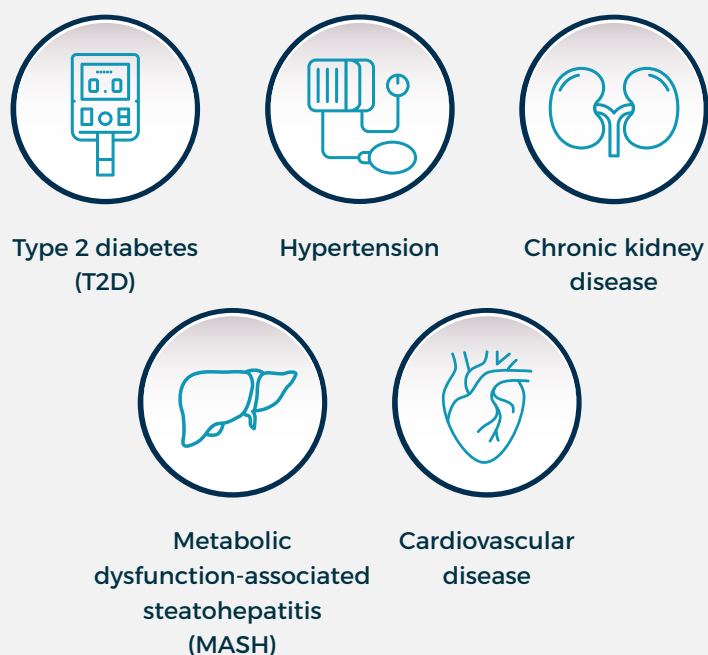


Comorbidities in Obesity

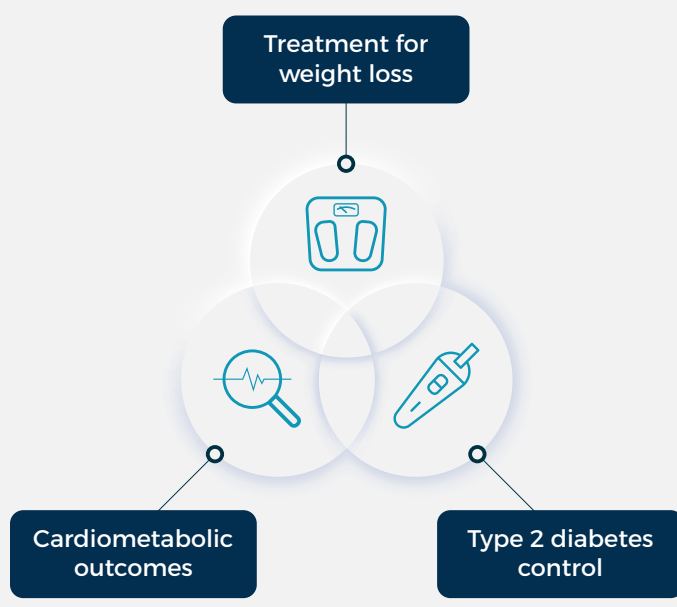
The Importance of an Integrated, Strategic Program



Obesity & Comorbidities



Management strategies overlap between the comorbid conditions – **treatment for weight loss influences T2D control and cardiometabolic outcomes.**



Research is ongoing with approved agents for comorbid conditions, specifically in MASH

- Contemporaneous development programs exploit physiological overlap between obesity and comorbidities, evaluating patients more holistically
- Capturing outcomes and healthcare utilization beyond weight loss highlights therapeutic impact on a broader scale
- Shifting sentiments may characterize obesity treatment as “platform technology” that can improve outcomes across overlapping patient populations



NCT04639414, a Phase IV study enrolling 192 patients in Germany and Austria, for GLP-1 treatment and/or SGLT2 in MASH.

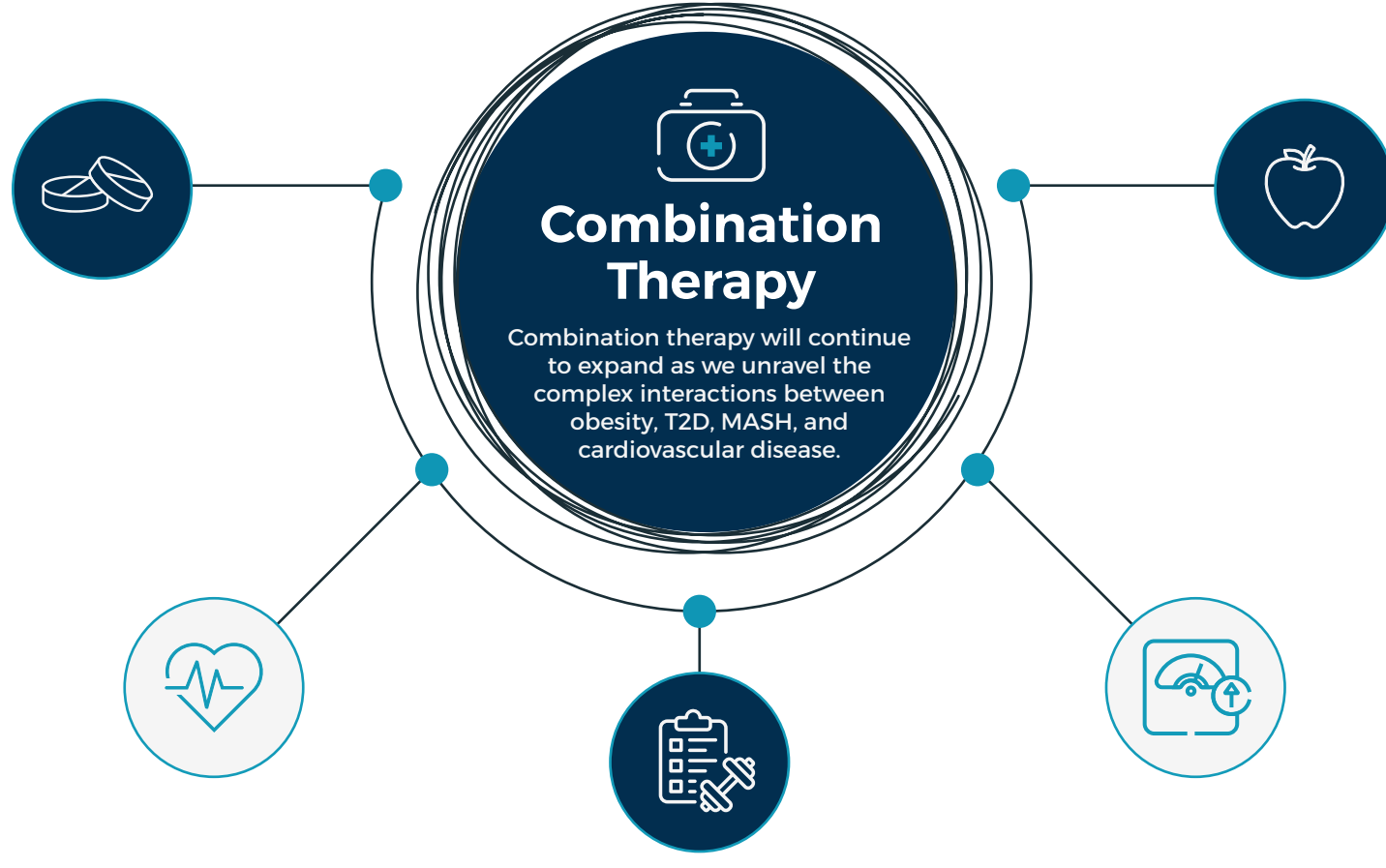


Researchers are investigating GLP-1 agonists, approved for treating T2D and obesity, in MASH. Semaglutide is currently under investigation for an ongoing Phase III trial.

Sponsors should proactively plan to address the impact of obesity management in the context of other comorbidities through:



- Innovative program strategies to both generate and test hypotheses
- Informed operational footprints that acknowledge geographical heterogeneity frequently encountered in complex disease management



Sponsors increasingly anticipate the need for subgroup analyses approached through either a priori or post-hoc stratification by:



Age



T2D status



Obesity



Concomitant medications (e.g., GLP-1 agonists)



Current clinical development programs are enrolling patients on stable doses of GLP-1 therapies or incorporating data analyses to evaluate the additive or synergistic effect on key clinical outcomes.

Although regulatory recommendations are evolving, EMA guidance formally recognizes the value of studying combinations of products, including standard of care, in the search for an efficacious MASH therapy.

Other stakeholders with unique data requirements that sponsors must acknowledge in a strategic program.

Drug Discovery



An exploration of unique targets and innovative formulation developments.

Standard of Care



Incorporation of observation in the context of clinical care for patients with several comorbidities.

Assuring Access



A variety of organizations that ultimately dictate product access by evaluating the totality of healthcare utilization for a given disease entity

GLP-1 Agonists & The Rebound Effect



Patients can develop an adaptation creating a rebound effect upon GLP-1 agonist discontinuation. The rebound effect is associated with:

- Regain in weight proportional to that previously lost while on therapy
- An increase in recognized risk factors for adverse cardiometabolic outcomes
- A negation of the additional benefit that had been obtained by behavioral and lifestyle interventions
- Recrudescence of maladaptive behavior ultimately leading to obesity

Beyond Medication

Pharmacological interventions

- GLP-1 Agonist
- Efficacy hinges on reduced caloric intake and lifestyle modification

Augmentation Therapy

- Incorporation of GLP-1 into obesity standard of care mandates study of additive and synergistic benefits with both approved and novel agents.
- Combination therapy may mitigate unwanted side effects, decrease required doses, and accelerate clinical benefits.

These benefits have the potential to lower the costs of obesity treatment, thereby increasing access and utilization.

Biosimilars

- The widespread success of GLP-1 agonists has spawned development of analogs and biosimilars.
- Demonstrating [value for biosimilars](#) requires strategic clinical development to address payer, physician, and patient sentiments regarding approved agents.
- Nuanced study design can [invigorate biosimilar development](#), by incorporating additional populations and analyzing new subgroups.
- Biosimilar development mandates [operational efficiency and regulatory agility](#) tailored to unique timelines and objectives.

Behavioral and lifestyle modifications



Cognitive behavioral therapy



Diet & nutrition coaching



Exercise counseling

Neuroplasticity

- Sustainable obesity treatment features positive changes to lifestyle and mental health
- Emerging sentiments suggest “a neuroplasticity hypothesis” to obesity and its treatment
- Evaluation of obesity therapy as a neurological intervention may reveal added benefits, requiring an understanding of new and existing behavioral approaches (e.g., cognitive behavioral therapy or psychedelics)

Design Impacts Operations — Lessons Learned

- Avoid obesity bias
 - Treat patients correctly
 - Use correct and caring language
 - Ensure equipment is adequately accessible for participants, including the scale and DEXA machine
- Consider drug availability considering GLP-1 shortage
- Prepare participants for realistic outcomes to avoid a mismatch of weight loss expectations and results
- Include side effects and mitigation strategies in the design
- A motivated population will increase enrollment and retention

Future of Obesity Care



- Using pharmacologic interventions and behavioral modification is likely more successful than relying on either approach alone.
- Incorporating frequency of physician-patient contact as a moderating variable in clinical care.
- Strategically designed clinical programs can optimize assessment of obesity and comorbid conditions through:
 - Retrospective evaluation of combination intervention studies
 - Controlled testing of pharmacologic efficacy on comorbidity outcomes
 - Optimizing trial design to harmonize across international regulatory guidance
 - More formal evaluation of the interaction of multiple treatment modalities