Rethinking success in the treatment of **overweight and obesity** through body composition:

What are we made of?

ObesityWeek® Corporate-Supported Symposium
sponsored by Wave Life Sciences

Saturday, November 14, 2026

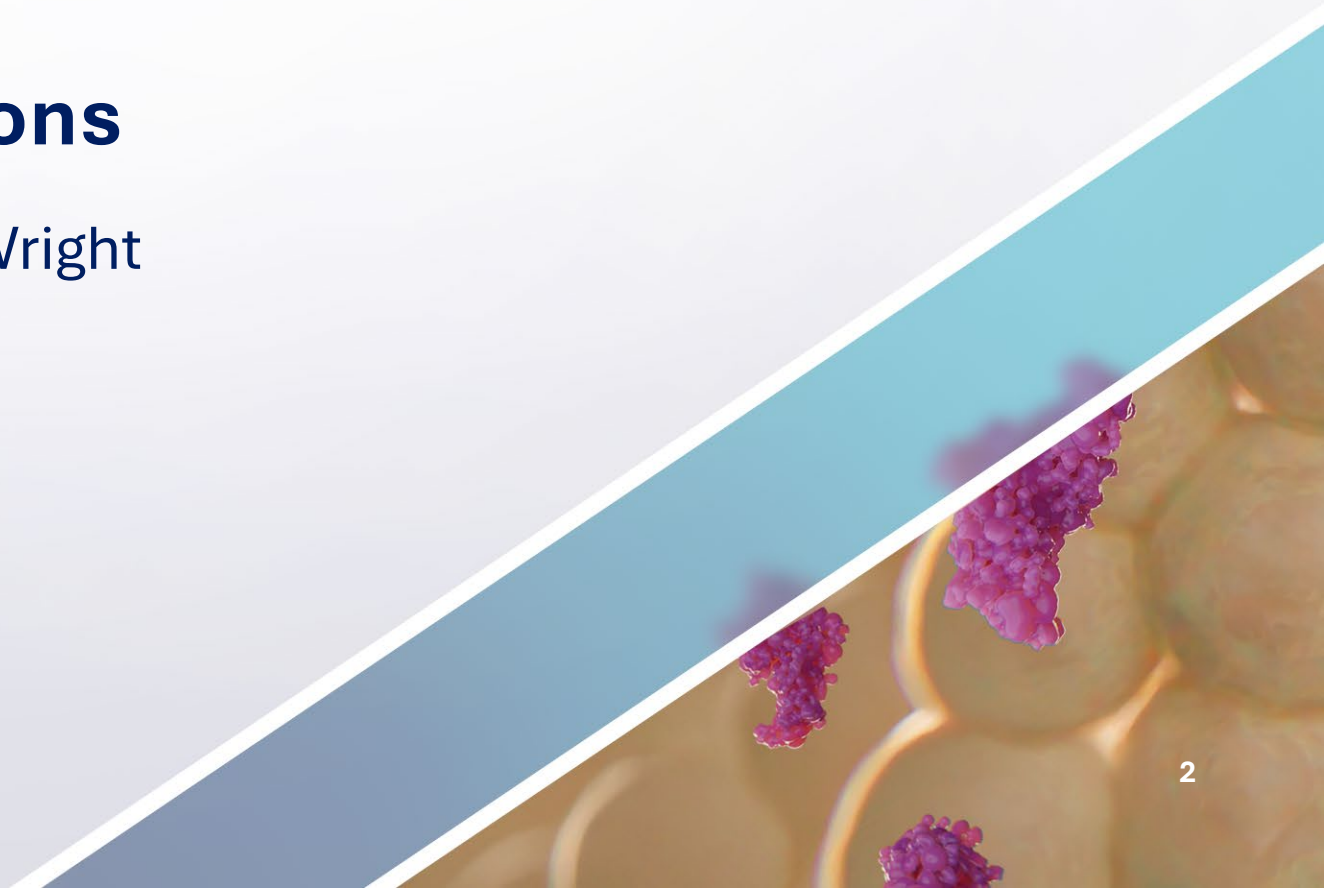
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This symposium is organized and sponsored by Wave Life Sciences
MRC--Obesity-2600045 | November 2026

Welcome and introductions

Dr. Angela Fitch & Dr. Christopher Wright

Co-Chairs



Meet our faculty



Dr. Angela Fitch MD, FACP, MFOMA, Dipl ABOM (Co-Chair)

Board Trustee, Obesity Action Coalition; Past President, Obesity Medicine Association;
Chief Medical Officer and Co-Founder, knownwell, Boston, MA



Dr. Christopher Wright MD, PhD (Co-Chair)

Chief Medical Officer, Wave Life Sciences, Cambridge, MA



Dr. Mehmet Furkan Burak MD

Co-Chair, Obesity Group, Endocrine Society;
Assistant Professor of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA



Dr. Erik Ingelsson MD, PhD

Chief Scientific Officer, Wave Life Sciences, Cambridge, MA

Disclosures

Dr. Angela Fitch has participated in advisory boards for AbbVie, Boehringer Ingelheim, Currax, Eli Lilly, Kailera, Metsera, Novo Nordisk, Samsung Health, Seca, Viking, and Zealand; served as a speaker for Abbott, Amgen, Boehringer Ingelheim, Currax, Eli Lilly, Kailera, Nestlé, Novo Nordisk, Rhythm, and Wave Life Sciences; and has received research funding from Eli Lilly, Roche/Genentech, Structure, Viking, and Wave Life Sciences

Dr. Christopher Wright is an employee and shareholder of Wave Life Sciences

Dr. Mehmet Furkan Burak has participated in an advisory board for Eli Lilly, and has served as a consultant, research partner and/or speaker for Halo Scape, Insulet, Kymera Therapeutics, Northstar, Tersus Life Sciences, and Wave Life Sciences

Dr. Erik Ingelsson is an employee and shareholder of Wave Life Sciences

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Our objectives today

1. Discuss body composition and lean mass preservation as important future treatment considerations in overweight and obesity
2. Review the role of the *INHBE*-Activin E pathway in regulating adipocyte lipolysis
3. Review how *INHBE* represents a promising therapeutic target for overweight and obesity, with potential to drive health gains by improving body composition
4. Consider emerging treatment approaches with the potential to impact body composition

INHBE, Inhibin βE; siRNA: short interfering ribonucleic acid

Our agenda today

Time (*Duration*)	Presentation	Speaker
11:45 AM–11:55 AM *(10 min)*	Welcome and introductions	Dr. Angela Fitch and Dr. Christopher Wright (Co-Chairs)
11:55 AM–12:10 PM *(15 min)*	Changing the treatment paradigm in overweight and obesity management	All Faculty
12:10 PM–12:35 PM *(25 min)*	Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass	All Faculty
12:35 PM–1:00 PM *(25 min)*	From genetic evidence to therapeutic hypothesis: The *INHBE*-Activin E pathway as a target for obesity management	Dr. Erik Ingelsson and Dr. Christopher Wright
1:00 PM–1:10 PM *(10 min)*	The next frontier: How may new therapies for overweight and obesity impact body composition?	Dr. Mehmet Furkan Burak and Dr. Angela Fitch
1:10 PM–1:15 PM *(5 min)*	Rethinking success: Where should obesity treatment go?	Dr. Angela Fitch and Dr. Christopher Wright (Co-Chairs)

Symposium essentials

Housekeeping

- Please **mute** your **mobile phone,** but keep it handy for voting!
- We'll **record the audio and slides, including audience responses** to questions.
- Please take a few minutes at the end to share your **feedback** by answering a **few short** questions on Slido.

Join the discussion

- We will be using **Slido** to vote, when prompted, **select your answer** to the poll.
- Through the symposium, **submit** your questions for the speakers under **Q&A** tab.
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Which of these is NOT true about Washington DC?

a. There is no J Street in Washington DC

b. The US Capitol dome is made primarily of cast iron

c. A Darth Vader sculpture can be found on Washington National Cathedral

d. George Washington is buried beneath the US Capitol

e. Washington DC was designed by Pierre Charles L'Enfant

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Which of these is NOT true about Washington DC?

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Overweight and obesity: A heterogenous, chronic disease of excess adiposity

A complex, multi-factorial disease

Overweight and obesity is a chronic, relapsing disease resulting from excess adiposity due to a **sustained energy imbalance** arising from a **complex interaction** of genetic, biological, behavioral, environmental and societal factors[1–5]

Associated with multiple comorbidities

Numerous **comorbidities**, including type 2 diabetes, cardiovascular disease, MASH, and some cancers are associated with overweight and obesity[1–3,6]

A substantial global burden

Approximately **2.6 billion adults** worldwide were living with overweight or obesity in 2024, representing a **substantial global health burden**[1]

Overweight and obesity is a chronic, complex, and relapsing disease requiring comprehensive, sustained care

MASH: metabolic dysfunction-associated steatohepatitis

1. World Health Organization. Obesity and overweight 2025. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed September 25, 2026). 2. World Health Organization. Obesity Day 2025: addressing the growing burden of obesity. https://www.emro.who.int/media/news/obesity-day-2025-addressing-the-growing-burden-of-obesity.html (accessed September 25, 2026). 3. Busebee et al. Mayo Clin Proc. 2023;98(12):1842–57. 4. Feng X *et al. Chin Med J (Engl)* 2025;139:182–99. Nadolsky et al. Endocrine Pract 2025;31(11):1351–94. 6. Grocic M *et al. Diabetes Obes Metab* 2026;28 Suppl 2:3–18.

Overweight and obesity: Pharmacological treatment progress and persistent unmet need

Early agents
e.g. orlistat, phentermine/topiramate, naltrexone/bupropion

GLP-1RAs (2005–early 2020s)
e.g. liraglutide, semaglutide

Dual/multi-agonists (2020s)
e.g. tirzepatide

Next-generation approaches

Bariatric surgery



~2–10% weight loss[1]

~5–20% weight loss[1]

~15–25% weight loss*[2–4]

?

~25–30% weight loss[2]

Pharmacological management of overweight and obesity has **progressed rapidly**; incretin-based therapies can result in ≥20% weight loss, and are associated with improvements in cardiometabolic health[1–2]

However, **loss of lean mass** (particularly muscle mass), **tolerability**, **dosing frequency** and **long-term treatment persistence** remain important considerations with incretin-based therapies[5–8]

There remains an **unmet need** in the treatment of overweight and obesity, and innovative approaches are warranted that **drive healthy, sustainable weight loss** while **preserving muscle mass**

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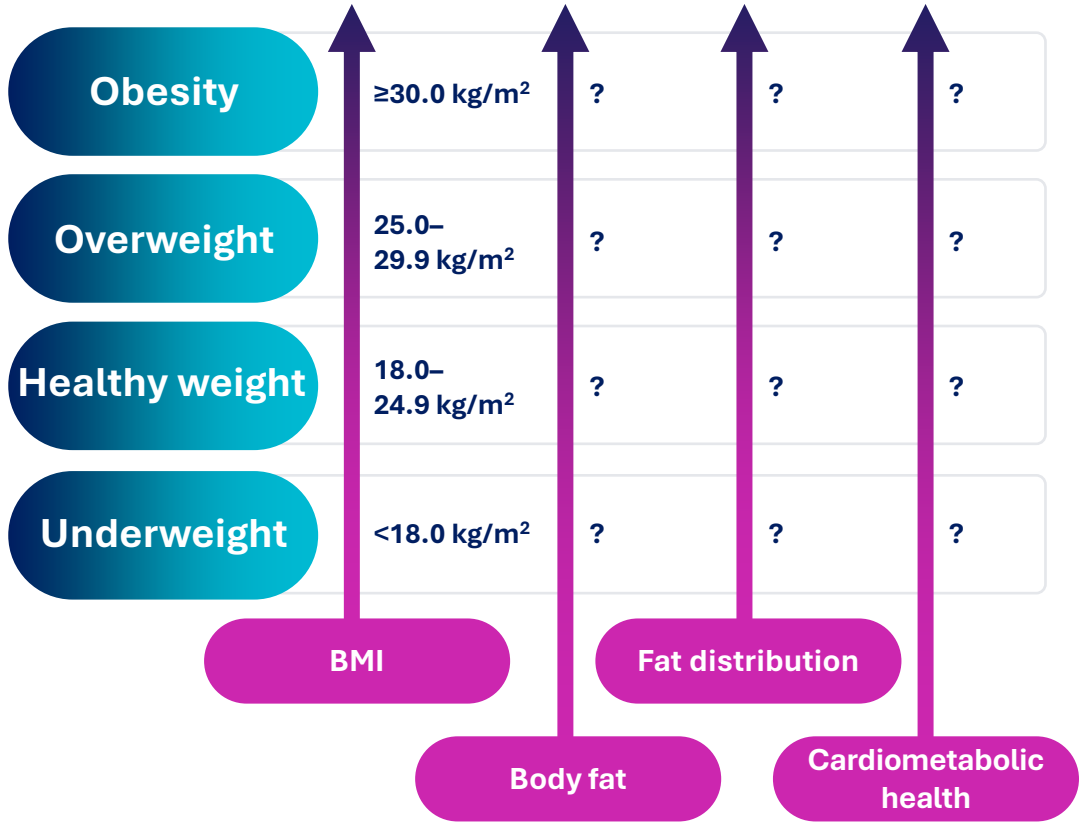
GLP-1RA, glucagon-like peptide 1 receptor agonist. 1. Idrees Z *et al. Cureus* 2022;14:e29262. 2. Heymsfield et al. *Obesity (Silver Spring)* 2025;33:1819–32. 3. Jastreboff AM *et al. N Engl J Med* 2022;387:205–16. 4. Jastreboff et al. *New Engl J Med* 2026 [Online ahead of print]. doi:10.1056/NEJMoa2604169. 5. Ghusn and Hurtado. *Obesity Pillars*. 2024;12:100127. 6. Wegovy Prescribing Information. 7. Gleason PP *et al J Manag Care Spec Pharm* 2024;30:860–7. 8. Gasoyan et al. *Obesity (Silver Spring)*. 2024;32:486–93.

Looking beyond weight loss: Defining more meaningful treatment outcomes

- **BMI and bodyweight** are useful screening measures, but they do not directly **capture body composition, fat distribution or individual health risk**[1–3]
- BMI substantially underestimates the true burden of obesity[4]
- Disease management should consider **obesity-related comorbidities**, **functional health** and **individual circumstances**[1]

Meaningful treatment goals can include:[1]

- Improving metabolic and cardiovascular health
- Supporting physical function and quality of life
- Reducing the risk of obesity-associated comorbidities
- Achieving and maintaining clinically meaningful weight loss



Treatment success should be defined according to **individual health needs and goals**, rather than weight loss alone

1. American Diabetes Association Professional Practice Committee for Obesity. BMJ Open Diabetes Res Care 2026;13:e005729. 2. Nadolsky et al. Endocrine Pract 2025;31(11):1351–94. 3. Rubino et al. Lancet Diabetes Endocrinol. 2025;13:221–62. 4. Fourman LT *et al. JAMA Netw Open* 2025;8:e2537619.

Moving beyond weight loss alone as a measure of broader health gains

There are limitations of using BMI alone in the diagnosis and management of obesity[1–4]

- BMI is not a direct measure of fat; it does not establish the fat distribution around the body, and cannot determine when excess body fat is a health issue

A considerable number of patients with clinically relevant excess adiposity are missed by BMI-based definitions

- In one study, defining obesity using adiposity rather than BMI alone increased prevalence from 42.9% to 68.6%[5]

BMI and body weight do not evaluate changes in body composition during weight loss

- Up to 20–50% of weight loss with incretin-based therapies may be attributed to lean mass loss,[6,7] which may be difficult to regain after treatment cessation

Clinical practice recommendations and scientific statements now recognize the importance of body composition in the management of overweight and obesity[1–4]

- The AACE,[1] the Lancet Commission on Obesity,[2] the Endocrine Society[3] and the ADA Standards of Care in Overweight and Obesity[4] recommend additional anthropometric measures to assess body fat beyond BMI, including waist circumference, waist-to-hip ratio and waist-to-height ratio

AACE: American Association of Clinical Endocrinology; BMI: body mass index. 1. Nadolsky *et al. Endocrine Pract* 2025;31(11):1351–94. 2. Rubino *et al. Lancet Diabetes Endocrinol* 2025;13:221–62. 3. Jastreboff *et al. Endocr Rev* 2026;bnag025. 4. American Diabetes Association Professional Practice Committee for Obesity. *BMJ Open Diabetes Res Care* 2026;13:e005729. 5. Fourman LT *et al. JAMA Netw Open* 2025;8:e2537619. 6. Sargeant et al. *Endocrinol Metab (Seoul)* 2019;34:247. 7. Heymsfield *et al. Obesity (Silver Spring)* 2025;33:1819–32

Looking beyond weight loss: The expanding pipeline for treatment of overweight and obesity

The classes of non-incretin therapies in development demonstrate that the field is expanding beyond weight loss to target body composition

Amylin analogs[1]

- Promote **satiety** and **reduce food intake** through central appetite-regulating pathways

Myostatin pathway inhibitors[2]

- Inhibit **myostatin/ activin signaling** with the aim of **preserving or increasing skeletal muscle mass**

INHBE-Activin E-ALK7 pathway inhibitors[3,4]

- **Inhibit Activin E signaling** via the ALK7 receptor with the expectation of **reducing inhibition of lipolysis**

CB1 inhibitors[5]

- Target endocannabinoid receptor signaling involved in **appetite** and **peripheral energy metabolism**

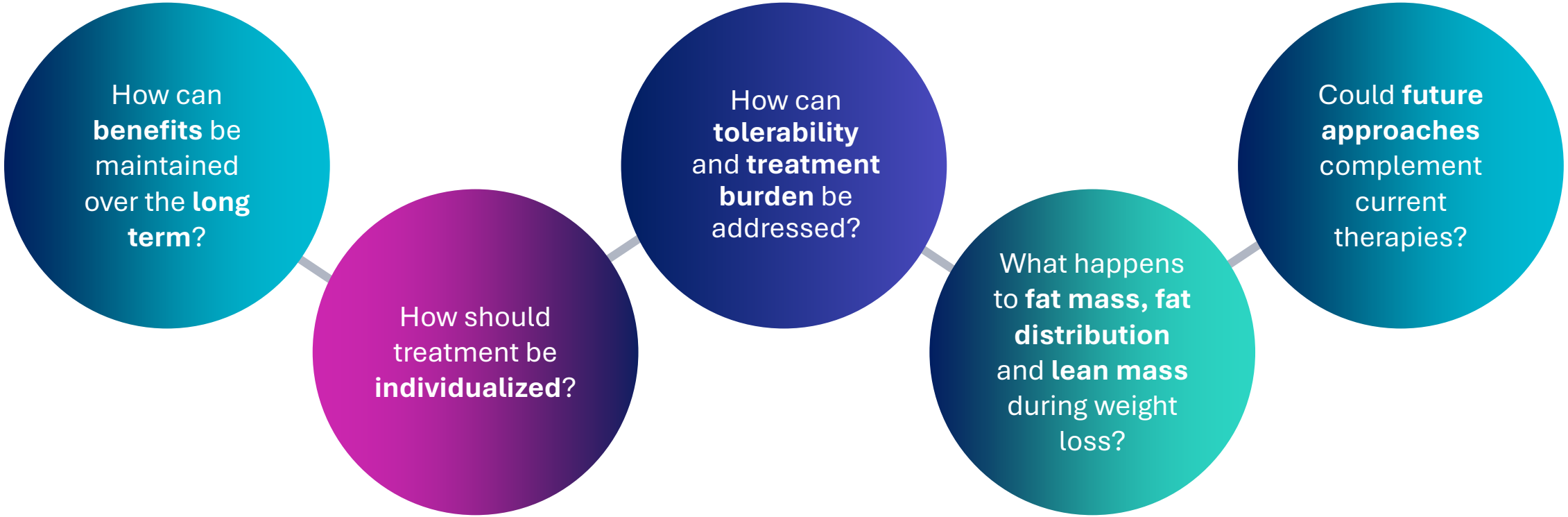
Glucagon receptor agonists[6]

- Increase glucagon receptor activation, which may **increase energy expenditure** and **hepatic lipolysis**, and **reduce appetite**

This list is not comprehensive and additional new mechanisms are being considered for pharmaceutical development, including (but not limited to) GPR75 antagonists[7] and mitochondrial uncouplers[8]

CB1, cannabinoid receptor 1; GLP-1, glucagon-like peptide 1; GLP-1RA, GLP-1 receptor agonist; *INHBE*, Inhibin βE. 1. Alhazmi A and le Roux CW. *Diabetes Obes Metab* 2026;28;42–50. 2. Baik J and Lee YS. *J Bone Metab* 2025;32:263–75. 3. Feng X *et al. Chin Med J (Engl)* 2025;139:182–99. 4. Zhao M *et al. JCI Insight* 2023;8:e161229. 5. Onimus O *et al. Br J Pharmacol* 2026;183:4953–68. 6. Winther JB and Holst JJ. *Diabetes Obes Metab* 2024;26:3501–12. 7. Jiang, Zhang. *Trends Cell Biol* 2025;35:102–4. 8. Demine et al. *Cells* 2019;8:795

Looking beyond weight loss: Body composition and broader outcomes matter for successful management of overweight and obesity



Should success be defined by weight loss alone, or by the quality and durability of that weight loss?

Changing the treatment paradigm in overweight and obesity management

Dr. Angela Fitch, Dr. Christopher Wright,
Dr. Mehmet Furkan Burak & Dr. Erik Ingelsson



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Meet the faculty

Reflections on the evolving overweight and obesity management landscape; from research to patient care



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Wave Life Sciences, Cambridge,
MA

Discussion | Changing the treatment paradigm in overweight and obesity management

Have your say

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Beyond total weight loss, which of the following outcomes matters most in your practice?

a. Improvement in obesity-associated comorbidities

b. Reduction in visceral adipose tissue

c. Preservation of muscle and physical function

d. Durability of benefit

e. Tolerability and treatment burden

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Beyond total weight loss, which of the following outcomes matters most in your practice?

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Discussion | Changing the treatment paradigm in overweight and obesity management

Have your say

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Which of the following outcomes would you consider to be unmet in the current treatment landscape?

a. Improvement in obesity-associated comorbidities

b. Reduction in visceral adipose tissue

c. Preservation of muscle and physical function

d. Durability of benefit

e. Tolerability and treatment burden

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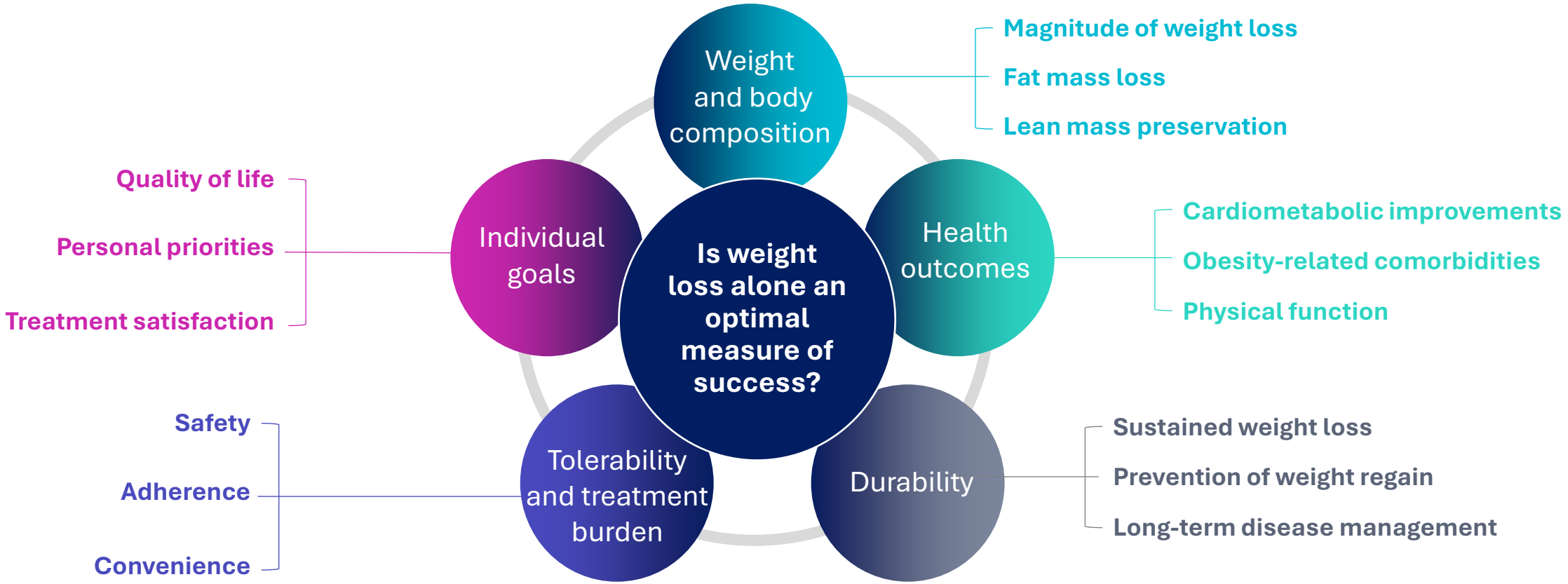


Which of the following outcomes would you consider to be unmet in the current treatment landscape?

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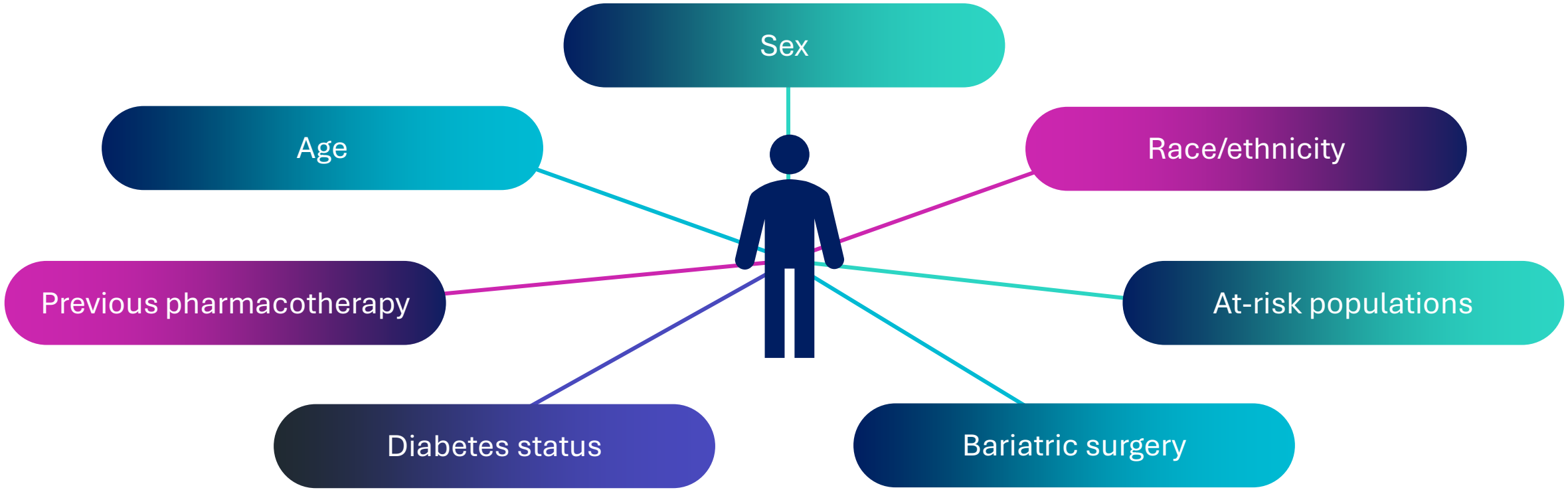
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Discussion | Changing the treatment paradigm in overweight and obesity



Discussion | Changing the treatment paradigm in overweight and obesity

Considerations for treatment individualization for patients with overweight and obesity across different patient characteristics and at-risk populations

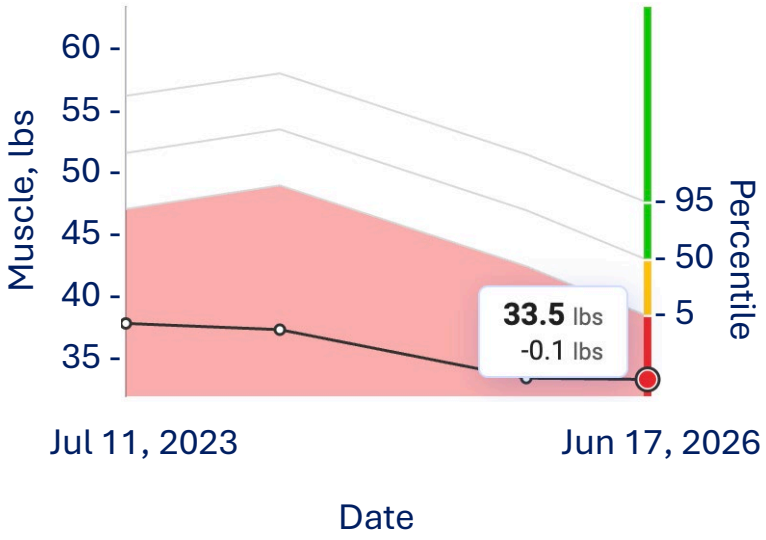


Patient case study

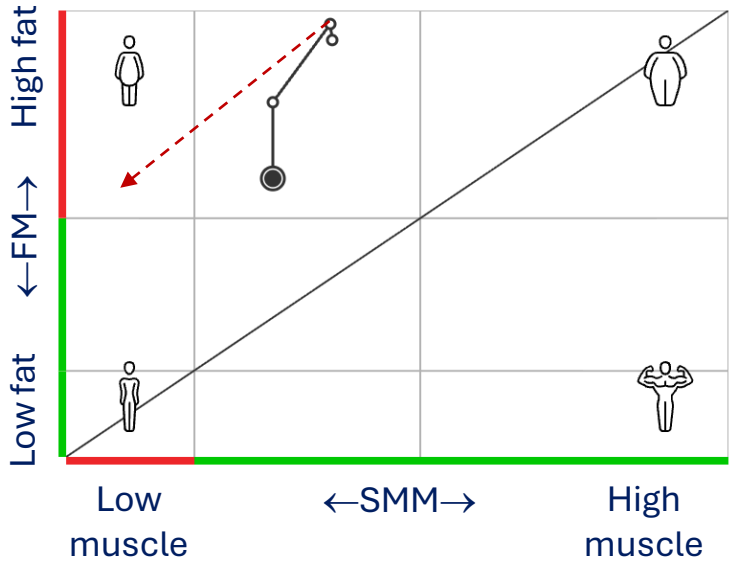


71-year-old patient
Underwent gastric bypass 20 years ago, followed by weight regain and treatment with semaglutide and now tirzepatide
Goes to water aerobics 2–3 times a week

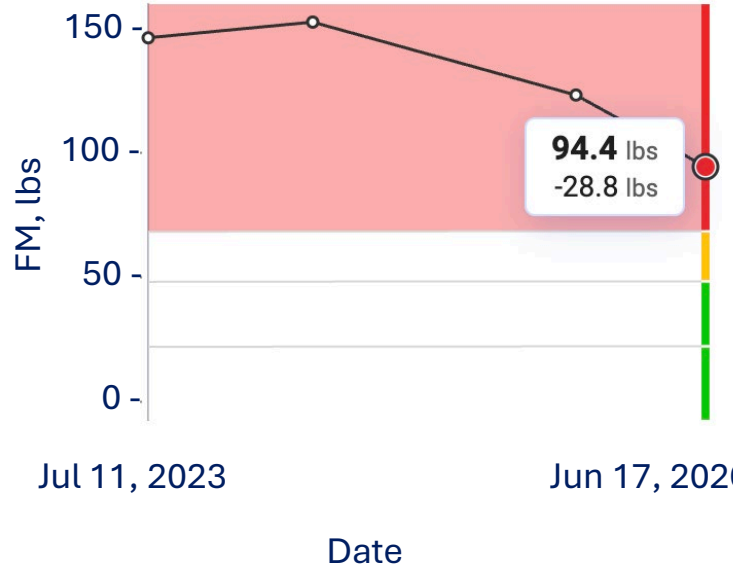
Muscle mass



Body composition



Fat mass



FM: fat mass; SMM: skeletal muscle mass

Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass

Dr. Angela Fitch, Dr. Christopher Wright,
Dr. Mehmet Furkan Burak & Dr. Erik Ingelsson

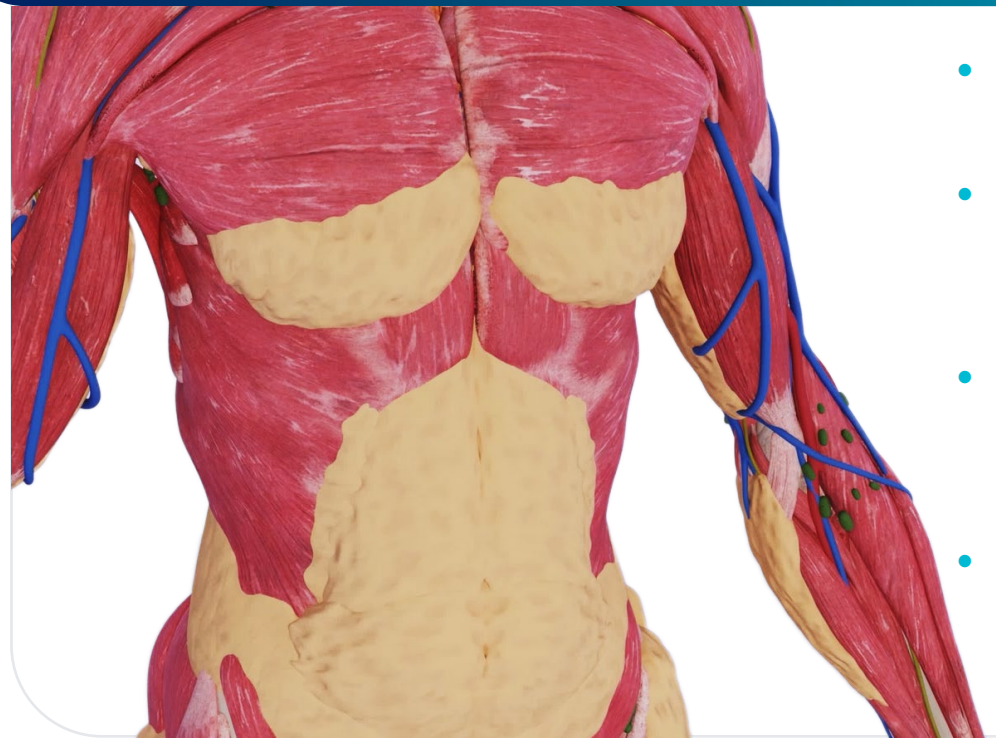


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Discussion | Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass

With current standard of care, up to 40% of weight loss is driven by lean mass loss[1–3]

A high level of lean mass is linked to many health benefits



- Higher basal metabolic rate[4]
- Improved insulin sensitivity and glucose homeostasis[5–7]
- Increased caloric expenditure post-exercise[8]
- Preserved muscle strength and function, and exercise performance[9]
- Contribution to reduced risk of weight regain[10]
- Increased bone density, strength, and function, supporting healthy ageing and longevity[11–13]
- Lower mortality[14]

1. Heymsfield et al. *Obesity (Silver Spring)* 2025;33:1819–32. 2. Kim JY, Kim NH. *Diabetes Metab J* 2026;50:844–62. 3. Locatelli JC *et al. Diabetes Care* 2024;47:1718–30. 4. Gitsi E *et al. J Clin Med* 2024;13:5862. 5. Zarini S *et al. Diabetes* 2026;75:1980–93. 6. Haines MS *et al. Int J Obes (Lond)* 2020;44:1851–8. 7. Paquin J *et al. Front Physiol* 2021;12:656909. 8. Lamont LS *et al. Appl Physiol Nutr Metab* 2010;35:23–6. 9. Calbert JAL *et al. Front Physiol* 2017;8:483. 10. Martins C *et al. Med Sci Sports Exerc* 2022;54:2031–6. 11. Riviati N *et al. Ann Geriatr Med Res* 2025;29:1–14. 12. Kirk B *et al. Age Ageing* 2025;54:afaf189. 13. Li C *et al. BMC Geriatr* 2022;22:597. 14. Sedlmeier AM *et al. Am J Clin Nutr* 2021;113:639–46

Discussion | Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass

Body composition as a driver of cardiometabolic health

Visceral fat is associated with obesity-associated comorbidities and mortality



Visceral fat is associated with:

- Subclinical cardiac changes and liver injury[1]
- Higher fasting glucose and HbA1c, and lower HDLs[2]
- Increased 10-year CVD risk[3]
- Increased risk of hepatic steatosis[4]
- Mortality[5,6]

Visceral fat reduction is beneficial for health



A reduction in visceral fat is associated with:

- Improved glucose homeostasis[7,8]
- Improved CVD risk factors[7–9]
- Lower liver enzymes and risk of hepatic steatosis[8,10]
- Lower inflammation[8,10]

CVD: cardiovascular disease; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; 1. Bai J *et al. Cardiovasc Diabetol* 2023;22:206. 2. Liu J *et al. Arterioscler Thromb Vasc Biol* 2011;31:2715–22. 3. Salle L *et al. Cardiovasc Diabetol* 2025;24:256. 4. Park BJ *J Gastroenterol Hepatol* 2008;23:900–7. 5. Xie C *et al. BMC Gastroenterol* 2025;25:238. 6. Sedlmeier AM *et al. Am J Clin Nutr* 2021;113:639–46. 7. Abdullah SR *et al. Front Endocrinol (Lausanne)* 2025;16:1576599. 8. Klein H *et al. BMC Med* 2025;23:57. 9. Guo X *et al. Nutr Metab (London)* 2019;16:44. 10. Sileo F *et al. Diabetes* 2026;75:2473-P

Discussion | Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass

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How often does body composition influence your assessment of obesity-related risk?

a. Routinely

b. In selected patients

c. Occasionally

d. Rarely

e. Never

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How often does body composition influence your assessment of obesity-related risk?

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Discussion | Beyond the scale: The clinical relevance of body composition, body fat distribution and lean mass

Have your say

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What tools do you use in your practice to assess body composition?

a. DEXA

b. Bioimpedance

c. MRI or CT

d. Anthropometric measures (waist circumference, WHR)

e. None of the above

CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; WHR, waist-to-height ratio

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What tools do you use in your practice to assess body composition?

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Discussion | Beyond the scale: the clinical relevance of body composition, body fat distribution and lean mass



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Fat mass and distribution

Lean mass and muscle quality and function

What is the clinical relevance of these outcomes?

Physical functioning and quality of life

Durability of weight loss

From genetic evidence to therapeutic hypothesis: The *INHBE*-Activin E pathway as a target for obesity management

Dr. Erik Ingelsson and Dr. Christopher Wright



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We are an RNA medicines company focused on delivering transformational therapies for people with serious and life-altering diseases



Building a leading RNA medicines company

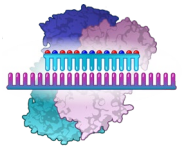
Differentiated RNA medicines platform and chemistry

PRISM

- **Proprietary chemistry**
- Leveraging deep insights in **human genetics**
- **In-house GMP** manufacturing

Translating genetic insights into potentially best-in-class medicines

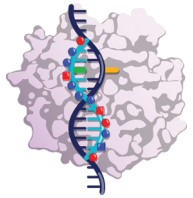
RNAi



WVE-007 (obesity)

- Differentiated mechanism focused on fat loss and muscle preservation

RNA editing



WVE-006 (AATD)
WVE-008 (liver disease)

- Restoration of functional protein production

Other modalities: **splicing, antisense silencing**

Unlocking emerging pipeline

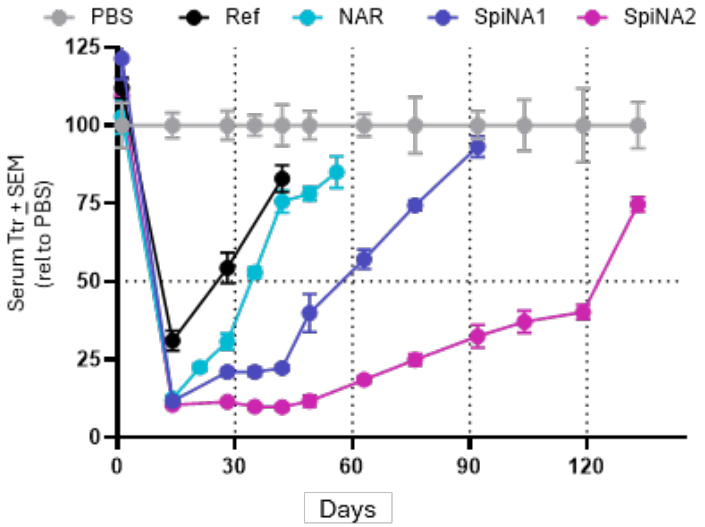
- **Extra-hepatic capabilities:** with RNAi and RNA editing
- **Bifunctional modalities:** single oligonucleotide constructs for dual RNAi silencing or RNAi silencing + RNA editing

AATD: alpha-1 antitrypsin deficiency; GMP: good manufacturing practice; RNA: ribonucleic acid; RNAi: ribonucleic acid interference

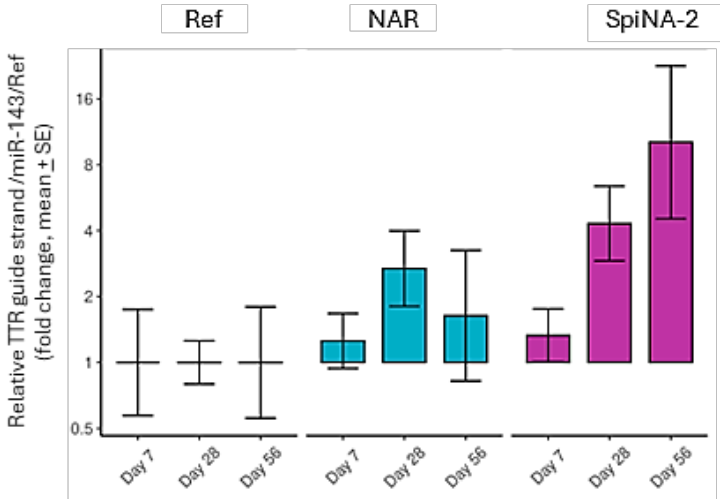
For over a decade Wave has been extending the frontiers of RNA therapies delivering breakthroughs in nucleic acid chemistry

RNAi — SpiNA

Protein reduction

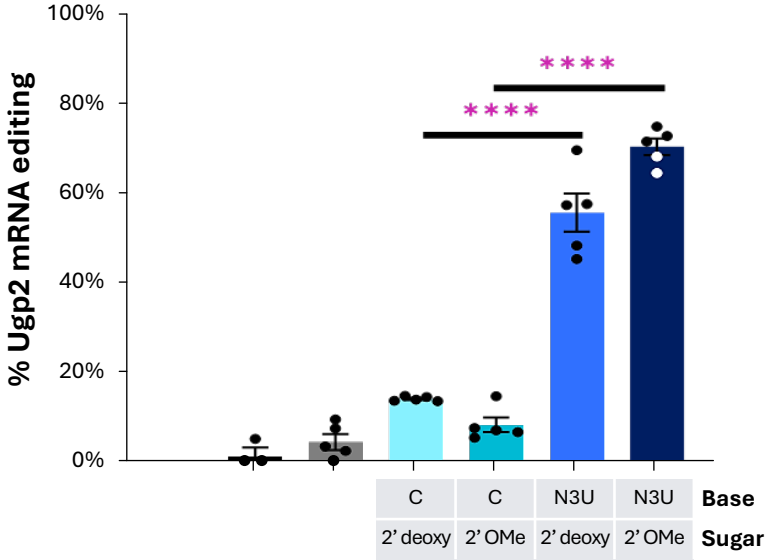


AGO2 loading



Substantial improvements in potency, duration of activity, and AGO2 loading with Wave's proprietary SpiNA design

RNA editing — AIMer



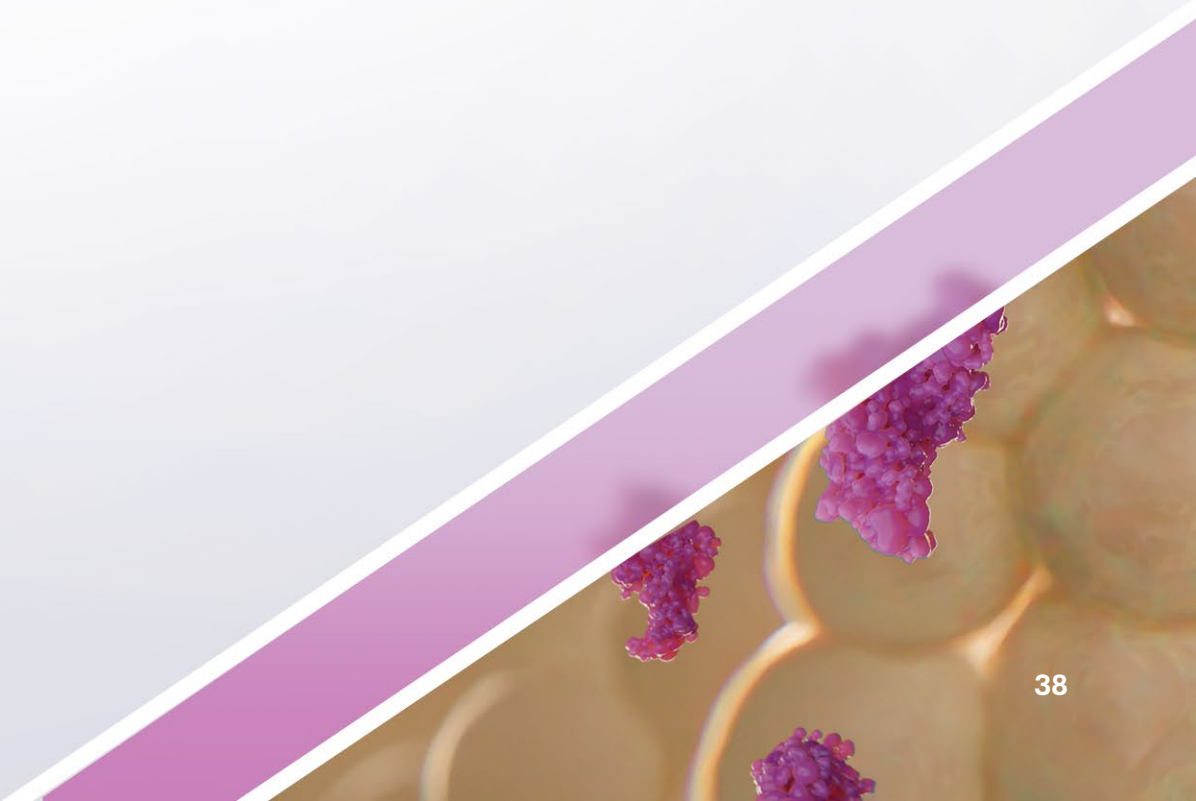
Increased RNA editing efficiency achieved with proprietary chemistry

Proprietary chemistry has dramatically increased potency and durability

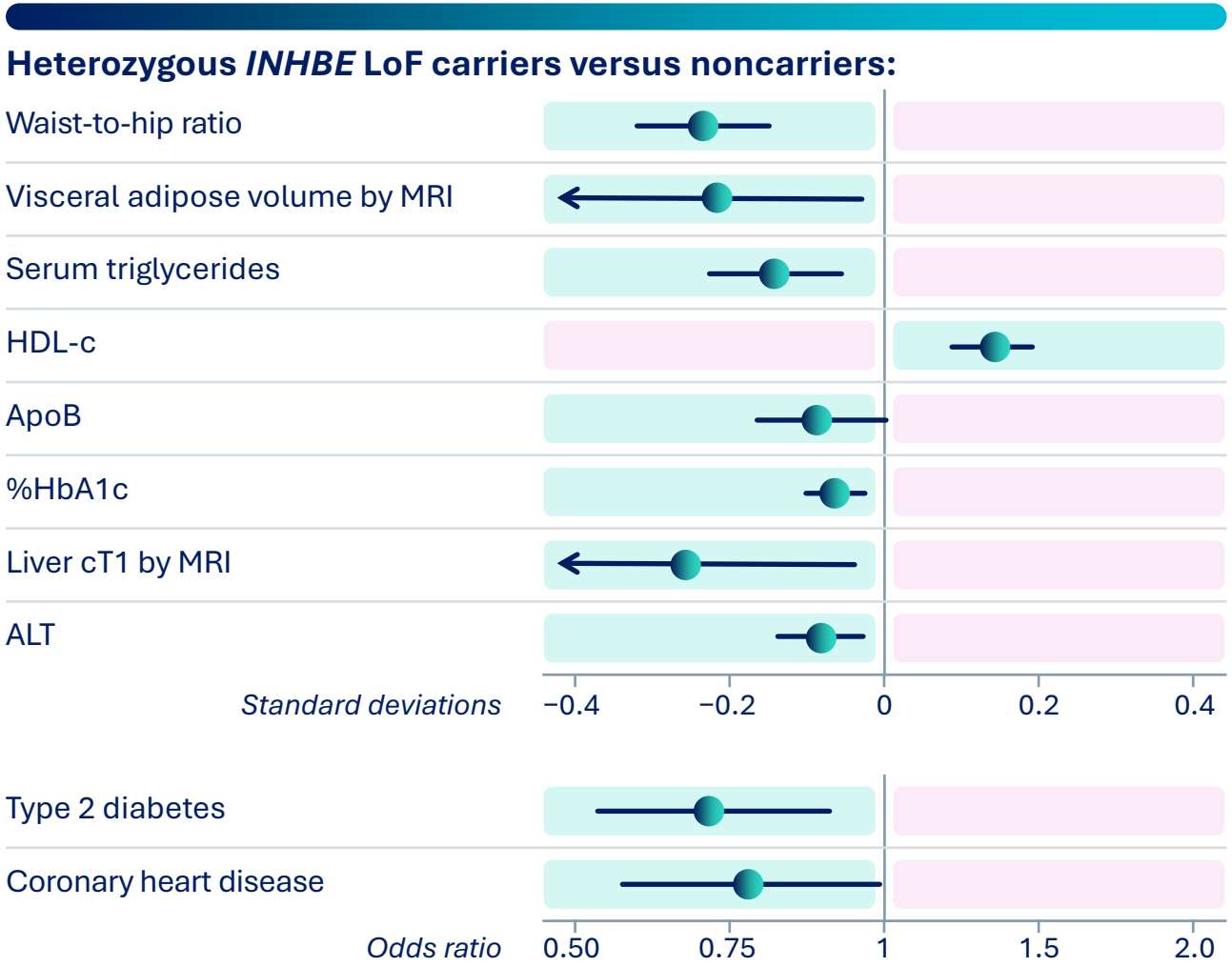
2'OMe, 2'-O-methylation; AGO2: Argonaute RNA-induced silencing complex catalytic component 2; mi-R: micro-ribonucleic acid; mRNA: messenger ribonucleic acid; NAR: *Nucleic Acids Res* publication (Liu W *et al. Nucleic Acids Res* 2023;51:4126–47); N3U: N-3-uridine; PBS: phosphate-buffered saline; Ref: reference; rel: relative; RNA: ribonucleic acid; RNAi: ribonucleic acid interference; SE: standard error; SEM: standard error of the mean; SpiNA: stereopure interfering nucleic acid; Ttr: transthyretin
https://wavelifesciences.com/science/publications/

INHBE biology and obesity

Dr. Erik Ingelsson



Human genetic data demonstrate that heterozygous *INHBE* LoF carriers have lower visceral fat and a healthier metabolic profile than noncarriers



Favorable traits:

- ✓ **Lower abdominal obesity**
- ✓ **Reduced visceral fat**
- ✓ **Lower triglycerides**
- ✓ **Higher “good” cholesterol**
- ✓ **Lower ApoB**
- ✓ **Improved glucose control**
- ✓ **Less liver inflammation/fibrosis**
- ✓ **Less liver damage**
- ✓ **Lower risk of type 2 diabetes**
- ✓ **Lower risk of CHD**

Waist-to-hip ratio and visceral adipose volume by MRI were BMI adjusted

ALT: alanine transaminase; ApoB: apolipoprotein B; BMI: body mass index; CHD: coronary heart disease; cT1: corrected T1; HbA1c: glycated hemoglobin; HDL-c: high-density lipoprotein cholesterol; *INHBE*: inhibin βE; LoF: loss of function; MRI: magnetic resonance imaging

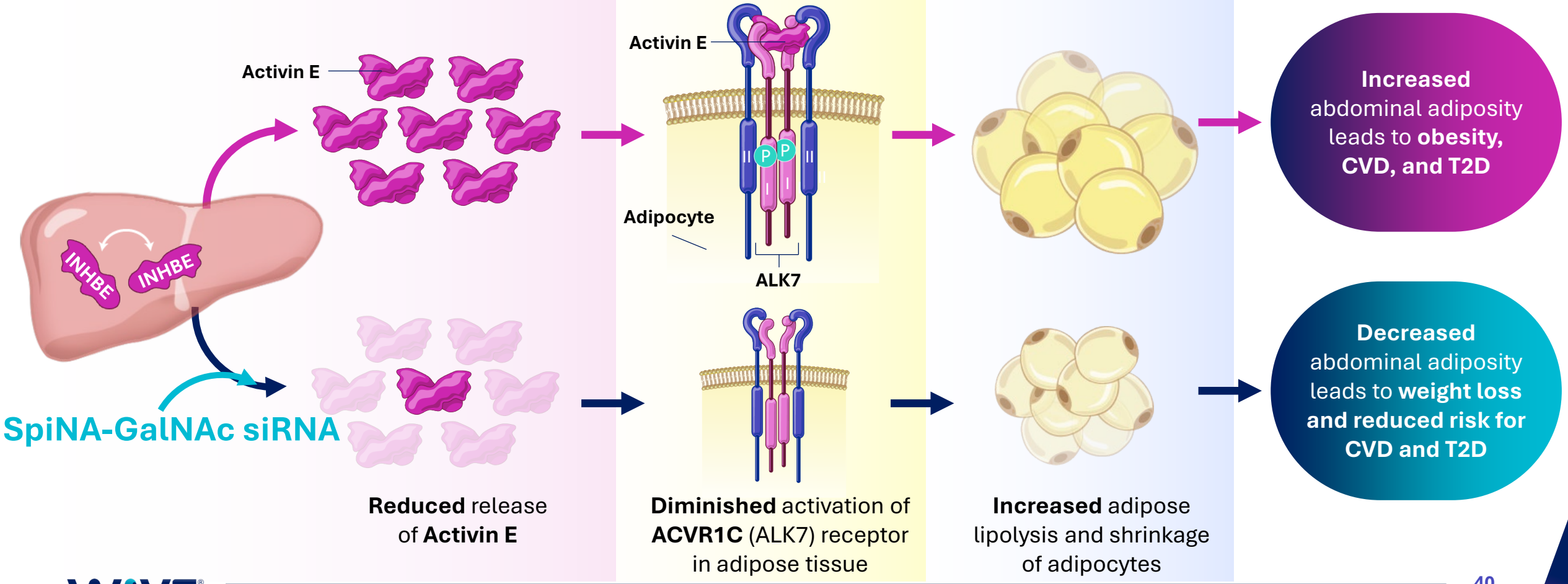
Akbari P *et al. Nat Commun* 2022;13:4844; Deaton AM *et al. Nat Commun* 2022;13:4319

How *INHBE* GalNAc-siRNA might address obesity-associated metabolic disease

Release of **dimerized** INHBE subunits creates the hepatokine **Activin E**

Activin E binds to and **activates ACVR1C** (ALK7) receptor in adipose tissue

Adipose lipolysis is blocked



Reduced release of **Activin E**

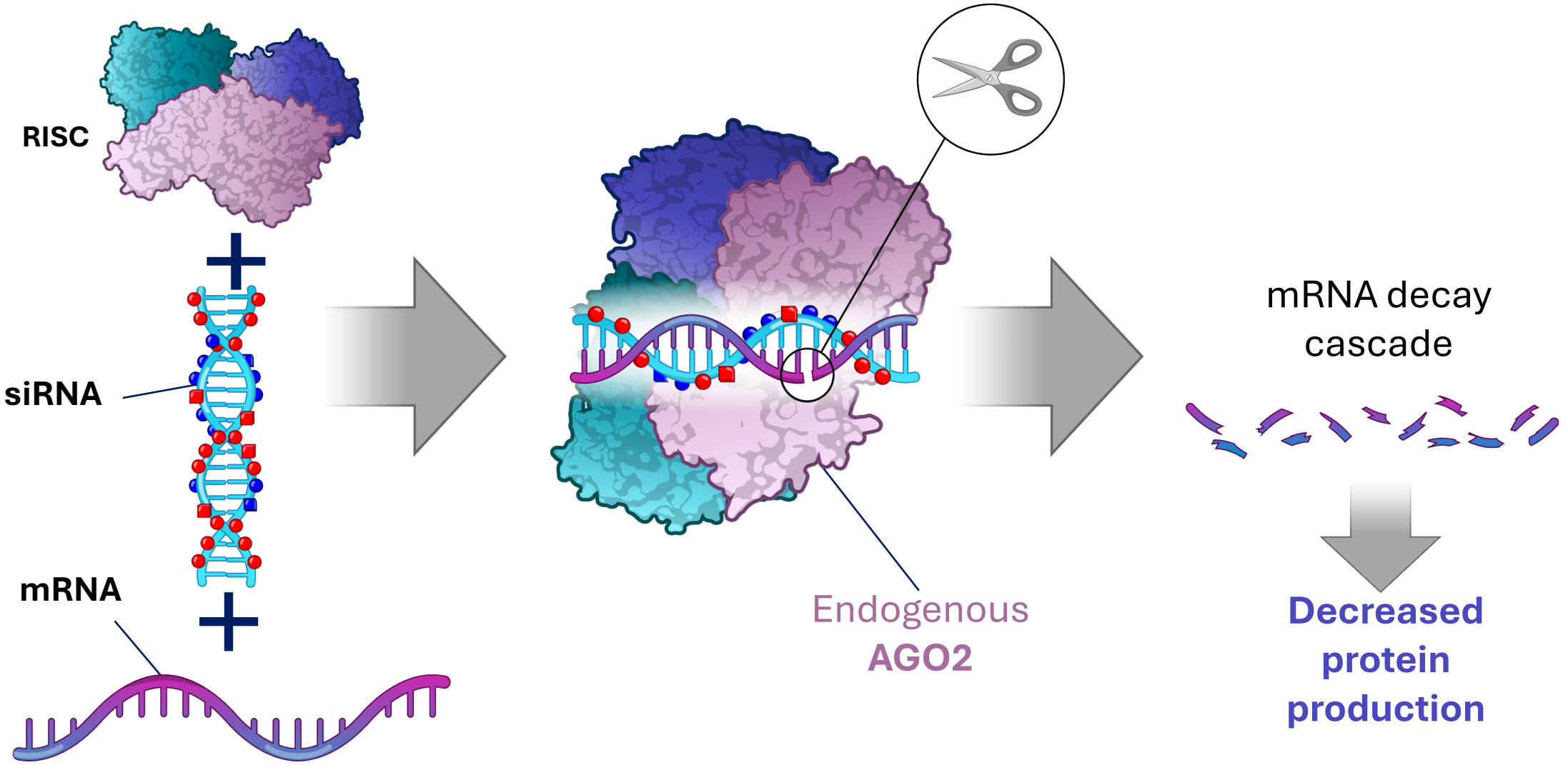
Diminished activation of **ACVR1C** (ALK7) receptor in adipose tissue

Increased adipose lipolysis and shrinkage of adipocytes

ACVR1C: activin A receptor type 1C; ALK7: activin receptor-like kinase 7; CVD: cardiovascular disease; GalNAc: N-acetylgalactosamine; *INHBE*: inhibin βE; mRNA: messenger ribonucleic acid; siRNA: short interfering ribonucleic acid; SpiNA: stereopure interfering nucleic acid; T2D: type 2 diabetes

Hashimoto O *et al. Cell Rep* 2018;25:1193–203; Vestal KA *et al. Biochem J* 2024;481:547–64; Adam RC *et al. Proc Natl Acad Sci U S A* 2023;120:e2309967120; Akbari P *et al. Nat Commun* 2022;13:4844; Deaton AM *et al. Nat Commun* 2022;13:4319

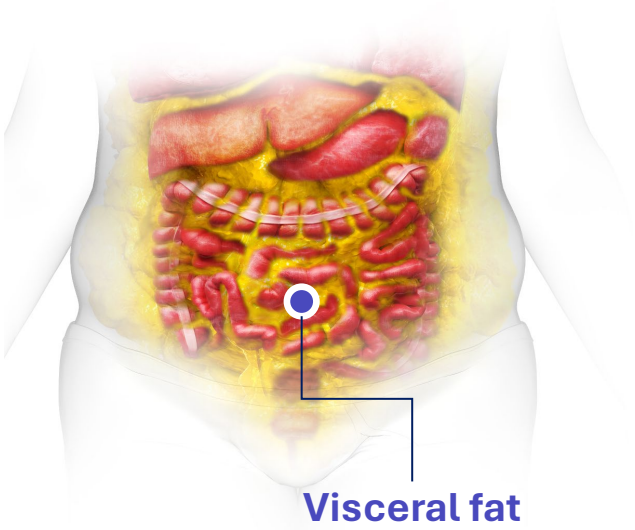
Oligonucleotide-directed gene silencing by RNA interference



AGO2: Argonaute 2; mRNA: messenger ribonucleic acid; RISC: ribonucleic acid-induced silencing complex; RNA: ribonucleic acid; siRNA: small interfering ribonucleic acid

The mechanism of WVE-007 is focused on lipolysis and directly reducing visceral and subcutaneous fat

Visceral fat drives insulin resistance and many cardiometabolic disorders



- MASH
- T2D
- CVD
- PMOS

Waist circumference is a clinical proxy for visceral fat

Reduced visceral fat is associated with multiple health benefits

Visceral fat decrease

≥5%

Improved insulin sensitivity[1–3]: Lower HbA1c, better lipid profile

≥5-10%

Reduced cardiovascular risk[4–6]: Reduced blood pressure, improved lipids, lower systemic inflammation

≥10%

Reduced liver fat (steatosis)[7–9]: Significant reduction in hepatic triglycerides, improved liver enzymes

Decreased hepatic fibrosis[7,8]: Resolution of steatohepatitis in up to 90% of people, fibrosis regression in many people

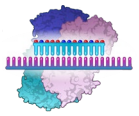
CVD: cardiovascular disease; HbA1c: glycated hemoglobin; MASH: metabolic dysfunction-associated steatohepatitis; PMOS: polyendocrine metabolic ovarian syndrome; T2D: type 2 diabetes

1. Gabriely I *et al. Diabetes* 2002;51:1016–21; 2. Campos RMDS *et al. Diab Vasc Dis Res* 2019;16:196–206; 3. Huang H *et al. Front Endocrinol* 2023;14:1144834; 4. Cesaro A *et al. Front Cardiovasc Med* 2023;10:1187735; 5. Khawaja T *et al. Curr Cardiol Rep* 2024;26:1297–307; 6. Hiuge-Shimizu A *et al. J Atheroscler Thromb* 2012;19:657–63; 7. Liao C *et al. PLoS One* 2023;18:e0289616; 8. Jung CH *et al. Endocrinol Metab* 2020;35:165–76; 9. Hanlon CL, Yuan L. *Clin Liver Dis* 2022;19:106–10

Treatment with WVE-007 (investigational *INHBE* GalNAc-siRNA) is expected to drive fat reduction and improve key measures of cardiometabolic health

Leading siRNA design (SpiNA)[1]

WVE-007 (*INHBE* GalNAc-siRNA)



- Proprietary, clinically validated chemistry
- Subcutaneous delivery (GalNAc)
- Potential for infrequent dosing (1 – 2x year)

Driving fat reduction

Reduction of *INHBE* mRNA and circulating Activin E

- ↑ Adipocyte lipolysis
- ↓ Adipocyte size
- ↓ Proinflammatory macrophages
- ↓ Fibrosis
- ↑ Insulin sensitivity

And improving clinical outcomes

Cardiometabolic outcomes

- ↓ Risk of CVD
- ↓ Risk of T2D

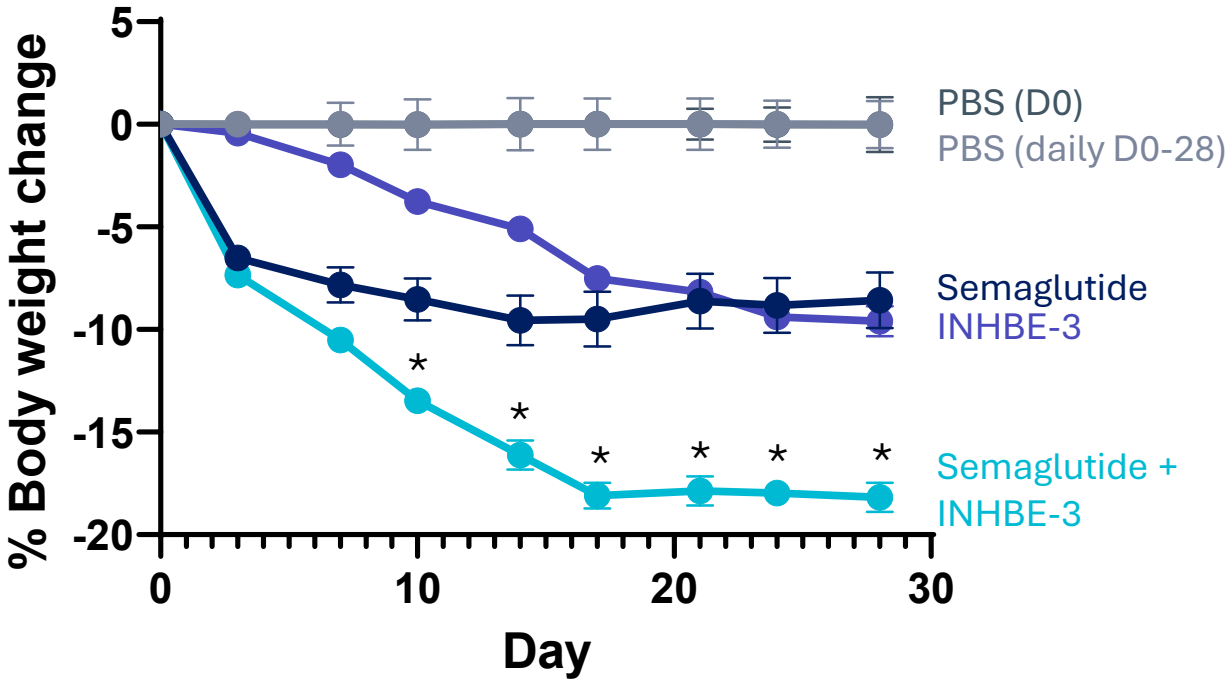
Preclinical data

CVD: cardiovascular disease; GalNAc: N-acetylgalactosamine; *INHBE*: inhibin βE; mRNA: messenger RNA; RNA: ribonucleic acid; siRNA: short interfering RNA; SpiNA: stereopure interfering nucleic acid; T2D: type 2 diabetes

1. SpiNA design is derived from Liu W *et al*. *Nucleic Acids Res* 2023;51:4126–47.

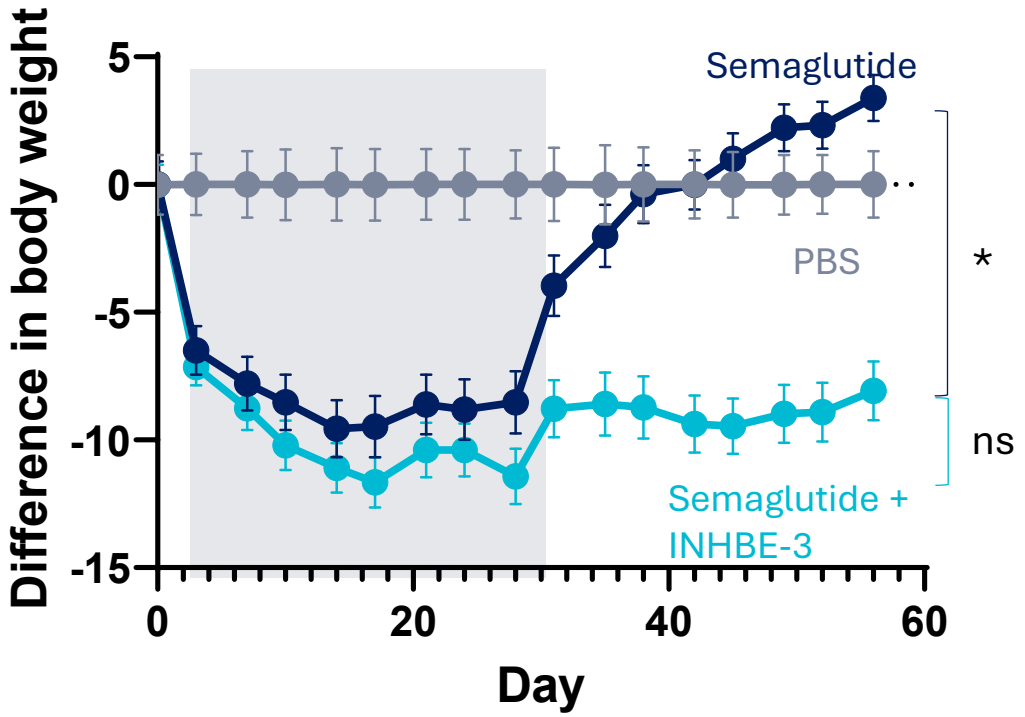
Treatment with *INHBE* SpiNA-GalNAc siRNA augments semaglutide-induced weight loss and suppresses weight regain in DIO mice

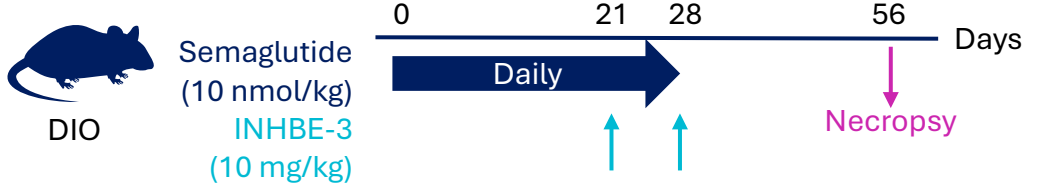
~2× greater overall weight loss when added to semaglutide





Curtails weight regain after the cessation of semaglutide

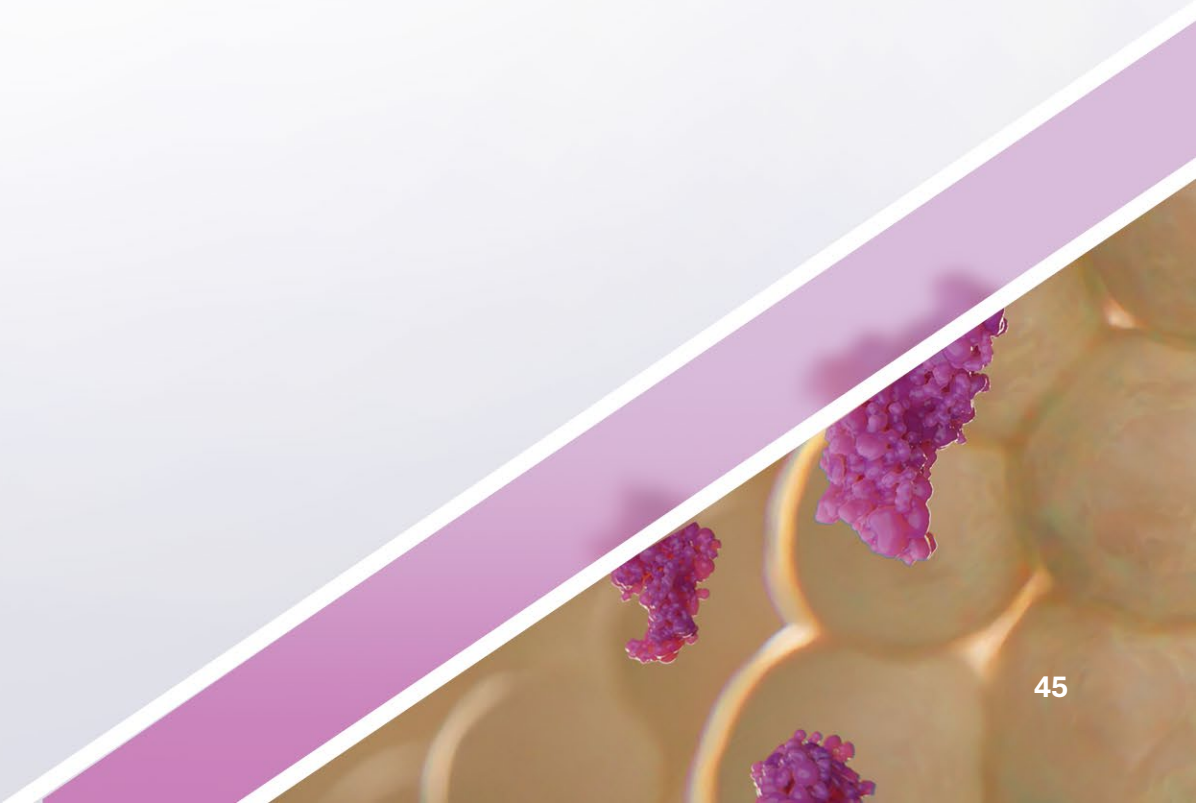




Stats: data presented as mean difference in baseline-adjusted weight percentage relative to PBS control on same day ± SEM (DIO mice; n = 10). Left: linear mixed-effects ANOVA with *post hoc* comparisons of marginal treatment effects for semaglutide vs. semaglutide + INHBE-3 siRNA per time point; *$p < 0.05$ vs. semaglutide group. Right: linear mixed-effects ANOVA with *post hoc* comparisons of marginal time point effects between day 28 and day 56 per treatment group; *$p < 0.05$. ANOVA: analysis of variance; DIO: diet-induced obesity; GalNAc: N-acetylgalactosamine; *INHBE*: inhibin βE; ns: nonsignificant; PBS: phosphate-buffered saline; SEM: standard error of the mean; siRNA: short interfering ribonucleic acid; SpiNA: stereopure interfering nucleic acid

WVE-007

Dr. Christopher Wright



WVE-007 is being evaluated across multiple use-cases

Potential to address more than one billion individuals with obesity globally

Monotherapy

Single agent in individuals living with obesity

- To induce fat loss with muscle preservation and favorable safety and tolerability
- **Status**: Phase 1 SAD study ongoing; Phase 2a MAD study initiated and actively enrolling

Combination

Add-on to incretin treatments

- To leverage an orthogonal mechanism to incretins for enhanced efficacy & tolerability
- **Status**: Phase 2a combination study initiated

Maintenance

An alternative maintenance therapy

- To prevent weight regain and maintain metabolic improvements upon incretin cessation
- **Status**: Integrated maintenance phase planned after incretin withdrawal in the combination study

SAD: single-ascending dose; MAD: multi-ascending dose
Phelps, NH, et al. 2024 Lancet 403, 1027

The INLIGHT™ trial, a phase 1/2a study, is evaluating investigational WVE-007 in adults with overweight or obesity

Randomized, double-blind, placebo-controlled (3:1) study of ascending doses of WVE-007

Phase 1, lower BMI (SAD)

- **BMI: 28–40 kg/m²**
- **HbA1c: ≤ 5.9%**
- **Otherwise healthy**
- Assessments include: safety and tolerability, PK, Activin E, body composition (DEXA), biomarkers, body weight
- No diet or exercise modifications

SAD cohort 4
600 mg (n = 32)

SAD cohort 3
400 mg (n = 32)

SAD cohort 2
240 mg (n = 32)

SAD cohort 1
75 mg (n = 8)
PK/PD and safety only (no DEXA)

Evaluate safety, tolerability, and PK

Phase 2a, higher BMI (MAD)

- **BMI: 35–50 kg/m²**
- Individuals with **higher BMI** and **comorbidities including T2D**
- In addition to Phase 1 assessments:
  - Body composition (MRI in addition to DEXA)
  - Liver fat (MRI-PDFF)
  - HbA1c
  - Lipid profile
- Diet and exercise counselling included

MAD high BMI + T2D cohorts
240 mg and 400 mg doses

MAD high BMI cohorts
240 mg and 400 mg doses

Evaluate safety, tolerability, and PK; assess metabolic and body composition improvements as well as weight loss

Evaluating WVE-007 in combination with tirzepatide in Phase 2a INLIGHT trial, followed by an integrated maintenance phase evaluating WVE-007 after tirzepatide withdrawal

BMI: body mass index; DEXA: dual-energy X-ray absorptiometry; HbA1c: glycated hemoglobin; MAD: multiple ascending dose; MRI: magnetic resonance imaging; PD: pharmacodynamics; PDFF: proton density fat fraction; PK: pharmacokinetics; SAD: single ascending dose; T2D: type 2 diabetes

ClinicalTrials.gov. NCT06842186. https://clinicaltrials.gov/study/NCT06842186 (Accessed November 9, 2026)

WVE-007 continues to be generally safe and well tolerated through 600 mg

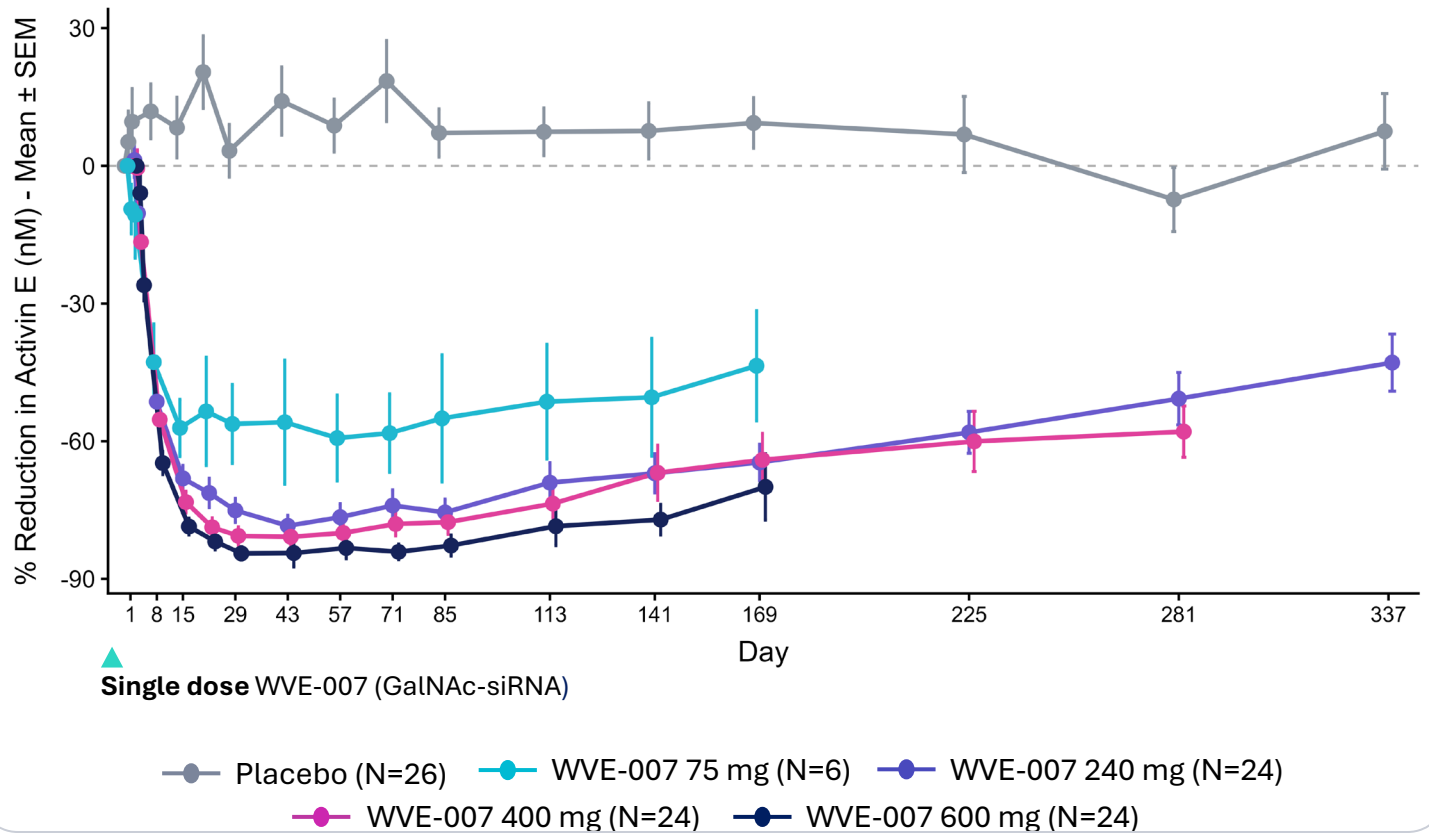
TEAE category, n (%)	Placebo N=26	WVE-007 75 mg N=6	WVE-007 240 mg N=24	WVE-007 400 mg N=24	WVE-007 600 mg N=24
Any TEAE	22 (84.6)	3 (50.0)	20 (83.3)	18 (75.0)	16 (66.7)
Mild	10 (38.5)	2 (33.3)	14 (58.3)	6 (25.0)	10 (41.7)
Moderate	11 (42.3)	1 (16.7)	6 (25.0)	10 (41.7)	6 (25.0)
Severe	1 (3.8)	0	0	2 (8.3)	0
Any drug-related TEAE	3 (11.5)	1 (16.7)	7 (29.2)	10 (41.7)	9 (37.5)
Mild or Moderate	3 (11.5)	1 (16.7)	7 (29.2)	10 (41.7)	9 (37.5)
Severe	0	0	0	0	0
Any drug-related serious TEAEs	0	0	0	0	0
Any TEAE leading to discontinuation	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0

- There were no discontinuations, no drug-related serious AEs, or deaths
- All drug-related AEs were mild or moderate
- No clinically meaningful changes in lipids or other clinical laboratory measurements including LFTs

Data as of August 28, 2026. Placebo includes participants randomized to placebo across all cohorts; there was 1 moderate drug related TEAE while the rest were mild
AE: adverse event; LFT: liver function test; TEAE: treatment-emergent adverse event

Potent, durable, and dose-dependent suppression of Activin E continues to support 1-2x yearly dosing regimen

Activin E change in INLIGHT™ trial



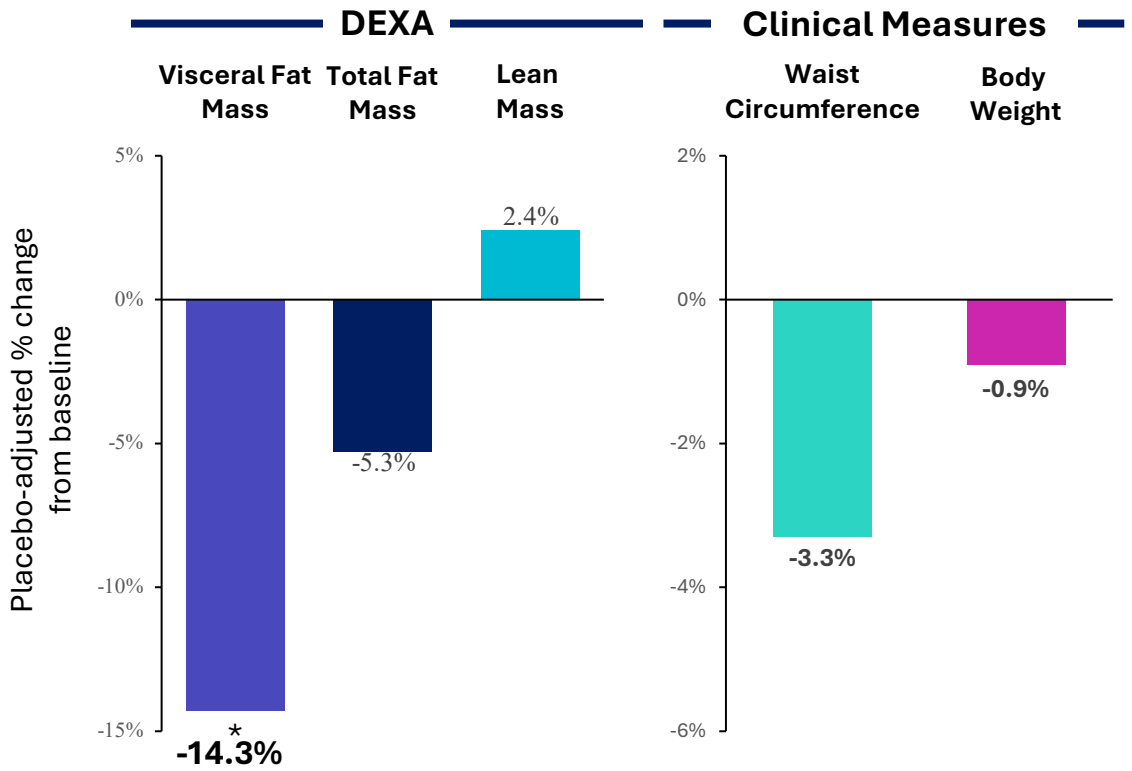
- Up to 88% Activin E mean suppression
- Greater than 80% mean max Activin E suppression across all cohorts ≥ 240 mg
- Significant Activin E reductions remain out to one year
- Durability supports once to twice-yearly dosing regimen

Data as of August 28, 2026. Left: figure shows sample means and SEMs. All MMRM baseline and placebo comparisons from Day 8 onwards are $p < 0.02$. INLIGHT is ongoing, and Activin E data is still being collected in long-term follow-up for some timepoints and participant groups shown above.

Potent and durable Activin E suppression led to improvements in body composition in Phase 1 SAD trial (otherwise healthy with BMI ~32 kg/m ^{2})

Body composition improvements

Initial 240 mg single dose cohort at 6 months



Additional data across top three cohorts

- 240 mg cohort: highest baseline BMI; A single dose led to placebo-adjusted decreases in visceral fat, total fat, and waist circumference, while lean mass was maintained through one year
- 400 mg and 600 mg cohorts: lower baseline BMI; Visceral fat and waist circumference were reduced relative to placebo, lean mass held steady, and total fat was little changed
- Across all three cohorts, larger treatment effects tracked with higher BMI and greater baseline adiposity

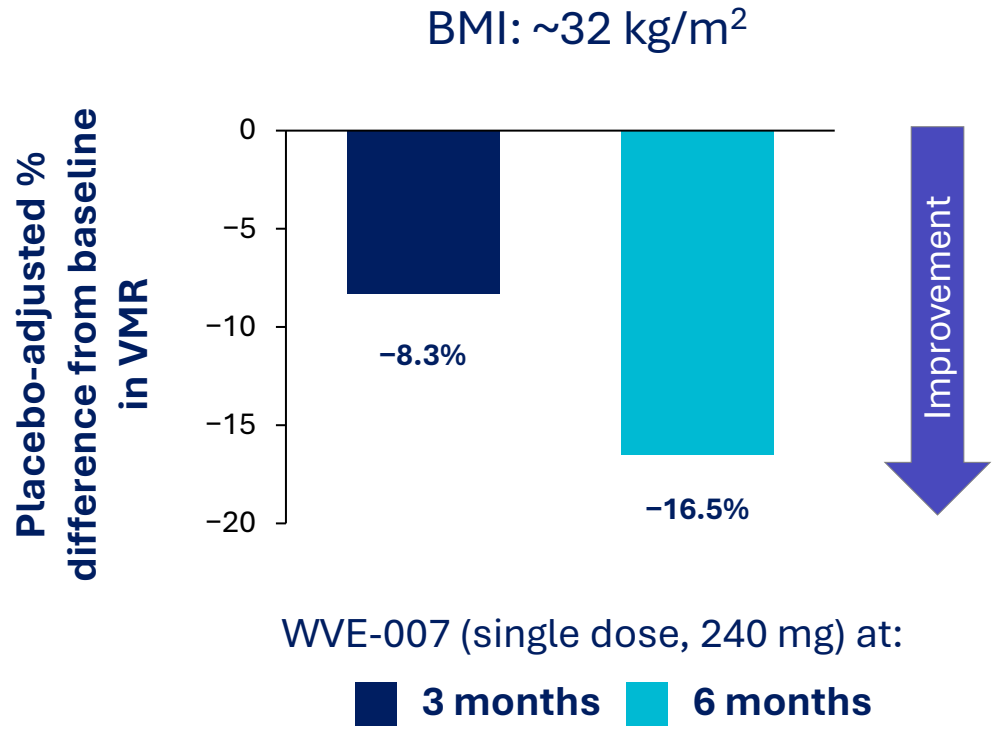
*p<0.05. Left: INLIGHT interim Phase 1 data reported March 26, 2026. Right: Interim data from Phase 1 INLIGHT study as of August 28, 2026. All reductions are placebo-adjusted % change from baseline were estimated using an MMRM model with fixed effects for treatment group, visit, treatment-by-visit interaction, and baseline as a covariate; estimates were based on geometric mean ratios. BMI: body mass index; DEXA: dual-energy X-ray absorptiometry; SAD: single ascending dose

A single dose of WVE-007 led to improvements in body composition by visceral fat-to-muscle ratio (VMR)

VMR

- VMR is a published measure of body composition that integrates harmful visceral fat and beneficial lean mass in a single index
- Lower VMR is associated with decreased risks of MASH/MAFLD,[1,2] T2D,[3] and cardiometabolic disorders (e.g., dyslipidemia, hypertension)[1,3]

Post hoc analysis: improvements in body composition by VMR at 3 months and 6 months[a]



INLIGHT interim Phase 1 data reported March 26, 2026. [a]Placebo-corrected VMR calculated based on changes from baseline in visceral fat and lean mass at 3 months and 6 months
BMI: body mass index; MAFLD: metabolic dysfunction-associated fatty liver disease; MASH: metabolic dysfunction-associated steatohepatitis; T2D: type 2 diabetes; VMR: visceral fat-to-muscle ratio

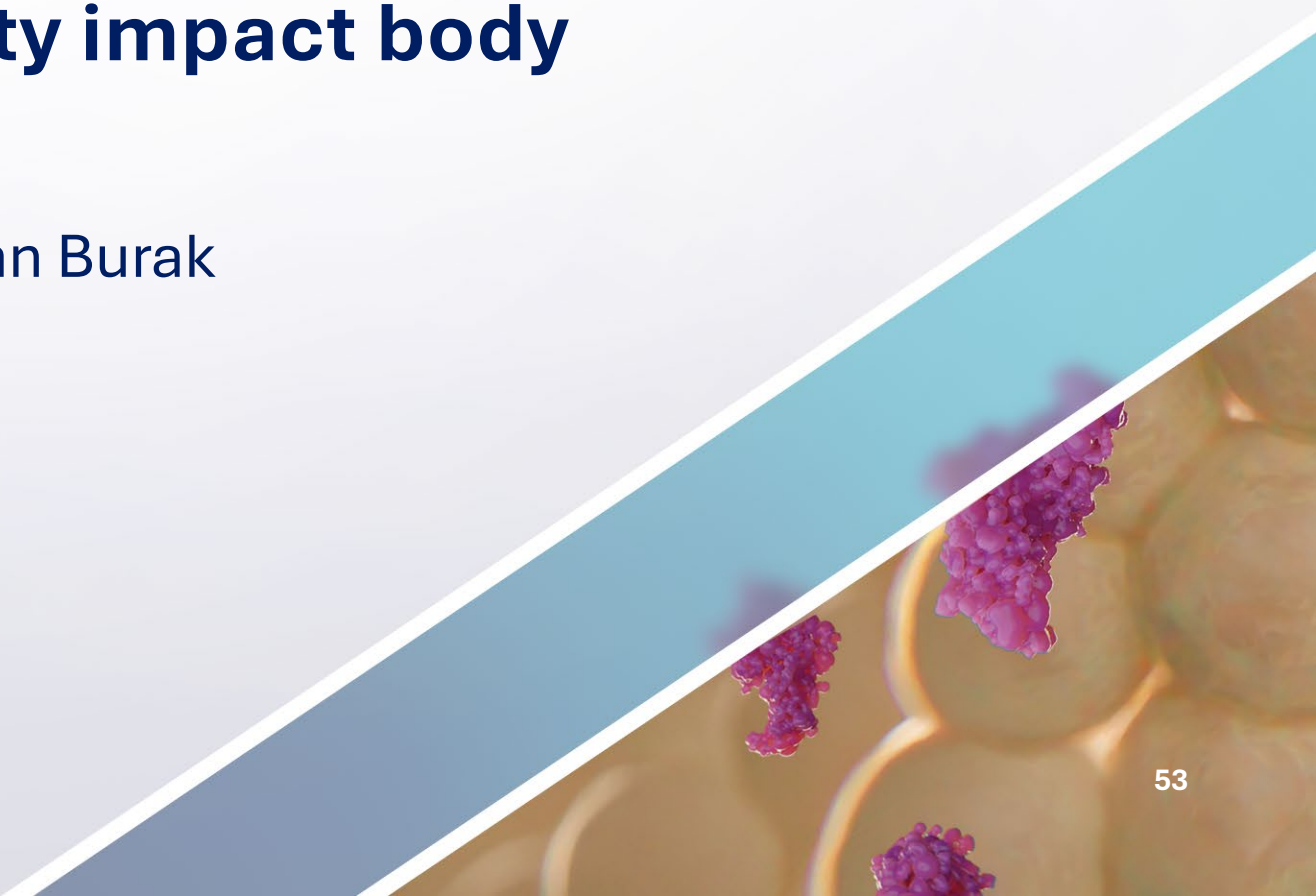
1. Zhang S *et al. Diabetes Metab Res Rev* 2023;39:e3597; 2. Liu C *et al. Lipids Health Dis* 2024;23:104; 3. Wang Q *et al. Diabetes Metab Syndr Obes* 2019;12:1399–407

Thank you to the participants, families, clinicians, and study site staff who are participating in this study



The next frontier: How may new therapies for overweight and obesity impact body composition?

Dr. Angela Fitch & Dr. Mehmet Furkan Burak



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Discussion | The next frontier: How may new therapies for overweight and obesity impact body composition?



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Endocrine Society;
Assistant Professor of Medicine,
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Harvard Medical School, Boston, MA

Discussion | The next frontier: How may new therapies for overweight and obesity impact body composition?

The evolving treatment landscape in overweight and obesity: An overview of non-incretin-based therapies in clinical development

Drug class	Agent	Company	Study	Phase
Amylin analogues	**Petrelintide**	Zealand Pharma/Roche	ZUPREME-3	3
	Eloralintide	Eli Lilly and Company	ENLIGHTEN-1	3
	AZD6234	AstraZeneca	SELENE 1	3
	ACCG-2671[b]	Aconcagua Bio, Inc. a wholly owned subsidiary of Structure Therapeutics	–	1/2
	PF-08653945[a]	Pfizer	SOLIS-1	2
	ABBV-295[b]	AbbVie	–	2
	Cagrilintide[b]	Novo Nordisk A/S	RENEW 1	3
Myostatin pathway inhibitors	**Bimagrumab**[c]	Eli Lilly and Company	–	2
	Trevogrumab + garetosmab[c]	Regeneron Pharmaceuticals	COURAGE	2
	Apitegromab[c]	Scholar Rock, Inc	EMBRAZE	2
	Taldefgrobep Alfa	Biohaven Therapeutics Ltd.	–	2
INHBE-Activin E-ALK7 pathway inhibitors	**WVE-007**	Wave Life Sciences	INLIGHT™	1/2a
	ARO-INHBE	Arrowhead Pharmaceuticals	–	1/2
	BC-006	BaseCure Therapeutics Inc.	–	2
	ALN-6222	Alnylam Pharmaceuticals	–	1
	SRSD384	Sirius Therapeutics Co., Ltd	–	1/2a
	RN3161	Rona Therapeutics Co., Ltd / Ikaria Bioscience Pty Ltd	–	1/2a
	SGB-7342	Suzhou Sanegene Bio Inc.	–	1
	CMS-D008	Shenzhen Kangzhe Biotechnology Co., Ltd	–	1
	HRS-5817	Atridia Pty Ltd	–	1
	LDR2515	Leaderna Therapeutics Ltd	–	1
	ARO-ALK7	Arrowhead Pharmaceuticals	–	1/2a
	ALN-2232	Alnylam Pharmaceuticals	–	1/2
CB1 pathway modulators	**CRB-913**	Corbus Pharmaceuticals	CANYON-1	1b
	Nimacimab[b]	Skye Bioscience, Inc.	CBeyond™	2
Glucagon receptor agonists[d]	**BI 456906/survodutide**	Boehringer Ingelheim	SYNCHRONIZE®-START	3
	DD01/zabopegdutide	Neuraly, Inc.	–	2
	NA-931/bioglutide[c]	Biomed Industries, Inc.	–	2
	LY3305677/mazdutide	Eli Lilly and Company	–	2/3[e]
	LY3437943/retatrutide	Eli Lilly and Company	TRIUMPH-9	3

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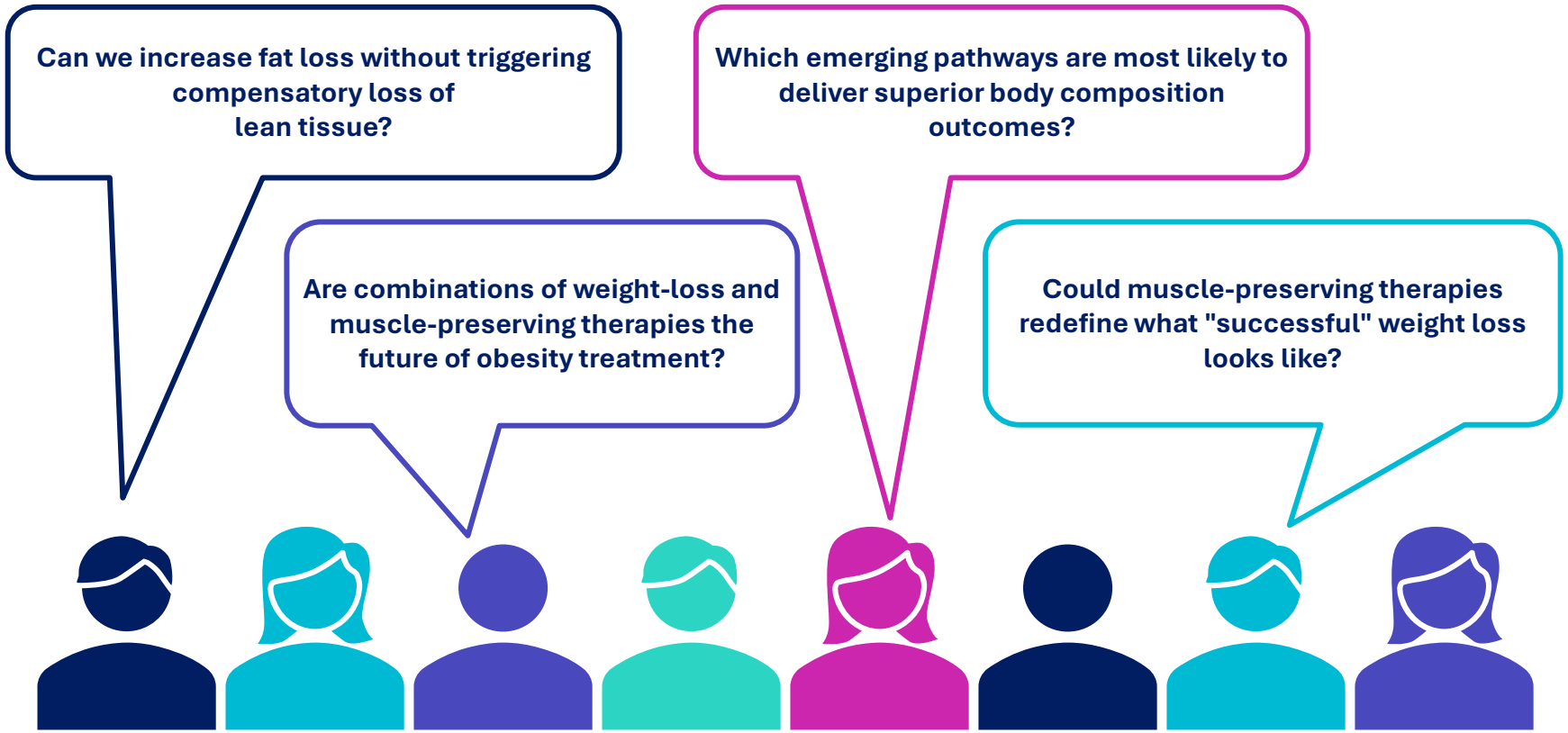
[a]Alone and in combination with PF-08653944. [b]Dual amylin and calcitonin receptor agonist. [c]In combination with a GLP-1RA. [d]Polyagonist therapies. [e]Approved in China for patients with a BMI ≥ 28 kg/m^2 or patients with a BMI ≥ 24 kg/m^2 and one or more obesity-associated comorbidity.

ALK7: Activin receptor-like kinase 7; CB1: cannabinoid receptor 1; GLP-1: glucagon-like peptide 1; GLP-1RA: GLP-1 receptor agonist; *INHBE*: Inhibin βE

Discussion | The next frontier: How may new therapies for overweight and obesity impact body composition?

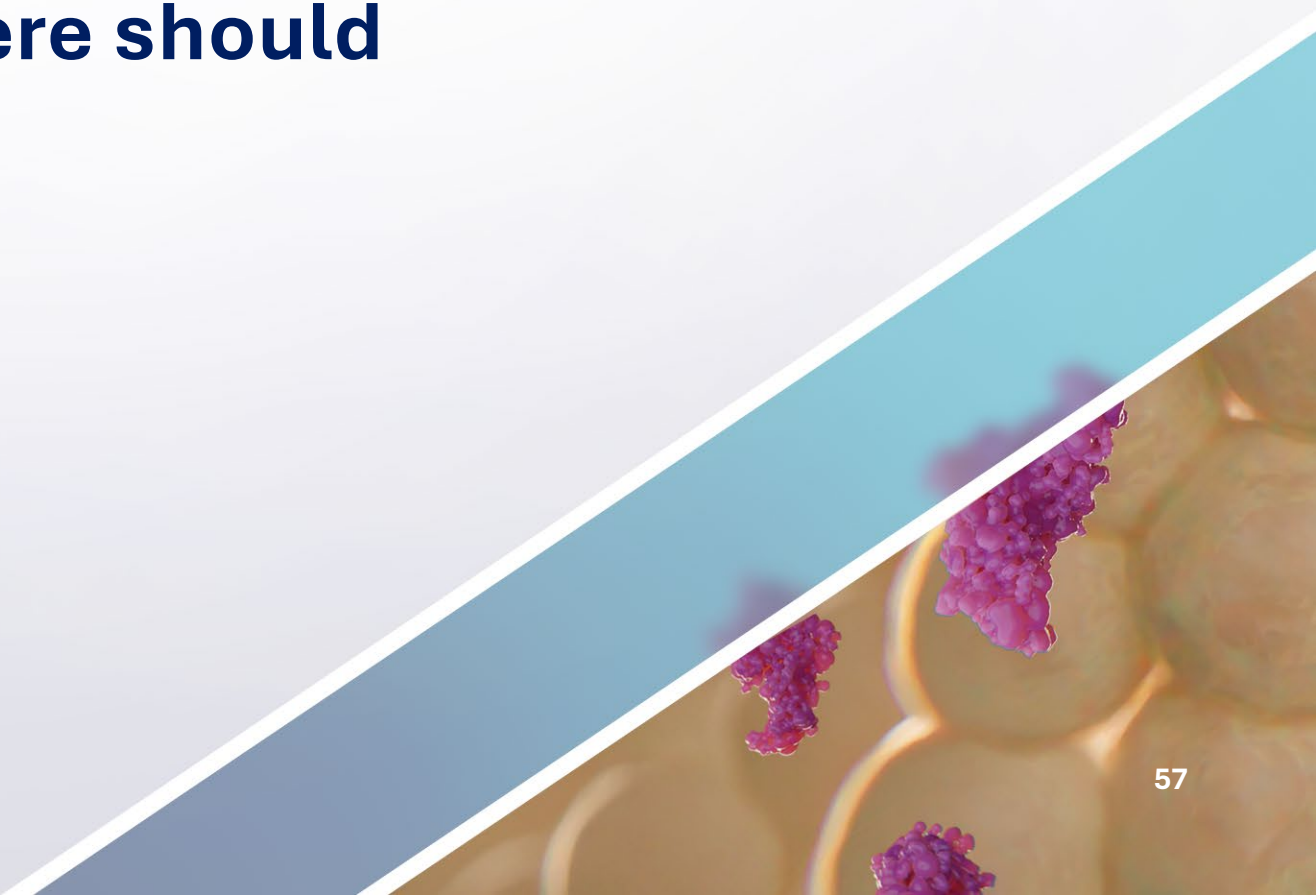


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Rethinking success: Where should obesity treatment go?

Co-chairs: Dr. Angela Fitch &
Dr. Christopher Wright



Rethinking success: Where should obesity treatment go?

Body weight is only part of the story

Body composition plays a vital role in metabolic health and should be an important consideration in obesity management

- People of the same BMI may have **different cardiometabolic** risk[1]



Fat mass

High fat mass increases the risk of mortality[2]
Visceral adipose tissue is associated with an increased cardiometabolic risk[1]

Reducing visceral adipose tissue decreases cardiovascular risk[3,4]

Lean mass

Low muscle mass index is associated with an increased risk of mortality[5,6]

Lean mass protects against mortality[2]
Muscle is a key endocrine organ and contributes to glucose homeostasis and metabolic regulation[7,8]

- Incretin-based therapies are effective at reducing body weight and total fat mass, but also reduce lean mass[7]
- There is increasing focus on integrating body composition and functional endpoints into clinical trials[8]

1. Britton KA *et al. J Am Coll Cardiol* 2013;A62:921–5. 2. Sedlmeier AM *et al. Am J Clin Nutr* 2021;113:639–46. 3. Hiuge-Shimizu A *et al. J Atheroscler Thromb* 2012;19:1006–18. 4. Klein H *et al. Circulation* 2026;154:16–27. 5. Kim D *et al. J Cachexia Sarcopenia Muscle* 2024;15:250–4. 6. Wang Y *et al. PLoS One* 2023;18:e0286745. 7. Iglesias P. *J Clin Med* 2025;14:4490. 8. Merz KE and Thurmond DC. *Compr Physiol* 2020;10:785–809. 9. Heymsfield SB *et al. Nat Med* 2026;32:869–82. 10. von Haehling S *et al. J Cachexia Sarcopenia Muscle* 2025;16:e70147.

Rethinking success: Where should obesity treatment go?

1. **Prioritize the quality of weight loss**, including reductions in total and visceral fat while preserving lean mass and physical function
2. **Deliver meaningful health gains,** such as improvements in cardiometabolic health, obesity-related comorbidities and quality of life
3. **Provide durable, individualized benefits** with acceptable tolerability and minimal treatment burden
4. **Consider body composition alongside bodyweight** when assessing treatment response and defining success
5. **Explore complementary treatment mechanisms** that may address persistent unmet needs and improve overall body composition

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