Application of Quantitative Decision Making in Early Clinical Development: A Case-Study

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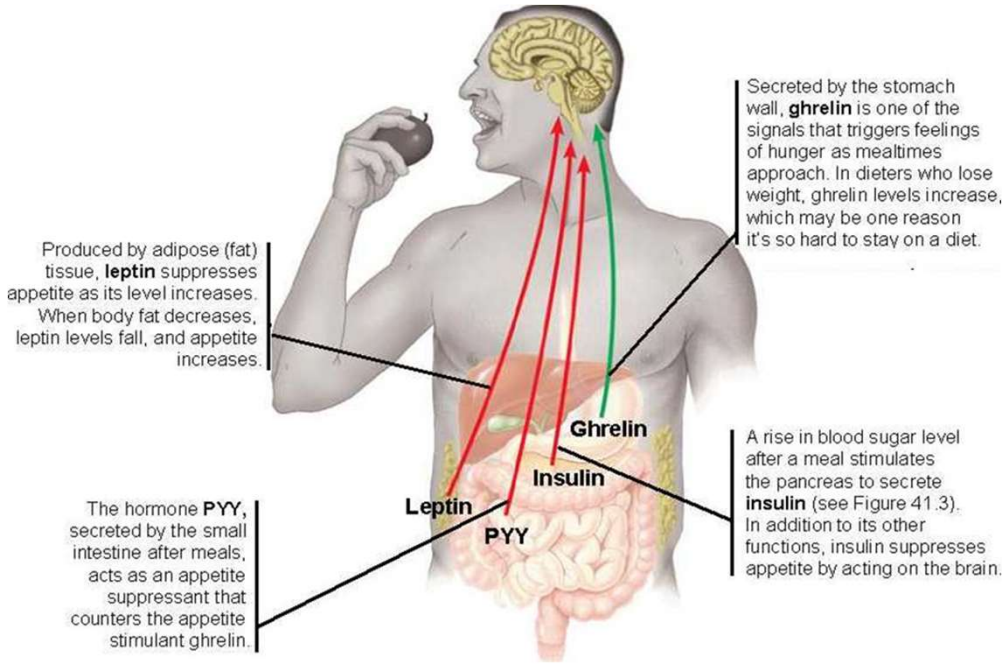
GSK

Disease Background

- Obesity is a complex disease involving an excessive amount of body fat
- Reduces quality of life and increases the risk of other diseases (heart disease, strokes, type 2 diabetes, high blood pressure, certain cancers)
- Lifestyle modification is the cornerstone of treatment, but it has limited efficacy and is insufficient in the majority of clinical cases
  - Drug-treatment rates for obesity are low due to limited approved safe and efficacious treatments
  - Drug-treatment rates may change as recently launched and imminent therapies are highly efficacious



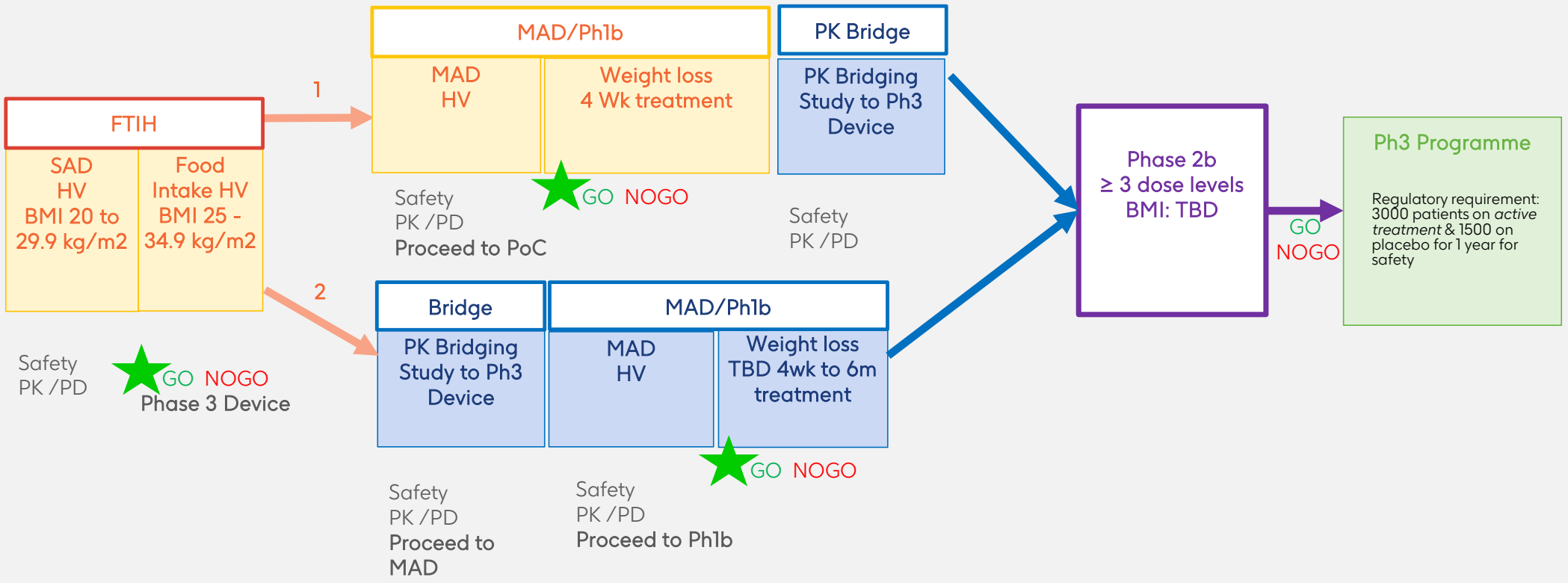
Considerations for Clinical Development Plan

Understanding of mechanism of action

- Inconsistent efficacy for mechanism in single and multiple dose food intake and short-term weight loss studies
- Reduced food intake in most clinical trials with lack of translation to short-term weight loss, potentially due to
  - Food intake did not result in reduced body weight, possibly due to lack of dose up-titration
  - May not dosing long enough in a limited sample size
- Substantial nausea associated with mechanism
  - Expectation that nausea and efficacy will both tolerate out over repeated exposures
  - Strong evidence to investigate up-titration of doses in early development
- Dose dependent reduction in food intake when given via IV infusion but other routes of administration less successful
- **Development plan required to build total data package with stepwise increase in N to minimise exposure and maximise early decision making**

Proposed Clinical Development Plan

Strategy: Build total data package with stepwise increase in N to minimise exposure and maximise early decision making



Single Dose Food Intake Study

- 4-period, single dose, placebo controlled crossover-study
- Aim is to identify a therapeutic dose which does not cause severe nausea and vomiting
- Challenges:
  - No clear specification of the definition/level of acceptable nausea
  - Multiple confounding factors for food calorie intake studies

- Timing of food relative to drug administration?
- How long will participants have to finish their meal?

- What meal to give? What if participants don't like the meal?
- Instructions for meal intake? Eat until comfortably full or completely full?

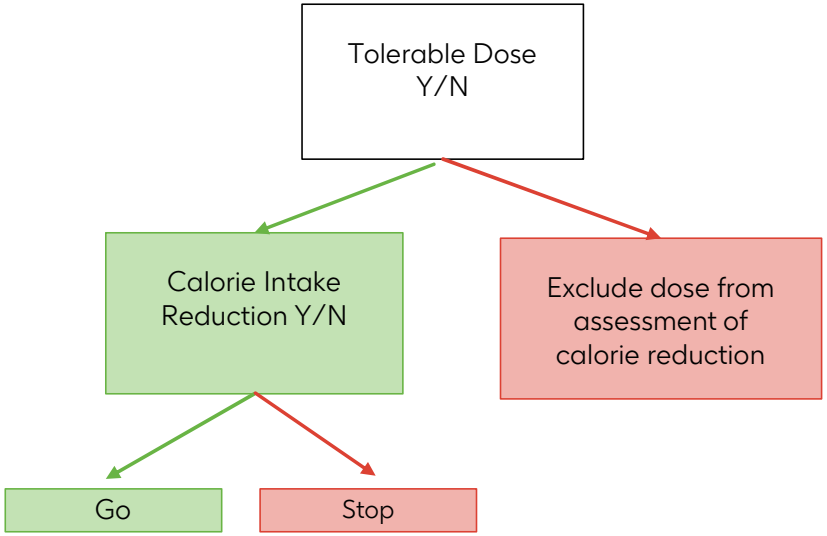
- How do we measure the calorie intake?
- How to objectively measure nausea?

CTCAE v5.0 definition of Nausea not suitable for a study with a molecule pharmacologically expected to affect appetite

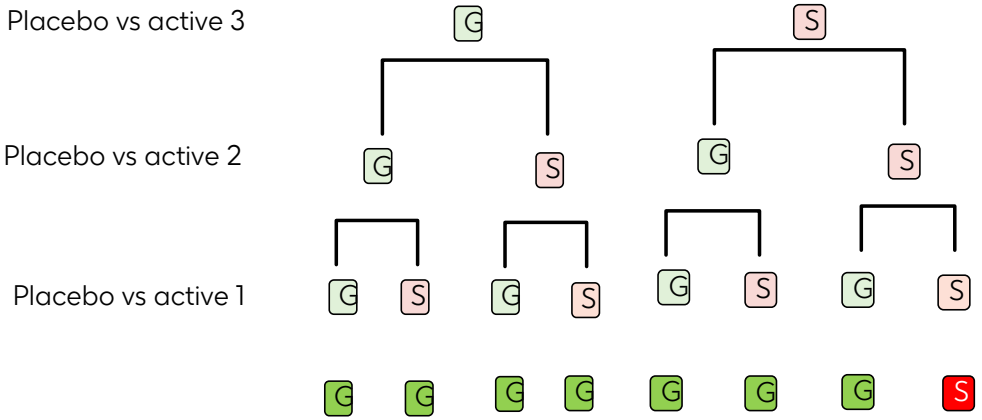
G1: Loss of appetite without alteration in eating habits
G2: Oral intake decreased without significant weight loss, dehydration or malnutrition
G3: Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indication

Decision Making Framework

Dose-Level Decision Making



Study Decision Making Framework



Overall outcome

G = Go, S = No-Go

Defining Decision Rules and Decision Making Framework

- Decision Making: Calorie intake reduction at a tolerable dose that we believe could lead to weight loss with multiple dosing

- No clear specification of the definition/level of acceptable nausea for tolerable dose
  - Exclude active treatment groups where observed proportion of nausea >=30%

- Calorie intake reduction for tolerable doses
  - Assess calorie intake reduction regardless of nausea or only for participants who tolerated the dose?
  - For participants with nausea on a tolerated dose: exclude or assess calorie intake reduction for based on participants highest tolerated dose?

Quantitative Decision Making

- Decision Making: Calorie intake reduction at a tolerable dose that we believe could lead to weight loss with multiple dosing

- Highest dose may not be maximum tolerate dose

- Considerations for QDM assessment
  - Unknown true % calorie reduction increasing with dose
  - Fixed or unknown true placebo calorie intake
  - Increasing true nausea rate with increasing dose
  - How to account for correlation between nausea and calorie intake

Understanding Impact of Nausea on Calorie Reduction

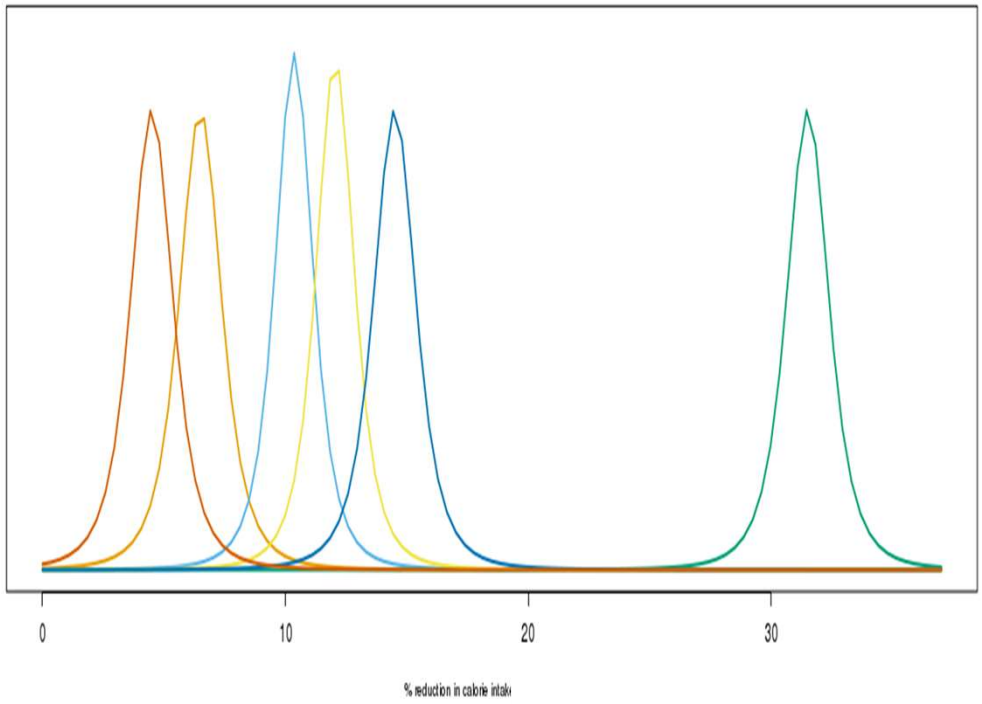
- Placebo Calorie Intake 1500 kCal
- Increasing Nausea rate between 0-35%

True % Reduction			Tolerability Not Assessed		Tolerable Dose and 50% reduction if participant had nausea		Tolerable Dose with no adjustment for participants with nausea	
Active 1 vs Placebo	Active 2 vs Placebo	Active 3 vs Placebo	Go	Stop	Go	Stop	Go	Stop
0%	3%	5%	1	99	86	14	9	91
2%	8%	10%	37	63	97	3	57	43
3%	12%	15%	93	7	>99	<1	89	11
7%	15%	20%	>99	<1	>99	<1	98	2
10%	18%	25%	>99	<1	>99	<1	>99	<1

Final decision: Calorie assessment on individual participated maximum tolerated active dose

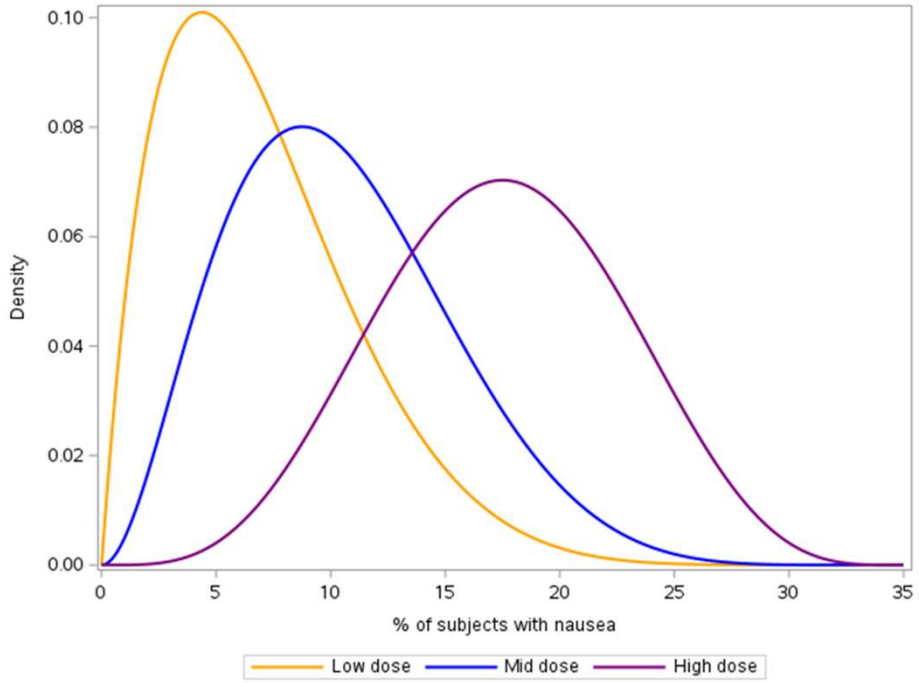
Literature Review

- 10 single dose studies identified with same mechanism
  - 3 studies discounted due to differences in time of food intake compared to dosing
  - 1 study discounted as did not collect calorie intake but informed nausea/vomiting rate
  - 2 studies discounted showed no/minimal effect on weight loss in type 2 diabetes patients, no data on food intake collected
- 4 relevant studies to inform assurance
  - Placebo intake consistent for 3 studies
  - Varied calorie reduction across studies

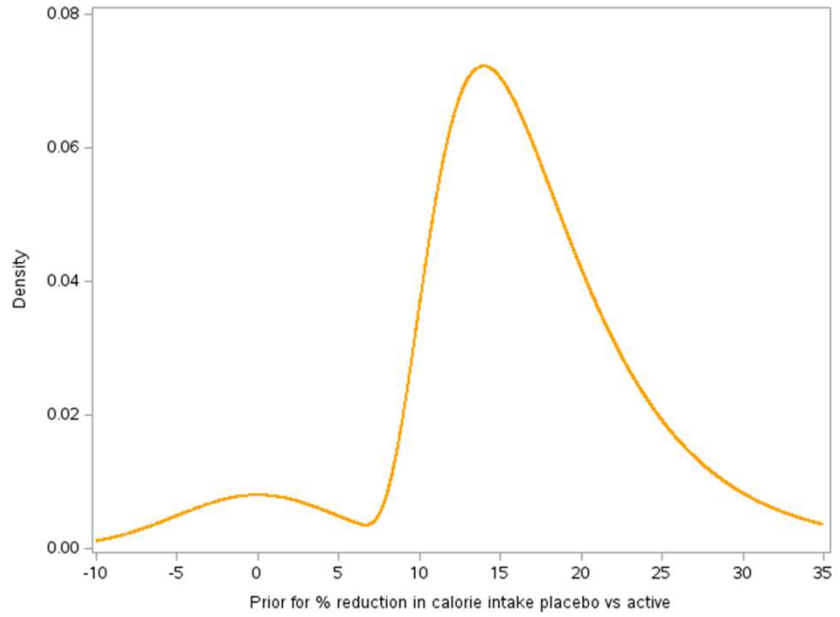


Prior Beliefs

Nausea



% Calorie Reduction



Placebo prior not shown

% Reduction in Calorie Intake

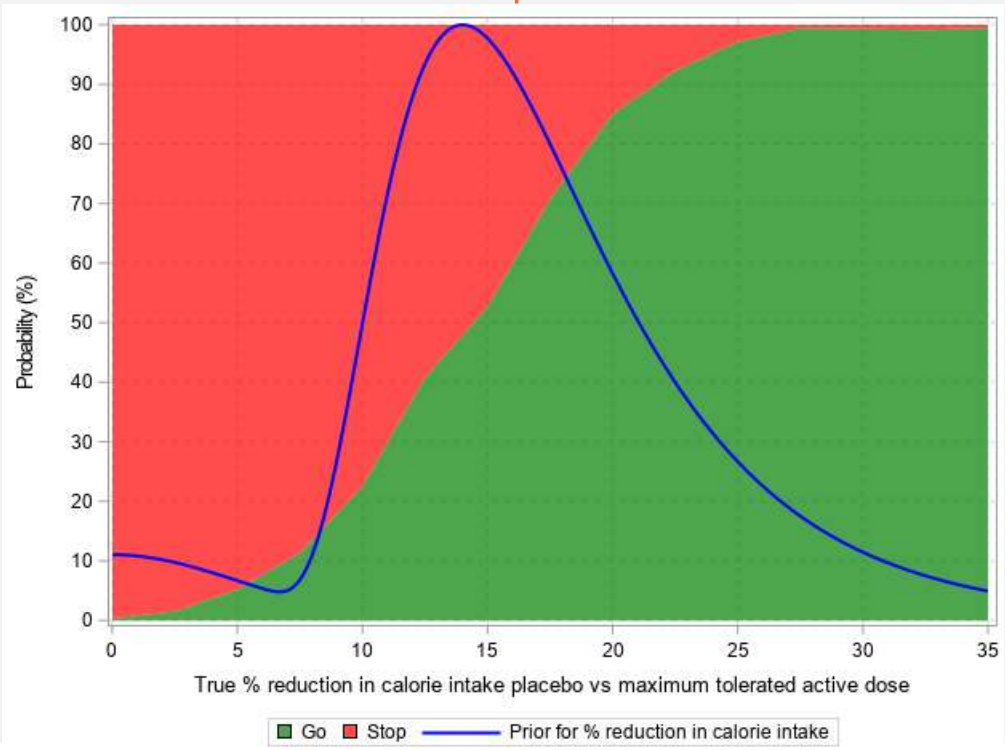
True % reduction placebo vs active 1	True % reduction placebo vs active 2	True % reduction placebo vs active 3	Calorie intake on placebo 1000kcal		Calorie intake on placebo 1500kcal	
			Probability of GO	Probability of STOP	Probability of GO	Probability of STOP
5	5	5	5%	95%	1%	99%
10	10	10	22%	78%	11%	89%
20	20	20	85%	15%	94%	6%
3	12	15	47%	53%	45%	55%
7	15	20	76%	24%	87%	13%
3	5	10	16%	84%	6%	94%
3	5	20	70%	30%	76%	24%

- Efficacy for maximum tolerable dose, where tolerable is defined on acceptable nausea rate
- Response on individual's maximum tolerated active dose is compared against placebo to assess the following rule:
- Response on maximum tolerated active dose is compared against placebo to assess the following rule:

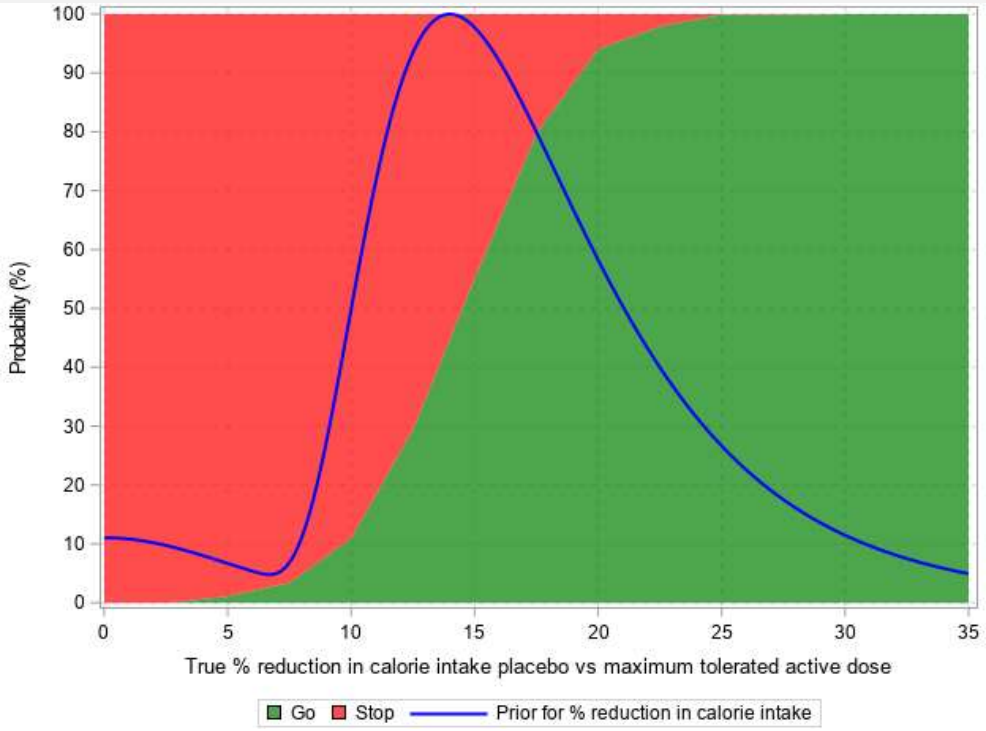
  Stop if P(true % reduction<15)>90%; Go otherwise
- Operating characteristics (OC) depend on the assumed calorie intake on placebo

Operating Characteristics for % Reduction in Calorie Intake

Calorie intake on placebo = 1000kcal



Calorie intake on placebo = 1500kcal

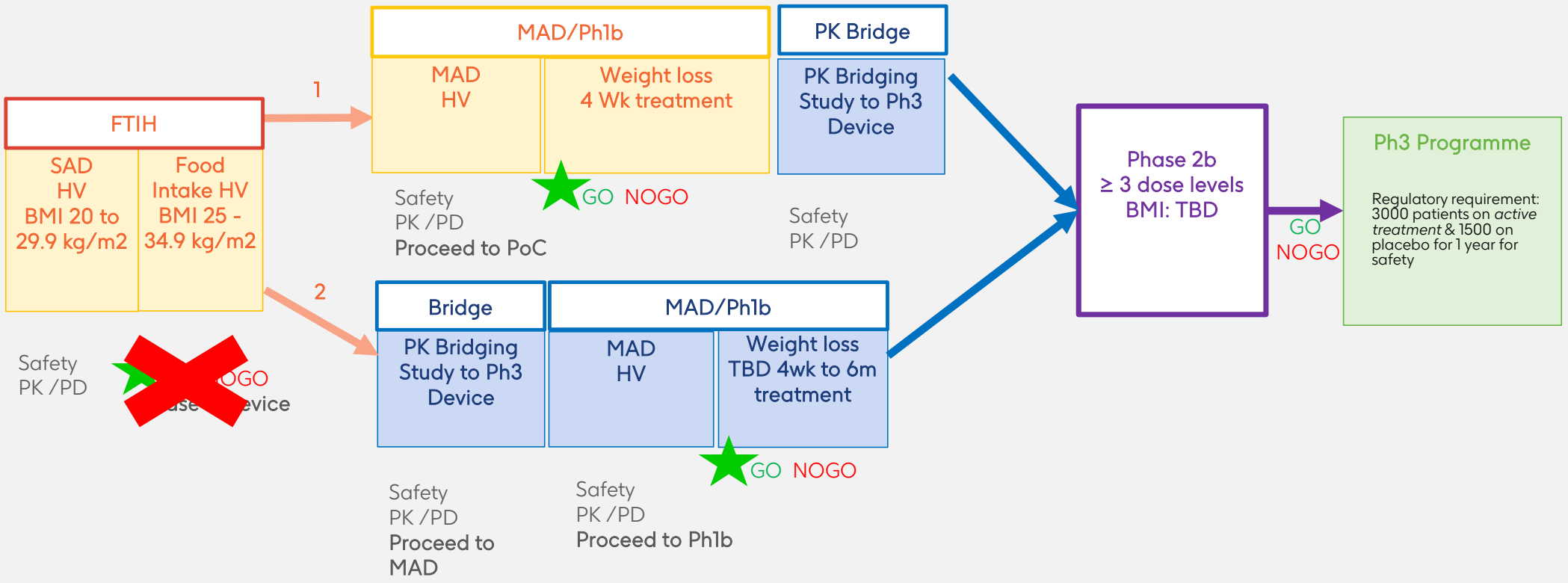


- Efficacy for maximum tolerable dose, where tolerable is defined on acceptable nausea rate
- Response on individual's maximum tolerated active dose is compared against placebo to assess the following rule:

  Stop if P(true % reduction<15%)>90%; Go otherwise
- Operating characteristics (OC) depend on the assumed calorie intake on placebo
- Assurance: 44%

Proposed Clinical Development Plan

Strategy: Build total data package with stepwise increase in N to minimise exposure and maximise early decision making



Conclusion

- QDM a key influential reason as to why the teams' initial beliefs about the asset were unfounded and hence why the programme was recommended for termination

- Team had a very high confidence asset would have an effect within single dose food intake study given mechanism
- However, the team's belief asset would achieve the desired effect was low, as highlighted by the thorough review of literature and understanding of multiple confounding factors for food calorie intake studies
- Resulting in a moderate assurance asset would achieve desired effect within single dose food intake study
- Literature review also highlighted poor translation between single dose food intake studies and short-term weight loss proof-of-concept studies
- No clear development plan that allowed build total data package with stepwise increase in N to minimise exposure and maximise early decision making for this asset