SUPPLEMENTARY DATA

EXSCEL Inclusion and Exclusion Criteria

Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this trial:

a) Patient has type 2 diabetes mellitus
b) Patient will be able to see a usual care provider at least twice a year
c) Patient has an HbA1c of ≥6.5% and ≤10.0% and is currently using one of the following treatment regimens:
    - Treatment with up to three (i.e. 0 – 3) oral AHAs (concomitant use of DPP-4 inhibitors is permitted)
    - Insulin therapy, either alone or in combination with up to two (i.e. 0 – 2) oral AHAs (use of basal and prandial insulins is permitted in any combination of individual or premixed insulins)

All patients should be on a stable diabetes management regimen, as assessed by the investigator, at time of enrolment.

HbA1c values must be from within the 3 months prior to randomisation. If multiple values are available, the most recent reported value should be used. A patient whose HbA1c is >10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA1c randomization eligibility (≥6.5% and ≤10.0%).

d) Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event.

A prior CV event is defined as *at least one of the following*:

- History of a major clinical manifestation of coronary artery disease i.e. myocardial infarction, surgical or percutaneous (balloon and/or stent) coronary revascularization procedure, or coronary angiography showing at least one stenosis ≥50% in a major epicardial artery or branch vessel
- Ischaemic cerebrovascular disease, including:
    - History of ischaemic stroke; strokes not known to be haemorrhagic will be allowed as part of this criterion; transient ischaemic attacks (TIAs) are not included

- History of carotid arterial disease as documented by ≥50% stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit

- Atherosclerotic peripheral arterial disease, as documented by objective evidence such as amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe-brachial pressure index less than 0.9, or history of surgical or percutaneous revascularization procedure

e) Female patients must not be breast feeding and agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant
f) Patient understands the trial procedures, alternative treatments available, the risks involved with the trial, and voluntarily agrees to participate by providing written informed consent
g) Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period, and agrees to communication between the trial site and the usual care provider in order to facilitate routine care
h) Patient is 18 years or older at enrolment

Exclusion Criteria

Each patient meeting any of the following criteria will be excluded from this trial.

a) Patient has a diagnosis of type 1 diabetes mellitus, or a history of ketoacidosis
b) Patient has a history of (≥2 episodes) of severe hypoglycaemia within 12 months of enrolment
c) Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g., BYETTA (exenatide), BYDUREON (EQW), VICTOZA (liraglutide), LYXUMIA (lixisenatide), albiglutide, taspoglutide or dulaglutide
d) Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial
e) Patient has a planned or anticipated revascularization procedure
f) Pregnancy or planned pregnancy during the trial period
g) Patient has medical history that indicates a life expectancy <2 years or might limit the individual's ability to take trial treatments for the duration of the trial
h) Patient has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose an unacceptable risk to the patient, confound the results of the trial e.g. if patient cannot comply with requirements of the trial, or likely to interfere with the patient's participation for the full duration of the trial
i) Patient has end-stage renal disease or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple MDRD-4 formula) of <30mL/min/1.73m^2
j) Patient has a known allergy or intolerance to exenatide
k) Patient has a history of gastroparesis

l) Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level of >40ng/L at baseline

NOTE: Serum for calcitonin measurement will be drawn at baseline. Patients may be randomized and initiate study medication prior to the results of the calcitonin measure being available. If a randomized patient is found to have an exclusionary serum calcitonin concentration, they will stop study medication and patients will continue to have follow-up and be part of the Intent-to-Treat analysis.

m) Patient has previously been randomized in EXSCEL
n) Patient has a history of pancreatitis
o) Is an employee of Amylin Pharmaceuticals, LLC, Bristol-Myers Squibb Company, or AstraZeneca.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study patients and that the results of the study can be used. It is imperative that patients fully meet all eligibility criteria.

Ancillary case report form used to collect calcitonin elevation follow-up data

1. Was the patient referred to their usual care provider for additional workup? (Yes/No/Not Available)
2. Was the patient referred to an endocrinologist or other thyroid specialist for additional workup? (Yes/No/Not Available)
3. **Was a repeat calcitonin level performed? (Yes/No/Not Available)
    a. If yes, DATE
    b. VALUE
    c. ULN
4. Is the patient taking, or have they taken within one month of the elevated calcitonin value, any of the following?
    a. Beta-blocker (Yes/No/Not Available)
    b. Glucocorticoids (Yes/No/Not Available)
    c. Chronic PPI (>2 months) (Yes/No/Not Available)
5. Does the patient have any of the following conditions:
    a. Hypercalcemia (Yes/No/Not Available)
    b. Hypergastrinemia (Yes/No/Not Available)
    c. Neuroendocrine tumors (Yes/No/Not Available)
    d. Renal insufficiency (Yes/No/Not Available)
    e. Chronic autoimmune thyroiditis (Yes/No/Not Available)
    f. Thyroid cancer (Yes/No/Not Available)
    g. History of radiation exposure (e.g. radioiodine treatment, head/neck irradiation) (Yes/No/Not Available)
6. Were any diagnostic tests or procedures performed (Yes/No/Not Available)

IF YES TO 6, TRIGGER REST OF FORM

7. Was a pentagastrin stimulation test performed? (Yes/No/Not Available)
    a. If yes: DATE
    b. Describe the results. (Dropdown: Normal/ Indeterminate/Diagnostic of medullary thyroid cancer
8. Was a thyroid ultrasound performed? (Yes/No/Not Available)
    a. If yes: DATE
    b. Describe the thyroid gland
        i. Size in cm
        ii. Parenchyma (Drop down: homogeneous or heterogeneous)
    c. Were any thyroid nodules identified? (Yes/No/Not Available) If yes,
        ** Thyroid nodule (repeat group i-viii)
        i. Size in cm (Format: number, one decimal place)
        ii. Location (Drop down: Right Upper Lobe/Right Lower Lobe/Left Upper Lobe/Left Lower Lobe/Isthmus)
        iii. Echogenicity (Drop down: hypoechoic/isoechoic/hyperechoic)
        iv. Calcifications (Drop down: none/microcalcifications/coarse (large) calcifications)
        v. Margins (Drop down: regular/irregular/not evaluated)
        vi. Vascularity (Drop down: central vascularity/peripheral vascularity/not evaluated)
        vii. Composition (Drop down: solid/cystic proportion/spongiform)
        viii. Shape (taller than wide/other (specify))
    d. Suspicious cervical lymph nodes in the central or lateral compartments (Yes/No/Not Available).
    e. Summarize any additional ultrasound findings. NARRATIVE (2 boxes)
9. **Was a fine needle aspiration (FNA) performed? (Yes/No/Not Available)
    a. If yes, DATE
    b. FNA clinical pathology findings (Drop down: non-diagnostic/benign/atypical cells of undetermined significance (ACUS)/follicular lesion of undetermined significance (FLUS)/suspicious for malignancy/malignant)
    c. If the clinical pathology was suspicious for malignancy or malignant, describe the tissue type. (Dropdown: Unknown/Papillary/Follicular/Medullary/Anaplastic/Poorly differentiated/ Other, specify)
    d. Summarize any additional results from the FNA. NARRATIVE (1 box)
10. Was genetic testing for germline *RET* mutations performed? (Yes/No/Not Available)

    a. If yes, was there a positive mutation? (Yes/No/Not Available)

11. **Was surgical intervention required? (Yes/No/Not Available)
    a. If yes, please provide the date of the procedure and ensure that the surgical intervention has been reported as an SAE. (DATE)
    b. Surgery type (Drop down: Partial thyroidectomy/Total thyroidectomy without lymph node dissection/ Total thyroidectomy with lymph node dissection / Other(Specify))
    c. Was malignancy discovered? (Yes/No/Not Available). If yes, please complete the questions below and ensure that the malignancy has been reported as an SAE.
        i. Staging (Dropdown: Stage 1, Stage 2, Stage 3, Stage 4)

ii. Is there evidence for persistent or recurrent disease? (Yes/No/Not Available)
iii. If Yes, please describe in the narrative below and include details of the treatment plan. Narrative (3 boxes)

d. Provide any additional narrative describing the surgical procedure. NARRATIVE (3 boxes)

12. Please use this space to describe any additional follow up not mentioned above AND to explain why "Not Available" was selected for any of the questions above.
    Narrative: (3 boxes)

**Denotes a repeated entry question

Criteria for adjudication of neoplasms

Excerpt from Clinical Events Committee Charter; version 6.0

6.8 Neoplasms

The following definitions will be utilized by the CEC for purposes of adjudication neoplasms:
Has a malignancy occurred? The CEC will answer yes to this question if the subject has either evidence of a new malignancy or the first recurrence (during the study period) of a previous cancer.

New malignancies:

1. New primary cancer in patients with or without pre-existing cancer, or
2. New metastatic cancer in patients without previous diagnosis of cancer, or
3. New metastatic cancer of a clearly distinct histology from any pre-existing cancer

Recurrence of previous cancer:

1. Evidence of first recurrence of a pre-existing cancer during the study period (histological, imaging, or clinical)

AND

2. History of this pre-existing cancer at the time of randomization (i.e. diagnosis of original cancer predates randomization)

AND

3. No evidence to indicate based on histological type or clinical picture that this is a different cancer.

Non-malignant neoplasms which are reported should be classified as benign neoplasms.
Progression of prior malignancy - does not meet EXSCEL definition of malignancy
Date of Initial Detections: This will be the date of initial detection by a treating physician, when the patient demonstrated either clinical symptoms or diagnostic testing results (for example, imaging, laboratory) with evidence of neoplasm that allows for a probable clinical diagnosis. Whichever date can be confirmed to occur first will be used.
Date of histological diagnosis: This will be the date that the diagnosis of Neoplasm was documented by histological and/or cytological evidence.

Status of Disease:

1. No evidence of disease: A patient who after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies.
2. Active disease: A patient who has evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy).
3. Stable/Inactive disease: A patient that has evidence of disease, but is not progressing, and has had no new and/or change in treatment since their previous evaluation
4. Cannot be determined: Is used to describe cases for which there is not enough information to indicate a classification.

SUPPLEMENTARY DATA

Table S1. Estimation of costs to local health care systems of routine serum calcitonin concentration monitoring

Follow-up activity	Code(s) assigned	Medicare fee schedule payment (US $)	Total amount per follow-up activity (US $)
Serum calcitonin measurement	82308*	33.08	33.08
Usual care provider visit	99213*	75.58	75.58
Thyroid specialist visit	99204*	169.98	169.98
Thyroid ultrasound	76536*	108.67	108.67
Fine Needle Aspiration (FNA)	99204*	169.98	404.24
	76942*	45.85	
	10022*	147.40	
	88172*	41.01	
Partial thyroidectomy	99204*	169.98	6677.13
	60220*	730.57	
	88307*	233.61	
	627†	5542.97	
Total thyroidectomy without lymph node dissection	99204*	169.98	6897.76
	60240*	951.20	
	88307*	233.61	
	627†	5542.97	
Total thyroidectomy with lymph node dissection	99204*	169.98	7313.26
	60252*	1366.70	
	88307*	233.61	
	627†	5542.97	
Pentagastrin stimulation test	80410*	99.24	231.56
	82308* x 4	132.32	
Genetic testing for germline RET mutations	81406*	282.88	282.88

*Current Procedural Terminology (CPT) code with associated 2018 Medicare reimbursement fee amount
†Diagnosis Related Group (DRG) code with associated 2017 Medicare reimbursement fee amount

Assumptions:

Serum calcitonin measurement: Assay of calcitonin (82308)

Usual care provider visit: Level 3 E/M code, established office patient non-facility fee (99213)

Thyroid specialist visit: Level 4 E/M code, new office patient non-facility fee (99204)

Thyroid ultrasound: non-facility procedure fee (76536)

Fine Needle Aspiration (FNA): non-facility thyroid specialist visit (99204) + non-facility procedure fee (76942, 10022) + cytopathologist analysis fee (88172)

Partial thyroidectomy: non-facility surgeon specialist visit (99204) + non-facility procedure fee (60220) + cytopathologist analysis fee (88307) + inpatient thyroid, parathyroid and thyroglossal procedures w/o cc/mcc fee

(627)

Total thyroidectomy without lymph node dissection: non-facility surgeon specialist visit (99204) + non-facility procedure fee (60240) + cytopathologist analysis fee (88307) + inpatient thyroid, parathyroid and thyroglossal procedures w/o cc/mcc fee (627)

Total thyroidectomy with lymph node dissection: non-facility surgeon specialist visit (99204) + non-facility procedure fee (60252) + cytopathologist analysis fee (88307) + inpatient thyroid, parathyroid and thyroglossal procedures w/o cc/mcc fee (627)

SUPPLEMENTARY DATA

Table S2. Baseline characteristics of participants with and without a serum calcitonin concentration elevation at baseline (>40 ng/L) or follow-up (≥50 ng/L) during the trial*

Characteristic	**Participants with elevated calcitonin N=75**	**Participants without elevated calcitonin N=12756**
Age at randomization (years)	66.0 (59.0, 71.0)	62.0 (56.0, 68.0)
Male	59 / 75 (78.7)	7916 / 12756 (62.1)
Ethnicity		
Hispanic or Latino	4 / 75 (5.3)	2667 / 12755 (20.9)
Not Hispanic or Latino	71 / 75 (94.7)	10088 / 12755 (79.1)
Race		
White	71 / 75 (94.7)	9696 / 12753 (76.0)
Asian	2 / 75 (2.7)	1278 / 12753 (10.0)
Hispanic	2 / 75 (2.7)	948 / 12753 (7.4)
Region		
Europe	32 / 75 (42.7)	5942 / 12756 (46.6)
North America	34 / 75 (45.3)	3009 / 12756 (23.6)
Latin America	5 / 75 (6.7)	2442 / 12756 (19.1)
Asia Pacific	4 / 75 (5.3)	1363 / 12756 (10.7)
European subcategories		
Western Europe	15 / 75 (20.0)	2320 / 12756 (18.2)
Eastern Europe	17 / 75 (22.7)	3622 / 12756 (28.4)
eGFR via MDRD (mL/min/1.73m^2)	66.0 (55.7, 87.0)	76.5 (61.6, 92.0)
>90	13 / 75 (17.3)	3698 / 12720 (29.1)
60-89	33 / 75 (44.0)	6318 / 12720 (49.7)
30-59	29 / 75 (38.7)	2694 / 12720 (21.2)
<30	0 / 75 (0.0)	10 / 12720 (0.1)

*Results are median (Q1, Q3) for continuous variables or n/N (%) for categorical variables