Real-world setmelanotide weight outcomes in French patients with acquired or congenital hypothalamic obesity

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Presentation: AD10.02

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ECO 2025 - Conflict Of Interest

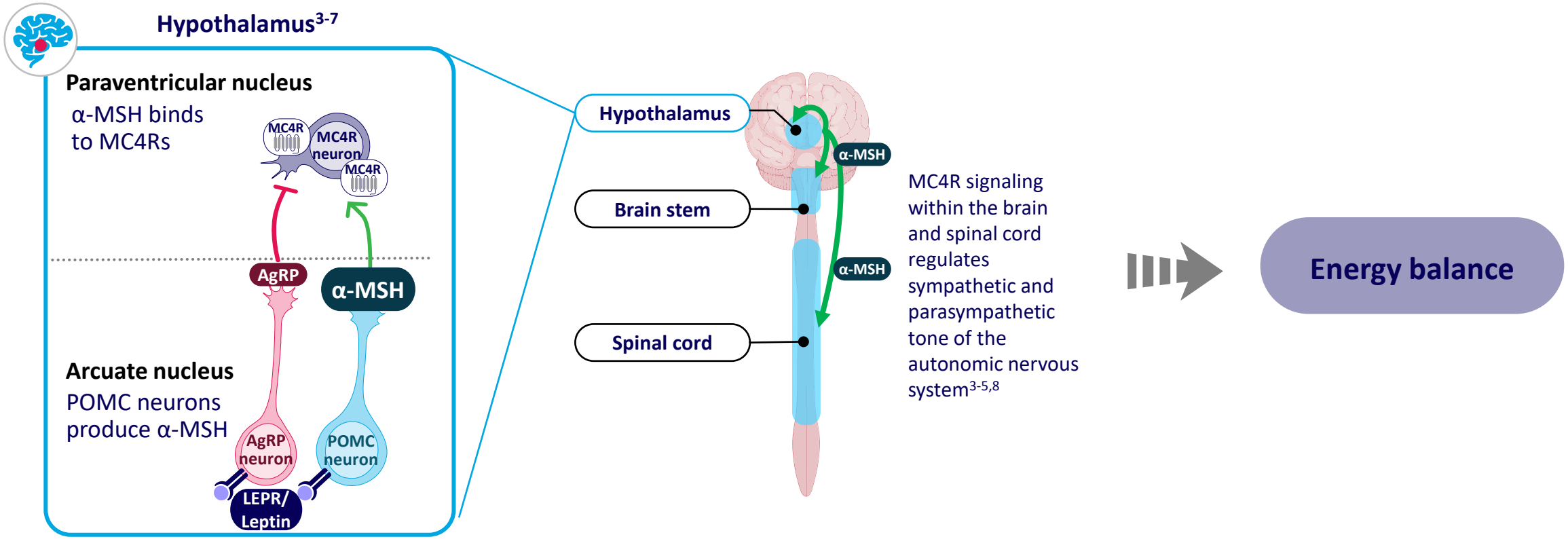
Name: Sarah Chalopin

☐ I have the following potential conflicts of interest to report:

- **☐ Research Contracts**
- **X Consulting**
- **☐ Employment in the Industry**
- **☐ Stockholder of a healthcare company**
- **☐ Owner of a healthcare company**
- **☐ Other(s)**

☐ I declare that I have no potential conflict of interest.

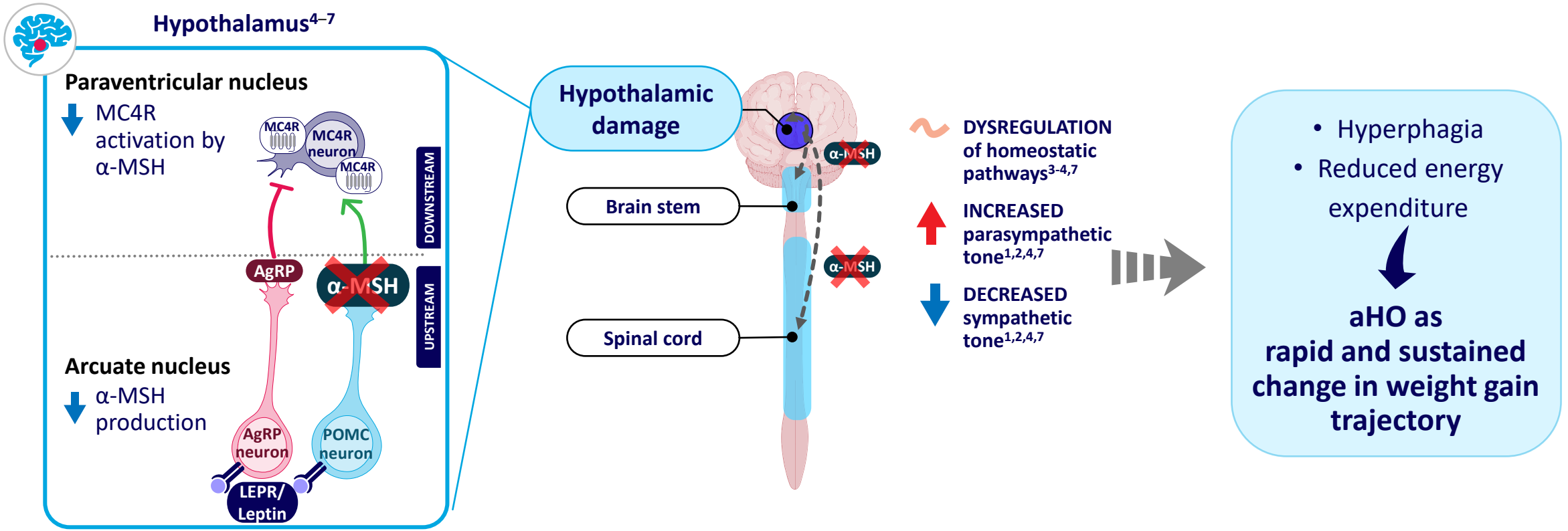
The central hypothalamus is a key regulator of energy balance, appetite and bodyweight through the MC4R pathway[1–3]



α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Farooqi IS. *Biol Psychiatry.* 2022;91(10):856–59; 2. Yeo GSH, et al. *Mol Metab.* 2021;48:101206; 3. Baldini G and Phelan KD. *J Endocrinol.* 2019;241(1):R1–R33; 4. Dimitri. *Front Endocrinol.* 2022;13:846880; 5. Hill, et al. *Neuroendocrinol.* 2017;104:330–346; 6. Hochberg, et al. *Obes Rev.* 2010;11:709–721; 7. Roth, et al. *Obesity (Silver Spring).* 2011;19:36–42; 8. Sohn, et al. *Cell.* 2013;152:612–619.

Development of acquired hypothalamic obesity (aHO)[1–3]

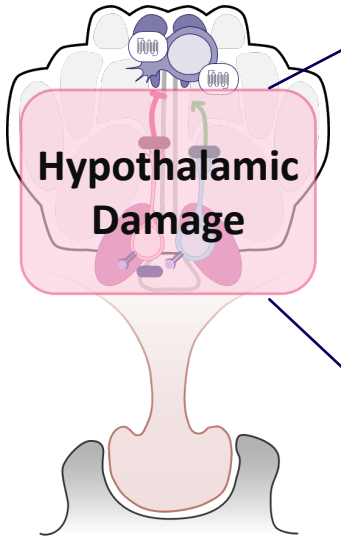


Hypothalamic damage can be associated with dysregulations in hormonal balance, heart rate, blood pressure, body temperature, circadian rhythms and visual impairment[1,4]

α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Abuzzahab, et al. *Horm Res Paediatr.* 2019;91:128–136; 2. Roth. *Front Endocrinol (Lausanne).* 2011;2:49; 3. Roth, *et al. Metabolism.* 2010;59:186–194; 4. Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880; 5. Baldini G and Phelan KD. *J Endocrinol.* 2019;241(1):R1–R33; 6. Hochberg, et al. *Obes Rev.* 2010;11:709–721; 7. Roth, et al. *Obesity (Silver Spring).* 2011;19:36–42.

Both paediatric and adult patients can develop HO as a consequence of diverse brain changes[1]



Causes may include[2–9]

- Presence and/or treatment of (supra)sellar tumours of different histology including:
  - **Craniopharyngiomas**
  - Pituitary tumours
  - Germ cell tumours
  - Chiasmatic hypothalamic gliomas
- Inflammatory diseases (e.g. sarcoidosis, histiocytosis)
- Traumatic brain injury
- Stroke
- Viral infections

Congenital forms[10]

- Congenital defects are much rarer than acquired forms
- Congenital brain malformations include
  - **Rathke´s cleft cysts**
  - Congenital hypopituitarism
  - Optic nerve hypoplasia
  - Congenital cavernous malformation

The weight gain and appetite changes accompanying HO are often unresponsive to existing therapies for obesity[2–4]

aHO, acquired hypothalamic obesity; HO, hypothalamic obesity.

1. Muller HL, et al. *Nature review: Disease primers.* 2022;8:24; 2. Abuzzahab, et al. *Horm Res Paediatr.* 2019;91:128–136; 3. Roth. *Front Endocrinol (Lausanne).* 2011;2:49; 4. Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880; 5. Baldini, et al. *J Endocrinol.* 2019;241:R1–R33; 6. Hochberg, et al. *Obes Rev.* 2010;11:709–721; 7. Sohn, et al. *Cell.* 2013;152:612–619; 8. Müller HL, et al. *Nat Rev Dis Primers.* 2019;5(1):75; 9. Müller HL. *Handb Clin Neurol.* 2014;124:235–253; 10. Tessaris D, et al. *Children (Basel).* 2021;8(7):531.

Background and objective

In a **Phase 2**, open-label trial of setmelanotide, an MC4R agonist, patients with acquired HO experienced consistent and clinically meaningful responses after **16 weeks of treatment**, which were maintained or increased for most patients through a 12-month long-term extension trial[1]

To analyse **real-world outcomes** of paediatric and adult patients with acquired or congenital HO treated with a **minimum of 3 months of treatment** with **setmelanotide in France** under pre-marketing early access authorisation

HO, hypothalamic obesity; MC4R, melanocortin-4 receptor.

1. Roth CL, et al. *Lancet Diabetes Endocrinol* 2024;12:380–389.

Methodology

- Patients with acquired or congenital HO were treated with setmelanotide in 14 different care units in France
- Acquired HO:
  - **10 patients** <18 years old
  - **20 patients** ≥18 years old
- Congenital HO:
  - **4 patients <18 years old**
  - **1 patient ≥18 years old**

- Outcomes included
  - **Mean change in BMI or BMI z-score***
    - *Physician-reported height and weight was used to calculate BMI and BMI z-scores*
  - **Changes in hunger scores** (if available)
    - *A reduction of ≥1 point was considered as a meaningful within-person changes in hunger*[1]
  - **Safety**, evaluated by adverse event frequency

*BMI z-score per International Obesity Task Force (IOTF) methodology.
BMI, body mass index; HO, hypothalamic obesity.
1. Roth CL, et al. *Lancet Diabetes Endocrinol* 2024;12:380–389.

Patient characteristics

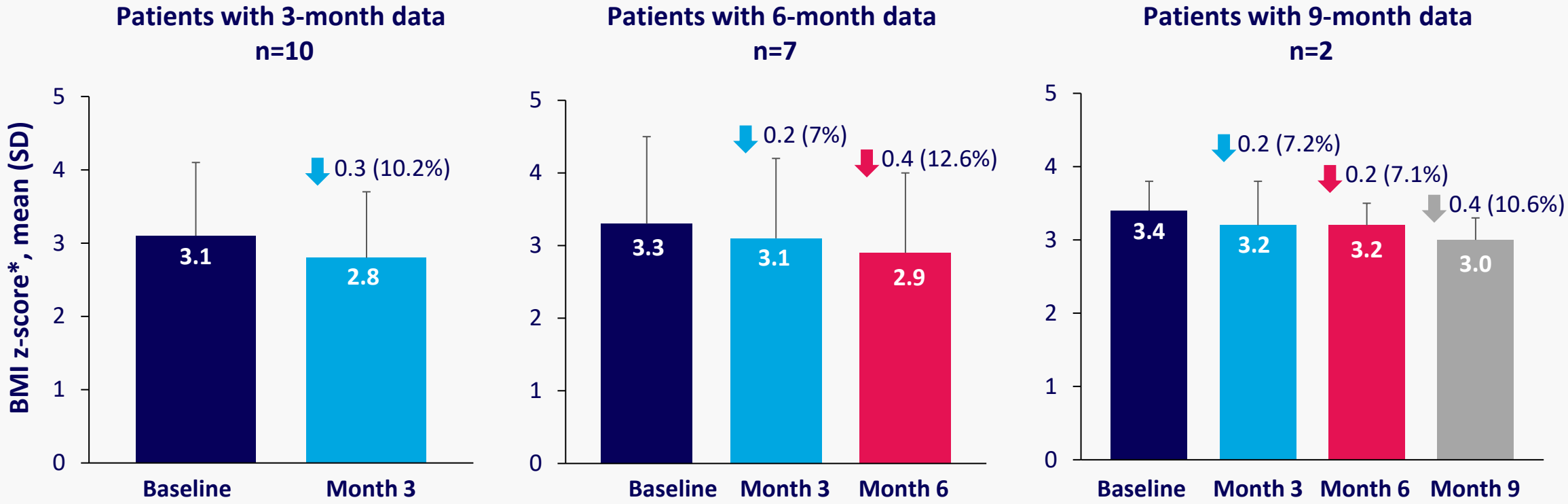
	Acquired hypothalamic obesity		Congenital hypothalamic obesity	
	Paediatric (n=10)	**Adult (n=20)**	**Paediatric (n=4)**	**Adult (n=1)**
Age at setmelanotide initiation, mean (SD), y	**12.7 (3.5)**	**31.5 (7.1)**	**13.3 (3.5); range 9–17 y**	**32.0**
Sex, n (%)				
Female	5 (50)	13 (65)	1 (25)	1
Male	5 (50)	7 (35)	-	-
Age at onset of obesity, mean (SD), y	9.7 (4.3); n=8	15.5 (8.7); n=17	2.5 and <1 (n=2)	-
Age at tumour resection, mean (SD), y	6.7 (4.6); n=9	14.3 (8.8); n=17	-	-
Weight at baseline, mean (SD), kg	87.5 (27.4)	128.1 (28.6)	104.3 (36.6)	97.5
BMI at baseline, mean (SD), kg/m²	35.9 (9.5)	**48.3 (21.6)**	-	**39.6**
BMI z-score at baseline, mean (SD)*	**3.1 (1.0)**	N/A	**3.7 (0.5)**	N/A
Concomitant treatment, n (%)				
GLP-1 receptor agonist	1 (10)	**11 (55)**	0	0
≥1 hormonal replacement therapy	9 (90)	20 (100)	4 (100)	1
aHO aetiology				
Craniopharyngyoma	**4**	**17**	-	-
AQP4 antibody encephalitis	1	-	-	-
Astrocytoma	3	-	-	-
Ganglioma	1	-	-	-
Inflammatory viral disease affecting the pituitary gland	1	-	-	-
Langheransian histiocytosis	0	2	-	-
Neuroglial tumour	0	1		
cHO aetiology	N/A	N/A	SOD n=2; PSIS n=1; Hamartoma n=1	Rathke's cleft cyst

*BMI z-score per International Obesity Task Force (IOTF) methodology.

aHO, acquired hypothalamic obesity; cHO, congenital hypothalamic obesity; BMI, body mass index; GLP-1, glucagon-like peptide-1; PSIS, pituitary stalk interruption syndrome; SOD, septo-optic dysplasia; SD, standard deviation.

BMI z-score outcomes in paediatric patients with aHO

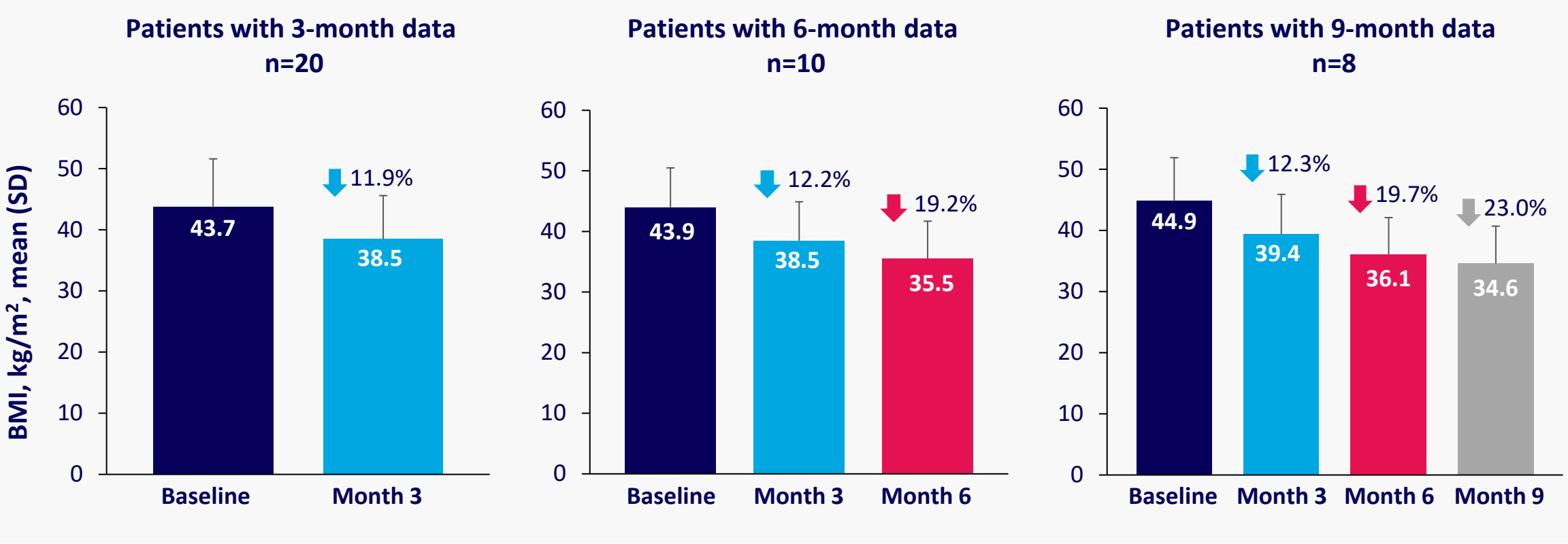
- BMI z-score decreased from baseline at all timepoints analysed, with up to a **0.4-point reduction** at 6 and 9 months of treatment with setmelanotide



*BMI z-score per International Obesity Task Force (IOTF) methodology. A clinically meaningful reduction in BMI z-score is defined as a ≥0.2-point reduction[1,2]
aHO, acquired hypothalamic obesity; BMI, body mass index; SD, standard deviation.

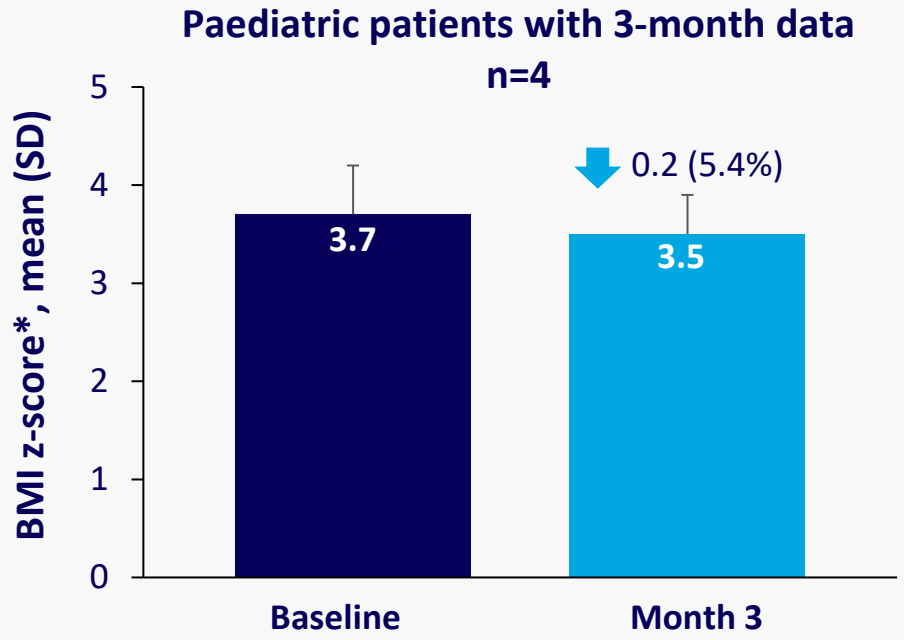
BMI outcomes in adult patients with aHO

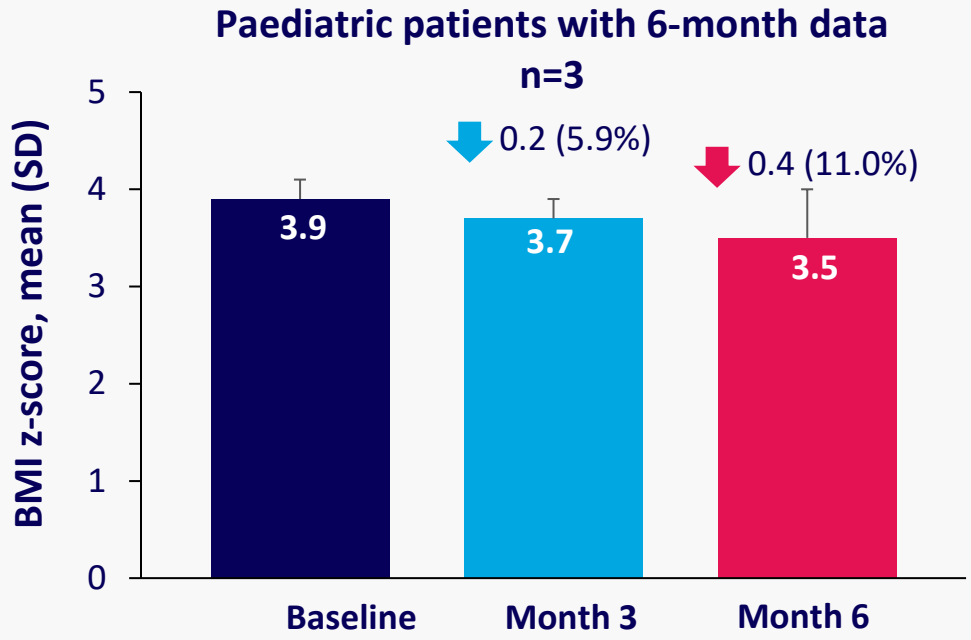
- BMI decreased from baseline at all timepoints analysed, with up to a **23% reduction at 9 months** of treatment with setmelanotide



aHO, acquired hypothalamic obesity; BMI, body mass index; SD, standard deviation.

Weight outcomes in patients with cHO





- A 15-year-old **paediatric patient with cHO** showed a reduction in BMI z-score from Baseline (4.1) to Month 3 (3.6), Month 6 (3.0) and Month 9 (2.3), reflecting a **reduction of 1.8 points (43.9%) after 9 months** of setmelanotide treatment
- The one **adult patient with cHO** experienced a reduction in BMI from baseline (39.6 kg/m^2) to Month 3 (35.5 kg/m^2) and Month 6 (33.7 kg/m^2), reflecting a **reduction of 14.8% after 6 months** of setmelanotide treatment

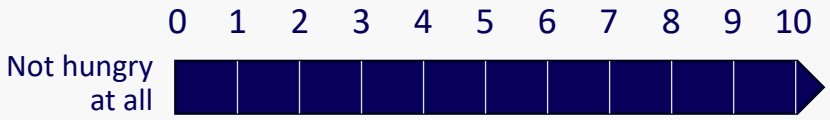
*BMI z-score per International Obesity Task Force (IOTF) methodology. A clinically meaningful reduction in BMI z-score is defined as a ≥0.2-point reduction[1,2]
BMI, body mass index; cHO, congenital hypothalamic obesity. 1. Haqq et al. Lancet Diabetes Endocrinol 2022; 2. Roth et al. Lancet Diabetes Endocrinol 2024.

Hunger score outcomes in adult patients with aHO

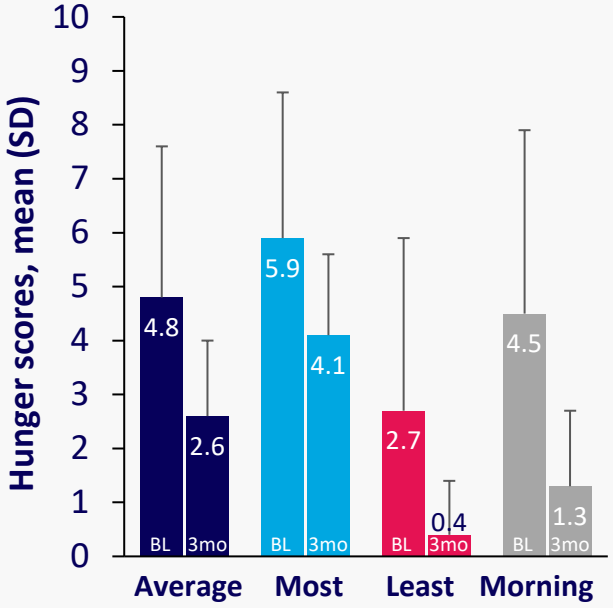
Hunger was assessed using the following questions

1. Over the past 24 hours, on average, how hungry have you felt?
2. Over the past 24 hours, how hungry did you feel when you were most hungry?
3. Over the past 24 hours, how hungry did you feel when you were least hungry?
4. This morning, when you woke up early in the day, how hungry did you feel?

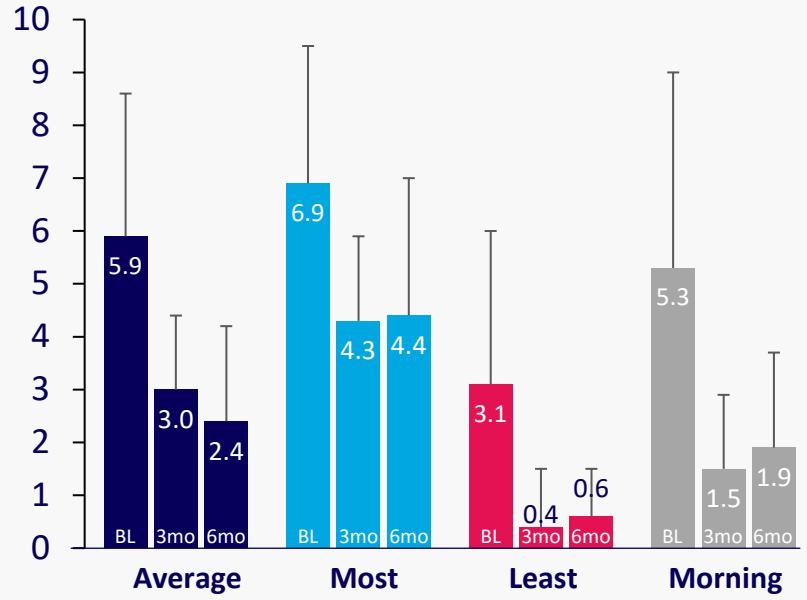
Hunger was scored from 0 to 10



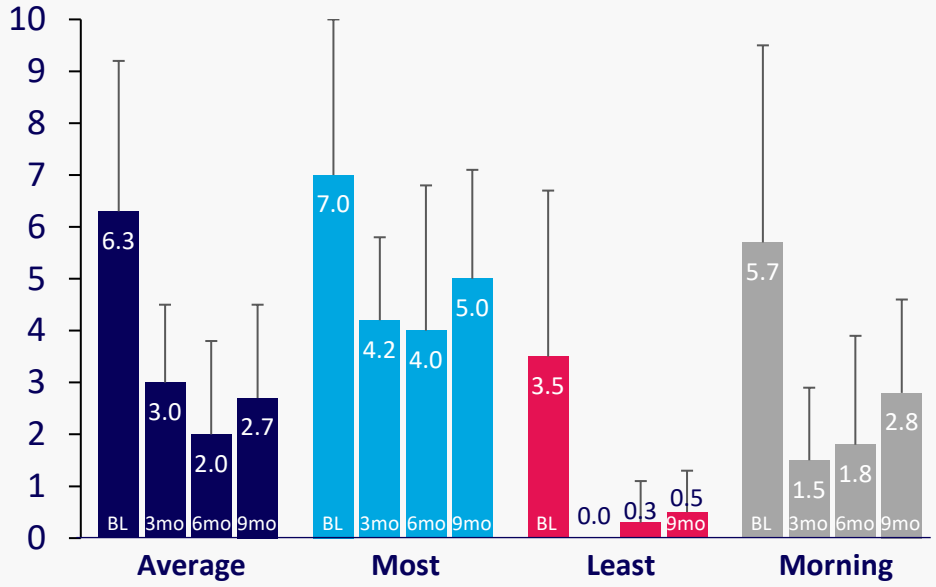
Patients with 3-month data
n=16



Patients with 6-month data
n=8



Patients with 9-month data
n=6



aHO, acquired hypothalamic obesity; mo, months. A meaningful within-person change in hunger has been defined as a reduction of at least 1 point in hunger score[1,2]

1. Haqq et al. Lancet Diabetes Endocrinol 2022; 2. Roth et al. Lancet Diabetes Endocrinol 2024.

Safety outcomes

- During treatment with setmelanotide patients mostly reported injection-site reactions, hyperpigmentation and nausea
- No new safety concerns were observed
- One paediatric patient with aHO suffered from a serious AE requiring hospitalisation
  - Sudden loss of consciousness without prodroma, absence of abnormal movements, absence of urine loss. Not considered related to setmelanotide treatment; treatment was stopped for 4 days

Adverse event, n (%)	aHO adult n=20	aHO paediatric n=10	cHO n=5	ALL n=35
Injection site reactions	8 (40%)	1 (10%)	2 (40%)	11 (31.4%)
Hyperpigmentation	5 (25%)	0%	2 (40%)	7 (20.0%)
Nausea	4 (20%)	0%	0%	4 (11.4%)
Asthenia	3 (15%)	0%	0%	3 (8.6%)
Headache	3 (15%)	0%	0%	3 (8.6%)

AE, adverse event; aHO, acquired hypothalamic obesity; cHO, congenital hypothalamic obesity.

Study limitations

1

Real-world studies rely on methods that are inadequate for identifying all possible adverse events

2

Real-world studies are subject to the presence of substantial missing data

3

This real-world study was not designed to accurately capture hunger scores

Conclusions

These real-world data demonstrate a clinical benefit of setmelanotide treatment on BMI and hunger in patients 6–42 years of age with acquired or congenital HO

- These **real-world** data demonstrate that patients with aHO or cHO who received **≥3 months of setmelanotide** under pre-marketing early access authorisation in France showed **consistent reduction in weight** outcomes
- Adult patients with aHO reported **meaningful decreases in hunger scores** after 3 and 6 months of treatment with setmelanotide
- Outcomes were consistent with Phase 2 data
- Setmelanotide was generally **well tolerated** with the most frequent AEs being **injection site reactions** and **skin hyperpigmentation**

AE, adverse event; aHO, acquired hypothalamic obesity; cHO, congenital hypothalamic obesity.