Project Title: Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry

Liraglutide injection NDA 022341

Liraglutide injection NDA 206321

Exenatide extended-release for injectable suspension NDA 022200

Exenatide extended-release injectable suspension NDA 209210

Dulaglutide Injection BLA 125469

Semaglutide Injection NDA 209637

Semaglutide Tablets NDA 213051

Semaglutide Injection NDA 215256

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1 Introduction

Human glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were first indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Long-acting GLP-1 RAs were subsequently approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g. hypertension, T2DM, or dyslipidemia).

GLP-1 RAs stimulate glucose-dependent insulin release, slow gastric emptying, inhibit inappropriate postprandial glucagon release, and reduce food intake. These effects are mediated by a G-protein coupled receptor, GLP-1R, which is widely distributed throughout a variety of tissues.

1.1 Background from GLP-1 Receptor Agonists Preclinical Development Programs

Nonclinical studies in rodents of clinically relevant doses of GLP-1 RAs showed dose-related and treatment-duration dependent increases in the incidence of thyroid C-cell tumors (adenomas and carcinomas). The clinical relevance of rodent thyroid findings observed with GLP-1 RAs is unknown. Information regarding the preclinical development programs for specific GLP-1 RAs can be found in Appendix F.

1.2 Background from GLP-1 Receptor Agonists Clinical Development Programs

Because of the changes observed in rodents including a GLP-1 RA- induced increase in serum calcitonin that preceded pathologic changes to the C-cell, serum calcitonin was monitored as a biomarker of C-cell pathology in the clinical development programs of the GLP-1 RA products. Results varied across the development programs, and are summarized in Appendix F.

1.3 Background Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) is the human equivalent of C-cell carcinoma in rodents. MTC is a rare form of human cancer. The annual age-adjusted incidence of thyroid cancer in general in the United States is 9.6 per 100,000[1], based on data from the National Cancer Institute Surveillance, Epidemiology and End Results program (SEER). MTC accounts for a small percentage of thyroid cancer overall, with estimates of the proportion ranging from approximately 1.6 - 5%.[1,2,3] The age-adjusted incidence rate of MTC for the period 2001 through 2005, as reported by the North American Association of Central Cancer Registries (NAACCR), is 0.2 per 100,000.[4]

MTC occurs sporadically in 75% - 80% of cases.[2] The remaining cases are associated with familial syndromes, including multiple endocrine neoplasia syndromes (MEN2A and 2B) or familial medullary thyroid carcinoma (FMTC).[5] Activating RET proto-oncogene mutations

generally are present in the familial MTC syndromes; these same germline mutations may also be found in approximately 6% of patients, with apparently sporadic varieties.[6,7] In addition, 20 - 50% of sporadic cases harbor a somatic RET mutation.[8,9,10]

Based on the available animal and clinical evidence, a post-approval active surveillance program for MTC is being established in order to evaluate further the potential association between treatment with long-acting GLP-1 RAs and the occurrence of MTC in humans.

1.4 Description of the MTC Registry

This active surveillance program will monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the United States population. Given the very low incidence of MTC in the general population, the expected rate of exposure to long-acting GLP-1 RAs, the anticipated long latency of the potential outcome under study and the limited data on underlying risk factors for development of MTC other than RET proto-oncogene mutations, an active surveillance program is the most efficient means of identifying a possible association between MTC and products in the long-acting GLP-1 RAs class. Given the uncertainty of the association of MTC in humans treated with these drugs, a study duration of at least fifteen years from the time of market introduction of the first long-acting GLP-1 RA was thought to provide evidence of an association, if one exists. If such an association is identified, a case-control study will be initiated to quantify the association.

The MTC registry is a Food and Drug Administration (FDA) post-marketing requirement for long-acting GLP-1 RA products. Because of the rarity of MTC and in order to minimize inconvenience to patients, physicians, and state cancer registries, FDA encouraged sponsors of long-acting GLP-1 RAs to work collaboratively to conduct this registry. Consequently, the MTC Registry Consortium has been formed for this purpose.

The MTC Registry Consortium refers to the Sponsors with approved long-acting GLP-1 RAs who have a contractual agreement to participate in the MTC Registry. A list of the current participating companies is shown in Appendix J. As additional Sponsors receive FDA approval for their compounds, it is expected that they will also participate in this MTC Registry. It is anticipated that the MTC registry will continue for 15 years after FDA approval of each respective compound (or for the duration agreed upon between each respective Sponsor and FDA).

This active surveillance program for cases of MTC will be conducted with assistance from the North American Association of Central Cancer Registries (NAACCR). NAACCR is a collaborative umbrella organization for cancer registries, government agencies, professional organizations, and private groups in North America interested in improving the quality and use of cancer registry data. All of the central cancer registries in the U.S. and Canada are members of NAACCR, including those that participate in SEER.

In addition, NAACCR develops and promotes uniform data standards for cancer registration, certifies population-based cancer registries, aggregates and publishes data from central cancer registries, and promotes the use of cancer surveillance data and systems for cancer control and epidemiologic research.[11]

2 Objectives

The objectives of this MTC Surveillance Study are:

1. To systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the U.S. through NAACCR to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the U.S. market.

2. To establish a registry of incident cases of MTC in adults (18 years of age and older) in the U.S. in order to characterize their medical histories and possible risk factors, including history of treatment with long-acting GLP-1 RAs.

3 Methods

3.1 Monitoring MTC Incidence in the U.S.

As per objective #1 above, cancer registry data will be collected through NAACCR to monitor the annual incidence rates of MTC in the United States (U.S.) adult population during the conduct of the active surveillance program. The data collected through NAACCR are the most complete source of aggregate data on the incidence of medullary thyroid cancer in the U.S., and are collected from all participating registries in all U.S. states. Incidence rates from 2001 until the time of U.S. market introduction of the first long-acting GLP-1 receptor agonist (January 2010) will serve as a baseline. Reports of case counts by state will be obtained on an annual basis and monitored during the conduct of the registry. Annual incidence rates will be documented for the 15-year period after each long-acting GLP-1 RAs approval, or for a time period agreed upon with the FDA. Trends by age and gender will be examined to identify any possible increases.

3.2 Establishing a Registry of Incident Cases

This active surveillance program and case-series registry will identify incident cases of MTC that occur in targeted States in the U.S., as per objective #2, and evaluate the characteristics of those cases.

Cases will be identified from state/regional population-based cancer registries. Participation of central cancer registries from many of the most populous states is critically important in order to capture a substantial percentage of all cases of MTC that occur in the U.S. Therefore, registries that have an average of at least 10 reported cases of MTC per year and meet the NAACCR standards for data collection quality and timeliness will be invited to

participate in the surveillance program. This sample will be augmented, if any of the targeted state registries refuse to participate, by adding additional state registries until the estimated, projected sample reaches at least 75% of incident cases in the U.S. In areas where a population-based registry is unable or unwilling to participate, comprehensive cancer center registries may be directly invited to participate. During the conduct of the registry, as described in Section 3.1 above, annual reports of all MTC cases in the U.S. by state will be obtained from NAACCR. Case counts in the participating registries will be monitored and compared to the overall incidence to ensure the 75% sample goal is reached. Based on the historical rate of ~590 cases annually across the entire U.S. population, 450 new cases per year would be expected in the participating state registries (representing 75% of the U.S. population). Therefore, it is expected that there will be approximately 110 new cases each quarter in the participating state registries. On a quarterly basis, participation rates and exact 95% confidence limits will be calculated. Figure 1 shows the expected participation rates and confidence limits for the first year. These estimates will be used to assess the participation rate for the registry. If the interim monitoring indicates that the registry may fall short of the 75% goal, corrective actions will be instituted.

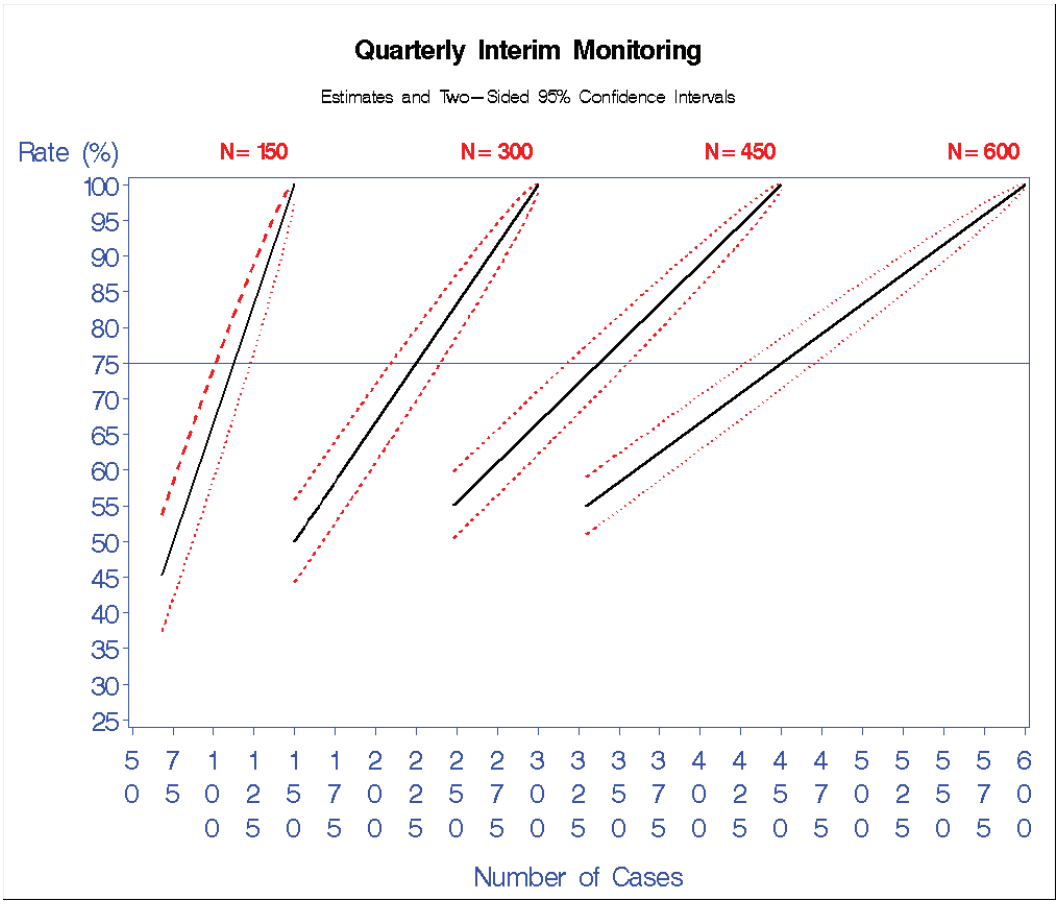


Figure 1 Expected Participation Rates and Confidence Limits for the First Year

Historical data on MTC incidence obtained through NAACCR are shown in Appendix A. In order to be included in these data listings, participating registries have to meet standards for certification, adhere to submission deadlines, and agree to have their data included; data from 40 states are included for the periods 2001 – 2005 and 2005 - 2009.[12,13] The remaining ten state registries did not have their data included in the listings because they did not meet the NAACCR data standards described above.

Based on this information, it is expected that a minimum of 20 U.S. states (listed in Appendix A) will be asked to participate in the case series registry. Inclusion of these participating registries is expected to capture approximately 75% of the incident cases of MTC in the U.S. based on historical data from 2001-2005, when a total of 2375 cases were reported over the five year period. Appendix C shows a population-based estimate of the number of cases that may have occurred in the ten states not included in Appendix A. Approximately 587 additional cases would have been expected in these states over the same 5-year reporting period based on state population estimates and the overall rates of MTC. Some of these state registries may be considered for inclusion if the issues that led to exclusion of their data are resolved.

3.2.1 Medullary Thyroid Cancer Case Definition

A case of MTC will be identified using the histological criteria in Table 1.

Table 1 Classification of Medullary Thyroid Cancer

Primary Site	C73.9 (Thyroid)
Histology	8345 Medullary carcinoma with amyloid stroma (C73.9) Med
	8346 Mixed medullary-follicular carcinoma (C73.9) Med
	8347 Mixed medullary-papillary carcinoma (C73.9) Med
	8510 Medullary carcinoma, NOS Med
	8512 Medullary carcinoma with lymphoid stroma Med
	8513 Atypical medullary carcinoma (C50._) Med

International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) Codes

3.3 Registry Outreach

An active outreach program will be implemented to help raise awareness about the registry and to encourage inclusion of data from all incident cases of MTC in participating states. Leading experts at thyroid cancer referral centers in the United States will be contacted and provided with information about the registry. Consideration will be given to having a booth at the Annual Meeting of the American Thyroid Association (and potentially other professional meetings of relevance) describing the MTC Registry and seeking support from members for active cases. Participation from leading thyroid cancer experts is anticipated to increase the active participation of physicians with access to the relevant clinical data on incident cases.

In addition, organizations such as the American Thyroid Association, The Endocrine Society, American Association of Clinical Endocrinology (AACE) and ThyCa (The Thyroid Cancer Survivors' Association, Inc.) may be contacted to solicit their involvement in making physicians and patients aware of the registry through their educational programs and on-line resources. This will include the development of a manuscript describing the project for submission to *Thyroid*, the official journal of the American Thyroid Association.

3.4 Registry Participation

An agreement will be established with each registry selected for participation in the case-series registry study based on the individual requirements of each registry. Dedicated cancer registry personnel who can facilitate the patient consent process will be identified at each registry whenever possible. The Study Coordinating Center (SCC) is available to conduct the necessary physician and patient outreach as needed for the MTC Registry. Compensation will be provided to the registry (if permissible) for the work involved in identifying MTC cases and recruiting MTC patients and their physicians. Each participating registry or cancer center will be required to obtain Institutional Review Board (IRB), relevant Department of Health, or Ethics Committee approval of the MTC Registry Document/Project Manual prior to inclusion of cases in the registry.

3.5 Patient Enrollment

Each participating registry will be asked to identify all cases of MTC in their database that were diagnosed on or after FDA approval of the first long acting GLP-1 RA in January 2010 with the date of first MTC diagnosis. As new MTC cases are identified prospectively, each participating registry will be asked to provide report only once (avoid duplicate reporting of the same case) for each case of MTC diagnosed after 25-Jan-2010 as soon as available (based on the registry's specific standard operating procedures (SOPs)). A case of MTC will be identified from the registry database using the criteria indicated in Table 1.

The methods for recruiting patients into the case-series registry will be developed based on the requirements of the reporting registry. Methods that will be used to recruit patients will include:

(1) Direct invitation of patients

In registries where direct patient contact is possible, the participating registry will be asked to send a written invitation to the patient to participate in the case series registry. The patient will then be directly contacted to explain the study and to request consent to release his/her name to the SCC. As a courtesy, the patient's physician will be notified of the case series registry study.

After appropriate informed consent is obtained by the registry staff, patient identifying data will be transferred to the SCC. The SCC staff will contact the patient by phone, further explain the study, and confirm his/her consent to participate. A telephone interview will be

conducted to obtain from the patient (or his/her proxy) additional information related to demographics, risk factors, and comorbid conditions. If the patient indicates that he/she has diabetes or has taken a diabetes medication, he/she will be asked which diabetes medication(s) and/or any GLP-1 RAs he/she may have used. If a patient indicates that he/she has taken medication for chronic weight management, he/she will be asked what medication they have taken. The patient will also be asked to identify his/her primary care physician, endocrinologist or thyroid specialist and oncologist. A Medical Record Authorization form will be sent to the patient for signature and returned to the SCC. This form will allow the SCC to contact the physician(s) to complete the Physician Verification Form. Physicians will be compensated $150 per completed Verification Form. In most states, the legal requirement for hospitals is that cancer diagnoses must be reported to their respective state registry within 6 months. Given this requirement and the generally good prognosis of MTC, it is expected that the SCC will be able to obtain information from the patient directly in most cases. If the patient is unable to participate in the phone interview, he/she will be asked to indicate a proxy, family member or caregiver familiar with his/her medical history who is authorized to provide information as a proxy. In the event that the patient is deceased, information will be collected from the patient's proxy, if available (depending upon state cancer registry requirements). Alternatively, a Medical Record Authorization form will be sent to the proxy for signature so that the necessary information can be collected from the physician(s) familiar with the patient's medical information.

Patients (or patient's proxy, if applicable) will be compensated $75.00 for their time to complete the telephone interview.

(2) Patient recruitment through the diagnosing physician

Some state or regional registries may be unable to contact a patient directly. In these situations, the patient's physician identified in the registry records will be asked to provide the required information for the case-series registry study or to recruit directly the patient for the study. The reporting registry or the SCC will send a written invitation to the physician indicating the name(s) of the patient(s) from whom information is sought. The registry will then provide the physician's name to the SCC (if not previously provided) and the SCC will follow-up with the physician to determine interest in participating in the study. If the physician agrees, he/she will be provided with a written invitation to send to the identified patient(s). The invitation will direct the patient to call the SCC and enroll in the study as per scenario #1 above.

If the state cancer registry is unable to contact the patient, the registry will be asked to provide the required data directly without specific patient identifiers. In this situation, the SCC will receive initials, year of birth, gender, date of MTC diagnosis and MTC histology, if approved by a state's IRB/Committee. The patients will be identified through a unique number or other identifier. No patient identifying information, such as patient initials, will be passed onto the Sponsor(s).

If allowable by the reporting registry, the proxy will be contacted to complete a data collection form for any patient who is deceased.

3.6 Data Collection

Initial data on each incident case will come from the reporting state cancer registry or comprehensive cancer center in the standard NAACCR format. The United BioSource Corporation (UBC) SCC will complete a manual duplicate check for the new patient case information received from the state cancer registries in the electronic data capture system (EDC) to determine if patient profile was previously created. All efforts will be made to identify duplicates. Depending on the circumstances as noted above, patient-identifying information may not be supplied for some cases. However, the basic NAACCR dataset will be provided for each MTC case so that the characteristics of those patients who are not included in the case-series registry study can be compared with those who are included.

Data to be obtained directly from patients will be collected by telephone interview using a standard questionnaire administered by a trained SCC interviewer. Data to be obtained from physicians will be collected using a data collection form.

The following data will be collected from the reporting registries for each incident MTC case:

- Reporting source
- Unique patient identifier (ID number assigned by the registry)
- Basic demography (sex, race, ethnicity, date of birth)
- Usual occupation and industry
- Primary site
- Topography of cancer
- Morphology of cancer
- Date of MTC diagnosis
- Age at MTC diagnosis
- Comorbidities
- Extent of spread outside the thyroid
- First course of treatment
- Primary surgical procedure
- Chemotherapy
- Date of last contact
- Vital status
  - Date of death, if deceased

The following data will be collected by the SCC directly from the patient or his/her proxy (via telephone interviews):

- Additional demographic information
- Date of MTC diagnosis

- Family history of cancer (including history of MEN2A or MEN 2B, history of FMTC, history of RET proto-oncogene mutations)
- Results of RET proto-oncogene testing
- Comorbid conditions (type 2 diabetes, previous history of cancer, hypothyroidism, hyperthyroidism, obesity)
- All current and previous long-acting GLP-1 RA use
  - Dose
  - Duration of use
  - Start date (month/year, if available)
- All current and previous diabetes medication exposures [including dipepetidyl peptidase (DPP) 4 inhibitors and insulin]
  - Dose
  - Duration of use
  - Start date (month/year, if available)
- All current and previous weight management medication exposures
  - Dose
  - Duration of use
  - Start date (month/year, if available)
- For patients who report use of diabetes medication or medication for weight management, verification of the specific medications prescribed by a Health Care Professional will be obtained whenever possible
- Other medication exposures (including proton pump inhibitors, H2 blockers, vitamin B12)
- History of surgery including gastric or intestinal bypass surgery
- Events leading to diagnosis (for example, calcitonin screening, thyroid nodule, thyroid ultrasound, thyroid scan, fine needle aspiration, surveillance related to family history)
- Radiation exposure (including exposure related to prior cancer treatment, neck irradiation as treatment for acne or other conditions)
- Lifestyle factors such as smoking and alcohol use
- Height and weight
- Environmental exposures
  - Occupational history
  - Radioiodine exposure, nuclear fallout

Similar questions will be included on the data collection form for physicians if the patient is unable to provide data directly.

3.7 Registry Procedures

3.7.1 Patient Contact

The SCC staff will follow due diligence procedures (including 3 telephone calls made at differing times of day, both during and after usual business hours) to follow up with the

patient. If these 3 telephone contacts have been exhausted with no response from patient, the SCC staff will send a hard to reach letter via a traceable courier.

3.7.2 Duplicate Records

Central cancer registries have thorough procedures in place to identify and consolidate duplicate reports. In order for registries to be certified by NAACCR, the duplicate rate is maintained at a very low level (<2 duplicate reports/1000 records).

3.7.3 Patient/Proxy and Physician Contact

In order to encourage the collection of the highest quality data possible in the registry, it is preferred that information be collected from patients or their proxies directly. Whenever possible, exposure to a long-acting GLP-1 RA will be verified by the patient's physician.

3.7.4 Registry

The overall background incidence of MTC in the U.S. is ~ 0.2 cases/100,000 person-years. This estimate is based on aggregate data from state cancer registries collected through NAACCR over the past decade. The MTC Registry Consortium intends to identify and collect information for approximately 75% of the incident cases of MTC in the U.S. All cases of MTC identified by the participating state cancer registries will be included in the analyses. Using the data supplied by NAACCR for 2001 through 2005, and assuming the states identified for participation because of the relatively large numbers of cases of MTC based on historical data continue to have similar incidence rates, then approximately 450 cases of MTC will be identified per year for possible inclusion in the case-series registry. The actual number of participating patients may be smaller, based on participation rates by patients and physicians.

3.7.5 Increased Risk Detection

The required number of person-years to detect relative risk ratios from 2.0 to 5.0 by increments of 0.5 is displayed in Appendix G. Sample sizes are calculated using a background rate of 0.2 cases per 100,000 person-years of observation based on the historical data from state cancer registries explained in Section 3.7.4 above and displayed in Appendix A. The sample sizes indicated are for a one-sided significance level of 0.05 and 80% power. Since this study is primarily interested in identifying an MTC rate in excess of the background rate, the alternative hypothesis is a one-sided hypothesis, i.e., that the rate in patients taking a long-acting GLP-1 RA is greater than the background rate. In addition, a one-sided test at the 0.05 level is powered to detect a higher rate if such a rate exists.

3.7.6 Latency

The latency period for the purpose of this project is defined as the time period from initial exposure to any long-acting GLP-1 RAs to a diagnosis of MTC. There is currently no knowledge of the length of this latency period, but this project is expected to address this issue by conducting the surveillance for 15 years beyond the initiation of the observation period or whatever duration is agreed to by each Sponsor and FDA. Appendix H shows a

table that represents the expected number of exposed patients over the study duration. For any given year, the project credits ½ the patients with a total year of exposure or the equivalent of all the patients with ½-year exposure.

3.8 Study Considerations and Limitations

When interpreting ecologic data, disentangling the effects of individual risk factors can be extremely challenging. Therefore, incidence rates of MTC in the U.S. will be monitored through an active surveillance program through state cancer registries. Specifically, the project will examine secular trends before and after the introduction to the U.S. market of long-acting GLP-1 RAs. Two important limitations of this analysis are: (1) a relatively small number of individuals will likely be exposed to long-acting GLP-1 RAs and (2) variation in the background incidence of MTC. To detect an impact of long-acting GLP-1 RAs on the incidence of MTC, even if one or more long-acting GLP-1 RAs were associated with MTC, there would have to be sufficient use of these agents in the population to distinguish an increase in the incidence due to exposure to these agents from typical background fluctuations in the rate of MTC. If the number of people exposed to long-acting GLP-1 RAs is small owing to limited uptake of a product or limited uptake of the class, then the number of exposed cases contributed to the registry will be correspondingly small. Further, the background rate will fluctuate apart from any impact of long-acting GLP-1 RAs. The incidence during the years before the introduction of the first long-acting GLP-1 receptor agonist will provide an indication of the random fluctuations in the background rate. Even small increases above this background fluctuation will be noted and could indicate the introduction of a new risk factor.

In addition, the MTC Registry will examine information obtained from cases about exposure to potential risk factors, including long-acting GLP-1 RAs. Information regarding possible screening techniques introduced due to a concern about a potential increased risk will also be considered, as new screening can lead to an increased incidence through earlier detection of prevalent cases, as opposed to a true increase in occurrence. It is acknowledged, however, owing in part to the rarity of the event (MTC) and the expected number of exposed people, that the registry may be unable to detect an association with long-acting GLP-1 RAs. For this reason, efforts are ongoing including other pharmacovigilance strategies of which this registry is one component.

It should be noted that the case-specific data collected from this registry would not be a total count of all cases of MTC (other than the data collected to monitor overall U.S. incidence) nor a scientific sample from cancer registries. Performing demographic comparisons between cases included and not included may help determine the representativeness of the cases included in the case series (see Section 4, Analysis).

4 Analysis

4.1 All Identified Cases of MTC

Data presented will include the number of patients enrolled in the registry compared to the number of MTC cases reported in the NAACCR database across the entire U.S. population, in order to ensure the inclusion of a significant portion of all incident cases of MTC in the U.S. Data will be captured to evaluate the lag time between the date of cancer diagnoses and inclusion of data into the sentinel databases and the timeliness of subject interviews after diagnosis.

The demographic characteristics of all identified cases of MTC, as well as the cases in the case-series registry, will be summarized using descriptive statistics. Tumor histology, topography, morphology, and method of diagnosis will be described and tabulated for both groups. The characteristics of those cases included in the case-series registry will be compared to the full cohort of cases. Comparisons will be evaluated between the originating registry and the overall NAACCR database through the use of 95% confidence intervals.

Each year NAACCR is provided with the patient IDs for all patients who have consented to participate in the MTC registry, they will provide the MTC data for the MTC cases with the corresponding patient IDs which NAACCR is scheduled to receive in November of the preceding year.

The data to be provided by NAACCR include:

- Date of first MTC Diagnosis
- Gender
- Race
- Age
- Computed Ethnicity
- Spanish / Hispanic Origin
- Primary Site Code
- Topography of Cancer
- Morphology of Cancer Code
- Age at Diagnosis

NAACCR will verify the data provided on cases for which informed consent has been given allowing matching with registries and will provide any missing MTC data that reside in NAACCR files on these cases.

4.2 All Cases in the Case-Series Registry Study

Descriptive statistics will be used to characterize potential risk factors, including drug exposures, radiation exposure, lifestyle factors, environmental exposures, and other characteristics (including family history of MEN syndromes or FMTC history). For patients with diabetes, exposure to long-acting GLP-1 RAs will be characterized by dose and duration of exposure prior to the diagnosis of MTC. For patients with obesity treated with medication for weight management, exposure to a long-acting GLP-1 RA will be characterized by dose and duration of exposure prior to the diagnosis of MTC.

It is expected that because of the association of long-acting GLP-1 RAs with thyroid C-cell abnormalities in studies in rodents, patients taking long-acting GLP-1 RAs will be subject to increased thyroid screening and surveillance (including serum calcitonin measurement, thyroid ultrasound, and thyroid examination) as compared to patients taking other medications for their diabetes or weight management. It is likely that this intensified screening may potentially influence the detection and characteristics of the MTC cases reported in this population. Indeed, enhanced surveillance may result in diagnosis of MTC earlier in the course of its natural history (microcarcinoma) or be based on minimal elevations in serum calcitonin.[15] This hypothesis will be explored in the analysis. In addition, data from other surveillance programs conducted by Sponsors in agreement with FDA could potentially be used to enhance this analysis.

4.3 Sensitivity Analysis

A sensitivity analysis assessing the impact of missing information of potential risk factors, including drug exposures, radiation exposure, lifestyle factors, environmental exposures, and other characteristics will be performed. Details of the sensitivity analysis will be contained in the statistical analysis plan.

5 Ethical, Regulatory, and Administrative Requirements

5.1 Committee/Institutional Review Board Approval

The MTC Registry Document/Project Manual will be approved by the required IRB or Committee prior to any registry activities being initiated by a reporting registry.

5.2 Privacy Protection and Confidentiality

All data collected during the registry will be held in accordance with all applicable privacy laws. Patient names and contact information will be provided to the SCC only after informed consent is obtained by the applicable party, unless the state cancer registry's policy allows

submission of patient data to the SCC which will then obtain patient consent. The electronic data capture (EDC) system used for data collection encrypts all identifiable information and patient identifiers are stored separately from the de-identified patient data. The Sponsors of the MTC Registry Consortium will only receive de-identified information from the MTC registry.

The date of paper destruction is 01 Dec 2041, at which time the Sponsors must be notified ahead of time of the state cancer registries' intent to destroy materials, so documents can be obtained from the state cancer registries, if it is their company policy at that time. This data destruction date is 15 years following 15 Sept 2026 when the final study report is due to FDA or whatever duration is agreed to by each Sponsor and FDA. The Sponsors request that they be notified prior to any project data destruction by the state cancer registry.

5.3 Registry Oversight

A Registry Data Monitoring Committee (RDMC) and Steering Committee are being established and will include clinicians and scientists with expertise in cancer epidemiology, endocrinology (diabetes, thyroid, and obesity), and biostatistics. The MTC Registry Consortium plans to invite representatives from the leadership of the American Thyroid Association and the Endocrine Society to participate on the committees and provide subject-matter expertise for the program. The RDMC will be responsible for performing an on-going and independent evaluation of accumulated data from the MTC registry.

The Steering Committee will be responsible for the scientific leadership of the MTC Registry, and the overall governance of the Registry. The Steering Committee will maintain the scientific integrity of the MTC Registry in alignment with scientific best standards and regulatory needs and in accordance with applicable laws, regulations, and guidelines. The Registry Data Monitoring Committee (RDMC), after review of the data, will make their recommendation (which could include changing the design of the registry to a case-control study if warranted) to each of the sponsors' designated contact and, subsequently to the Steering Committee. The non-Sponsor majority on the Steering Committee will then make their recommendation(s) (which could include the possibility of converting the registry to a case-control study) to the Sponsors. The final decision would be made by the Sponsors after consultation with FDA.

5.4 Regulatory Reporting

Information on the progress of the study will be provided to FDA by the individual Sponsors at the interval agreed upon with FDA after the approval of their respective products. It is assumed that a single report will be provided by each individual sponsor annually for submission to the FDA in addition to responding to any Information Requests; the study will be conducted over a period of 15 years (or whatever duration is agreed to with the FDA by each respective Sponsor) for each approved product, based on the date of their product's FDA approval. Annual reports will contain information about the registry's operation

including participation of state registries, MTC case identification, and patient participation in interviews. The reports will also provide information on long-acting GLP-1 receptor agonist-associated cases and how they were first identified (through the case series registry, as published case reports, or as spontaneously submitted adverse event reports). The reports will include an evaluation of the effectiveness of the registry in meeting the objective of successfully obtaining data for a substantial proportion of the incident cases of MTC in adults in the U.S. A final study report will be provided to the agency within 6 months of the completion of the study.

5.4.1 Safety

Serious Adverse Events (SAEs) and Adverse Events (AEs) that are identified as spontaneous reports as a result of the data collected in the MTC registry will be submitted to Safety Departments of the relevant Sponsor(s) using the standard method of spontaneous SAE and AE reporting. MTC cases reported as AEs in clinical trials or reported spontaneously will be cross-referenced with MTC cases reported in the registry. A separate Adverse Event Reporting Plan will document how adverse events will be handled in the MTC Registry.

5.4.2 Potential Premature Termination of Study

The study could be terminated prematurely at the direction of FDA.

5.5 Publishing

Each participating MTC Registry Consortium Sponsor will be the owner of their product's data collected from the MTC Registry, which will be identified only to that Sponsor with respect to product exposure in a case of MTC. Data regarding another Sponsor's product will be de-identified to all other Sponsor's with respect to product exposure in a case of MTC. The MTC Registry Consortium will establish a uniform procedure for analyzing, publishing, and disseminating findings from this study. The MTC Registry Consortium will submit the MTC Registry Document/Project Manual, information on the overall process, the methodology, the comparative yield of the case series registry and other surveillance methods, and the results of the study for publication in a peer-reviewed medical journal. Co-authors of publications may include participating physicians, MTC Consortium members, members of the Steering Committee, and/or other relevant thought leaders who contribute substantially to the publication. Publications will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines.

6 References

1. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006, based on November 2008 SEER data submission, posted to the SEER web site, 2009.

2. Roman S, Mehta P, and Sosa JA. Medullary Thyroid Cancer: Early Detection and Novel Treatments, Curr Opin Oncol 2008, 21:5-10.

3. Roman S, Lin R, and Sosa JA. Prognosis of Medullary Thyroid Carcinoma: Demographic, Clinical, and pathologic Predictors of Survival in 1252 cases, Cancer 2006, 107:2134-42.

4. North American Association of Central Cancer Registries. Personal Communication. June 2009.

5. Fialkowski EA, Moley JF. Current Approaches to Medullary Thyroid Carcinoma, Sporadic and Familial, J Surg Oncol 2006, 94:737-47.

6. Jiminez C, Min HU, Gagel RF. Management of Medullary Thyroid Carcinoma, Endocrinolo Metab Clin North Am 2008, 481-96.

7. Elisei R, Romei C, Cosci B, et al. RET Genetic Screening in Patients with Medullary Thyroid Cancer and Their Relatives: Experience with 807 Individuals at One center, J Clin Endocrinol Metab 2007, 92:4725-29.

8. Ball DW. Medullary Thyroid Cancer: Monitoring and Therapy. Endocrinol Metab Clin North Am 2007, 36:823-837.

9. Hofstra RMW, Landsvater RM, Ceccherini I, et al. A Mutation in the RET Protooncogene Associated with Multiple Endocrine Neoplasia Type 2B and Sporadic Medullary Thyroid Carcinoma. Nature 1994; 367:375-376.

10. Blaugrund JE, Johns MM, Eby YJ, et al. RET Proto-oncogene Mutations in Inherited and Sporadic Medullary Thyroid Cancer. Hum Mol Genet 1994;3:1895-1897.

11. North American Association of Central Cancer Registries. NAACCR Bibliographies. Retrieved May 13, 2010 from NAACCR website: http://www.naaccr.org/LinkClick.aspx?fileticket=WjJgQcV5Tog%3d&tabid=95&mid=477.

12. North American Association of Central Cancer Registries. Registry Certification. Retrieved May 13, 2010 from NAACCR website: http://www.naaccr.org/LinkClick.aspx?fileticket=vExruQwCdB4%3d&tabid=87&mid=427.

13. North American Association of Central Cancer Registries. Cancer Data Standards. Retrieved May 13, 2010 from NAACCR website: http://www.naaccr.org/Certification/USCert2007.aspx.

14. Amylin Pharmaceuticals: Thinking long-term: Bydureon a likely blockbuster. Deutsche Bank Securities Inc. Global Market Research Report. September 23, 2010. pp 48, 52.

15. Etit D, Faquin WC, Gaz R, Randolph G, DeLellis RA, Pilch BZ, Histopathologic and clinical features of medullary microcarcinoma and C-cell hyperplasia in prophylactic thyroidectomies for medullary thyroid carcinoma: a study of 42 cases, Arch Pathol Lab Med 2008; 132(11):1767-73.

Appendix A: Rates and Frequency Counts of Medullary Thyroid Cancers Among the CINA 2001-2005 US Combined Registries

Rates[1] and Frequency Counts of Medullary Thyroid Cancers[2] Among the CINA 2001-2005 U.S. All Registries Combined and by State.

Registry	Male and Female	
	Rate	Count
United States	0.20	2,375
Alabama*	0.20	43
Alaska	^	^
Arkansas	0.21	30
California	0.17	289
Colorado	0.19	43
Connecticut	0.32	58
Delaware	0.18	8
Florida	0.21	193
Georgia	0.17	72
Hawaii	0.11	7
Idaho	0.25	17
Illinois	0.17	103
Indiana	0.19	61
Iowa	0.19	29
Kentucky	0.21	45
Louisiana*	0.18	36
Maine	0.66	45
Massachusetts	0.22	73
Michigan	0.16	83
Minnesota	0.19	49
Missouri	0.25	72
Montana	0.19	9
Nebraska	0.10	9
Nevada	0.13	16
New Hampshire	0.23	16
New Jersey	0.22	99
New Mexico	0.14	13
New York	0.27	264
North Dakota	^	^
Oklahoma	0.14	25
Oregon	0.17	31

Registry	Male and Female	
	Rate	Count
Pennsylvania	0.25	168
Rhode Island	0.29	16
South Carolina	0.16	34
South Dakota	^	^
Texas*	0.21	193
Utah	0.29	27
Washington	0.19	61
West Virginia	0.28	27
Wyoming	^	^

Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.
^Statistic not displayed due to fewer than 5 cases.
*Rates and counts for Alabama, Louisiana, and Texas are based on data from 2001 through June 2005 because of Hurricanes Katrina/Rita
[1]SEER*Stat File Citation: NAACCR Incidence - CINA Analytic File, 1995-2005, for Expanded Races, Standard File, North American Association of Central Cancer Registries.
[2] Medullary Thyroid Cancers Defined as (Malignant Cases): Primary Site C73.9 and the following histologies:
8345 Medullary carcinoma with amyloid stroma (C73.9) Med
8346 Mixed medullary-follicular carcinoma (C73.9) Med
8347 Mixed medullary-papillary carcinoma (C73.9) Med
8510 Medullary carcinoma, NOS Med
8512 Medullary carcinoma with lymphoid stroma Med
8513 Atypical medullary carcinoma (C50._) Med
Data obtained from NAACCR June 2009

CINA= Cancer in North America

Appendix B: Rates and Frequency Counts of Medullary Thyroid Cancers 2005-2009 NAACCR Call For Data Analysis 2005-2009 US Combined Registries

2005-2009 NAACCR Call For Data Analysis[1]
2005-2009 Rates and Frequency Counts of Medullary Thyroid Cancers[2]

Registry	Male and Female	
	Rate	Count
United States	0.24	3,417
Alabama*	0.21	48
Alaska	0.23	8
Arizona	0.21	69
California	0.21	366
Colorado	0.22	51
Connecticut	0.36	67
Delaware	0.12	6
Florida	0.21	212
Georgia	0.23	103
Hawaii	0.12	8
Idaho	0.27	20
Illinois	0.21	140
Indiana	0.17	56
Iowa	0.19	30
Kentucky	0.26	56
Louisiana*	0.22	44
Maine	0.41	30
Maryland	0.21	63
Massachusetts	0.36	126
Michigan	0.19	101
Minnesota	0.25	68
Mississippi*	0.16	21
Missouri	0.32	100
Montana	0.31	17
Nebraska	0.24	24
Nevada	0.19	26
New Hampshire	0.28	20
New Jersey	0.25	117
New Mexico	0.29	28
New York	0.29	303
North Carolina	0.23	109

Registry	Male and Female	
	Rate	Count
United States	0.24	3,417
North Dakota	0.22	7
Ohio	0.21	136
Oklahoma	0.22	42
Oregon	0.21	42
Pennsylvania	0.28	194
Rhode Island	0.38	21
South Carolina	0.25	57
South Dakota	0.12	5
Tennessee	0.26	84
Texas*	0.23	229
Utah	0.24	26
Washington	0.18	65
West Virginia	0.27	29
Wyoming	^	^

Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.

^Statistic not displayed due to fewer than 5 cases.

*Rates and Counts for Alabama, Louisiana, Mississippi and Texas exclude data from July 2005 through December 2005 because of Hurricanes Katrina/Rita.

[1]SEER*Stat File Citation: NAACCR Incidence - CINA Analytic File, 1995-2009, for Expanded Races, Standard File - Vintage 2009 Populations, North American Association of Central Cancer Registries.

[2]Medullary Thyroid Cancers Defined as (Malignant Cases): Primary Site C73.9 and The following histologies:
8345 Medullary carcinoma with amyloid stroma (C73.9) Med
8346 Mixed medullary-follicular carcinoma (C73.9) Med
8347 Mixed medullary-papillary carcinoma (C73.9) Med
8510 Medullary carcinoma, NOS Med
8512 Medullary carcinoma with lymphoid stroma Med
8513 Atypical medullary carcinoma (C50._) Med

http://web2.facs.org/cstage0205/thyroid/Thyroid_xce.html

Data obtained from NAACCR May 29, 2012

Appendix C: Estimated Incident Cases of Medullary Thyroid Cancer in Remaining States

Estimated Incident Cases of Medullary Thyroid Carcinoma in Remaining Ten States 2001-2005[1]

State	Population	# Cases Expected
Arizona	6,500,180	65
Kansas	2,802,134	28
Maryland	5,633,597	56
Mississippi	2,938,618	29
North Carolina	9,222,414	92
Ohio	11,485,910	115
Tennessee	6,214,888	62
Vermont	621,270	6
Virginia	7,769,089	78
Wisconsin	5,627,967	56
Total :		587

[1] Crude estimate of state rates determined by multiplying state population X 0.2/100,000 PYs X 5 (not age-adjusted)

In order to be included in the NAACCR Cancer in North America (CINA) analysis, states have to meet standards for certification, meet the submission deadlines, and agree to have their data included.

Appendix D: Estimated Incident Cases of Medullary Thyroid Cancer in Remaining States

Estimated Incident Cases of Medullary Thyroid Carcinoma in Remaining States 2005-2009[1]

State	Population	# Cases Expected
Kansas	2,802,134	28
Vermont	621,270	6
Virginia	7,769,089	78
Wisconsin	5,627,967	56
Total :		168

[1] Crude estimates of state rates determined by multiplying state population X 0.2/100,000 PYs X 5 (not age-adjusted)

In order to be included in the NAACCR CINA analysis, states have to meet standards for certification, meet the submission deadlines, and agree to have their data included.

Appendix E: List of Abbreviations

AACE	American Association of Clinical Endocrinology
AE	Adverse Event
AUC	Area Under Curve
BMI	Body Mass Index
CINA	Cancer in North America
DPP	Dipeptidyl peptidase
EAC	Event Adjudication Committee
EDC	Electronic Data Capture
EQW	Exenatide Once Weekly
FDA	Food and Drug Administration
FMTC	Familial Medullary Thyroid Carcinoma
GLP-1	Glucagon-like peptide 1
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
ICD-O	International Classification of Diseases for Oncology
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
MEN2A	Multiple endocrine neoplasia syndrome 2A
MEN2B	Multiple endocrine neoplasia syndrome 2B
MRHD	Maximum Recommended Human Dose
MTC	Medullary thyroid cancer
NAACCR	North American Association of Central Cancer Registries
NDA	New Drug Application

NOS	Not Otherwise Specified
RDMC	Registry Data Monitoring Committee
RET	Ret proto-oncogene
SAE	Serious Adverse Event
SCC	Study Coordinating Center
SEER	Surveillance, Epidemiology and End Results Program
SOPs	Standard Operating Procedures
T2DM	Type 2 Diabetes Mellitus
UBC	United BioSource Corporation
ULN	Upper Limit of Normal
U.S.	United States

Appendix F: Background from GLP-1 Receptor Agonists Development Programs

F.1 Background of Preclinical Development Programs

F.1.1 Liraglutide

***Liraglutide (T2DM)*:** A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Human relevance of thyroid C-cell tumors in mice and rats is unknown and could not be determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)].[1]

Liraglutide (weight management): A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1, and 3 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 43-times the

[1] US Prescribing Information, Version 10 for Victoza®, NDA 022341.

exposure in obese humans, respectively, at the maximum recommended human dose (MRHD) of 3 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1 and the 3 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 7-times the exposure in obese humans, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the Rearranged during Transfection (RET) proto-oncogene in thyroid C-cells. Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)].[2]

F.1.2 Exenatide extended-release aqueous and lipid based injectable suspension

A 104-week carcinogenicity study was conducted with exenatide extended-release in aqueous suspension (Bydureon) in male and female rats at doses of 0.3, 1.0, and 3.0 mg/kg (2-, 9-, and 26 times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. These doses correspond to 2.4-fold (low dose), 23-fold (mid dose), and 74-fold (high dose) the human systemic exposure with exenatide extended-release lipid suspension (Bydureon BCise), based on AUC. A statistically significant increase in thyroid C cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27%-31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically

[2] US Prescribing Information, Version 4 for Saxenda®, NDA 206321.

significantly higher incidence of C-cell carcinomas occurred in the high-dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (non-statistically significant versus controls) were noted in the low-, mid-, and high-dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection-site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown, [see Boxed Warning and Warnings and Precautions (5.1)].[3, 4]

F.1.3 Dulaglutide

A 2-year carcinogenicity study was conducted with dulaglutide in male and female rats at doses of 0.05, 0.5, 1.5 and 5.0 mg/kg (0.2-, 3-, 8- and 24-fold the MRHD of 4.5 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. In rats, dulaglutide caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) compared to controls, at ≥3-fold the MRHD based on AUC. A statistically significant increase in C-cell adenomas was observed in rats receiving dulaglutide at ≥0.5 mg/kg. Numerical increases in thyroid C-cell carcinomas occurred at 5 mg/kg (24 times the MRHD based on AUC) and were considered to be treatment-related despite the absence of statistical significance.[5]

A 6-month carcinogenicity study was conducted with dulaglutide in rasH2 transgenic mice at doses of 0.3, 1.0, and 3.0 mg/kg administered by subcutaneous injection twice weekly. Dulaglutide did not produce increased incidences of thyroid C-cell hyperplasia or neoplasia at any dose.[5]

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies.[5]

F.1.4 Semaglutide s.c.

***Semaglutide (T2DM)*:** In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [5-, 17-, and 59-fold the maximum recommended human dose (MRHD) of 1 mg/week, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (2-, 5-, and 17-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (>2X human exposure).[6]

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.4-, 1-, and 6-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in

[3] US Prescribing Information, Revised April 2018 for Bydureon®, NDA 022200.
[4] US Prescribing Information, Revised October 2017 for Bydureon® Bcise, NDA 209210.
[5] US Prescribing Information, Revised 03 September 2020 for Trulicity®, BLA 125469.
[6] US Prescribing Information, Version 1 for Ozempic®, NDA 209637.

thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, at clinically relevant exposures.[6]

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies [see Boxed Warning and Warnings and Precautions (5.1)].[6]

***Semaglutide (weight management)*:** In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day (2-, 8-, and 22- fold the maximum recommended human dose [MRHD] of 2.4 mg/week, based on AUC) were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (0.6-, 2-, and 5-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (greater than or equal to 0.6 times human exposure).

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.2-, 0.4-, and 2-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at greater than or equal to 0.01 mg/kg/day, at clinically relevant exposures.[7]

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

F.1.5 Semaglutide tablets

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [9-, 33-, and 113-fold the maximum recommended human dose (MRHD) of RYBELSUS 14 mg, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (3-, 9-, and 33-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (>3X human exposure).[6]

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.8-, 1.8-, and 11-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, at clinically relevant exposures.[6]

[7] US Prescribing Information, Version 1 for Wegovy™, NDA 215256

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies [*see Boxed Warning and Warnings and Precautions (5.1)*].[8]

F.2 Background of Clinical Development Programs

F.2.1 Liraglutide

Liraglutide (T2DM)*:* Because of the changes observed in rodents, including a liraglutide-induced increase in serum calcitonin that preceded pathologic changes to the C-cell, serum calcitonin was monitored as a biomarker of C-cell pathology in the clinical development program that involved more than 5,000 subjects over a period of up to 2 years' exposure to liraglutide. The mean calcitonin levels were in the lower part of the normal range across all groups throughout the treatment period, with no consistent dose-dependent or time-dependent differences between liraglutide and the active comparator group. Additionally, there was no difference in the proportion of outliers (those subjects who had a shift in calcitonin value to levels ≥ 2 X the upper limit of normal) across treatment groups.

In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza and one non-Victoza-treated patient developed elevated calcitonin concentrations while on treatment.[1]

Liraglutide (weight management): In Saxenda® clinical trials, papillary thyroid carcinoma confirmed by adjudication was reported in 7 (0.2%) of 3291 Saxenda®-treated patients compared with no cases among 1843 placebo-treated patients. Four of these papillary thyroid carcinomas were less than 1 cm in greatest diameter and 4 were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings identified prior to treatment. One MTC case occurred in a placebo patient shortly after randomization.

Calcitonin was monitored as a biomarker of C-cell pathology in the clinical development program of liraglutide 3.0 mg for weight management that involved more than 5500 overweight or obese subjects exposed for 56 weeks. Although the clinical significance of calcitonin fluctuations below 50 ng/L in patients without MTC is unknown, all confirmed cases of elevated calcitonin concentration (≥ 20 ng/L) were subject to ongoing blinded review by an independent external group of thyroid experts.

More patients treated with Saxenda® in the clinical trials were observed to have high calcitonin values during treatment, compared with placebo. The proportion of patients with calcitonin greater than or equal to 2 times the upper limit of normal at the end of the trial was

[8] US Prescribing Information, Version 1 for Rybelsus®, NDA 213051.

1.2% in Saxenda®-treated patients and 0.6% in placebo-treated patients. Calcitonin values greater than 20 ng/L at the end of the trial occurred in 0.5% of Saxenda®-treated patients and 0.2% of placebo-treated patients; among patients with pre- treatment serum calcitonin less than 20 ng/L, none had calcitonin elevations to greater than 50 ng/L at the end of the trial.

F.2.2 Exenatide extended-release aqueous and lipid based injectable suspension

Serum calcitonin was monitored as a biomarker of C-cell pathology in a subset of patients in the clinical development program for both exenatide extended-release aqueous and lipid suspensions. There were no clinically meaningful changes in calcitonin concentrations with exenatide once weekly therapy or active comparators within the treatment durations evaluated (up to 84 weeks). Mean calcitonin concentrations remained within the normal range during treatment with EQW or non-exenatide comparators, with no meaningful changes from baseline and no apparent differences between the treatment groups.[3,4]

F.2.3 Dulaglutide

Serum calcitonin was serially measured in patients in the initial Phase 2 and Phase 3 clinical development program. Treatment with dulaglutide was not associated with mean increases in serum calcitonin. A similar proportion of patients treated with placebo (0.4%) or dulaglutide (0.7%) had any treatment emergent serum calcitonin ≥ 20 pg/ml. Only 7 patients across the initial development program (N=6005) had post-baseline values for serum calcitonin ≥35 pg/ml. These cases were characterized by elevated baseline calcitonin levels, pre-existing thyroid disorders or single elevations in calcitonin. Across the Phase 2 and Phase 3 development program there has been one case of MTC identified in a patient treated with dulaglutide. This patient had baseline calcitonin values ~ 8 times the ULN and was subsequently found to have a RET proto-oncogene germline mutation, consistent with pre-existing disease. Results from studies with calcitonin monitoring conducted following the original Phase 2/3 development program have been consistent with the initial development studies.

F.2.4 Semaglutide s.c.

***Semaglutide (T2DM)*:** Calcitonin was monitored as a biomarker of C-cell pathology in the clinical development program of semaglutide for type 2 diabetes. Treatment with semaglutide was not associated with mean increases in serum calcitonin. Across the cardiovascular outcomes trial and phase 3a glycemic control trials, a small proportion of subjects had post-baseline events of calcitonin ≥20 ng/L both with semaglutide, placebo and pooled comparators. Proportion of subjects with post-baseline calcitonin levels >ULN, >20 ng/mL, >50 ng/L and >100 ng/L were comparable with semaglutide, placebo and pooled comparators. In the cardiovascular outcomes trial, 2 subjects in the semaglutide 0.5 mg group had post-baseline calcitonin levels above 100 ng/L at 1 or more occasions during the trial. Neither of the subjects had thyroid events. No cases of MTC were reported with semaglutide in the phase 3a glycemic control trials or cardiovascular outcomes trial.

***Semaglutide (weight management)*:**

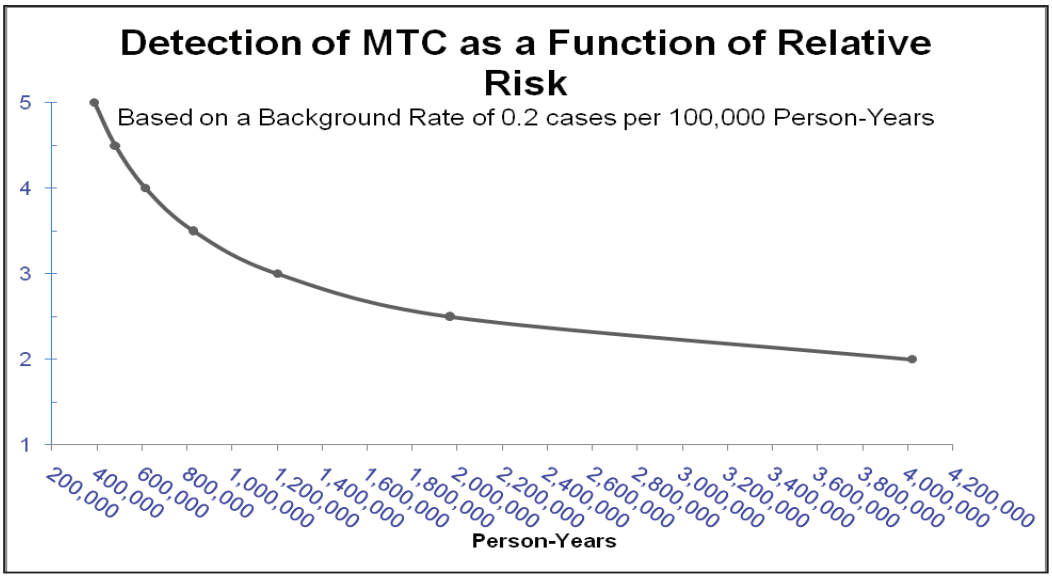
Calcitonin was monitored as a biomarker of C-cell pathology in the clinical development program of semaglutide injection for weight management. In the phase 3a dose escalation group, calcitonin levels were higher for males than for females. The central tendencies were stable over time showing only minor fluctuations with no differences between semaglutide 2.4 mg and placebo. The ratio to baseline levels of serum calcitonin at the end-of-treatment visit were similar for semaglutide 2.4 mg and placebo.

No events of MTC were reported in the phase 3a semaglutide injection for weight management. In the phase 3a dose escalation group, one subject had elevated calcitonin values of >50 ng/L at screening. No subjects had elevated calcitonin values of >100 ng/L.

F.2.5 Semaglutide tablets

Calcitonin was monitored as a biomarker of C-cell pathology in the clinical development program of semaglutide tablets for type 2 diabetes. Ratio to baseline levels of serum calcitonin were stable over time and similar with semaglutide tablets, active comparator and placebo at the end of treatment with increases of ≤1% with semaglutide tablets and increases of ≤3% with comparator/placebo. A similar proportion of subjects treated with semaglutide tablets and active comparator/placebo (9.2% vs 9.0%) or semaglutide tablets and placebo (9.4% vs 8.9%) had maximum post-baseline calcitonin levels >ULN, and no subjects with semaglutide tablets had maximum post-baseline calcitonin levels >100 ng/mL. With semaglutide tablets and active comparators/placebo, maximum post-baseline calcitonin levels >50 ng/mL were present in 0.2% vs <0.1% of subjects, respectively. There was no indication of a dose-response with semaglutide tablets in the proportion of subjects with maximum post-baseline calcitonin levels in the 78-week long-term safety trial or in other trials evaluating dose response. In the cardiovascular outcomes trial of semaglutide tablets versus placebo, both on a background of standard of care, mean levels of calcitonin were stable over time and similar in the two treatment groups. There were no events of MTC in any of the Phase 3a pool trials; one event of medullary thyroid microcarcinoma was reported in the cardiovascular outcomes trial in a subject treated with semaglutide tablets; this subject had been diagnosed with thyroid nodules approximately 1 year before enterring the trial and had elevated calcitonin levels at baseline (30 ng/mL).

Appendix G: Increased Risk Detection



Required Number of Person-years of GLP-1 receptor agonist exposure to Detect Relative Risk Ratios

Appendix H: Estimated GLP-1 Agonist Exposure

Calendar Year /Study Year	New Patients on GLP-1 Receptor Agonists	Expected Cumulative Number of Patients for Follow-up	Expected Number of Years of Follow-up for These Exposed Patients
2010/1	50,000	25,000	15
2011/2	403,000	251,500	14
2012/3	480,000	693,000	13
2013/4	570,000	1,218,000	12
2014/5	678,000	1,842,000	11
2015/6	780,000	2,571,000	10
2016/7	835,000	3,378,500	9
2017/8	960,000	4,276,000	8
2018/9	1,040,000	5,276,000	7
2019/10	1,120,000	6,356,000	6
2020/11	1,200,000	7,516,000	5
2021/12	1,351,000	8,791,500	4
2022/13	1,453,000	10,193,500	3
2023/14	1,555,000	11,697,500	2
2024/15	1,657,000	13,303,500	1

The data presented in the table are derived based on published predictions of current and future long-acting GLP-1 RA usage.[14]

Appendix I: Registry/Project Manual Approval Form

Approval of MTC registry document/project manual version 8.0

PPD

Clinical Development and
Research-Diabetes
Clinical Development, Medical and
Regulatory Affairs
Novo Nordisk Inc.

Signature and Date PPD

PPD

Clinical Development and
Research
Clinical Development, Medical and
Regulatory Affairs
Novo Nordisk Inc.

Signature and Date PPD

Responsible AstraZeneca Pharmaceuticals LP:

PPD

Pharmacovigilance Excellence
AstraZeneca R&D

Signature and Date PPD

Responsible Eli Lilly and Company:

PPD

Lilly Diabetes
Eli Lilly and Company

Signature and Date

PPD

Appendix J: MTC Consortium Sponsors

Novo Nordisk, Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

AstraZeneca AB
C/O AstraZeneca Pharmaceuticals LP
1 MedImmune Way
Gaithersburg, MD 20878

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DocuSign

Certificate Of Completion

Envelope Id: CDE9503ADEE84D49A10E782AAF54D1F8
Status: Completed
Subject: Please DocuSign: MTC Case Series Registry Protocol_v8.0 dated 03Feb2022_FINAL-revised.pdf
Source Envelope:
Document Pages: 45
Signatures: 6
Envelope Originator:
Certificate Pages: 3
Initials: 0
PPD
AutoNav: Enabled
PPD
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
2/14/2022 3:48:52 PM
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	PPD I approve this document I approve this document	Sent: 2/14/2022 4:07:19 PM Viewed: 2/16/2022 9:28:48 AM Signed: 2/16/2022 9:29:57 AM
Electronic Record and Signature Disclosure: Accepted: 2/16/2022 9:28:48 AM PPD		
PPD Security Level: Email, Account Authentication (Required)	PPD PPD PPD I approve this document I approve this document	Sent: 2/14/2022 4:07:20 PM Viewed: 2/15/2022 4:56:02 AM Signed: 2/15/2022 4:57:05 AM
Electronic Record and Signature Disclosure: Accepted: 2/15/2022 4:56:02 AM PPD		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	 I approve this document	Sent: 2/14/2022 4:07:22 PM Viewed: 2/15/2022 12:21:51 PM Signed: 2/15/2022 12:22:27 PM

Electronic Record and Signature Disclosure:
Accepted: 2/15/2022 12:21:51 PM
PPD

PPD Security Level: Email, Account Authentication (Required)	 I approve this document	Sent: 2/14/2022 4:07:21 PM Viewed: 2/15/2022 2:20:21 PM Signed: 2/15/2022 2:22:32 PM

Electronic Record and Signature Disclosure:
Accepted: 2/15/2022 2:20:21 PM
PPD

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	2/14/2022 4:07:22 PM
Certified Delivered	Security Checked	2/15/2022 2:20:21 PM
Signing Complete	Security Checked	2/15/2022 2:22:32 PM
Completed	Security Checked	2/16/2022 9:29:57 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Electronic Record and Signature Disclosure created on: 1/30/2020 11:41:39 PM
Parties agreed to: PPD

I hereby consent to that AstraZeneca Worldwide https://www.astrazeneca.com may disclose personal information such as; full name, email address, and any other information you may supply on the electronic form to AstraZeneca affiliates and third party service providers throughout the world in relation to the handling and administration of the Electronic Signature Service solution. This consent relates to any electronic records or signatures associated with the electronic contract.
AstraZeneca and the third party administering this service store and process personal information that AstraZeneca collects from you for the purposes of operating the Electronic Signature Service solution.
This also applies after termination of the Agreement. Processing of your personal information will be done in accordance with applicable law.
You may request access to your personal data and withdraw agreement to this processing at any time by contacting us in writing at PPD .
Personal details and electronic signatures of signatories contained in contracts cannot be removed once the contract has been executed and will remain part of such contracts until these are destroyed in accordance with applicable law and AstraZeneca internal data retention policies.