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<table>
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<th>Topic</th>
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| Introduction               | David Reese, MD  
Executive Vice President, Research and Development, Amgen                  |
| AMG 133 Program Update     | Narimon Honarpour MD, PhD  
Vice President, Clinical Development, Amgen                                |
| Q&A                        | All                                                                      |
OBESITY: A COMPLEX AND HETEROGENEOUS DISEASE WITH STRONG GENETIC UNDERPINNINGS THAT CAUSES A WIDE VARIETY OF GRIEVOUS ILLNESSES

- Complex biology
- Causal driver of many diseases
- Strong genetic underpinnings
- Substantial patient heterogeneity
- No “one-size fits all” approach

NASH = nonalcoholic steatohepatitis; Afib = atrial fibrillation.
AMGEN IS TACKLING OBESITY USING DIVERSE AND INNOVATIVE APPROACHES

HUMAN GENETIC VALIDATION
- Target discovery
- Unraveling patient heterogeneity

BIOLOGY DRIVES MODALITY CHOICE
- Large molecule
- Small molecule
- siRNA
- Others

MULTI-ASSET PORTFOLIO
- Incretin based
- Non-incretins
- Novel genetics

MULTI-SPECIFIC MOLECULES
- e.g., AMG 133

siRNA = small interfering ribonucleic acid.
A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SINGLE AND MULTIPLE ASCENDING DOSE STUDY OF AMG 133 IN SUBJECTS WITH OBESITY

NARIMON HONARPOUR
VICE PRESIDENT CLINICAL DEVELOPMENT
AMG 133, A FIRST-IN-CLASS ANTIBODY-PEPTIDE CONJUGATE TARGETING OBESITY

GIPR INHIBITORY ANTIBODY

AMG 133

GLP-1R activation

GLP-1R activation and GIPR inhibition

GLP-1R activation

GIPR inhibition

STUDY POPULATIONS OF GIPR VARIANTS

Japanese
Genome-wide association study¹

European
Genome-wide association study²,³

Whole exome sequencing in UK-Biobank and N. America⁴

GIPR expression

BMI

GIPR = Gastric Inhibitory Polypeptide Receptor; GLP-1 = Glucagon-like peptide-1; GLP-1R = Glucagon-like peptide-1 receptor.

¹. Nature Genetics 2012; 44 (3):302-6
². Nature Genetics 2010; 42 (11):937-48 (deCODE is collaborator)
³. Nature Genetics 2013; 45 (5):501-12 (deCODE is collaborator)
⁴. Science 2021; 373 (6550)

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AMG 133 PHASE 1 STUDY DESIGN AND OBJECTIVE

• A Phase 1 randomized, double-blind, placebo-controlled study with single and multiple ascending dose cohorts.

• Enrolled obese subjects (BMI ≥30.0 kg/m² to ≤40.0 kg/m²) without other medical conditions to receive either subcutaneous AMG 133 or placebo.

• Evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 133 in subjects with obesity and without other medical conditions.

• Reporting on safety, pharmacokinetic parameters, and pharmacodynamics (body weight change).

BMI, body mass index; kg = kilogram.
**STUDY SCHEMA**

**Single Ascending Dose Cohorts**
AMG 133: Placebo (6:2) SC x 1

- 21 mg
- 70 mg
- 140 mg
- 280 mg
- 560 mg
- 840 mg

*One IV cohort for bioavailability not included in current data set

**Multiple Ascending Dose Cohorts**
AMG 133: Placebo (6:2) SC Q4W x 3

- 140 mg Q4W x 3
- 280 mg Q4W x 3
- 420 mg Q4W x 3

**3 cohorts not included due to ongoing trial/analysis; 1 with digital tools and 2 with 2- or 4-week dose escalation strategies

SC, subcutaneous; IV, intravenous; mg = milligram; Q4W, every 4 weeks.
# BASELINE CHARACTERISTICS AND SUBJECT DISPOSITION

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single Ascending Dose (N = 49)</th>
<th>Multiple Ascending Dose (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 12)</td>
<td>AMG 133 (N = 37)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.7±13.4</td>
<td>48.5±10.9</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>8 (66.7)</td>
<td>24 (64.9)</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>97.2±12.4</td>
<td>100.3±14.0</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>32.8±2.1</td>
<td>33.6±3.0</td>
</tr>
<tr>
<td>Hemoglobin A1C, mean ± SD, %</td>
<td>5.38±0.35</td>
<td>5.52±0.41</td>
</tr>
</tbody>
</table>

N, total number of subjects treated in each cohort. n, number of patients with observed data. BMI, body mass index; SD, standard deviation.

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A SINGLE DOSE OF AMG 133 PROMOTES SUSTAINED WEIGHT LOSS

A total of 12 subjects were randomized to the placebo group across cohorts. 6 subjects were randomized to the AMG 133 group at each dose level. 1 subject was replaced in the 140 mg dose group.

SC = subcutaneous; \( t_{1/2} \) = half-life; mg = milligram.
RAPID AND SUBSTANTIAL WEIGHT LOSS WITH DURABILITY OF EFFECT AFTER LAST DOSE ADMINISTERED

- A total of six subjects were randomized to the placebo group across cohorts.
- 6 subjects were randomized to the AMG 133 group at each dose level.
- 2 subjects were replaced in the 420 mg dose group.

**Body Weight**

**Mean % body weight change from baseline after multiple doses**

- **Placebo**
- **140 mg**
- **280 mg**
- **420 mg**

SC = subcutaneous; mg = milligram.
SAFETY AND TOLERABILITY FROM SINGLE AND MULTIPLE ASCENDING DOSE COHORTS

• No safety concerns were identified that would preclude further development

• The majority of TEAEs were mild and resolved within 48 hours

• Most TEAEs were GI-related with the most common being nausea and vomiting

• Among subjects with > 1 dose of AMG 133 (N=22):
  o > 90% of GI-related AEs were after the first dose
  o All GI-related AEs in this group were mild

*Per protocol, no education or dietary guidance was given to subjects

TEAE – treatment-emergent adverse event; GI = gastrointestinal; N = number of subjects treated; AE = adverse event.
SUMMARY AND CONCLUSION

AMG 133 is a GIPR antagonist + GLP1 agonist antibody-peptide conjugate taken into human testing based on human genetic insights and preclinical evidence.

The pharmacokinetics and pharmacodynamics of AMG 133 support dosing intervals of every 4 weeks or longer.

Reductions in body weight were dose proportional with up to 14.5% body weight loss at d85 following three monthly subcutaneous doses of 420 mg, each 4 weeks apart.

Durable weight loss with reductions observed for up to 150 days after the final (third) AMG 133 administration at higher doses.

Most TEAEs were mild, transient and associated with the first dose administered. TEAEs were most commonly GI-related.

The safety, tolerability and PK profile as well as the magnitude, rapidity, and durability of weight loss support further clinical development of AMG 133.
QUESTIONS?

DAVID REESE, MD