National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Semaglutide for managing overweight and obesity [ID3850]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Novo Nordisk	Yes.	Comment noted.
	GlaxoSmithKline	Yes.	Comment noted.
	British Obesity Society	We agree that this is an appropriate topic for NICE to appraise. Given its association with COID-19 morbidity and mortality, obesity management is important and a high priority.	Thank you for your comment. No change to the scope required.
	The UK Obesity Organisation	Yes – There are limited treatment options available for people living with obesity currently. Semaglutide offers a treatment that fits in between diet and exercise and bariatric surgery. There needs to be more options for PLWO because one size does not fit all.	Thank you for your comment. No change to the scope required.
Wording	Novo Nordisk	Yes.	Comment noted.
	GlaxoSmithKline	Yes.	Comment noted.

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	British Obesity Society	Yes.	Comment noted.
	The UK Obesity Organisation	Yes – I think the wording reflects the issues correctly.	Comment noted.
Timing Issues	Novo Nordisk	Given the high unmet need for additional clinically effective treatments for obesity and overweight in the NHS, the urgency of the proposed appraisal is high.	Thank you for your comment. No change to the scope required.
	British Obesity Society	We agree that this is an appropriate topic for NICE to appraise. Given its association with COVID-19 morbidity and mortality, obesity management is important and a high priority.	Thank you for your comment. No change to the scope required.
	The UK Obesity Organisation	COVID-19 has highlighted the need for more support and treatment options for people living with obesity. So I would say the urgency is pretty high for this.	Thank you for your comment. No change to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novo Nordisk	Based on the guidance outlined TA664 liraglutide is recommended alongside a reduced-calorie diet and increased physical activity for use in in adults who: • Have a body mass index (BMI) of at least 35 kg per m2 • Have pre-diabetes (non-diabetic hyperglycaemia (defined as a haemoglobin A1c level of 42 to 47 mmol per mol [6.0 to 6.4%] or a fasting plasma glucose level of 5.5 to 6.9 mmol per litre) • Have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia	Thank you for your comment. A description of the recommendations for liraglutide has been added to the background section of the scope.

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		• It is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service.	
	GlaxoSmithKline	No additional comment	Comment noted.
	British Obesity Society	This information is accurate and complete to date.	Comment noted.
	The UK Obesity Organisation	Please consider use of people first language in the document. The word obese is deemed as stigmatising.	Thank you for your comment. The scope has been amended to reflect this approach. “People who are overweight or obese” has been changed to “People living with overweight or obesity”.
The technology/ intervention	Novo Nordisk	**Current wording:** Semaglutide (Rybelsus, Novo Nordisk) binds to and activates the glucagon-like peptide-1 (GLP-1) receptor in order to increase insulin levels and suppress glucagon secretion. This action leads to the slowing of glucose absorption and lower post-meal blood glucose levels. It is administered by subcutaneous injection. **Proposed wording:** Semaglutide 2.4 mg (Brand Name TBC, Novo Nordisk) is a once-weekly subcutaneous injection that binds to and activates the glucagon-like peptide-1 (GLP-1) receptor in order to increase insulin levels and suppress glucagon secretion. This action leads to the slowing of glucose absorption and lower post-meal blood glucose levels.	Thank you for your comment. The scope has been amended to reflect that the brand name is yet to be confirmed. The proposed appraisal will only appraise semaglutide within its marketing authorisation and within the remit of the scope. It is therefore not necessary to

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		Current wording: Semaglutide has a marketing authorisation in the UK as an adjunct to diet and exercise for treatment of adults with insufficiently controlled type 2 diabetes mellitus, either as monotherapy when metformin is considered inappropriate due to intolerance, or in combination with other medicinal products for the treatment of diabetes. Semaglutide is available as once-daily oral tablet and once-weekly injectable preparations. **Proposed wording:** Semaglutide has a marketing authorization in the UK as an adjunct to diet and exercise for treatment of adults with insufficiently controlled type 2 diabetes mellitus, either as monotherapy when metformin is considered inappropriate due to intolerance, or in combination with other medicinal products for the treatment of diabetes. Semaglutide is available as once-daily oral tablet (Rybelsus®, 3 mg, 7 mg and 14 mg) and once-weekly injectable preparations (Ozempic®, 0.5 mg and 1.0 mg dose). **Current wording:** Intervention(s) Semaglutide **Proposed wording:** Semaglutide 2.4 mg	distinguish between doses from other indications.
	GlaxoSmithKline	No additional comment.	Comment noted.
	British Obesity Society	Yes.	Comment noted.

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	The UK Obesity Organisation	Yes, I believe this is correct.	Comment noted.
Population	GlaxoSmithKline	Yes, the population is defined appropriately.	Comment noted.
	British Obesity Society	Appropriate population data.	Comment noted.
	The UK Obesity Organisation	Yes the population is defined appropriately. I would stress that those with a BMI above 40 require access sooner than others.	Thank you for your comment. No change to the scope required.
Comparators	Novo Nordisk	Novo Nordisk would like to propose the following amendments to the Comparators section: **Orlistat (prescription dose)** is not a relevant comparator for semaglutide 2.4 mg. In section 3.2 of the final appraisal determination for technology appraisal 494, orlistat was not considered to be widely used by the clinical experts in clinical practice due to undesirable side effects leading to poor adherence and outcomes. These sentiments were again reflected in the recent appraisal of liraglutide for managing overweight and obesity [TA664] and were discussed at length during consultation. In section 3.4 of the final appraisal determination, it is stated that many people decide not to have orlistat or stop taking it because of undesirable, and socially unacceptable side effects. Therefore, based on this rationale, and the clear determination made in TA494 and TA664 orlistat should not be considered a relevant comparator. **Bariatric surgery** is not a relevant comparator in the appraisal for semaglutide 2.4 mg. Although bariatric surgery may be considered a last	Thank you for your comment. Although clinical expert comments in TA494 indicated that orlistat is not widely used, it is listed as an available treatment option in CG189. For completeness, it has been kept in the scope as a comparator. It is acknowledged that bariatric surgery is a treatment option when all appropriate non-surgical measures have been tried. Therefore,

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		resort treatment option for patients with obesity with a high BMI (a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease), in UK clinical practice it is not realistic that all patients will be offered bariatric surgery. In section 3.1 of the final appraisal determination for technology appraisal 494, clinical experts stated that only 0.1% of patients eligible for surgery actually have it. Again, this is reiterated in section 3.4 of the final appraisal determination for TA664. To account for bariatric surgery in the treatment pathway for obesity, this will be included in the economic model as an event. The rate of surgery would be based on the current incidence in the NHS and modifiable via sensitivity analysis. Consistent with the recommendation achieved through appraisal TA664 liraglutide 3.0mg is a relevant comparator in patients who: • Have a body mass index (BMI) of at least 35 kg per m^2 • Have pre-diabetes (non-diabetic hyperglycaemia (defined as a haemoglobin A1c level of 42 to 47 mmol per mol [6.0 to 6.4%] or a fasting plasma glucose level of 5.5 to 6.9 mmol per litre) • Have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia • It is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service The expected license recommends the use of semaglutide 2.4 mg as an adjunct to diet and exercise and therefore diet and exercise will continue to be a significant component for the ongoing management of obesity	bariatric surgery has been removed as a comparator. The scope has been updated to specify the population for whom liraglutide is an appropriate comparator.
	GlaxoSmithKline	Yes, the comparators are appropriate for this appraisal.	Comment noted.

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	British Obesity Society	Yes.	Comment noted.
	The UK Obesity Organisation	I think the comparators are fair for this appraisal.	Comment noted.

Outcomes	Novo Nordisk	The following outcomes were collected as part of the STEP-1 clinical trial:
		• Change from baseline at week 0 to week 68 in body weight (%)
		• Subjects who after 68 weeks achieve (yes/no):
		  ○ Body weight reduction ≥5% from baseline (week 0)
		• Subjects who after 68 weeks achieve (yes/no):
		  ○ Body weight reduction ≥10% from baseline (week 0)
		  ○ Body weight reduction ≥15% from baseline (week 0)
		  ○ Body weight reduction ≥20% from baseline (week 0)
		• Change from baseline at week 0 to week 68 in:
		  ○ Body weight (kg)
		  ○ BMI (kg/m^2)
		• Cardiovascular risk factors
		  ○ Change from baseline at week 0 to week 68 in:
		  ▪ Systolic blood pressure (mmHg)
		  ▪ Diastolic blood pressure (mmHg)
		  ▪ Lipids (mmol/L and mg/dL)
		  • Total cholesterol
		  • HDL cholesterol
		  • LDL cholesterol
		  • VLDL cholesterol
		  • Free fatty acids
			Thank you for your comment. We note that the trial outcomes broadly fall under the outcome measures in the scope and the company's intended modelled outcomes are consistent with the scope. Please note that work productivity is currently outside the remit of NHS and PSS perspective. No change to the scope required.

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		• Triglycerides ○ CRP (mg/L) ○ PAI-1 activity (AU/mL) • Clinical outcome assessments ○ Change from baseline at week 0 to week 68 in: ▪ Physical functioning score (SF-36) ▪ Physical function domain (5-items) score (IWQOL-Lite-CT) ▪ SF-36 ▪ IWQOL-Lite-CT • Subjects who after 68 weeks achieve (yes/no): ○ Responder definition value for SF-36 physical functioning score ○ Responder definition value for IWQOL-Lite-CT physical ○ Function domain (5-items) score • Glucose metabolism ○ Change from baseline at week 0 to week 68 in: ▪ HbA1c (% and mmol/mol) ▪ FPG (mmol/L and mg/dL) ▪ Fasting serum insulin (mIU/L) • Other body weight-related endpoints ○ Waist circumference (cm)# ○ Soluble leptin receptor (ng/mL) ○ Leptin (ng/mL) ○ Body composition (as assessed by DEXA in a subset of ○ subjects): ▪ Total fat mass (kg and %) ▪ Lean body mass (kg and %) ▪ Visceral fat mass (kg and %) • Body weight (kg and %) in the DEXA subset of subjects • Safety endpoints	

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		• Number of TEAEs from baseline at week 0 to week 75
		• Number of SAEs from baseline at week 0 to week 75
		• Change from baseline at week 0 to week 68 in:
		  ○ Pulse (bpm)
		  ○ Amylase (U/L)
		  ○ Lipase (U/L)
		  ○ Calcitonin (ng/L)
		• Glycaemic status
		  ○ Change from baseline at week 0 to week 68 in glycaemic category (normo-glycaemia, pre-diabetes, T2D)
		• Use of medication for hypertension and dyslipidaemia
		  ○ Change from baseline at week 0 to week 68 in:
		  ▪ Antihypertensive medication (decrease, no change, increase)
		  ▪ Lipid-lowering medication (decrease, no change, increase)
		• Work productivity
		  ○ Change from baseline at week 0 to week 68 in the SPS-6, total score
		• Treatment discontinuation
		  ○ Subjects who from randomisation at week 0 to week 68 have permanently discontinued randomised trial product (yes/no)
		  ○ Time to permanent discontinuation of randomised trial product
		  ○ (weeks)
		• Liver indices
		  ○ Change from baseline at week 0 to week 68 in fatty liver index score category (<30, ≥30 and <60, ≥60)
		• Urinary incontinence
		  ○ Change from baseline at week 0 to week 68 in ICIQ-UI-SF, sum score (assessed in female subjects)
		• Diet and physical activity	

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		○ Number of days per week with at least one entry in the food diary from baseline at week 0 to week 68 ○ Number of minutes per week of physical activity from baseline at week 0 to week 68 Modelled outcomes include, life expectancy, health-related quality of life measures, cardiovascular events, incidence of type 2 diabetes, weight progression over time. **Proposed change** Percentage body fat should not be included as an outcome. Glycaemic status should be included as an outcome. **Rationale:** Section 1.2.2 of NICE clinical guidelines 189, suggests using BMI as a practical estimate of percentage body fat (adiposity) in adults. In section 1.2.6 it also does not advocate percentage body fat as a measurement of overweight or obesity via bioimpedance. This is also supported in section 5.1.3 of the NICE Evidence Review for clinical guideline 43, which states there is a weak association between BMI and percentage adiposity: "Adiposity is defined as the amount of body fat expressed as either the absolute fat mass (in kilograms) or as the percentage of total body mass. Absolute adiposity is highly correlated with body mass, but percentage adiposity is relatively uncorrelated with body mass". Furthermore, percentage body fat is not routinely collected in UK clinical practice, was not considered relevant to the recent appraisal of liraglutide for managing overweight and obesity [TA664]. Treatment with semaglutide 2.4 mg is associated with improvements in glycaemic status, clinically meaningful weight loss and improvements in other	Comment noted. Outcomes amended.

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		comorbidity markers for patients with obesity. It is anticipated that a proportion of patients treated with semaglutide 2.4 mg will revert to a normal glucose levels, greatly reducing the risk of diabetes onset. As such, glycaemic status is a relevant outcome to be included within the appraisal.	
	GlaxoSmithKline	Yes, we agree with the listed outcomes.	Comment noted.
	British Obesity Society	Yes.	Comment noted.
	The UK Obesity Organisation	Yes – I think these outcomes will capture the most important health related benefits.	Comment noted.
Economic analysis	Novo Nordisk	The costs and benefits of semaglutide 2.4 mg vs the relevant comparators will be modelled over a lifetime horizon with ability for sensitivity analyses at different time horizons.	Thank you for your comment. No change to the scope required.
	GlaxoSmithKline	No additional comment.	Comment noted.
	British Obesity Society	Given the data available, the economic analysis is appropriate.	Comment noted.
	The UK Obesity Organisation	This looks appropriate to me.	Comment noted.
Equality and Diversity	Novo Nordisk	Socioeconomic status has an influence on the incidence and the impact of obesity. The lack of effective treatment options available on the NHS for the medical management of obesity and lack of well-established obesity services means that there may be inequity in access to available treatment options.	Thank you for your comment. These equalities considerations are formally addressed in

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		Obesity services are not available universally across England, and only a fraction of patients who are eligible for these Tiers are referred and seen. There is also lack of awareness of the services available and their clinical outcomes accompanied with a certain reluctance to seek help amongst the patients with obesity. For BMI an adjustment will be considered for the BMI threshold for treatment in patients from non-European descent. This is in line with the wording used in the background for the scope, which some ethnic groups may be at increased risk of some ill health conditions at lower BMI than people of European family origin, and therefore some adjustment may be appropriate. This is similarly reflected in the recent approval of liraglutide for managing overweight and obesity [TA664] in a population with a BMI of at least 35 kg per m^2 (adjust accordingly using lower thresholds for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population).	the Equalities Impact Assessment form.
	GlaxoSmithKline	No additional comment.	Comment noted.
	British Obesity Society	Proposed remit does not need changing.	Comment noted.
	The UK Obesity Organisation	Stigma is rife when it comes to obesity, I would like to think that the complexity of obesity is fully understood when evaluating this proposal. Working to 12-week timelines etc. are just not appropriate for people living with obesity. We cannot treat chronic conditions with acute solutions. I hope this will be taken into consideration.	Thank you for your comment. No change to the scope required.
Other considerations	Novo Nordisk	Based on clinical guidelines and the prior NICE technology appraisal of liraglutide [TA664], Novo Nordisk believe there remains a substantial unmet need amongst patients with BMI ≥27 with comorbidities. This group is of a particular priority for treatment with semaglutide 2.4 mg, especially those with	Thank you for your comment. No change to the scope required.

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		comorbidities who may not be eligible for or be able to access liraglutide 3.0mg. If evidence permits, analyses will be explored specifically for sub populations given the ongoing need for efficacious and well tolerated treatment options for patients with overweight or obesity and additional comorbidities.	
	GlaxoSmithKline	No additional comment.	Comment noted.
	The UK Obesity Organisation	The urgency that has been highlighted re COVID-19 and the lack of support and treatment options for people living with obesity (PLWO) should be considered here.	Thank you for your comment. No change to the scope required.
Innovation	Novo Nordisk	Although the recent approval of liraglutide for managing overweight and obesity [TA664] is a welcome step change in providing access to a clinically effective treatment, this approval still represents a relatively small subset of the overall overweight and obese population. For patients with BMI ≥27 with comorbidities, many will not be eligible for treatment with liraglutide 3.0 mg, and therefore a strong clinical need remains for efficacious treatments with tolerable adverse effects profiles.	Thank you for your comment. The appraisal committee will consider whether there are any innovative aspects of semaglutide that are not adequately captured by the QALY estimate.
	GlaxoSmithKline	No additional comment.	Comment noted.
	British Obesity Society	This innovation could make a significant impact on health-related benefits, opening up effective treatment to those unable to tolerate alternative, daily injected medication.	Thank you for your comment. No change to the scope required.
	The UK Obesity Organisation	Yes – Liraglutide has shown some great outcomes and safety data. Semaglutide has shown even greater outcomes re health benefits and weight loss. The fact that it is available in tablet and injectable form offers flexibility for people.	Thank you for your comment. No change to the scope required.

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		Some of the weight loss data for Semaglutide is not far from what can be achieved with bariatric surgery, obviously this would be a huge step forward if people can achieve this with an oral drug or injectable, rather than the risks and costs associated with surgery.	
Questions for consultation	Novo Nordisk	**Have all relevant comparators for semaglutide been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the NHS for overweight and obesity?** Liraglutide 3.0 mg should be considered for patients with a BMI ≥35 with prediabetes and high CV risk according to TA664. No pharmacotherapy plus diet and exercise should also be considered for these patients and for those patients with obesity who fall outside of this criteria. **How should 'standard care without semaglutide' be defined?** Please see responses as provided above. The relevant comparators for this appraisal are liraglutide (for those who have a body mass index (BMI) of at least 35 kg per m^2, have non-diabetic hyperglycaemia and have a high risk of cardiovascular disease) and standard of care is likely to involve general counselling on lifestyle measures, which is defined as diet and physical activity in section 1.3.6 of NICE clinical guideline 189. **Are the outcomes listed appropriate?**	Thank you for your comment. No further change to the scope required. Thank you for your comment. Liraglutide is listed as a comparator. Thank you for your comment. These are listed as comparators in the scope. Thank you for your comment. Please see response in the

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		As mentioned above, percentage body fat is not considered an appropriate measure for BMI and should not be listed as an outcome. The other outcomes listed are appropriate, however they are not exhaustive. Therefore additional suggested outcomes not listed in the scope e.g. impact on glycaemic status and prediabetes will be presented alongside those listed. **Are there any subgroups of people in whom semaglutide is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As explained in the 'Other considerations' section above, based on clinical guidelines and the prior NICE technology appraisal of liraglutide [TA664], Novo Nordisk believe there is a substantial unmet need for patients with BMI ≥27 with comorbidities for whom there are limited treatment options. Particularly those who are not eligible for treatment with liraglutide 3.0 mg. This group is a particular priority for treatment with semaglutide 2.4 mg. If evidence permits analyses will be explored specifically for this population given the ongoing need for efficacious and well tolerated treatment options for patients with obesity and additional comorbidities. If justified, further analyses will be presented on subpopulations with specific comorbidities and various BMI cut offs. **Where do you consider semaglutide will fit into the existing NICE pathway, Obesity?** As mentioned above, there remains a substantial unmet need for patient with obesity and various weight related comorbidities. If evidence permits, semaglutide 2.4 mg may be best positioned as a treatment for patients with BMI ≥27 with comorbidities in addition to diet and exercise. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people**	'outcomes' section above. Thank you for your comment. Semaglutide will be appraised within its marketing authorisation. No further change to the scope required. Thank you for your comment.

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		with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which semaglutide will be licensed;** Novo Nordisk does not believe the proposed remit and scope could exclude any people protected by the equality legislation who fall within the patient population eligible for semaglutide. • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** Novo Nordisk does not believe the proposed remit and scope could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population. • **could have any adverse impact on people with a particular disability or disabilities.** Novo Nordisk does not believe the proposed remit and scope could have any adverse impact on people with a particular disability or disabilities. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.**	Thank you for your comment. Thank you for your comment. Thank you for your comment.

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		N/A **Do you consider semaglutide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes. Semaglutide provides a clinically efficacious and tolerable once-weekly treatment option for people with obesity. **Do you consider that the use of semaglutide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Obesity is a complex condition that impacts on a patient's physical, social and psychological wellbeing. Accounting for all of these aspects in an economic model is also complex. Novo Nordisk has developed an obesity model which takes into account conditions which have a strong relationship with obesity according to the WHO and therefore may underestimate health-related benefits associated with all conditions that may benefit from weight loss such as the risk of hospitalisation and mortality from infectious diseases including COVID-19. PHE's evidence review of excess weight and Covid-19 found people with obesity are at greater risk of hospitalisation, Intensive Care Unit (ICU) admission and death from Covid-19, with risk growing substantially as BMI increases. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**	Thank you for your comment. Thank you for your comment. Please see response in the 'innovation' section above. Thank you for your comment.

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		Novo Nordisk will include a utility value per BMI increment, which can be varied in a sensitivity analysis. A review of relevant epidemiology will be presented to substantiate the association between BMI and longer-term complications not directly measured in the model. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Obesity is considered a chronic disease that requires holistic, long-term management with appropriate interventions. Typically there has been underinvestment in weight management services damaging the ability for patients to routinely, and equitably access effective interventions. If approved semaglutide 2.4 mg would be introduced as a welcome additional to the current standard of care and increase opportunity for access to the patients most in need.	Thank you for your comment.
	The UK Obesity Organisation	I feel these have been answered above.	Comment noted.