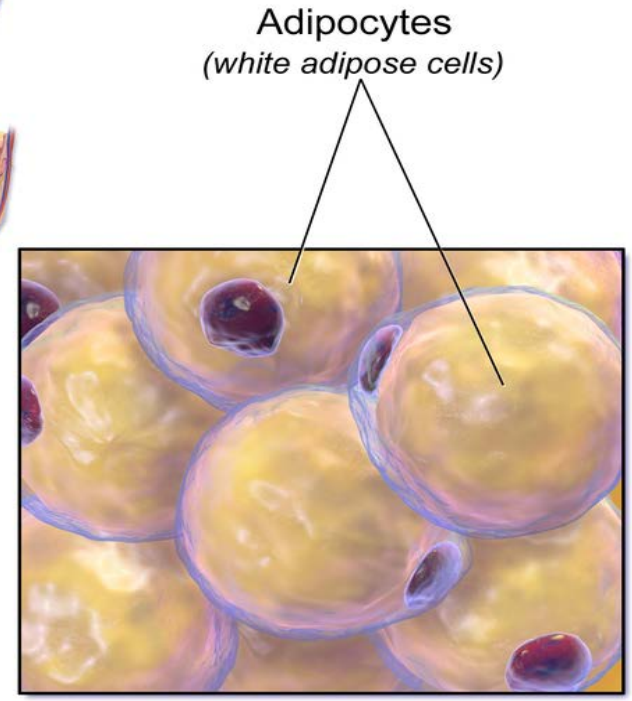
Medication	Company	Compound	Target Action	Study Phase	ClinicalTrials.gov Identifier
Beloranib	Zafgen	methionine aminopeptidase 2 (MetAP2) inhibitor	Decrease fat biosynthesis and enhance fat oxidation and lipolysis	Phase 3	NCT02179151
RM-493	Rhythm	melanocortin 4 receptor (MC4R) agonist	Activation of the MC4R to control pro-orexigenic pathways in the hypothalamus	Phase 2	NCT02311673
Intranasal Oxytocin	N/A	Oxytocin nasal spray	Bind oxytocin receptors to improve satiety and behaviors	Phase 2	NCT02013258
Intranasal FE 992097	Ferring	Oxytocin analog	Bind oxytocin receptors to decrease hyperphagia and behaviors Hyperpolarize hypothalamic neurons	Phase 2 completed	NCT01968187
Diazoxide	Essentialis	K^+-ATP channel agonist	whose activity is otherwise impaired by a defective leptin signaling pathway	Phase 2	NCT02034071
AZP-531	Alize	unacylated ghrelin analog	Increase unacylated ghrelin levels to improve blood glucose levels and weight	Not started	Not yet listed
Exanatide/ Liraglutide	AstraZeneca/ Novo Nordisk	GLP-1 Receptor Agonists	Suppress appetite and to induce weight loss	Phase 2	NCT01444898/ NCT01542242

J.L. Miller, Diseases, 2015

Methionine Amniopeptidase 2 *(MetAP2)* Inhibition

- Fumagillin - antimicrobial agent isolated in 1949 from *Aspergillus fumigatus* that inhibits MetAP2
  - MetAP2 promotes endotheliial cell proliferation
  - Angiogenesis requires endothelial cells to build new vessels
  - Fumagilin blocks angiogenesis
- Beloranib originally developed as anticancer agent with better safety profile than fumagilin
- Beloranib inhibits endothelial cell proliferation in adipocytes resulting in adipose cell apoptosis



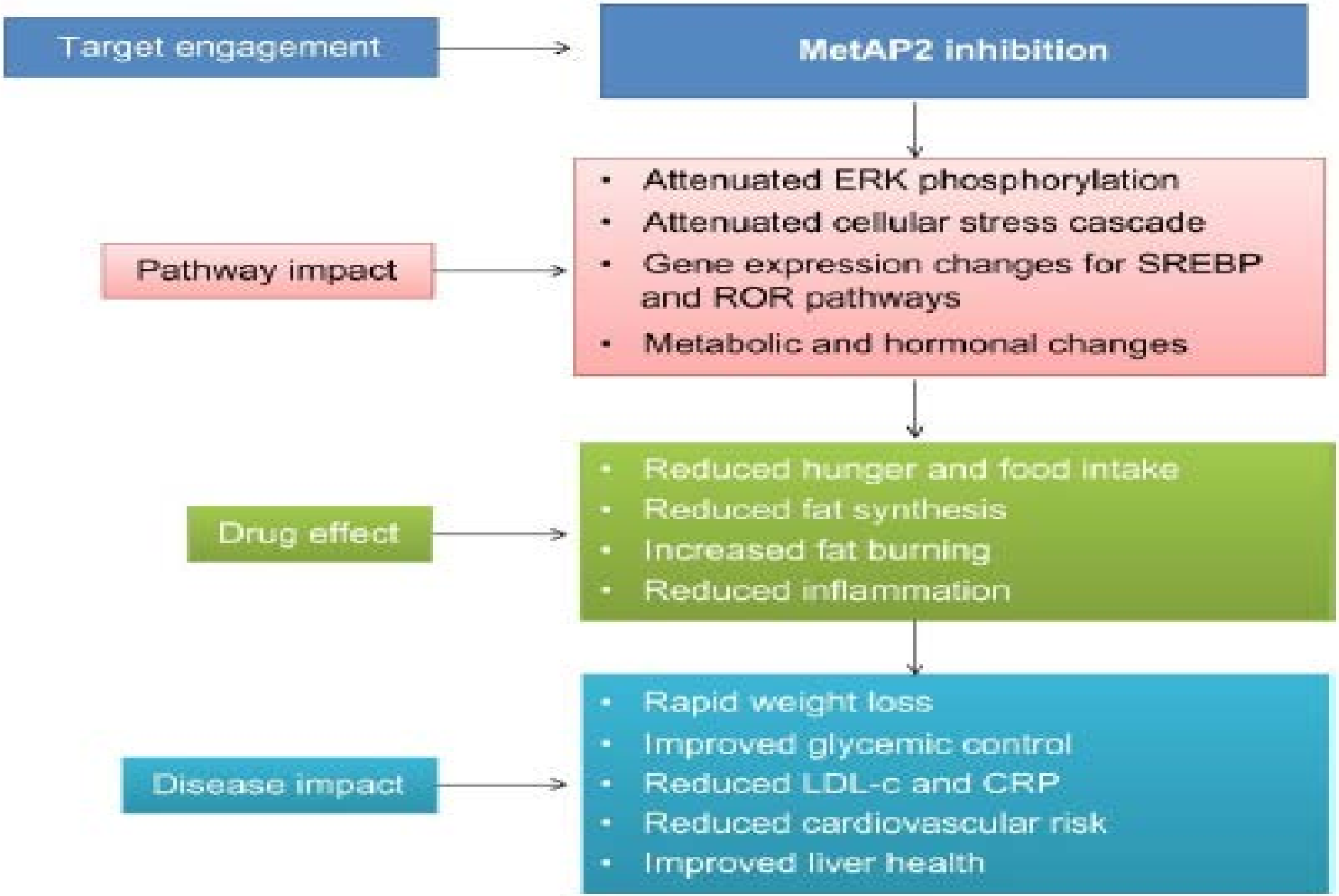


Adipose Tissue

Bruce Blausen, Blausen.com.
"Blausen gallery 2014"

- Act on the liver and adipose tissue to rebalance lipid metabolism and body composition and reduce hunger

Azione del Beloranib

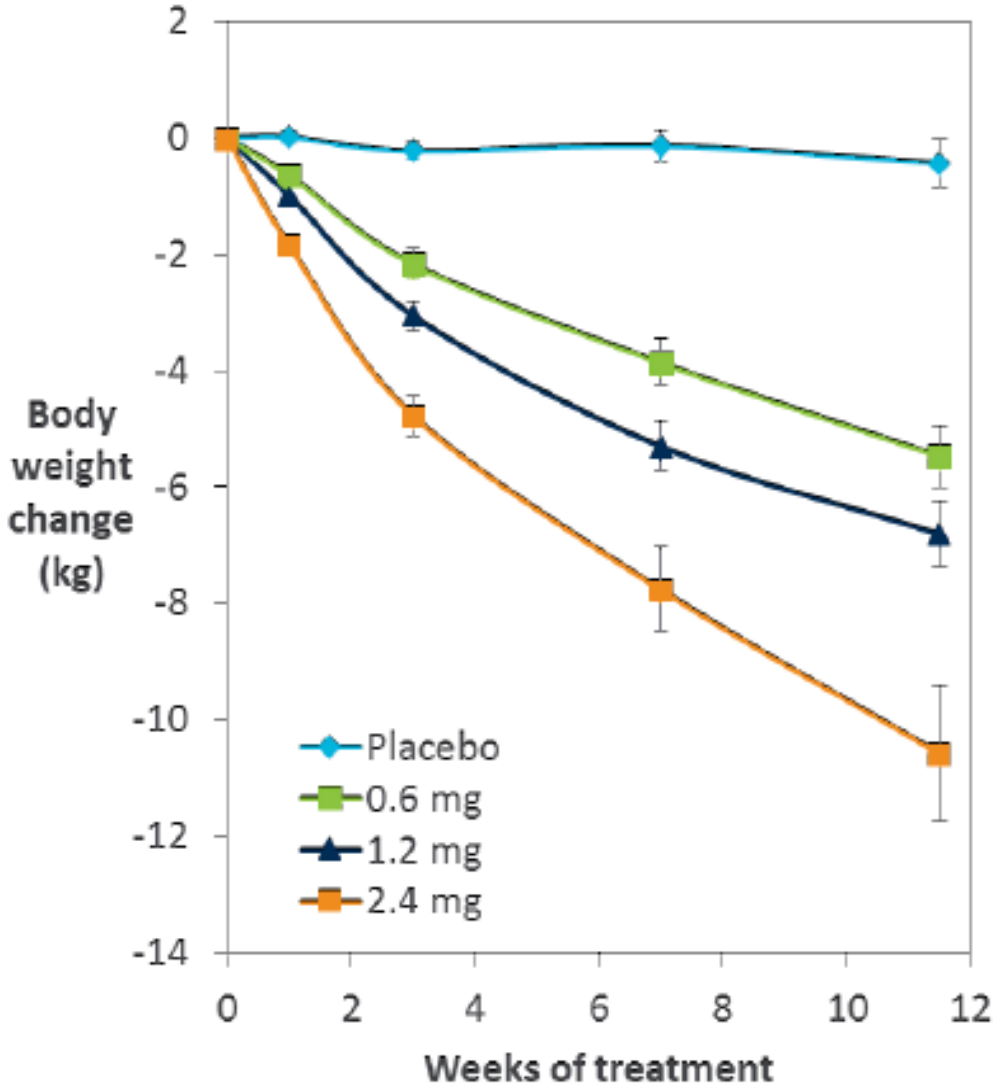


Beloranib – Consistent Impact on Weight and Hunger in "Exogenously" Obese Patients

Phase IIa study

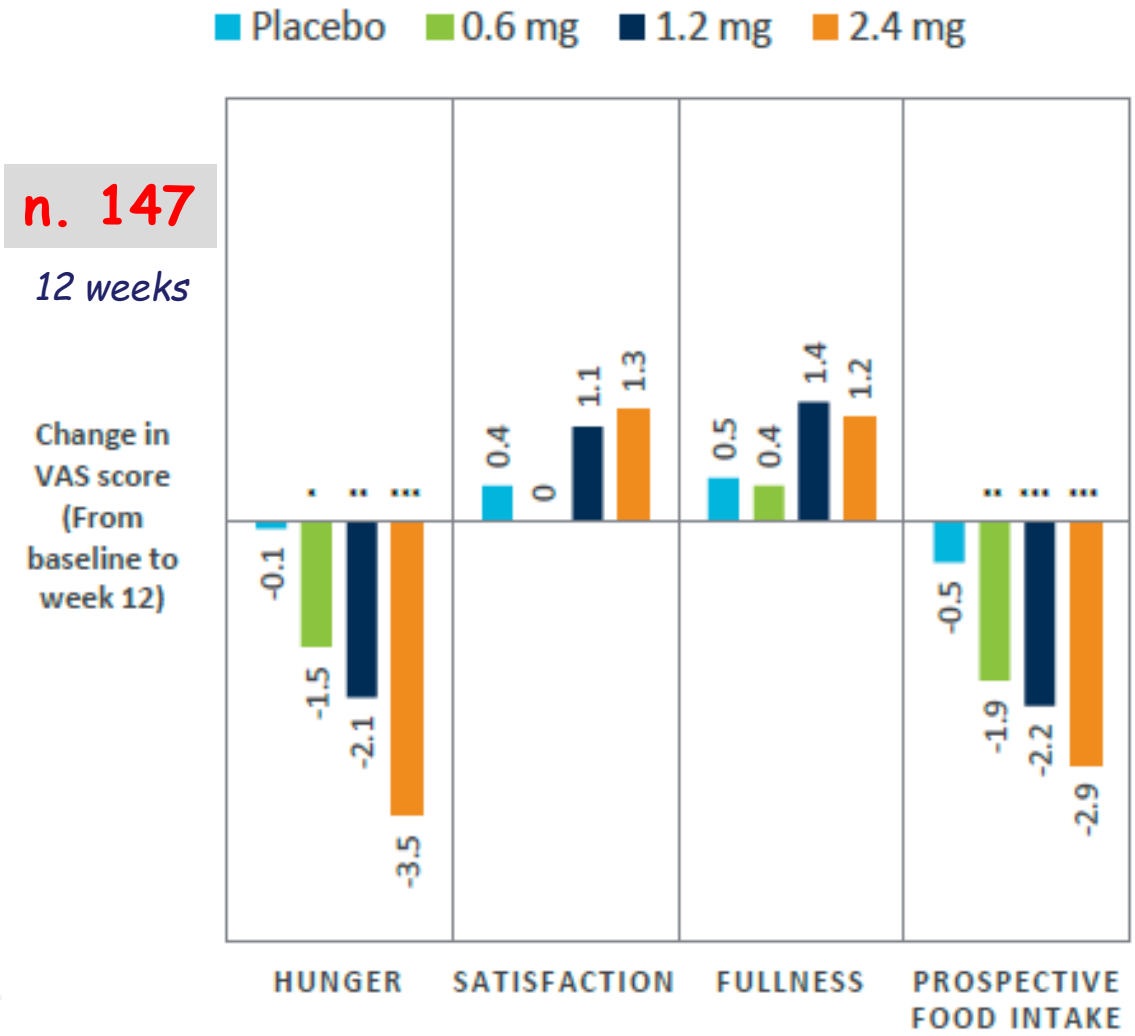
Results from ZAF-201 completer population

Kim DD, *et.al.* Diab Obesity Metab, March 2015



n. 147

12 weeks



BELORANIB *(protocollo ZAF-312)*

- Prodotto dalla Ditta Zafgen *(USA)*
- Già utilizzato su un ristretto numero di pazienti con PWS (n.108) e su alcuni pazienti che hanno sviluppato obesità in seguito ad un danno della regione ipotalamica *(craniofaringioma).*
- Tipo dello studio: randomizzato, doppio cieco, con placebo *(Fase III)*
- Durata dello studio: 12 mesi
- In Europa verranno inseriti n. 150 pazienti dai 12 anni in su *(60 placebo, 90 Beloranib).*
- Scopo: dimostrare l'efficacia del farmaco nell'iperfagia e nel calo ponderale, nonché la sicurezza e la tollerabilità.
- n. 5 Centri coinvolti in Italia:
  Ospedale Bambino Gesù, Istituto Auxologico Italiano, H. S.Raffaele Milano, Università di Padova, Università di Modena

Zafgen Pipeline

Novel Portfolio Leveraging Powerful MetAP2 Target in Metabolic Diseases

Drug Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Milestone
Beloranib Fumagillin-class MetAP2i	*Prader-Willi syndrome*	*Twice-weekly subcutaneous (SC) injection*				Initiate EU Phase 3 trial 1H 2015
Beloranib Fumagillin-class MetAP2i	*Hypothalamic injury*	*Twice-weekly (SC) injection*				Complete Phase 2a trial 1Q 2015
Beloranib Fumagillin-class MetAP2i	*Severe obesity*	*Twice-weekly (SC) injection*				Initiate Phase 2b trial 2H 2014
2nd Generation MetAP2i	*General obesity*	*SC Injection*				Candidate Nomination
ZGN-839 Novel chemical class MetAP2i	*NASH / Type 2 diabetes*	*Oral*				IND 1H 2015

Zafgen owns world-wide commercial rights to all compounds (exclusive of Korea for beloranib)

ZAF-211: Successful Proof of Concept Trial

The Largest Placebo-Controlled Multiple Dose Study for Obesity in PWS

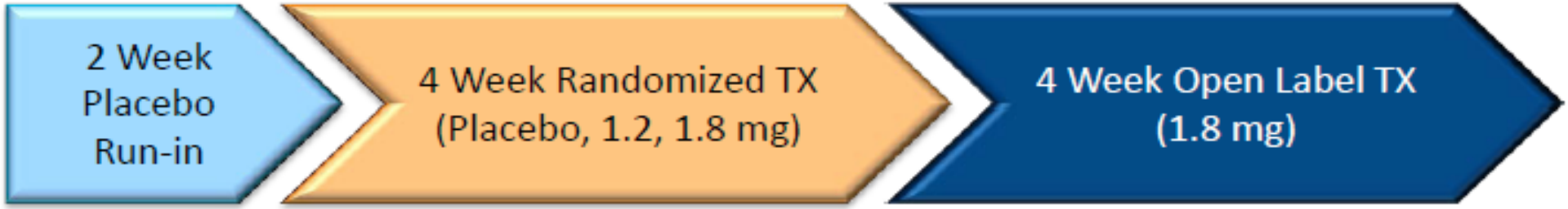
Phase IIa

Trial Population

- 17 Patients in group home setting
- Genetically confirmed PWS
- Obese – BMI average ~31 kg/m²
- 50% Increased food allowance

Key Readouts

- Biomarkers
- Hyperphagia-related behaviors
- Body composition and weight
- Safety and tolerability



Key Findings

- Well-tolerated – no safety signals
- Clear evidence drug pathway is responsive in PWS patients including LDL-c reduction
- Improved hyperphagia-related behaviors
- Reduced body fat content vs. placebo

} Planned registration endpoints

Ongoing Phase 3 Study in Patients with Prader-Willi Syndrome (ZAF-311)

- Randomized, double-blind, placebo-controlled
- 15 sites in US, 102 patients

Dose	# patients	6 month randomized treatment	6 month open label treatment
2.4 mg beloranib	34	2.4 mg	2.4 mg
1.8 mg beloranib	34	1.8 mg	2.4 mg
Placebo (2 arms to volume match the beloranib arms)	34	placebo	2.4 mg

- Dual primary endpoints of change in body weight and change in hyperphagia related behaviors
- Recruitment is ongoing

Key Study Population Criteria

- Male and female patients with Prader-Willi syndrome (genetically confirmed)
- Hyperphagia total score ≥13 (scale of 0-36)
- BMI ≥30 and ≤60 kg/m^2 for adults or BMI ≥95th percentile for adolescents for age and gender
- Age 12-65
- Patients with type 2 diabetes permitted
  - HbA1c <10%, FPG <240 mg/dL; no insulin use
- Stable body weight for 3 months
- No subjects unwilling or unable to have DXA scans
- Patients living in group homes (≥ 50% of time) are excluded

Glucagon-like peptide 1 (GLP-1)

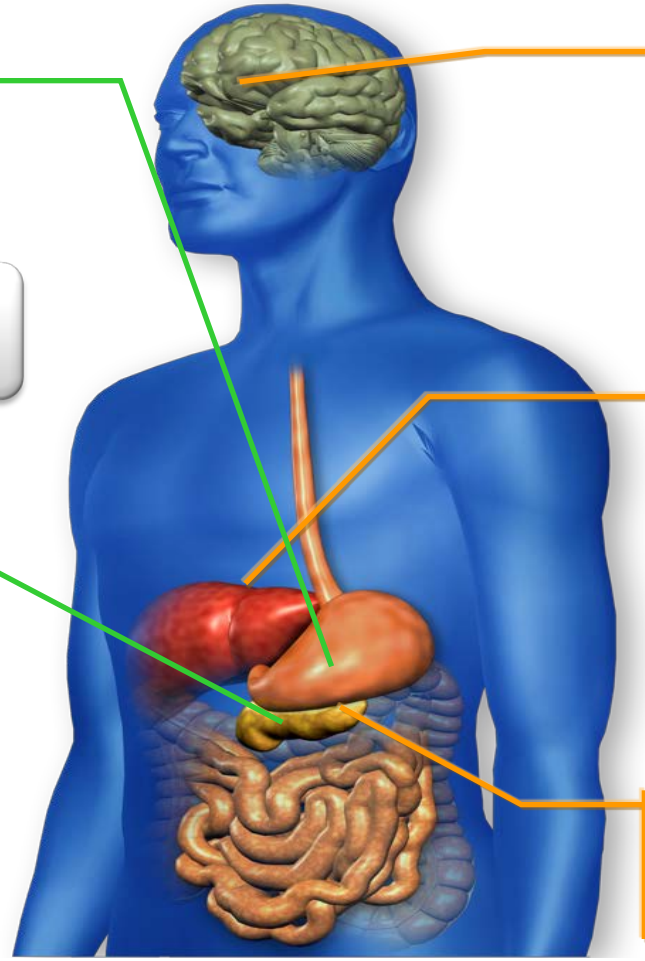
Hormone produced by the gastrointestinal tract (*cell L*) in response to incoming nutrients, and has important actions that contribute to glucose homeostasis

GLP-1 secretion meal induced

Glucose dependent action: insulin secretion when glycemia >110 mg/dl

B Cells: *insulin secretion and production*

A Cells: *glucagon secretion*

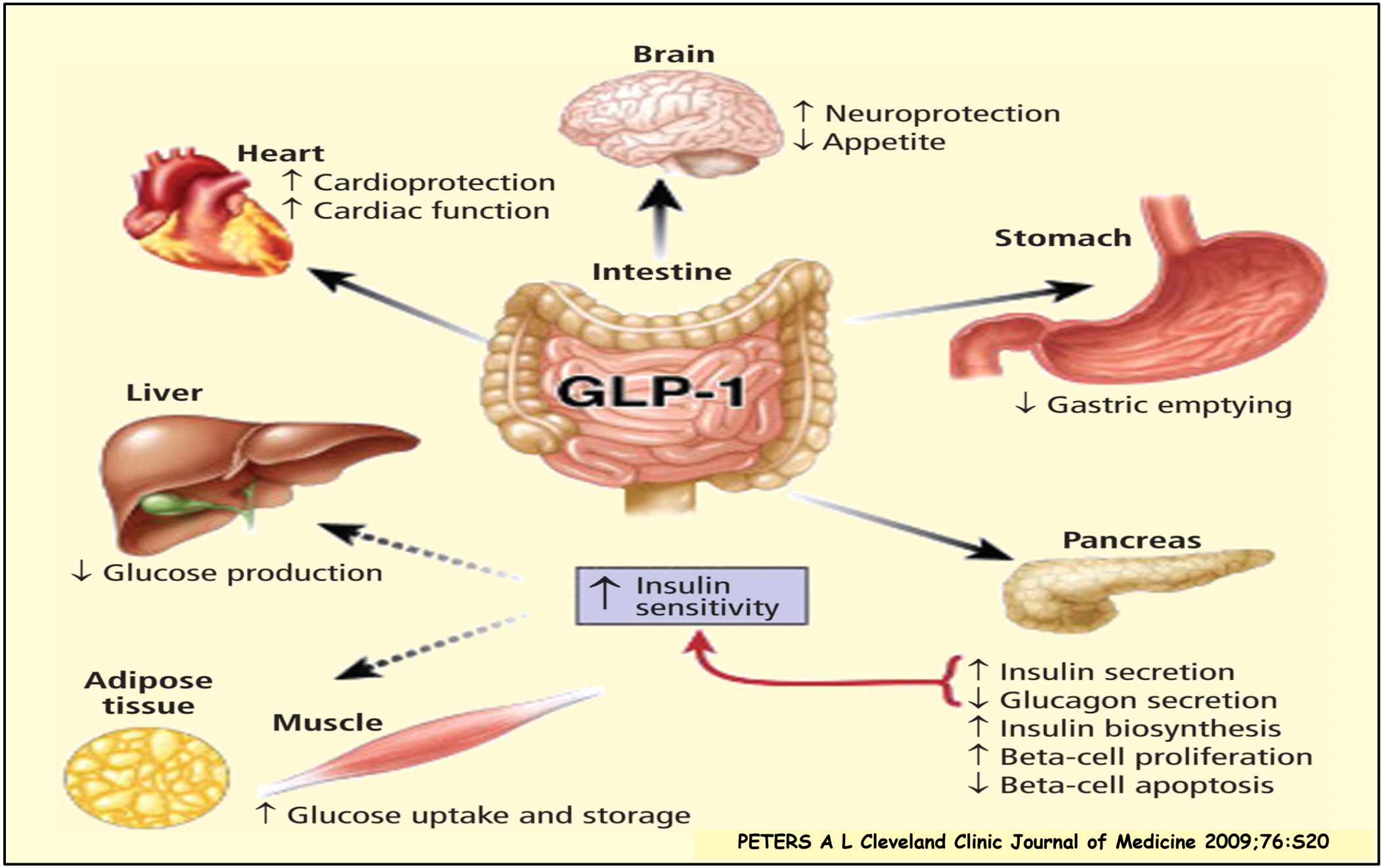


Satiety

Liver: glucose synthesis

Stomac: gastric emptying

GLP-1: half-life (*1-2 min*), inactivated by DPP-4 (*enzyme dipeptidyl peptidase-4*)



PETERS A L Cleveland Clinic Journal of Medicine 2009;76:S20

Use of GLP-1 Receptor Agonists in Prader-Willi Syndrome: Report of Six Cases

Danilo Fintini,[1] Graziano Grugni,[2] Claudia Brufani,[1] Sarah Bocchini,[1] Marco Cappa,[3] and Antonino Crinò[1]

Diabetes Care 2014;37:e76–e77 | DOI: 10.2337/dc13-2575

3 del15, 3 UPD (1 with IGT and 5 with T2DM)

None of them experienced GH therapy.

Table 1—Characteristics of the patients and variation of parameters and therapy during the period of therapy/observation of six PWS patients

All had a liver steatosis.

				Basal		12 months		24 months		
Patient	Sex	Age (years)	Therapy	BMI	HbA_{1c} % (mmol/mol)	BMI	HbA_{1c} % (mmol/mol)	BMI	HbA_{1c} % (mmol/mol)	Therapy
1	M	37.3	Lrg 1.2 Met 1,700	36	7.6 (60)	33	6.3 (45)	32.4	6.9 (52)	Testosterone 250 mg Ramipril 5 mg Calcitriol 0.5 µg
2	M	20.7	Exn 20 Met 3,000	28	8.2 (66)	28	7 (53)	26.5	6.8 (51)	Topiramate 40 mg
3	M	27.7	Lrg 1.2 Met 1,700	44	7.5 (58)	44	6.9 (52)	44	7.4 (57)	Ramipril 5 mg Candesartan 8 mg
4	F	30.4	Lrg 1.2 Met 3,000	50	8.7 (72)	48	7.3 (56)	48.1	7.8 (62)	Allopurinol 150 mg
5	F	37.1	Lrg 1.8 Met 2,000 Glic 30	30	8.3 (67)	31	8.6 (70)	30.2	9.3 (78)	Simvastatin 20 mg EEPP
6	F	34.5	Exn 20 Met 3,000	57	9.5 (80)	59	9.5 (80)	58.5	10.1 (87)	Furosemide 25 mg

All therapies are intended daily except for testosterone (patient 1), which was administered monthly. EEPP, estroprogestin; Exn, exenatide (µg/day); F, female; Glic, gliclazide (mg/day); Lrg, liraglutide (mg/day); M, male; Met, metformin (mg/day).

During the 24 months of treatment, we detected a tendency to decrease BMI, HbA_{1c} and waist circumference and a significant decrease of mean glycemia during continuous glycemic monitoring at 12 months in respect to baseline.

No side effects were reported in PWS patients. Mild reduction of appetite was observed by patients and parents, although not documented by questionnaire.

Protocollo LIRAGLUTIDE nella PWS

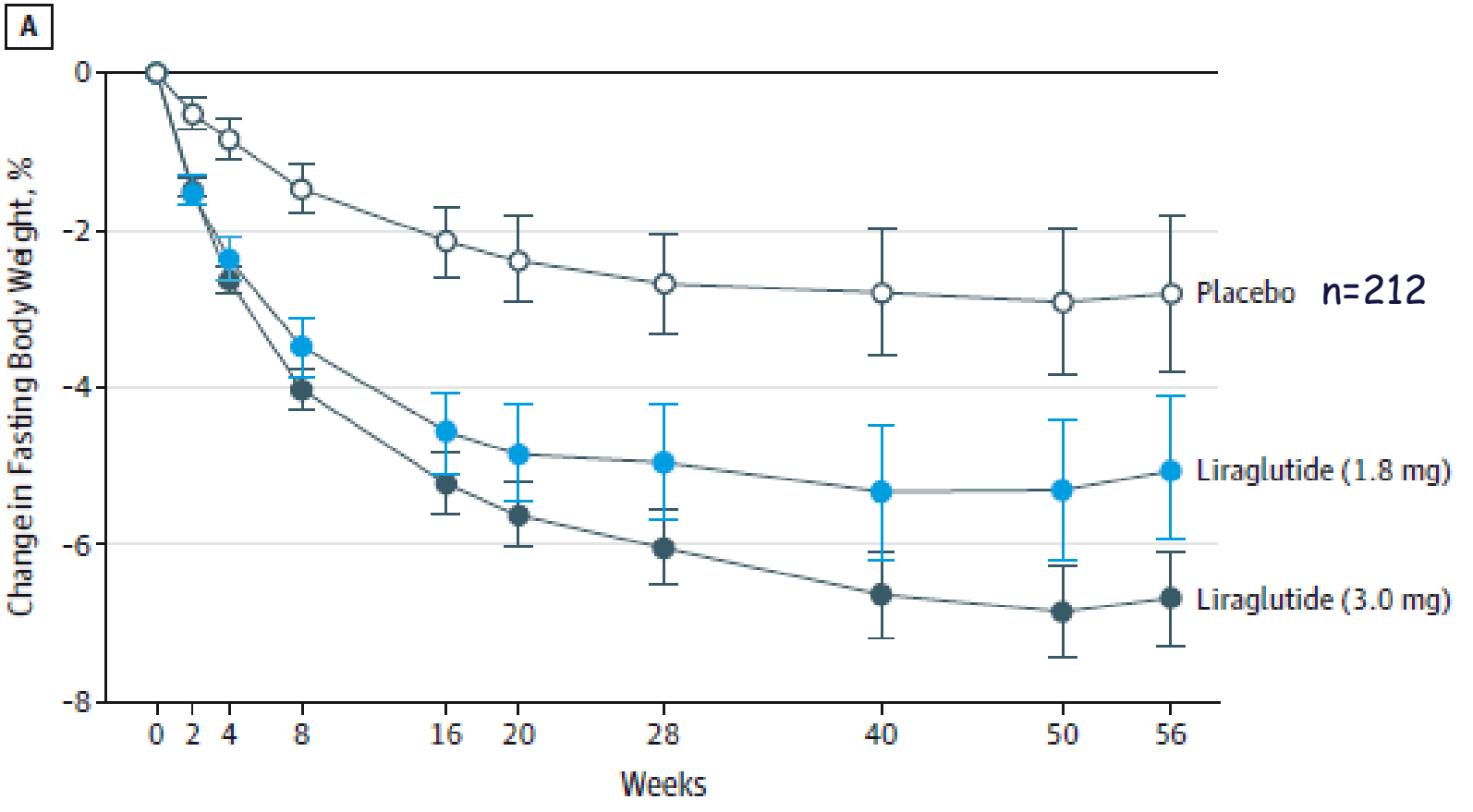
Studio NN8022-4179 SITE 401

- **Liraglutide** è un analogo del Glucagon-Like Peptide -1 (*GLP-1*) umano già disponibile in mono-somministrazione giornaliera iniettiva per il trattamento del Diabete mellito tipo 2.
- Sponsor: Azienda Farmaceutica Novo Nordisk S.p.A
- Studio randomizzato, con placebo in fase III
- Verranno trattati 60 pazienti con PWS *(n. 33 adolescenti 12-18 aa – parte A; n. 27 bambini 6-12 anni parte B)*
- Durata dello studio: 1 anno *(16 settimane doppio cieco; 36 settimane studio aperto)*
- The SCALE Obesity and Prediabetes study *(3731 pz – calo ponderale dell'8% dopo 56 settimane)*
- n. 8 Centri: Canadà, Nuova Zelanda, Australia, Italia, Turchia Francia, Olanda, USA

Original Investigation

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial



Davies MJ, JAMA, 2015

Protocollo Liraglutide in PWS

Key inclusion criteria

Part A

- Adolescents with PWS from 12 to <18 years with Tanner 2-5 puberty

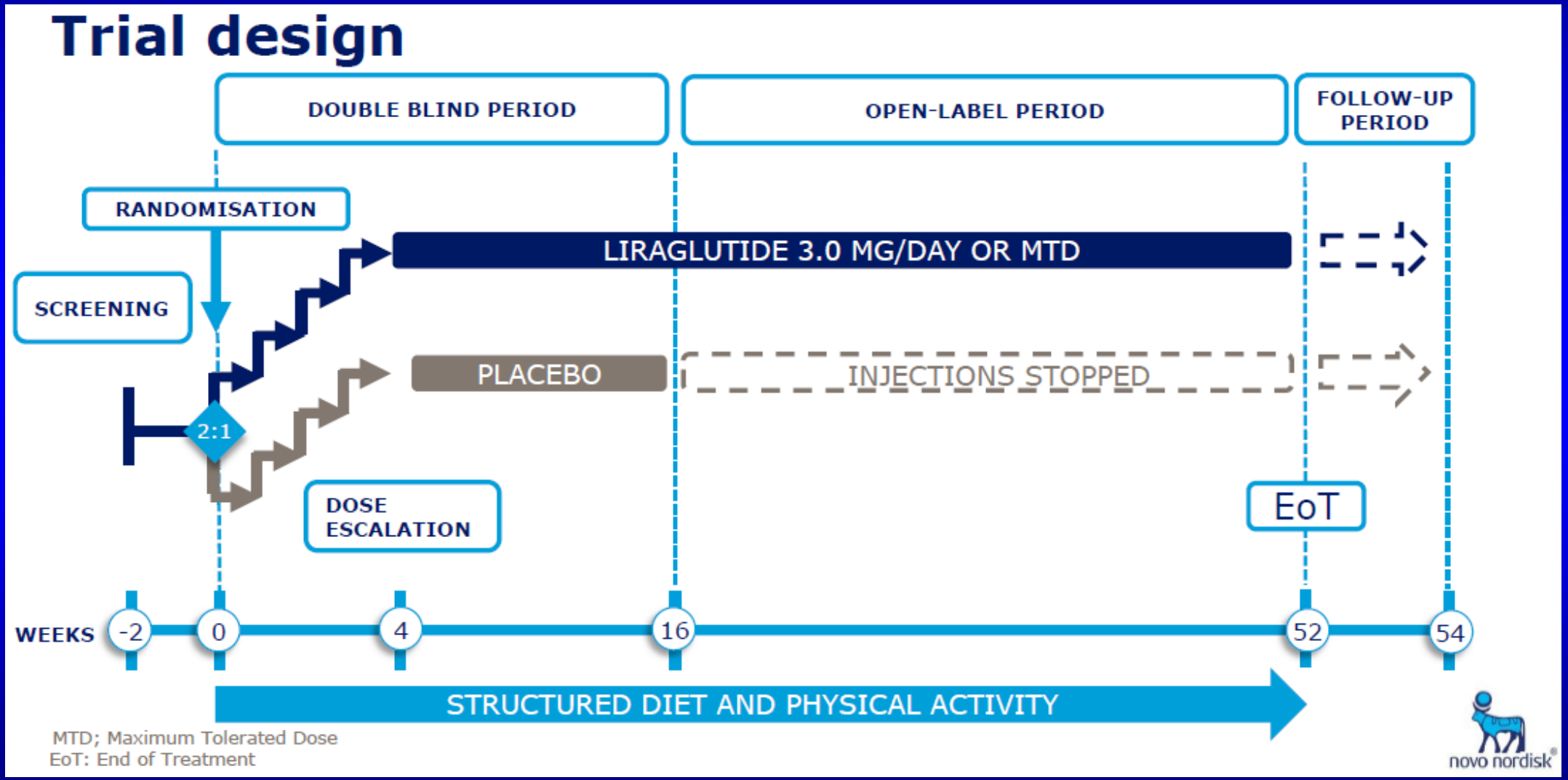
Part B

- Children with PWS 6 to <12 years with Tanner 1 puberty

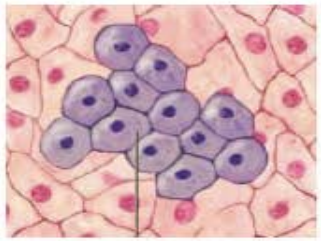
Parts A and B

- Confirmed diagnosis of PWS (by genetic testing)
- BMI corresponding[1] to ≥30 kg/m^2 for adults by international cut-off points and ≥95th percentile for age and gender
- Stable body weight during the previous 90 days before screening (<10 kg self-reported weight change)
- Testing has been performed to evaluate for adrenal insufficiency and documented in medical record

Effect of liraglutide for weight management in paediatric subjects with Prader-Willi syndrome

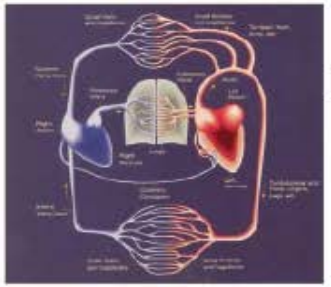


Biological Effects of Ghrelin



Modulation of cell proliferation and survival

Influence on food intake, sleep and behaviour

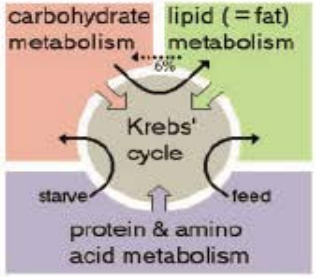


Influence on cardiac performances and vascular resistances

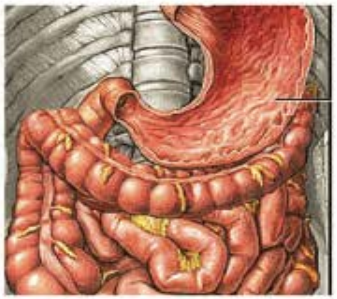
Stimulation of GH, PRL, ACTH and AVP secretion; Inhibition of gonadotropin secretion

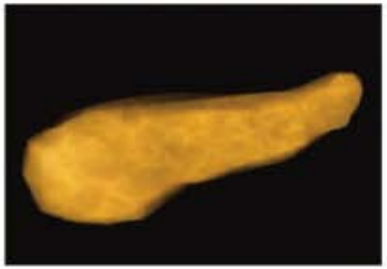
ghrelin

Influence on energy metabolism



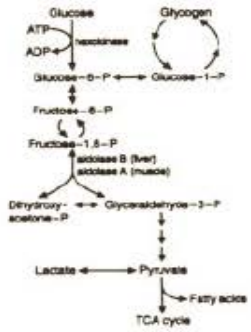
Influence on gastric acid secretion and motility





Influence of exocrine and endocrine pancreatic function

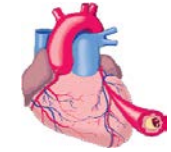
Influence on glucose metabolism

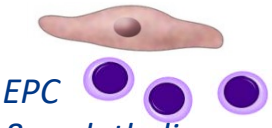


Pharmacological profile of UAG

Acylated ghrelin (AG) inhibition

Undirect tissular effects





AG

\+

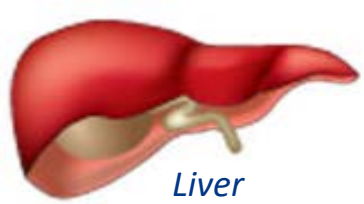
\-

UAG

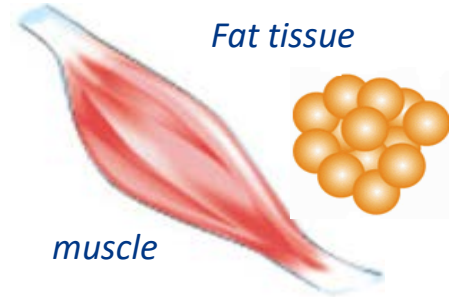
\+

\+

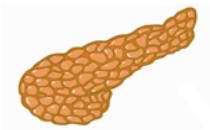
Glucose output



Glucose uptake
Insulin sensitivity



Trophic effect on beta-cells



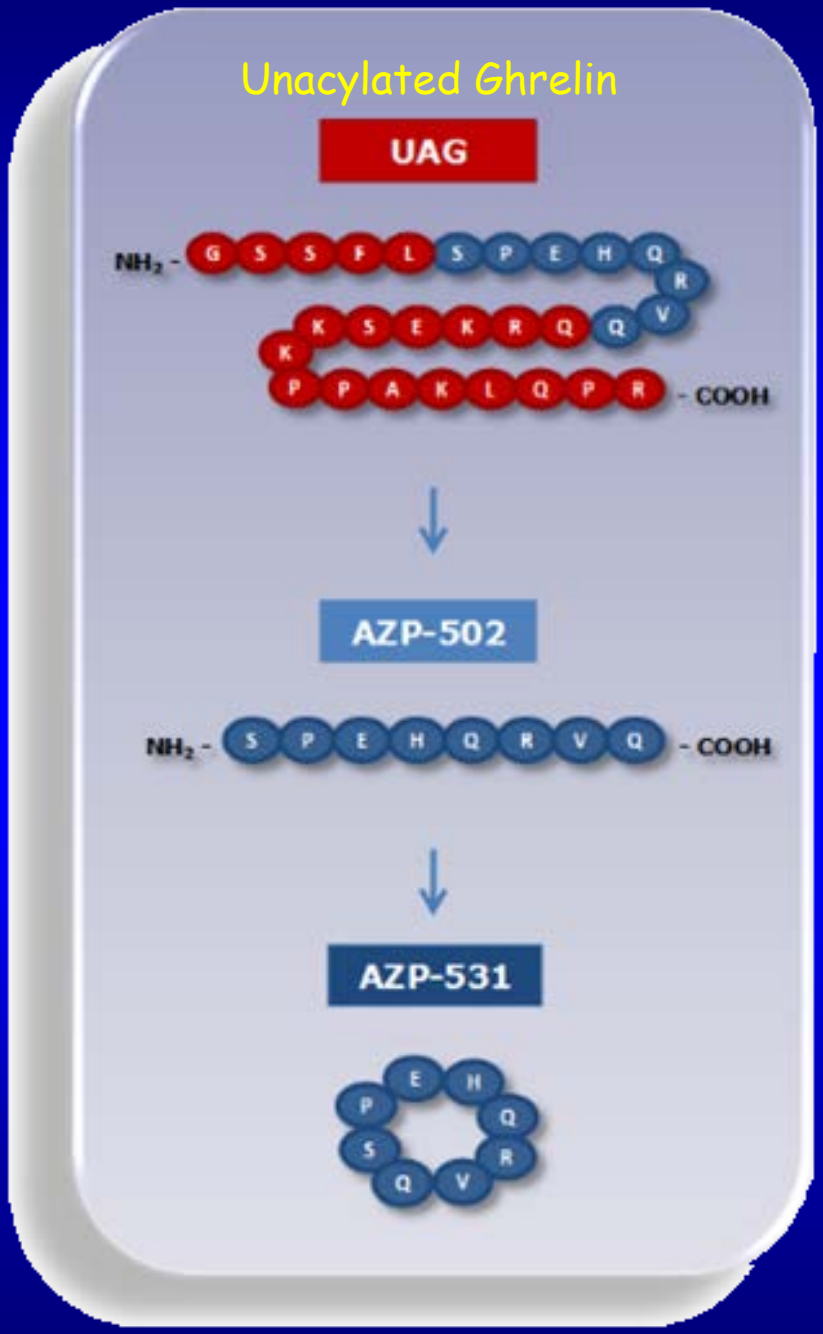
insulin

insulin

Supply

Elimination

Glucose balance

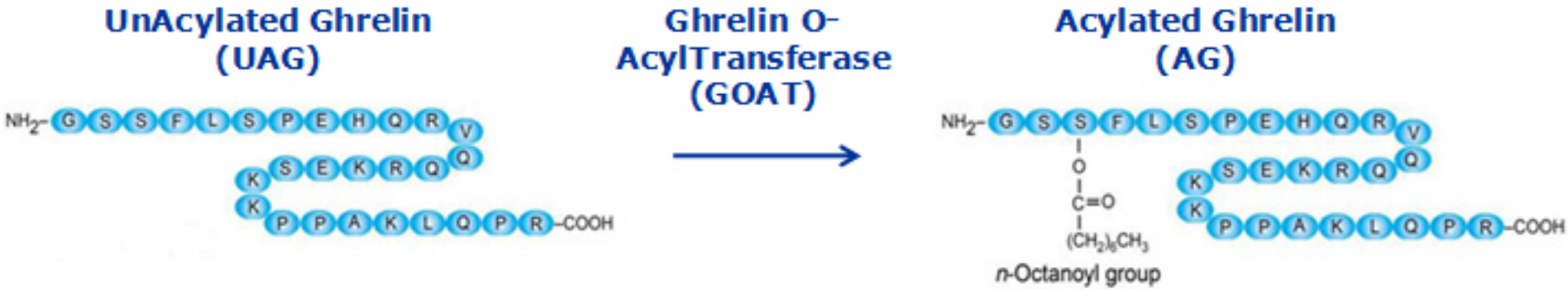


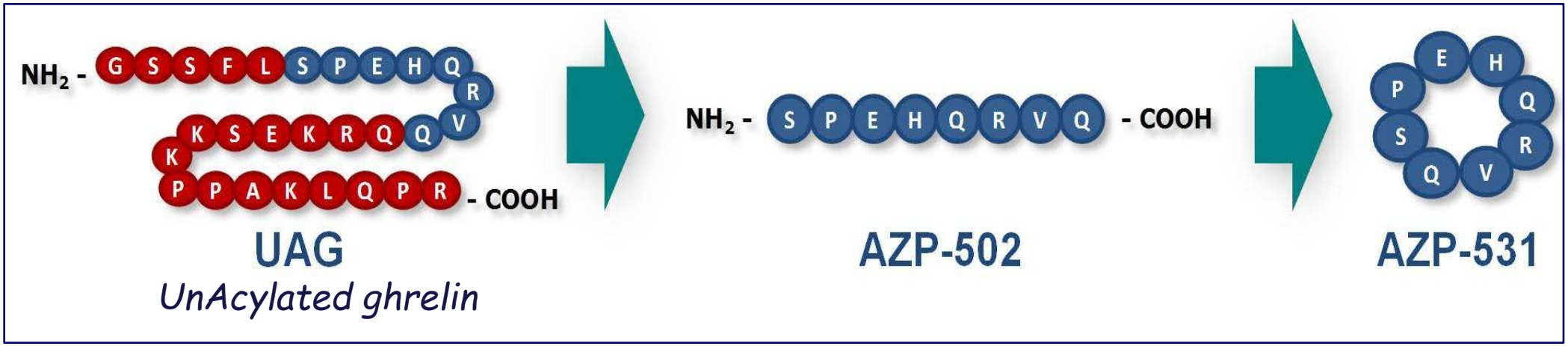
STUDIO con AZP-531
(analogo della grelina deacilata)

- Studio multicentrico in Fase IIa, randomizzato, in doppio cieco e controllato con placebo.
- Scopo: valutare gli effetti, la sicurezza e la tollerabilità di AZP-531 sul comportamento alimentare nella PWS.
- Sponsor: Ditta Alizè Pharma – Francia

Coordinatore dello studio:
Prof. Tauber *(Tolosa-Francia)*

Ghrelin , Unacylated ghrelin (UAG) and Analogs



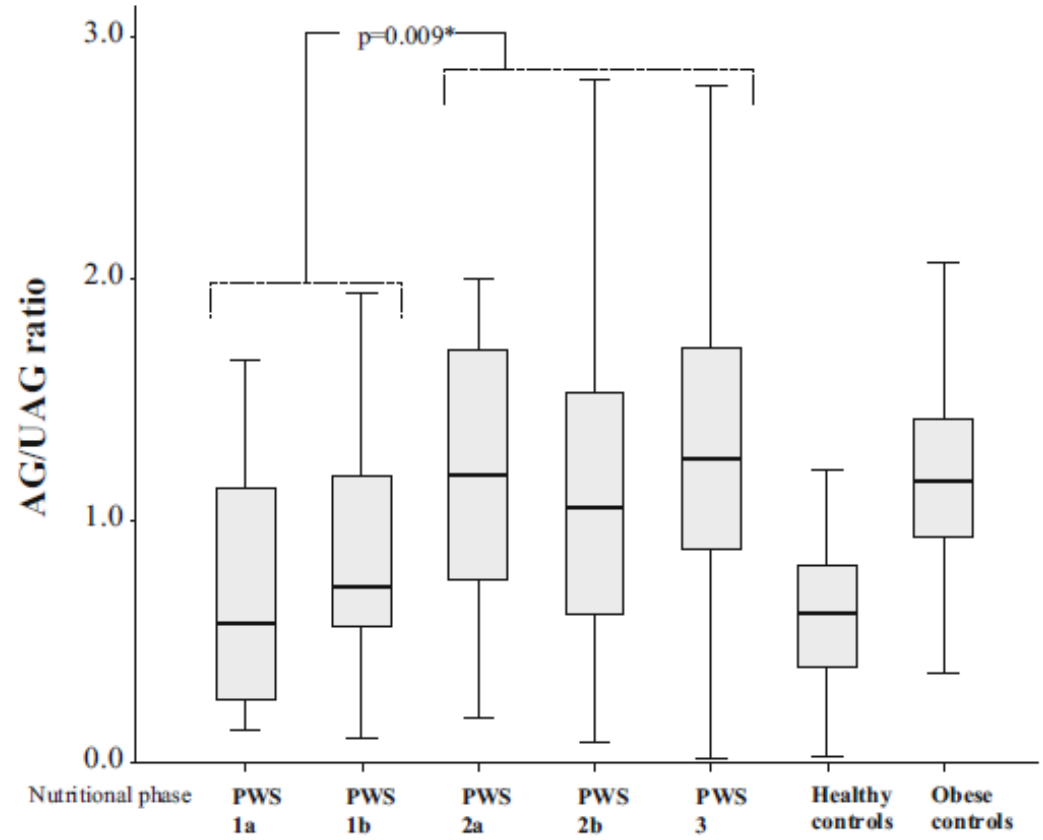


Elevated ratio of acylated to unacylated ghrelin in children and young adults with Prader–Willi syndrome

R. J. Kuppens[1,2] · G. Diène[3] · N. E. Bakker[1,2] · C. Molinas[3,4] · S. Faye[3] · M. Nicolino[5] · D. Bernoux[5] · P. J. D. Delhanty[6] · A. J. van der Lely[6] · S. Allas[7] · M. Julien[7] · T. Delale[7] · M. Tauber[3,8] · A. C. S. Hokken-Koelega[1,2]

138 pts (0,2-29,4 yr)

AG. As a group, PWS patients had higher AG but similar UAG levels as healthy controls (AG 129.1 vs 82.4 pg/ml, $p = 0.016$; UAG 135.3 vs 157.3 pg/ml, resp.), resulting in a significantly higher AG/UAG ratio (1.00 vs 0.61, $p = 0.001$, resp.). Obese subjects had significantly lower AG and UAG levels than PWS and controls (40.3 and 35.3 pg/ml, resp.), but also a high AG/UAG ratio (1.16). The reason for the higher AG/UAG ratio in PWS and obese was, however, completely different, as PWS had a high AG and obese a very low UAG. PWS patients without weight gain or hyperphagia had a similar AG/UAG ratio as age-matched controls, in contrast to those with weight gain and/or hyperphagia who had an elevated AG/UAG ratio. The switch to excessive weight gain in PWS seems to coincide with an increase in the AG/UAG ratio, even prior to the start of hyperphagia.



Endocrine, 2015

Pharmacological effects of AZP-531

AZP-531 and UAG have a comparable pharmacological profile

Non clinical pharmacological results	Tested Molecule(s)
▪ Improved pancreatic β-cell survival and proliferation	AZP-531, AZP-502, UAG
▪ Trophic effects on β-cells and restored glucose and insulin levels in STZ-rats	AZP-502, UAG
▪ Improved oxygen consumption rate in myotubes	AZP-531, AZP-502, UAG
▪ Improved glucose and FFA uptake in myotubes and adipocytes	AZP-502, UAG
▪ In HFD mice, prevention of insulin resistance, glucose intolerance, body weight gain, fat mass gain, inflammation in WAT and lipid accumulation in BAT	AZP-531, UAG
▪ Reversed AG-induced food intake in rat	AZP-531, UAG
▪ Protection of EPCs from oxidative stress and cell senescence	AZP-531, AZP-502, UAG
▪ Protection of C2C12 myotubes from oxidative stress	AZP-531, AZP-502, UAG
▪ Improved muscle protection and regeneration following hind limb ischemia in mice	AZP-531, UAG
▪ Reduced reperfusion injury following cardiac I/R in mice	AZP-531

STUDIO con AZP-531 *(analogo della grelina deacilata)*

- Pazienti PWS *(diagnosi genetica)* di età 18-40 anni *(12-18 in seguito).*
- Durata dello studio: 28 gg per paziente *(14 gg di terapia)*
- Somministrazione s.c. una volta al di x 14 gg *(da una infermiera)*
- Principio attivo e placebo *(2, 3 o 4 mg in funzione del peso)*
- Non affetti da diabete tipo 1 né in trattamento con insulina.
- Non devono usare farmaci che agiscono sull'appetito o sulla perdita
  di peso – *possono essere in terapia con GH.*
- Centri partecipanti in Italia: Ospedale Bambino Gesù, Istituto Auxologico Italiano *(n.10 in Italia compresa Francia).*
- Verranno inclusi complessivamente n. 40 soggetti randomizzati

Valutazioni	Screening	Randomizzazione / Basale	Periodo di trattamento			Follow-up
	Visita 1	Visita 2	Visita 3	Periodo di trattamento	Periodo di fine trattamento o sospensione prematura del trattamento	Telefonata e Visita 5 se necesaria
	Giorno-2	Giorno-1	Giorno 1	Da Giorno 2 a Giorno 13	Giorno 14 o prima	Giorno 28 ±3
Consenso informato	X					
Criteri di inclusione/esclusione	X	X				
Randomizzazione con IWRS		X				
Anamnesi medica	X					
Anemnesi della patologia	X					
Dati anagrafici	X					
QI (se disponibile)	X					
Trattamenti concomitanti	X	X	X	X	X	X
Esame obiettivo	X				X	X (se visita)
Segni vitali	X	X			X	X (se visita)
Test di gravidanza	X				X	
Analisi di laboratorio per la sicurezza[a]	X				X	X (se visita)
ECG a 12 derivazioni	X					
Presentazione delle NRS per formazione e adattamento	X					
Test di comprensione delle NRS[b]	X					
WC, peso[c], massa grassa[c*] BMI (calcolato automaticamente)		X			X	X (se visita)
Altezza		X				
NRS		X[h]	X[h]	X[i]	X[h]	
Glicemia, insulina, AG, UAG e hPP[d]		X	X		X	
Anticorpi anti-AZP-531[e]		X			X	
Questionario PWS sull'iperfagia		X			X	
DBC-P24		X			X	

Valutazioni	Screening	Randomizzazione / Basale	Periodo di trattamento			Follow-up
	Visita 1	Visita 2	Visita 3	Periodo di trattamento	Periodo di fine trattamento o sospensione prematura del trattamento	Telefonata e Visita 5 se necesaria
	Giorno-2	Giorno-1	Giorno 1	Da Giorno 2 a Giorno 13	Giorno 14 o prima	Giorno 28 ±3
CHI-S		X			X	
Raccolta Eventi Avversi (EA)		X	X	X[j]	X	X[k]
CGI-I e CHI-I					X	
Informazioni al medico di base		X				
Trattamento[f]			X	X	X	
IGF-1[g]			X		X	
Consegna di Diario del paziente, glucometro e fornitura di farmaco in studio			X			
Misurazione della glicemia a digiuno con glucometro (durante il periodo di trattamento)				X[l]		
Conteggio farmaco e adesione					X	
Raccolta e revisione del Diario del paziente; raccolta di tutte le fiale di farmaco,, usate o no					X	

Ricovero gg 3

Ricovero

Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients

Intranasal , *adult pts*

Table 3 Pre-post differences in the behavioural scores of the two groups and change comparison between OT treatment and placebo

Change in behavioural scores	Placebo group			OT group			OT vs. Placebo
	Mean	SD	P-value (Mann Whitney)	Mean	SD	P-value (Mann Whitney)	P-value (Wilcoxon*)
Isolation tendencies	-0.000	0.402	0.723	0.083	0.289	0.317	0.404
Sadness tendencies	-0.139	0.324	0.260	0.111	0.533	0.343	0.217
Depressive tendencies	-0.097	0.230	0.158	0.056	0.192	0.317	0.088
Self-depreciation	-0.056	0.192	0.317	0.056	0.192	0.317	0.166
Self-mutilation	0.042	0.203	0.530	0.194	0.354	**0.047**	0.236
Conflicts with others	0.083	0.314	0.735	0.208	0.498	0.150	0.532
Disruptive behaviour	0.056	0.457	0.812	0.389	0.385	**0.011**	0.070
Interest in friendship	-0.028	0.497	0.690	0.153	0.379	0.183	0.245
Interest in love affair	-0.000	0.632	1.000	-0.069	0.429	0.600	0.704
Trust in others	-0.069	0.399	0.850	0.167	0.333	0.084	0.222

* Wilcoxon test is based on individual changes.

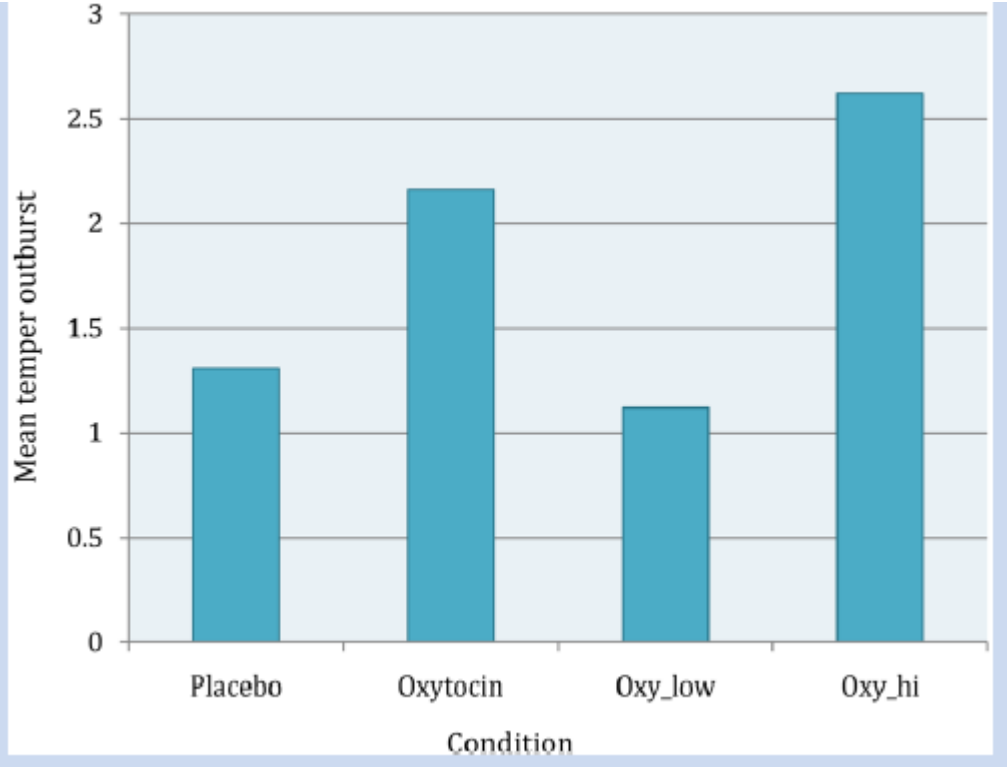
M. Tauber et al,OJRD, 6:47, 2011

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

A Double-Blind Randomized Controlled Trial of Oxytocin Nasal Spray in Prader Willi Syndrome

Stewart L. Einfeld,[1,2,3]* Ellie Smith,[4] Iain S. McGregor,[5] Kate Steinbeck,[6,7] John Taffe,[8] Lauren J. Rice,[2,3] Siân K. Horstead,[2,3] Naomi Rogers,[9] M. Antoinette Hodge,[4] and Adam J. Guastella[3]



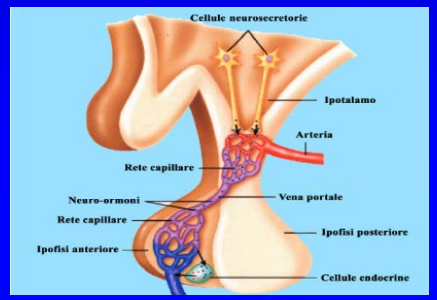
30 PWS
Aged 12-30 yrs

Oxytocin had little impact on any measure. The only significant difference found between the baseline, oxytocin, and placebo measures was an increase in temper outbursts (P=0.023) with higher dose oxytocin. The lack of effect of oxytocin nasal spray may reflect the importance of endogenous release of oxytocin in response to exogenous oxytocin.

Einfeld SL - Am J Med Genetics - 2014

EVOLUZIONE NATURALE nella PWS

Iperfagia → OBESITA'



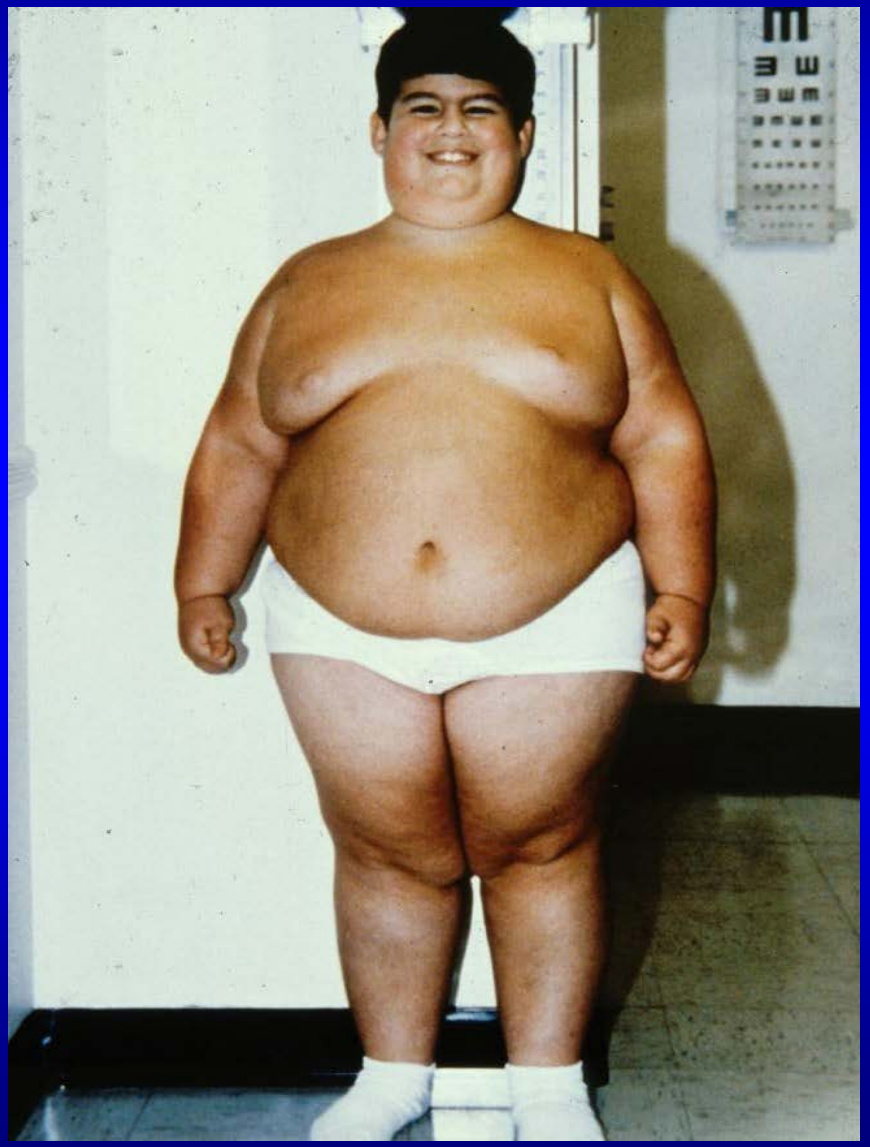
↓

Gravi complicanze

↓

MORTE PREMATURA

(in assenza di intervento)



Current treatment options for PWS

- Three principal treatment modalities:

Lifestyle modification
- Strict supervision on food intake
- Healthy diet and exercise
- Behavioural therapy
- Group homes

Secondary treatments
- Treatment for sleep disorders
- Physical therapy
- Orthopaedic treatment
- Special needs programs

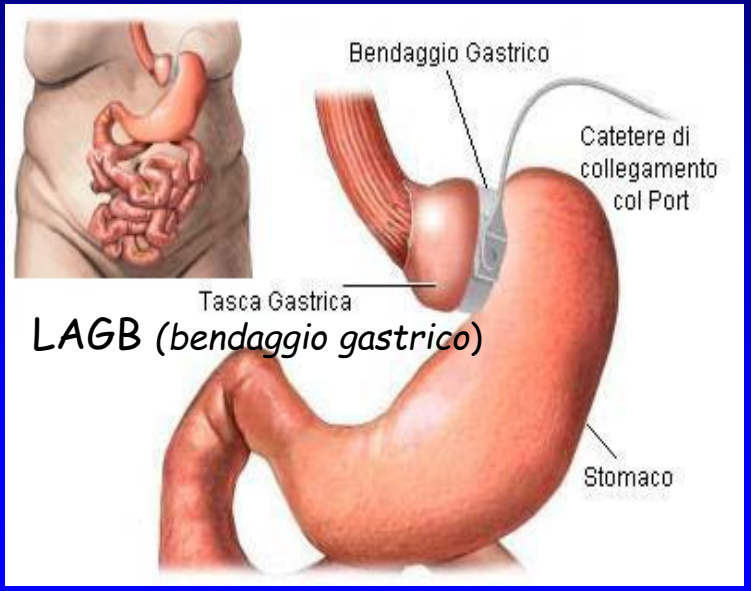
Pharmacotherapy
- Growth hormone therapy

- There is no approved treatment for obesity in PWS
- The **only approved treatment** for paediatric obesity is Orlistat (US only, >12 years old)
- Orlistat is not approved for the treatment of PWS patients

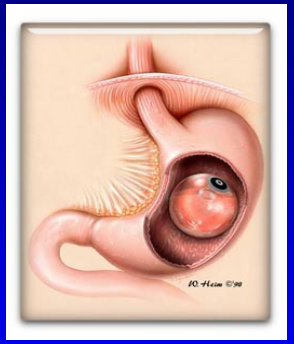
www.nichd.nih.gov/health/topics/prader-willi/conditioninfo/Pages/treatments.

novo nordisk®

Interventi di Chirurgia Bariatrica



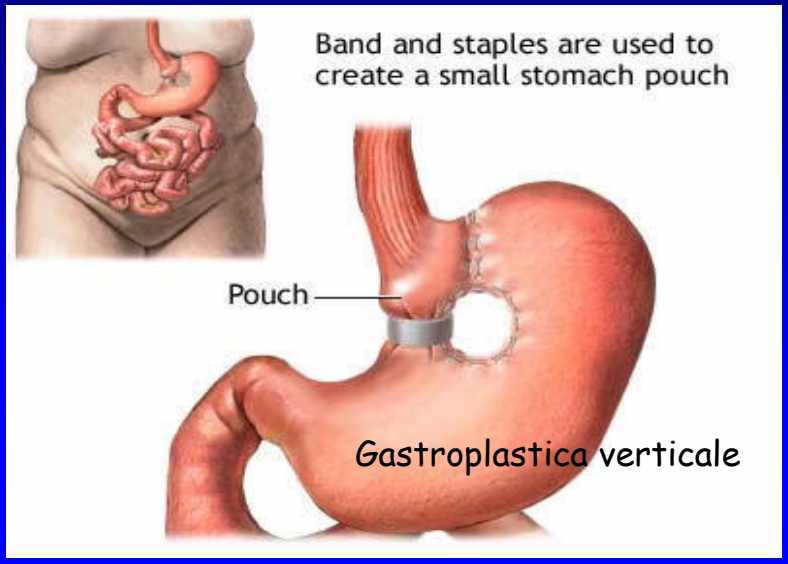
LAGB *(bendaggio gastrico)*



Restrittivi

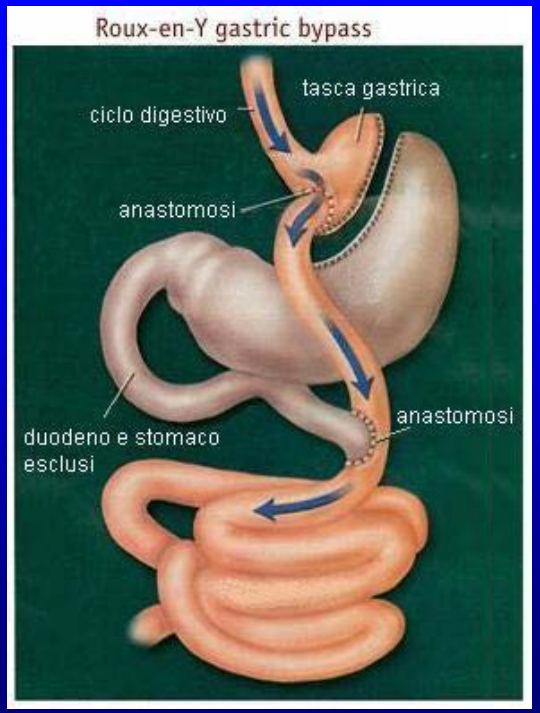
Malassorbitivi

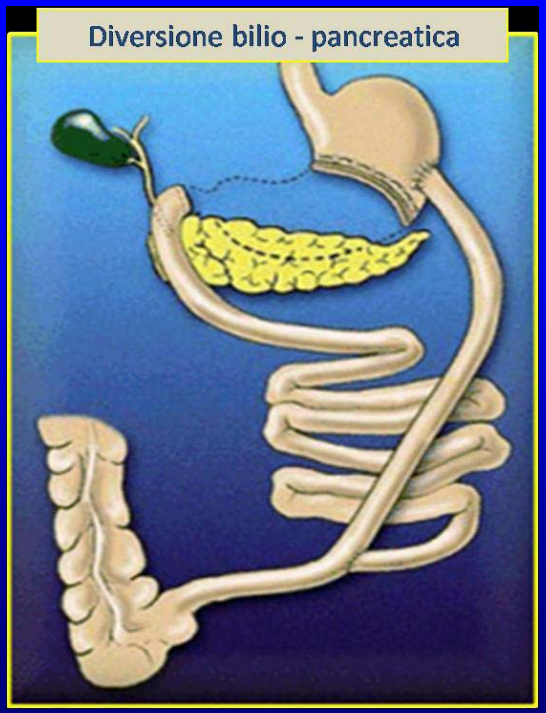
Misti



Gastroplastica verticale

LSG *(sleeve gastrectomy)*



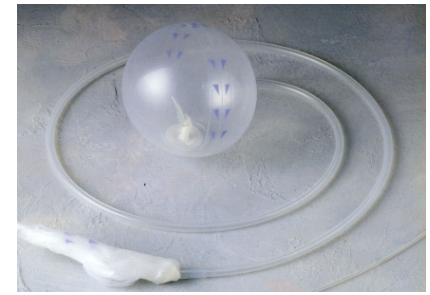


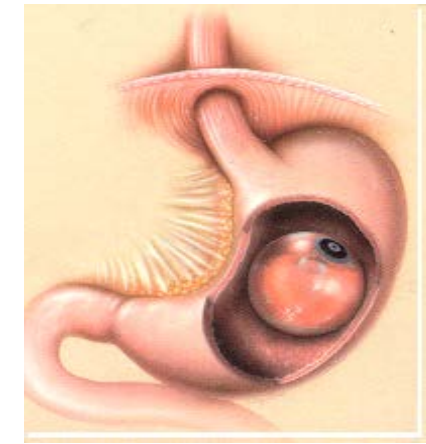
OBES SURG
DOI 10.1007/s11695-008-9509-8

RESEARCH ARTICLE

BioEnterics Intragastric Balloon for Treatment of Morbid Obesity in Prader–Willi Syndrome: Specific Risks and Benefits

F. De Peppo · G. Di Giorgio · M. Germani · E. Ceriati · P. Marchetti · C. Galli · M. G. Ubertini · S. Spera · G. Ferrante · M. Cuttini · M. Cappa · G. Castelli Gattinara · M. Rivosecchi · A. Crinò

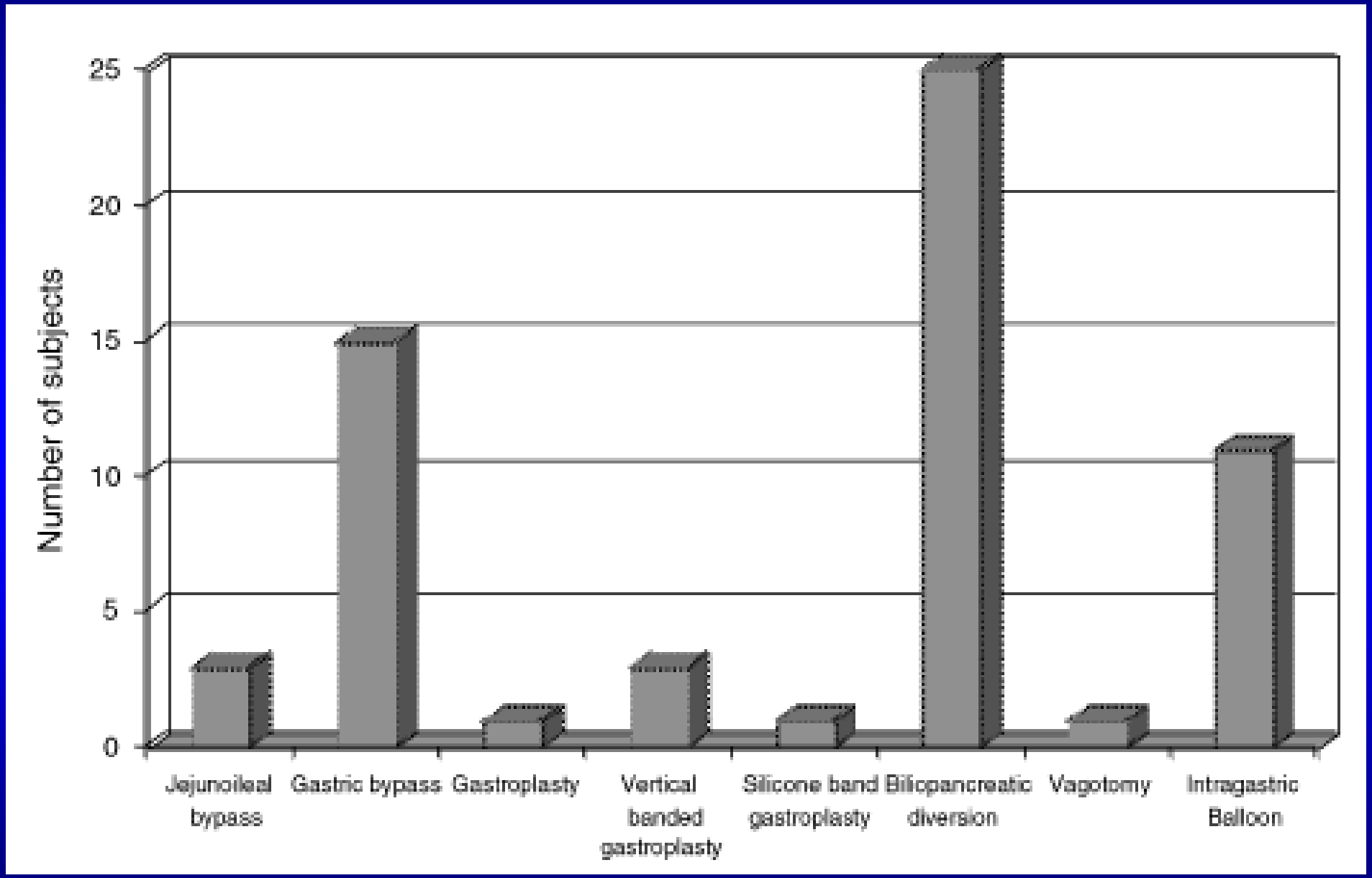




Received: 15 February 2008 / Accepted: 18 March 2008

Abstract
Background Obesity in Prader-Willi Syndrome (PWS) is progressive, severe, and resistant to dietary, pharmacological, and behavioral treatment. A body weight reduction is mandatory to reduce the risk of cardio-respiratory and metabolic complications. The aim of the study was to assess risks and benefits of BioEnterics Intragastric Balloon (BIB) for treatment of morbid obesity in PWS patients.
Methods Twenty-one BIB were positioned in 12 PWS patients (4 M, 8 F), aged from 8.1 to 30.1 years, and removed after 8±1.4 months (range: 5–10 months). Auxological, clinical, and nutritional evaluations were performed every 2 months. Variations in body composition were analysed by dual energy X-ray absorbiometry (DXA).
Results One patient (28.5 years, BMI: 59.3 kg/m^2) died 22 days after BIB positioning because of gastric perforation. In another case (26.2 years, BMI: 57.6 kg/m^2), BIB was surgically removed after 25 days because of symptoms suggesting gastric perforation (not confirmed). The remaining ten patients showed a significant decrease of BMI (p= 0.005) and of fat tissue as measured by DXA (p=0.012).

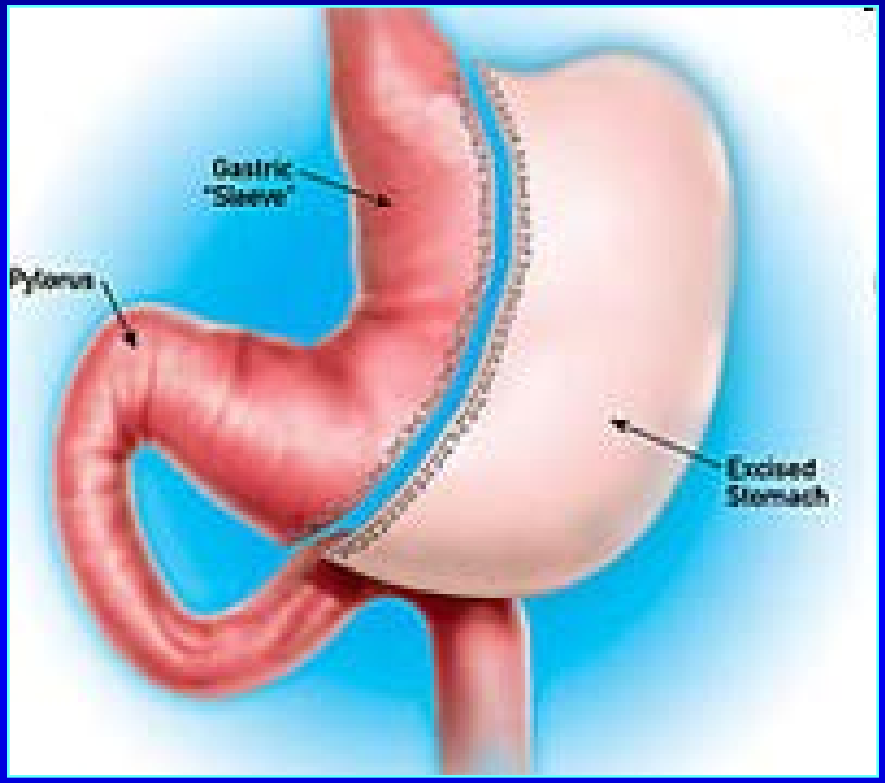
Types of bariatric procedures performed on individuals with PWS



A. Scheimann, J Pediatr Gastroenterol Nutr, 2008

Vertical Sleeve Gastrectomy (VSG)

- In laparoscopia
- Parzialmente restrittivo
- Preliminare all'intervento di DBP *(ma anche come intervento isolato)*
- Senso di sazietà precoce
- Da sola determina significativa e importante perdita di peso (~60%)



- Alternativa sicura al bypass gastrico con minori rischi nutrizionali.
- Modificazione della secrezione di entero-ormoni (⬇ ghrelina)
- Mortalità operatoria: ~ 0.2%
- Non ancora risultati a lungo termine *(possibile ripresa ponderale)*

Ghrelin Level and Weight Loss After Laparoscopic Sleeve Gastrectomy and Gastric Mini-Bypass for Prader–Willi Syndrome in Chinese

Anthony K. W. Fong · Simon K. H. Wong · Candice C. H. Lam · Enders K. W. Ng

Obesity Surgery, 2012

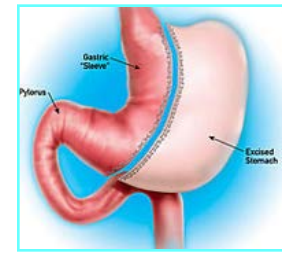
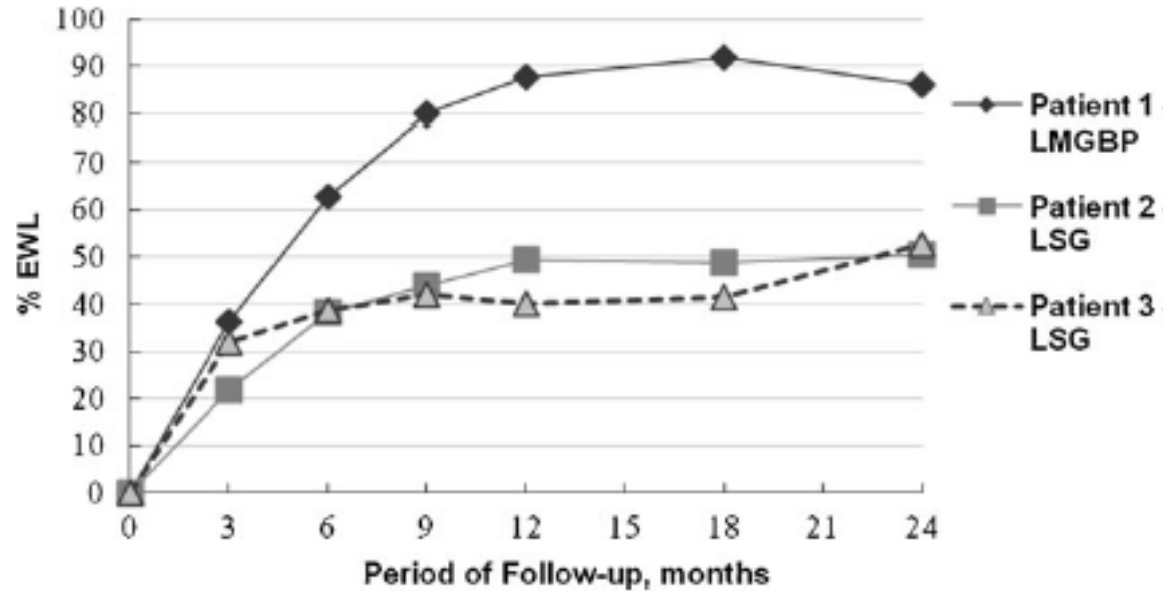


Table 1 Patient data and follow-up results

	Patient 1/LWK	Patient 2/LKY	Patient 3/CCY
Age (years)	15	23	18
Gender	M	F	F
FU (months)	36	24	33
Initial body weight (kg)	120.7	96.4	102.8
Pre-op BMI (kg/m^2)	50	46	44
Type of surgery	LSG	LSG	LMGBP
Operation time (min)	95	85	120
Total weight loss (kg)	32.8	24.5	38.1
% excessive weight loss			
At 12 months	49.3 %	40.1 %	87.8 %
At 24 months	50.5 %	52.8 %	86.2 %
Ghrelin level (pg/ml)			
Before operation	294.9	860.2	2,247.5
1 year after operation	119.7	238.5	1,201.2

BMI body mass index, *LSG* laparoscopic sleeve gastrectomy, *LMGBP* laparoscopic mini-gastric bypass

Fig. 1 Percentage of excessive weight loss over time. *%EWL* percentage of excessive weight loss (excessive body weight defined as initial body weight – ideal body weight at BMI 25 kg/m^2). *LMGBP* laparoscopic mini-gastric bypass, *LSG* laparoscopic sleeve gastrectomy



OBES SURG (2008) 18:1047–1049
DOI 10.1007/s11695-008-9543-6

CURRENT STATUS

Efficacy of Laparoscopic Sleeve Gastrectomy (LSG) as a Stand-Alone Technique for Children with Morbid Obesity

H. Till · S. Blüher · W. Hirsch · W. Kiess

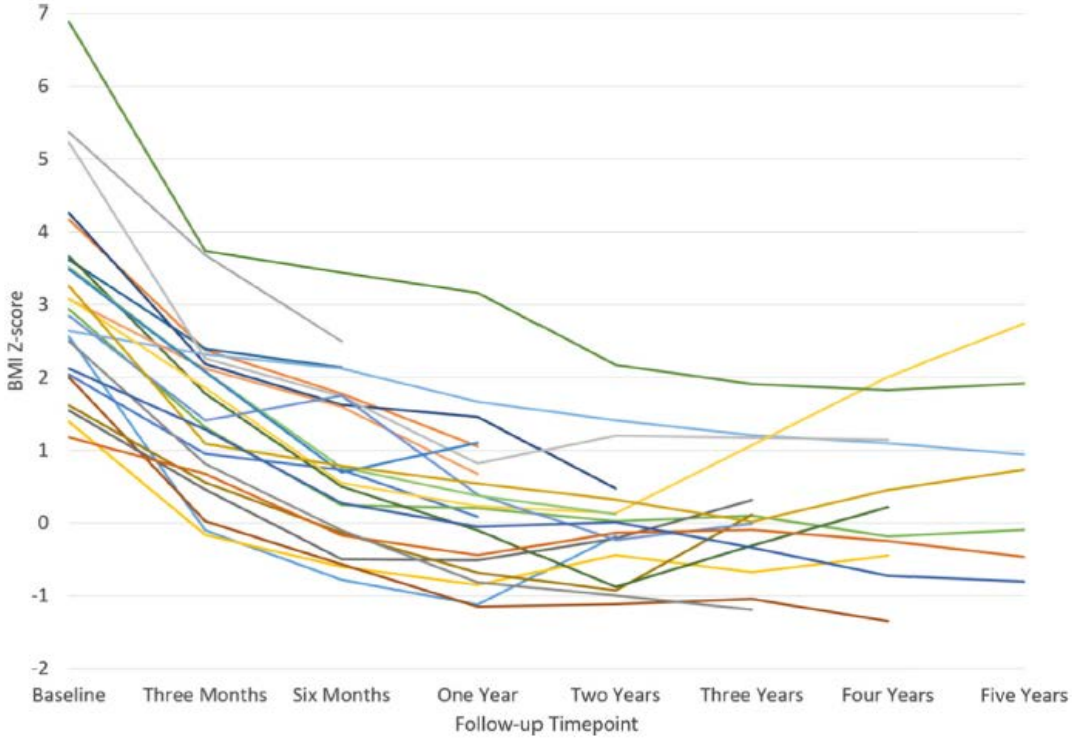
Table 1 Patient data, follow-up results, and metabolic changes

	Patient 1, MK pre/postop.	Patient 2, JE pre/postop.	Patient 3, AS pre/postop.	Patient 4, LR pre/postop.
Age (years)	16	8	17	17
FU (months)	19	9	6	10
Weight (kg)	121/83	112/85,9	140,7/115	132,2/111,7
BMI (kg/m^2)	40,6/28,4	56,3/40	49,3/40,6	47,4/40,1
BMI SDS	3,61/2,07	4,43/3,67	4.25/3,65	4.4/3,84
Comorbidities	Mental retardation (U), cholelithiasis (R), arterial hypertension (R)	Prader–Willi (U), sleep apnea (R), psoriasis (I), glucose intolerance (I)	Cholelithiasis (R), steatosis hepatis (I), polycystic ovary syndr (U), glucose intolerance (I), dyslipidemia (I)	Cholelithiasis (R), steatosis hepatis (R), hyperinsulinism (I), impaired glucose tolerance (R), arterial hypertension (I)

The metabolic effect of LSG can nicely be shown by the improvement or resolution of many comorbidities.
U=unchanged, I=improved, R=resolved

Laparoscopic sleeve gastrectomy in children and adolescents with Prader-Willi syndrome: a matched-control study

Aayed R. Alqahtani, M.D., F.R.C.S.C., F.A.C.S.[a,*], Mohamed O. Elahmedi, M.B.B.S.[a], Awadh R. Al Qahtani, M.D., M.Sc., F.R.C.S.C.[a], Jaehoon Lee, Ph.D.[b], Merlin G. Butler, M.D., Ph.D., F.F.A.C.M.G.[c]



- 24 PWS pts
  (mean age 10,7; 6<8 yr old, range 4,9-18)
- BMI: *46.2 ± 12,2*
- Follow-up: *5 yrs*
- *No mortality or major morbility was observed*

CONCLUSIONS

PWS children and adolescents underwent effective weight loss and resolution of co-morbidities after LSG, without mortality, significant morbidity, or slowing of growth. LSG should be offered to obese PWS patients with heightened mortality particularly because no other effective alternative therapy is available.

Experience with sleeve gastrectomy in adolescent obese subjects and in Prader-Willi Syndrome

Danilo Fintini 1,Sarah Bocchini1, Romina Caccamo2, Graziano Grugni3, Marco Cappa4, Francesco De Peppo2, Antonino Crinò1

1 Autoimmune Endocrine Disease Unit, 2 Surgery Unit, 4Endocrinology and Diabetes Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy3, Italian Auxological Intitute Foundation, Piancavallo, Verbania, Italy

3 PWS (2 M; aged 15.9±4.4yrs; range 10.9-19.3) and 6 age matched obese controls (OB; 1 M; aged 15.6±2.8; range 10.5-18.5).

Mean±SD	*Before Surgery*		*12 months after surgery*		*p (0-12 months)*	
	PWS	Obese	PWS	Obese	PWS	Obese
BMI (Kg/m²)	43.1 ±0.9	57.2±17.8	37.6±4.6	39.5±7.4	<0.05	<0.05
BMI-SD	4.5 ±1.4	7.5±2	3.7±1.7	6.1±0.6	<0.05	<0.05
Waist circumference (cm)	107±21	120±9.1	98±15.5	106.8±8.8	<0.05	<0.05
HbA1C (mmol/mol)	44.7±8.3	36.4±2.4	38±6.2	33±1.7	<0.05	NS
HOMA-IR	13.8±19.4	5±2	2±0.9	3.5±2.3	<0.01	<0.05

Conclusion

Our data, although preliminary showed that sleeve gastrectomy in adolescent with PWS, as in obese patients, improve positively BMI, and may normalize glycemic control and insulin resistance. Statistically difference were found among parameters even though the sample is very small and there is widespread distribution of data. These results need to be confirmed on higher number of pts with a longer follow up.

Poster presented at: ESPE 2015 BARCELONA

Chirurgia bariatrica nella PWS

- Rappresenta un'arma terapeutica efficace per il trattamento del paziente PWS con obesità severa o molto severa, in cui tutte le altre opzioni terapeutiche sono risultate fallimentari.
- La letteratura scientifica ha ampiamente acclarato che la chirurgia bariatrica non solo determina la riduzione del peso corporeo, ma contribuisce al controllo ed alla risoluzione delle comorbidità associate all'obesità che configurano la sindrome metabolica - come l'ipertensione arteriosa, il diabete mellito tipo 2, le dislipidemie, la NAFLD e l'OSAS – migliorando la qualità della vita dei pazienti.
- L'approccio chirurgico in tali pazienti deve essere effettuato sempre con molta prudenza (*possibili complicanze specifiche a breve e a lungo termine*) e la scelta dovrebbe scaturire da una decisione multidisciplinare che valuti i rischi e i benefici.

INCONTRO SULLA SINDROME DI PRADER-WILLI
Sabato 12 aprile 2014
CERIMONIA DI CONSEGNA DELLA MY KEY

Seminar Room - 3° Padiglione - Sede di Palidoro (Roma)
Ospedale Pediatrico Bambino Gesù

Indicazioni alla chirurgia bariatrica in età pediatrica e adolescenziale

Criteri più restrittivi e prudenti rispetto all'adulto (*indicazioni EASO e ASMBS*):

- BMI ≥ 35 kg/m^2 ed almeno una comorbilità grave tra DMT2, OSAS moderata-grave (*MOHAI >15*), pseudotumor cerebri, NASH con fibrosi significativa.
- BMI ≥ 40 kg/m^2 con comorbilità minore tra cui OSAS lieve (*MOHAI >5*), ipertensione arteriosa, dislipidemia, ridotta tolleranza ai carboidrati.
- Obesità di lunga durata e fallimento di un trattamento intensivo di almeno 12 mesi.
- Consapevolezza e autonomia decisionale nell'accettare il trattamento proposto, i contenuti di un consenso informato, il percorso pre e post-operatorio.
- Le controindicazioni sono sovrapponibili a quelle per gli adulti (*disturbi psichici severi, dipendenza da alcool e droga, incapacità a prendersi cura di sè e non "compliance ad un prolungato protocollo di follow-up, ridotta aspettativa di vita, alto rischio anestesiologico).*
- In individui con obesità sindromica o con ritardo mentale (*e in particolare la sindrome di Prader-Willi*) è opportuno una attenta valutazione multidisciplinare a causa della loro variabilità nel dimostrare motivazione, conoscenza e compliance. Ogni decisione, anche sul tipo di intervento, va sempre considerata caso per caso.

Mechanism of action of UAG and analogs

Alizé Pharma

INDIRECT EFFECTS

Inhibition of the AG activity and/or levels

Improvement of glucose control

Reduction of AG-induced food intake

Therapeutic potential in metabolic diseases associated with high [AG] or [AG]/[UAG]

DIRECT EFFECTS

Cell protection against oxidative stress and tissue regeneration

pancreatic β cells, EPCs,

vessels, cardiomyocytes, muscle…

Therapeutic potential in ischemic diseases, cardioprotection, muscle wasting and metabolic diseases

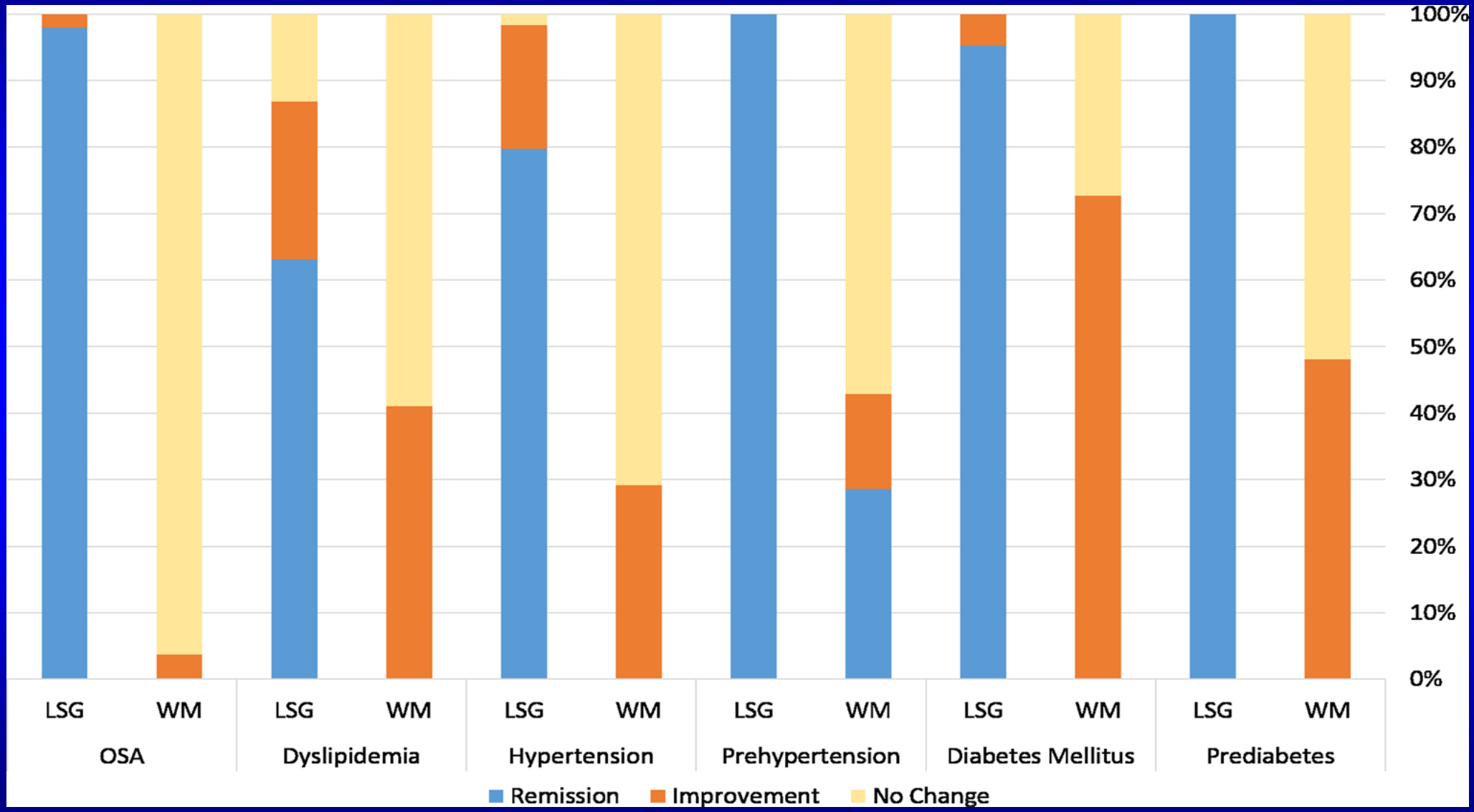
PWS

T2DM

I/R

Cachexia

Comorbidity resolution in children and adolescents with LSG



Alqahthani AR et al Obes Surg 25:910, 2015