EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)
Clinical Study Protocol D5551C00003, BCB109

A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Phase 3b/4

Original Protocol:	24 December 2009
Amendment 01:	11 November 2010
Amendment 02:	10 May 2011
Amendment 03:	23 April 2012
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Amendment 06	09 March 2016

Protocol Approved By:

PPD

13-Jun-2016

Stephanie Gustavson, MD, PhD — Date

Director - CVMD Global Medicines Department

PPD

IND Number: 67,092

EUDRACT: 2010-021069-63

SPONSOR:

Amylin Pharmaceuticals, LLC (a wholly owned subsidiary of AstraZeneca)

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Wilmington, Delaware 19897-0001

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Amylin Pharmaceuticals, LLC sponsors the Investigational New Drug Application

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PROTOCOL AMENDMENT 06: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol D5551C00003, BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **D5551C00003, BCB109**

Amendment Number: **06**

Amendment Purpose: **Date: 09 March 2016**

The purpose of this non-substantial amendment is two-fold:

1. to update the protocol based on US Food and Drug Administration (FDA) recommendation for the study analysis, and
2. to update the procedures for handling all Clinical Events (as defined in Protocol Appendix 1) to be consistent throughout the study.

As per the protocol, the EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events (confirmed cardiovascular-related death, nonfatal myocardial infarction or nonfatal stroke) and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). The primary statistical analysis was initially planned to include all adjudicated cardiovascular events with onset dates up to and including the primary endpoint event cut-off date. As per FDA recommendation, the primary statistical analysis has been updated to include all adjudicated primary endpoint events with onset dates up to and including the Trial Termination Visit date (rather than the primary endpoint event cut-off date). Any events occurring between the Trial Termination Visit and the safety follow-up phone call (scheduled 70 days after last dose of study medication) will not be adjudicated and will not be included in the primary analysis, as agreed by the FDA. The FDA also made recommendations for updating the censoring strategy, which has been incorporated in the protocol amendment.

The procedure for serious adverse event (SAE) reporting described in Protocol Section 10.3.1 and Protocol Appendix 1 will be updated to reflect that Clinical Events (as defined in Protocol Appendix 1) occurring after the primary endpoint event cut-off date (e.g., during either the time period up to the Trial Termination Visit or during the safety follow-up period) will continue to be collected and reported in the same way as they have been throughout the study. There will be no switch to collecting and managing Clinical Events as SAEs after the primary endpoint cut-off date as previously described in the protocol.

This amendment will also address administrative changes in the study.

Administrative Changes:

- To inform that as of January 2015, the EXSCEL Executive Committee co-chair, PPD , has been replaced by PPD
- To inform that while Amylin LLC remains the sponsor for the study, as of 1 February 2014, Amylin LLC is wholly owned by AstraZeneca.
- To inform that as part of the ownership transfer of Amylin, a new study code D5551C00003 was generated to comply with AstraZeneca internal procedures. Trial reference codes H80-MC-GWDQ, BCB109 and D5551C00003 refer to the same clinical study, known as EXSCEL.

In the table below, the changes in individual sections are presented in the revised text with all deletions addressed as a strikethrough and all additions shown in bold.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
3 Trial Governance	EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of Bristol-Myers Squibb. EXSCEL will be Co-Chaired by PPD and sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired PPD	EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of **AstraZeneca** ~~Bristol-Myers Squibb~~. EXSCEL will be Co-Chaired by PPD sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by PPD
4.1 Design Description Paragraph 2	Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued); all patients will be expected to have follow-up through this date (see Section 6).	Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). **Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established**; all patients will be expected to have follow-up ~~through this date~~ **until the Trial Termination Visit** (see Section 6).

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
4.2 Trial Duration	It is anticipated that enrollment will occur over approximately a five year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the data cut-off date for primary endpoint events.	It is anticipated that enrollment will occur over approximately a ~~five~~ **5-**year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the **Trial Termination Visit** ~~data cut-off date for primary endpoint events~~.
6.1 Trial Procedures - Overview	Paragraph 3: The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued; all patients will be expected to have follow-up through this date). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established.	Paragraph 3: The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued)~~ all patients will be expected to have follow-up through this date)~~. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. **All patients will be expected to have follow-up until this visit.**

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
	Paragraphs 5 and 6: After the Trial Termination Visit patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the telephone contact visit performed. These patients will have their final assessment of serious adverse experiences and hospitalizations completed at the Trial Termination Visit. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	Paragraphs 5 and 6: After the Trial Termination Visit patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. **Note that any events occurring between the Trial Termination Visit and the safety follow-up phone call will not be adjudicated and will not be included in the primary analysis**. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the **safety follow-up** telephone contact visit performed. These patients will have their final assessment of **Clinical Events**, serious adverse experiences and hospitalizations completed at the Trial Termination Visit. **Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date)** ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
6.13 Trial Termination Visit	Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. …. If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the primary endpoint event cut-off date.	Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. **All patients will be expected to have follow-up until this visit.** At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. …. If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the **Trial Termination Visit** ~~primary endpoint event cut-off date~~.
6.14 Post-Treatment Telephone Contact	After the Trial Termination Visit, patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Note that all serious adverse experiences, hospitalizations, and reportable study events with an *onset* date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	After the Trial Termination Visit, patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. **Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date)** ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an *onset* date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).
8.3 Additional Efficacy Endpoints	• Number of episodes of severe hypoglycemia requiring medical assistance.	• ~~Number of episodes of severe hypoglycemia requiring medical assistance.~~

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.5 Primary Analysis	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e.* until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). All patients will be expected to have follow-up through this date. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the primary endpoint event cut-off date.	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e.* **the Trial Termination Visit and** until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). **Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established.** All patients will be expected to have follow-up ~~through this date~~ **until this visit**. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date. **Note that any event occurring between the Trial Termination Visit and the safety follow-up date (70 days after the administration of the last dose of trial medication) will not be adjudicated and will not be included in the primary analysis. Events occurring during this period will be summarized descriptively.**
9.7.1 Intent-To-Treat Population	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the primary endpoint event cut-off date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the primary endpoint event cut-off date. Every effort will be made to collect CV events through the primary endpoint event cut-off date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date. Every effort will be made to collect CV events ~~through~~ **until** the **Trial Termination Visit** ~~primary endpoint event cut-off date~~ even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.7.1.1 On-Treatment Analysis	An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred within 70 days of the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized.	An on-treatment analysis using the ITT population will be performed for the primary and some secondary endpoints as sensitivity analyses. This analysis will include only those events that occurred **through** ~~within 70 days of~~ the last dose of study medication or the **Trial Termination Visit** ~~primary endpoint event cutoff~~ date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. **The on-treatment censoring scheme will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.**
9.7.2 Per-Protocol Population	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or primary endpoint event cut-off date, whichever occurs first), such as: • Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first.	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or **the Trial Termination Visit** ~~primary endpoint event cut-off~~ date, whichever occurs first), such as: • Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the **Trial Termination Visit** ~~primary endpoint event cut-off~~ date, whichever occurs first.
9.8 Safety Data Analysis	Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed and tabulated by high level group terms (HGLT), as assigned by the MedDRA dictionary.	Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed and tabulated **as described in the SAP** ~~by high level group terms (HGLT), as assigned by the MedDRA dictionary~~.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.9 Subgroup Analyses	Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed: • Class of AHA therapy at entry (mono or combination) • Race (Black, Caucasian, Asian, Other) • Region (North/South America, Europe or South Africa, Rest of world) • Gender (Male, Female) • Age (<65 or ≥65) • Baseline HbA1c (<8.0% or ≥8/0%) • Baseline BMI (<30 or ≥30 kg/m^2) • Duration of diabetes (<5 years or ≥5 years) • Baseline eGFR (<60 mL/min or ≥60 mL/min) • History of previous cardiovascular event (e.g., previous MI or stroke)	Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed: • Class of AHA therapy at entry (mono or combination) • Race (**Indian [American] or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Hispanic, Other** ~~(Black, Caucasian, Asian, Other~~) • **Geographic** region (**North America, Latin America, Europe and Asia Pacific)** (~~North/South America, Europe or South Africa, Rest of world~~) • Gender (Male, Female) • Age (<65 or ≥65) • Baseline HbA1c (<8.0% or ≥8.0%) • Baseline BMI (<30 or ≥30 kg/m^2) • Duration of diabetes (<5, **5-14, ≥15 years** ~~or ≥5 years~~) • **eGFR groups (in mL/min/1.73 m^2)** – **(<60 or ≥60)** – **Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15** ~~Baseline eGFR (<60 mL/min or ≥60 mL/min)~~ • History of previous cardiovascular event (e.g., previous MI or stroke)

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
9.11 Economic Analysis	The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient. Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care vs. usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol.	The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient. Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care vs. usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol. **For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment.**

<table>
<tr><th>SECTION</th><th>AMENDMENT 05 TEXT</th><th>AMENDMENT 06 TEXT</th></tr>
<tr><td>10.3.1 Recording Adverse Events</td><td>SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) through the primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

<table>
<tr><th>Table 1</th><th>List of events to be recorded in each eCRF reporting module*</th></tr>
<tr><td>eCRF reporting module to be used</td><td>List of events to be recorded in this eCRF reporting module:</td></tr>
<tr><td>Clinical Event eCRF (events with onset date up to and including the primary endpoint event cut-off date)</td><td>- Clinical Events that meet the criteria of an SAE (i.e. serious adverse event) and are listed in Appendix 1
- All non-serious (or serious) events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminuria, hyperlipidemia/dyslipidemia, hypertension, or gout
- All neoplasia events
- All pancreatitis events</td></tr>
<tr><td>SAE eCRF</td><td>- Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are <u>not</u> listed in Appendix 1 and all events above with an onset date after the primary endpoint event cut-off date
- All episodes of pancreatitis
- All episodes of any type of neoplasia/cancer
- Any AE or SAE resulting from an overdose of study drug
- Any event that is recorded in the Clinical Event eCRF, that the investigator considers a SUSAR, with the exception of possible Primary or Secondary trial endpoints (i.e. all events listed in Appendix 1, Section I)</td></tr>
<tr><td colspan="2">* Trial sites will be provided with an ‘EXSCEL Event Reporting’ flow chart that can be referenced to help identify which events should be reported in which eCRF reporting module.</td></tr>
</table></td><td>SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) throughout the trial (including the 70 day safety wash-out period after last dose of study medication) <s>through primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module</s>. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

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- All non-serious (or serious) events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminuria, hyperlipidemia/dyslipidemia, hypertension, or gout
- All neoplasia events
- All pancreatitis events</td></tr>
<tr><td>SAE eCRF</td><td>- Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are <u>not</u> listed in Appendix 1 <s>and all events above with an onset date after the primary endpoint event cut-off date</s>
- All episodes of pancreatitis
- All episodes of any type of neoplasia/cancer
- Any AE or SAE resulting from an overdose of study drug
- Any event that is recorded in the Clinical Event eCRF, that the investigator considers a SUSAR, with the exception of possible Primary or Secondary trial endpoints (i.e. all events listed in Appendix 1, Section I)</td></tr>
<tr><td colspan="2">* Trial sites will be provided with an ‘EXSCEL Event Reporting’ flow chart that can be referenced to help identify which events should be reported in which eCRF reporting module.</td></tr>
</table></td></tr>
</table>

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
10.3.2 Safety Reporting	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List and "Clinical Events" with onset dates after the primary endpoint event cut-off date will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. **This will be applicable throughout the duration of trial including the 70 day wash-out period**. **There will be no switch to collecting and reporting Clinical Events as SAEs. Thus, the exemption from routine SAE reporting of events listed in Protocol Appendix 1 will remain for the entire trial duration, including the safety wash-out phase.** In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List ~~and "Clinical Events" with onset dates after the primary endpoint event cut-off date~~ will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.

SECTION	AMENDMENT 05 TEXT	AMENDMENT 06 TEXT
12.1 Executive Committee (EC)	The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be P -PPD n EC charter will outline the committee membership and structure and delineate operating procedures.	The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be PPD . An EC charter will outline the committee membership and structure and delineate operating procedures.
Appendix 2 TRIAL PLAN (PROTOCOL BCB109)	Table 1 Footnote 9: [9] Patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).	Table 1 Footnote 9: [9] Patients will be contacted by telephone to check for any **Clinical Events**, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. ~~Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences~~ (see Section 10.3.1).

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AE	Adverse Event
AHA	Antihyperglycemic agent
Amylin	Amylin Pharmaceuticals, LLC
ARO	Academic Research Organization
BP	Blood Pressure
CEC	Clinical Events Committee
CHF	Congestive heart failure
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
DTU	Diabetes Trials Unit
EC	Executive Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQW	Exenatide once weekly
EQ-5D	EuroQol 5 Dimensions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	Hemoglobin A1c
HLGT	High level group term
IFU	Instructions for use
IRB	Institutional Review Board
ITT	Intent-to-Treat
MDRD	Modification of Diet in Renal Disease Study Group method for eGFR
MI	Myocardial infarction
OC	Operations Committee
PCI	Percutaneous coronary intervention
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
UKPDS	United Kingdom Prospective Diabetes Study

CLINICAL STUDY PROTOCOL

1 INTRODUCTION

1.1 Background

Type 2 diabetes mellitus is a leading public health issue. Often regarded as a mild disease, it is the fourth leading cause of death in developed countries and the number of people worldwide with diabetes is predicted to exceed 300 million by the year 2025.[1] Diabetes remains the leading cause of blindness, end stage renal disease, and lower extremity amputations and confers a two to four times greater risk of heart disease and strokes.

The majority of people with type 2 diabetes mellitus (T2DM) die as a result of cardiovascular disease (CVD). Epidemiological analysis of UKPDS data from patients with newly-diagnosed T2DM showed that potentially modifiable risk factors for CVD were a raised LDL cholesterol, a low HDL cholesterol, hyperglycemia, hypertension, and smoking.[2] Elevated glucose levels were also the major determinant of microvascular complications. A number of trials in people with T2DM have shown that their CVD risk can be reduced by lowering LDL cholesterol,[3,4] blood pressure,[5,6] glycated hemoglobin,[7,8] or all three risk factors.[9]

1.2 Rationale for Conduct of the Study

Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials[10] showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies. The addition of BYETTA to titrated basal insulin therapy has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue).[11]

Exenatide once weekly (EQW; BYDUREON), is an extended release formulation of exenatide that is administered once weekly rather than twice daily. EQW has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as an adjunct to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and SU, or a combination of metformin and TZD therapy to improve glycemic control in adult patients with type 2 diabetes mellitus.

In a 30-week, randomized, open-label trial, EQW treatment resulted in a significantly greater improvement in glycemic control, as measured by glycated hemoglobin (HbA_{1c}), compared to exenatide administered twice daily.[12] Furthermore, treatment with EQW for one year (52 weeks) showed net reductions of 2.0% in HbA_{1c}, 0.06 mmol/l (2.2 mg/dl) LDL cholesterol, 6 mmHg in systolic blood pressure and 4 kg in body weight.[13] Thus, EQW represents a novel therapeutic

approach to the treatment of T2DM that could potentially impact the occurrence of cardiovascular events in patients mediated by improvements in multiple CV risk factors, as well as reducing glycemia.

EXSCEL (EXenatide Study of Cardiovascular Event Lowering) is a pragmatic, long-term, placebo-controlled, double-blinded trial which seeks to characterize the effects of EQW on cardiovascular-related outcomes in patients with type 2 diabetes when added to the current usual care for glycemic control in a standard care setting.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of EXSCEL will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes.

Objective: To compare the impact of including EQW in addition to usual care *vs.* usual care without EQW on major CV outcomes as measured by the primary CV composite endpoint of CV-related death, nonfatal myocardial infarction (MI), or nonfatal stroke.

Hypotheses:

Efficacy: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

Safety: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.

2.2 Secondary Objectives

The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1) All cause mortality
2) Each of the components of the primary composite CV endpoint
3) Hospitalization for acute coronary syndrome (ACS)
4) Hospitalization for congestive heart failure (CHF)

2.3 Additional Objectives

Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

1) Revascularization procedures. This will include percutaneous coronary intervention (PCI) with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting
2) Time to initiation of first co-interventional agent (i.e., next antihyperglycemic agent [AHA] or chronic insulin therapy)
3) Number of episodes of severe hypoglycemia

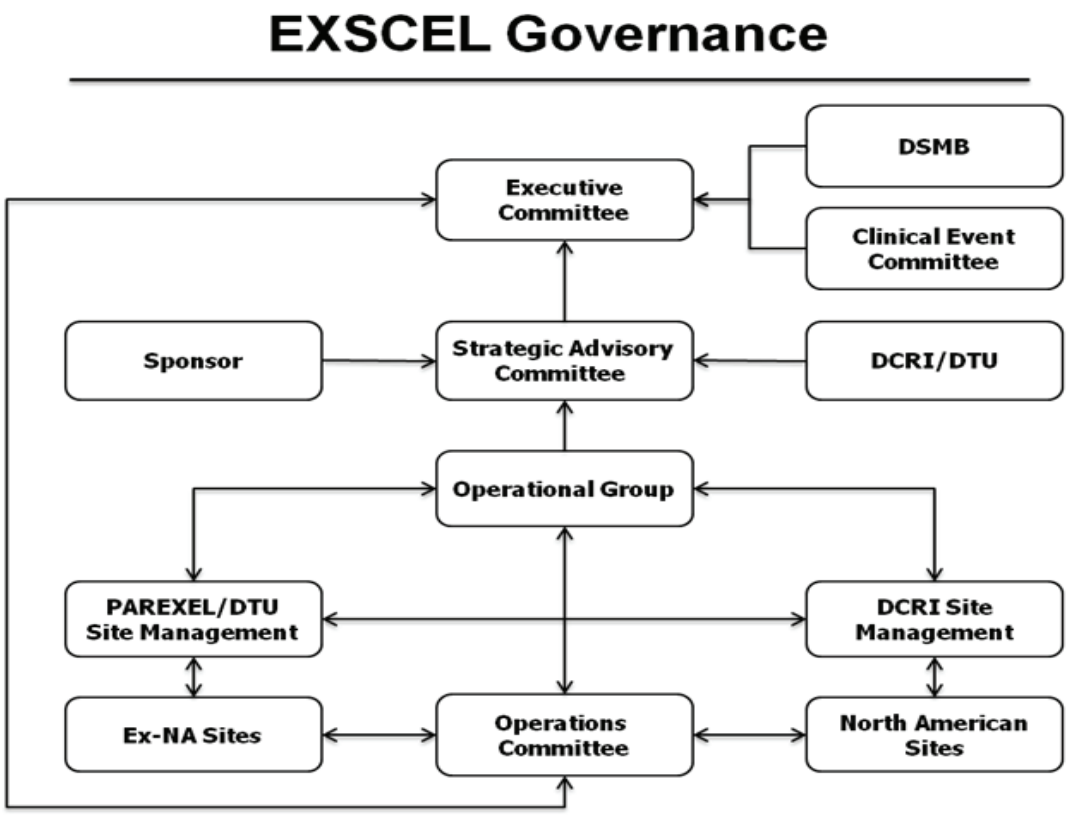
4) Absolute values of and changes in markers of cardiovascular risk including: HbA_{1c}, body weight, blood pressure, lipid profile
5) Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire
6) Medical resource use and total direct medical costs
7) Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide

3 TRIAL GOVERNANCE

EXSCEL is a multinational pragmatic trial that will be conducted at approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of AstraZeneca. EXSCEL will be Co-Chaired PPD and sponsored and funded by Amylin.

The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired by Professors Adrian Hernandez and Rury Holman (see Section 12.1).

Figure 1: EXSCEL Governance



4 TRIAL DESIGN

4.1 Design Description

EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA_{1c} ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event (see Section 6.3).

Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for the conduct of the Trial Termination Visit will be established; all patients will be expected to have follow-up until the Trial Termination Visit (see Section 6).

The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments; patients will be enrolled in the Americas (North/South America), Europe and Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period.

There is no requirement to achieve glycemic equipoise between randomized groups but all patients during the double-blind treatment period will have their AHA regimens adjusted as deemed necessary by their usual care provider with the addition or substitution of other AHAs, including insulin, but excluding GLP-1 receptor agonists, to achieve appropriate individualized glycemic goals in line with national guidelines. Adjustments in AHA medications are permitted any time after randomization, but usual care providers will be asked to avoid this until HbA_{1c} levels begin to reflect the initial effect of randomized study medication. Prior to randomization, it is anticipated that all patients will have received counseling regarding appropriate diet and level of physical activity as part of usual care for type 2 diabetes. Per usual care, HbA_{1c} values should be measured locally. An NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay[14] should be used if available.

4.2 Trial Duration

It is anticipated that enrollment will occur over approximately a 5-year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5

years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the Trial Termination Visit.

4.3 Post Trial Access to Therapy

At the end of the trial, the sponsor will not continue to supply study drug to patients/investigators. The investigator should ensure that the patient receives appropriate standard of care to treat the condition under study according to national treatment guidelines.

5 TRIAL POPULATION

5.1 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 HbA_{1c} 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 the time of enrollment.

HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is >10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} 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 (see Section 6.3) 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
- Ischemic cerebrovascular disease, including:
  - History of ischemic stroke; strokes not known to be hemorrhagic will be allowed as part of this criterion; transient ischemic 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 enrollment

5.2 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 (≥2 episodes) of severe hypoglycemia within 12 months of enrollment

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 of <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 <30 mL/min/1.73m^2 (see Appendix 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 > 40 ng/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.

6 TRIAL PLAN

6.1 Trial Procedures - Overview

A schedule of procedures to be performed during the trial is found in Appendix 2. The intent of this large, pragmatic, global trial is to integrate the trial-specific procedures into usual clinical care visits and to use routine clinical care assessments and laboratory values whenever possible as an efficient strategy for protocol implementation and data collection. At randomization (Visit 1) patients will be provided with the patients' instruction for use (IFU) and will be trained by study personnel to administer the study medication injection. Patients will be seen at one week (±3 days) and have their self-injection observed. Then patients will be seen at 2 months (± 2 weeks) after randomization to again confirm competency with dosing study medication. The next visit will be six months (±1 month) after randomization. Thereafter, patients will be seen every six months (±1 month) until study close out (Figure 2).

At all visits post randomization there will be an assessment of Clinical Events and Serious Adverse Events (see Section 10.3.1), as well as a review of concomitant medication, and adherence to study therapy. At semi-annual and annual visits, additional procedures will include blood pressure, body weight, heart rate, review of laboratory values and dispensing of study drug as described in Appendix 2.

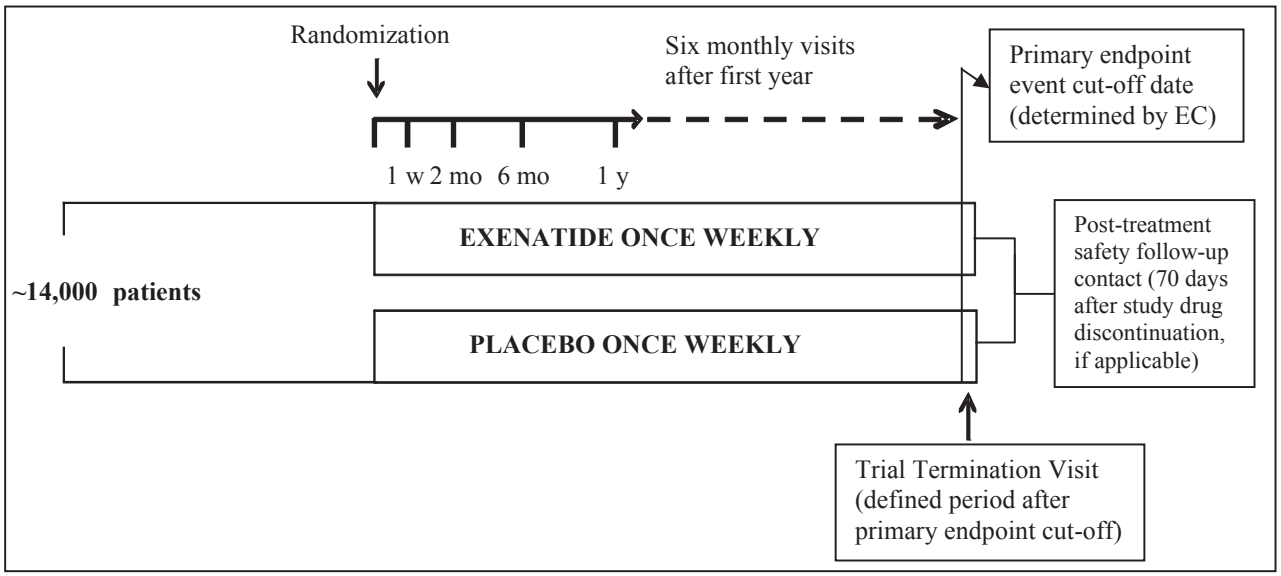
The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. All patients will be expected to have follow-up until this visit.

NOTE: Patients who have temporarily or permanently discontinued trial medication should continue with their regular visit schedule. **ALL** patients should have a Trial Termination Visit (including patients who have previously discontinued trial medication).

After the Trial Termination Visit patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Note that any events occurring between the Trial Termination Visit and the safety follow-up phone call will not be adjudicated and will not be included in the primary analysis. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the safety follow-up telephone contact visit performed. These patients will have their final assessment of Clinical Events, serious adverse experiences and hospitalizations completed at the Trial Termination Visit.

Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date) (see Section 10.3.1).

Figure 2: EXSCEL Study Design



6.2 Pre-Enrollment and Enrollment Procedures

Informed consent, and if feasible, randomization will occur at the initial trial visit for patients satisfying all inclusion and exclusion criteria. Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1 (recommended guidance for management of serum creatinine values will be provided to each site). For patients who require a repeat visit *e.g.* key lab data not available at Visit 1, randomization will be delayed until all information is available. It should be noted that patients may still be randomized at Visit 1 even if calcitonin results are pending.

6.3 Method of Assigning Patients to Treatment Groups (Visit 1)

An Interactive Voice Response System (IVRS) will be used to enroll those patients satisfying all inclusion and exclusion criteria. This automated system will randomize eligible patients and dispense double-blind trial medication. Each site user will be given an identification number and a password to access the IVRS. Patients will be randomly allocated at Visit 1 in a 1:1 ratio, stratified by whether or not they have had a prior CV event, to receive one of the following two interventions:

Treatment 1: EQW 2 mg subcutaneous injection, administered once weekly

Treatment 2: Matching placebo subcutaneous injection, administered once weekly

The IVRS will be programmed to ensure the expected overall proportion of randomized patients with a prior CV event is approximately 70%. With transition to Amylin-labeled trial medication (beginning in 2013), the IVRS was programmed to ensure at least 80% of newly randomized patients have a history of a prior CV event (previously was programmed to ensure approximately 60% of patients had a prior CV event).

The generation of the randomized allocation schedule for trial treatment assignment will be the responsibility of the IVRS provider. Prior to database lock, these codes will be provided in strict confidence only to the facility packaging trial medication and to the DSMB independent statistical group. Immediately upon database lock the codes will be transmitted to the DTU and DCRI data management groups for incorporation into the trial database.

6.4 Treatments Administered

In accordance with standard guidelines for care in all countries participating in the trial, it is anticipated that all patients will receive counseling about appropriate diet and exercise interventions as part of usual care.

EQW and matching placebo will be supplied as subcutaneous injections and will be administered once weekly.

As exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment, trial medication must be discontinued if a patient's eGFR drops below 30 mL/min/1.73 m^2, based on two consecutive serum creatinine determinations (See Section 6.12). As part of standard of care, serum creatinine should be, at minimum, among labs drawn annually. If serum creatinine has not been performed on an annual basis, then study personnel should prompt usual care providers to perform serum creatinine measurement. If serum creatinine remains unavailable, then it should be performed at the next visit by study personnel. If the investigator recognizes that the eGFR has decreased sufficiently to necessitate trial medication cessation, he/she should determine whether or not repeat/confirmatory testing has occurred and undertake this if necessary. If the need for drug discontinuation is confirmed, the situation will be explained to the patient and the patient will be asked to stop the study drug and encouraged to continue follow up off study drug until the end of the trial. If deemed necessary by the investigator, an unscheduled visit can be performed to discuss study drug discontinuation and the importance of subsequent follow up. Drug discontinuation will be managed at the trial

site through the IVRS system. Drug discontinuation visit procedures should be followed as outlined in Section 6.11.

6.5 Concomitant Therapy

Concomitant medications will be used at the discretion of the usual care provider (or investigator if also the usual care provider), who will be informed of the patient's enrollment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists is contraindicated during the trial period. If an open-label GLP-1 receptor agonist therapy is started whilst on study medication, then the investigator will inform the usual care provider about the possibility of double dosing and encourage the discontinuation of open-label GLP-1 agonist therapy. However, if an open-label GLP-1 receptor agonist therapy remains, then study drug should be discontinued to avoid potential double dosing. Usual care providers will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. AHAs will be captured by name and total daily dose at the time of study visits, while other relevant concomitant medications may be collected only as drug classes.

During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals based on clinical care practice guidelines published by national and international societies. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication.

Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA_{1c} levels begin to reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA_{1c} goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial medication following initiation of insulin.

6.6 Precautions to Minimize Rates of Hypoglycemia

At the screening/randomization visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with patients. Patients who experience severe hypoglycemia will be asked to notify both their usual care provider, as well as trial personnel. Usual care providers will be responsible for the adjustment of non-trial AHA medications in order to prevent or minimize the occurrence of further hypoglycemia.

All episodes of severe hypoglycemia will be reviewed and recorded. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently

disoriented or incapacitated as to require help from either a family member or from medical personnel (whether or not this assistance was actually provided). For example, if a family member or other bystander brought the patient a snack or drink to help raise his blood sugar even though the patient was capable of doing this himself, the episode would not be considered severe.

Combination therapies with insulin and sulfonylurea have an increased risk of hypoglycemia. To minimize this risk, patients whose diabetes is well controlled may require a reduction in the insulin or sulfonylurea dose when allocated study medication. EXSCEL will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Patients receiving sulfonylurea/insulin combinations will be explicitly reminded of the symptoms and proper management of hypoglycemia before starting study drug.

6.7 Laboratory and Anthropometric Measurements

Laboratory values *i.e.* HbA_{1c}, serum creatinine, lipid profile [LDL-C, TC, TG, HDL-C]) will be obtained where available as per the patient's usual care assessments. Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in Appendix 2.

6.8 Calcitonin Sample Collection

Serum calcitonin concentrations will be monitored throughout the patient's participation in the trial (See Section 10.4). Samples will be collected at baseline, annually and at the Trial Termination visit.

6.9 Genetic and Biomarker Sample Collection

In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient.

In addition, a subset of patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), year 1 and at the Trial Termination visit.

6.10 Resource Utilization Quality of Life Data for Economic Evaluation

As part of this trial, data will be collected to inform cost-effectiveness analyses that are relevant to major health care systems around the world. The economic analyses will be undertaken by a team led by the University of Oxford and Duke University. Resource use information will be collected from case report forms on number, type and duration of hospitalizations, number of outpatient physician visits, and use of antihyperglycemic and cardiovascular agents. The EQ-5D instrument, consisting of 5 questions, will be used to measure health utilities which are essential to estimating quality-adjusted survival for the cost-effectiveness analysis. This instrument will be administered at baseline, at 6 months, at subsequent annual visits, and at the Trial Termination visit.

An outline statistical analysis plan for this evaluation is reported in Section 9.11; a detailed analysis plan and study report will be developed and reported separately.

6.11 Temporary or Permanent Discontinuation of Trial Medication

Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for when protocol-specified reasons apply (Section 6.12), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial medication (Section 6.18).

Unless resumption of trial medication is considered unsafe or is refused by the patient, the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded.

All randomized patients who permanently discontinue trial medication should have a drug termination visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Necessary procedures are indicated in Appendix 2. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit; patients should continue with their regular visit schedule until the end of the trial, including semi-annual in-person visits, as well as the annual calcitonin measurement. If patients cannot attend visits in person, they will be followed via telephone contact for all subsequent visits.

NOTE: *After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).*

6.12 Permanent Discontinuation of Trial Medication Per Protocol

Reasons for protocol-specified discontinuation from the trial medication are listed below**.** All patients will be followed until resolution *i.e.* return to baseline values or diagnosis determined, or new stable state established, based on investigator assessment, for any adverse event or laboratory safety test abnormality resulting in discontinuation.

a) Severe Hypoglycemia: repeated (2 or more) episodes since the prior trial visit of severe hypoglycemia *i.e.* in which patient required medical assistance, despite down-titration or interruption/discontinuation of non-trial AHAs.

- ***Note****: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia.*

b) Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to additional risk by continuing in the trial or does not allow the patient to adhere to the requirements of the protocol.

c) Severe, irreversible renal dysfunction (confirmed by two consecutive eGFR <30 ml/min/1.73m^2) or renal replacement therapy.

d) Annual calcitonin measurement ≥50 ng/L

6.13 Trial Termination Visit

Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule **all** patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. All patients will be expected to have follow-up until this visit. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2.

NOTE: ***All patients should have a Trial Termination Visit. Patients who have discontinued trial medication prior to the end of the trial must, at minimum, have a Trial Termination telephone contact.***

If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the Trial Termination Visit.

6.14 Post-Treatment Telephone Contact

After the Trial Termination Visit, patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Clinical Events (as defined in Protocol Appendix 1) will continue to be collected and reported in the same way as they have been throughout the entire study (i.e., prior to the cut-off date) (see Section 10.3.1).

6.15 Withdrawal of Consent

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient explicitly withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information.

Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

When a patient withdraws consent from future follow-up prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time (Section 6.13).

6.16 Lost to Follow-Up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above as well as the usual care provider. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death.

If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. Where specific consent has been obtained from the participant, the site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

6.17 Breaking the Blind

The IVRS will be used to unblind patients to the randomized treatment assignment only if absolutely necessary. Disclosure envelopes will not be supplied with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Prior to unblinding, the investigator is required to speak with a trial hotline physician (Section 6.18). Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.

6.18 Trial Hotline

Clinicians at DCRI and DTU operate the trial hotline. It is available at all times to answer urgent clinical questions from sites concerning enrolled patients as well as questions to determine whether a particular patient qualifies for enrollment or performance of study procedures.

7 TRIAL MEDICATIONS

7.1 Trial Medication Supply

Investigational Materials will be provided by the Sponsor as EQW 2 mg and matching placebo.

7.2 Formulation, Packaging, and Storage

EQW (formulation AC2993 F17) is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactic-co-glycolic acid (PLG). The vial containing the white to off white dry powder (2.8 mg of exenatide in EQW microspheres to deliver 2 mg of exenatide) must be stored in a refrigerator between 2ºC and 8ºC (36°F and 46°F) and protected

from light. EQW matching placebo is the identical formulation with the active ingredient omitted.

The Microsphere Diluent for suspension of the EQW and matching placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. The Microsphere Diluent must be stored between 2°C and 25°C (36°F and 77°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Instructions for Use (IFU). The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose.

7.3 Dispensing of Trial Medication

Study materials will be provided to patients by the investigator, medically qualified subinvestigator, or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than patients participating in the study.

A supply of study medication will be dispensed for each patient, according to their assigned treatment group (EQW or Placebo). A 6 month supply of study medication will be distributed to patients at the study site during Visit 1 and at subsequent visits indicated in Appendix 2. Patients should bring used and unused study medication vials to the site at each visit so medication compliance can be assessed.

7.4 Dose Administration Procedures, Route, and Schedule

Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen, thigh, or back of the upper arm. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly. The same anatomical region can be used for the injection but the site should be rotated (e.g. different quadrants of the abdomen can be used in a weekly rotation).

At Visit 1 (Day 0), a medically qualified staff member will demonstrate the preparation of EQW or matching placebo for the patient or a designated caregiver and will administer the first dose of study medication. Patients will subsequently self administer study medication (or have it administered by a caregiver) once weekly (± 3 days) relative to the date of the first dose of EQW or matching placebo (Visit 1 [Day 0]). Patients will be seen one week as well as two months after randomization to confirm competency with study medication. On weeks with no scheduled study-site visits, patients may opt to return to the study site to have the injection procedure monitored by study-site personnel, although such visits will not be required. During scheduled study visits, patients must bring their study medication treatment kit with them to the clinic and will self administer EQW or matching placebo as directed by study-site personnel.

Adjustments to dosing regimens are not permitted. If a patient is unable to tolerate study medication (e.g., patient experiences adverse events that are judged by the investigator to be unacceptable) the termination of study medication can be considered. Patients who terminate

study medication will be followed up, per the protocol, for the remainder of the study unless the patient opts to withdraw consent for further follow-up.

7.5 Randomization Schedule and Blinding Procedures

Patients who meet all study requirements based on inclusion and exclusion criteria will be randomized at Visit 1 (Day 0). Patients will be randomly assigned to 1 of 2 treatment groups (EQW or Placebo). Randomization will be in the ratio of 1:1 (EQW:Placebo) and will be carried out centrally in a manner blocked within site and stratified by whether a participant has or has not had a prior cardiovascular event, to achieve a balanced distribution of patients across treatment groups.

Sufficient study medication will be provided to the study site for enrollment of all patients. Study medication kits will be labeled with unique package numbers (this is not the patient randomization number). At Visit 1 (Day 0), study site personnel must contact the interactive voice response system (IVRS) to randomly assign patients. The study-site personnel must call the IVRS at all subsequent visits (except Visits 2, 3 and Trial Termination) to record the visit and confirm the kit assignment. The calls to the IVRS will ensure the resupply of additional kits required for upcoming visits. If medication is allocated to a patient incorrectly, the sponsor must be notified. At Trial Termination, the site must call the IVRS to record study termination. The sponsor, the study-site personnel, and the patients will be blinded to treatment allocation.

7.6 Drug Accountability

Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. In addition, the study-site personnel must contact IVRS to verify receipt of study medication. The sponsor (or designee) should be notified immediately about any irregularities, discrepancies, or damage.

A drug accountability log will be provided to record all study medication dispensed to or returned from each patient. Upon completion of the study, all used and unused EQW or matching placebo vials and copies of completed drug accountability logs should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment; however, if the site manager/CRA approves, the site can destroy the material instead of returning the used and unused study drug. The study site personnel must maintain documentation of any missing or unreturned study medication.

8 EFFICACY ASSESSMENTS

Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. The definitions of the events to be adjudicated by the Clinical Events Classification Committee (CEC) and the committee procedures will be included in the CEC Charter (Section 12.4). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.

8.1 Primary Efficacy Endpoint

- **Time to first confirmed CV event in the primary composite CV endpoint**
  Defined as the time from randomization to first confirmed CV-related death, nonfatal MI or nonfatal stroke.

8.2 Secondary Efficacy Endpoints

- **Time to all-cause mortality**
  Defined as time from randomization to death due to any cause.
- **Time to first confirmed CV event for each component of the primary composite endpoint**
  Defined as time from randomization to a confirmed CV-related death, fatal or nonfatal MI, or fatal or nonfatal stroke.
- **Time to hospitalization for acute coronary syndrome**
  Defined as time from randomization to a confirmed hospital admission for unstable angina, ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.
- **Time to hospitalization for heart failure**
  Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.

8.3 Additional Efficacy Endpoints

- **Time to revascularization procedure**
  Defined as time from randomization to time of first cardiovascular or peripheral revascularization procedure. This will include percutaneous coronary intervention with or without stenting, coronary artery bypass grafting, revascularization and/or stenting for peripheral arterial disease, carotid endarterectomy, or carotid stenting.
- **Time to initiation of first co-interventional agent**
  - Additional AHA
  - Chronic insulin therapy
- **Absolute values and change from baseline in:**
  - HbA1c
  - Body weight
  - Blood pressure
  - Lipid profile
- **Quality of life assessed by the EQ-5D (EuroQol 5 Dimension) questionnaire**
- **Medical resource use and total direct medical costs**
- **Incremental cost-effectiveness analysis of exenatide once weekly as part of usual care compared with usual care without exenatide**

9 STATISTICAL METHODS

This section outlines the statistical analysis strategy related to the primary and secondary study objectives with the full details given in a separate Statistical Analysis Plan (SAP). If any substantive changes are made to these objectives or the statistical methods after the study has begun then the protocol will be amended, provided that it is prior to any unblinding, consistent with ICH Guideline E9. The study database will only be locked and unblinded once medical/scientific review has been performed, protocol violations have been identified and the data have been declared final and complete. The statistical analyses for this study will be the responsibility of the University of Oxford Diabetes Trials Unit.

9.1 Baseline Characteristics

Demographic characteristics *e.g.* gender, age, race, body weight, will be summarized for each treatment group. In addition, duration of diabetes, alcohol intake, smoking status, cardiovascular medical history, baseline laboratory results and concomitant medications will be summarized by treatment group.

9.2 Sample Size

The primary endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke. The study is designed to assess the primary efficacy objective of superiority of EQW to placebo through the following hypothesis:

H0: upper limit of the 95% CI of the HR [exenatide:placebo] ≥1

versus

H1: upper limit of the 95% CI of the HR [exenatide:placebo] <1

In order to test the above hypothesis with 85% power and 2-sided α=0.05, a total number of 1360 composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With this number of events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo.

In addition, with the following assumptions made for this study,

- An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled
- A planned accrual period of 5-6 years
- An estimated annual lost-to-follow up rate of 1%
- An anticipated treatment discontinuation rate of 5% per year

it is expected that a total of 14000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 confirmed composite CV events.

9.3 Randomization

Randomization via an Interactive Voice Response System (IVRS) will be 1:1 EQW to Placebo, blocked within each site, and stratified by whether a participant has or has not had a prior cardiovascular event (see Section 5.1).

9.4 Primary Hypothesis

The primary efficacy hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular endpoint, defined as the time from randomization to the first confirmed CV-related death, nonfatal MI or nonfatal stroke with the patients analyzed as randomized.

The primary safety hypothesis is that EQW will be non-inferior to placebo with respect to the primary composite cardiovascular endpoint, with patients analyzed as randomized.

9.5 Primary Analysis

The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, *i.e.* the Trial Termination Visit and until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. All patients will be expected to have follow-up until this visit. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the Trial Termination Visit date. Note that any event occurring between the Trial Termination Visit and the safety follow-up date (70 days after the administration of the last dose of trial medication) will not be adjudicated and will not be included in the primary analysis. Events occurring during this period will be summarized descriptively.

Kaplan-Meier curves for time to the first occurrence of a primary composite endpoint event will be used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time to first occurrence of the primary composite endpoint event for the EQW treated group to that of the placebo treated group and its 95% confidence interval will then be estimated using a Cox proportional hazards model stratified by baseline CV risk group (prior CV event or no prior CV event) and using treatment group as covariate.

The primary safety hypothesis will be assessed by a non-inferiority analysis with the non-inferiority margin of 1.30, i.e., non-inferiority will be concluded if the upper limit of the confidence interval is less than 1.30.

The primary efficacy hypothesis of superiority will be then assessed by the 95% confidence interval for the hazard ratio of EQW to placebo, i.e., superiority will be concluded if the 95% confidence interval does not include 1 (upper limit of 95% confidence interval < 1).

9.6 Secondary Efficacy Analyses

The secondary efficacy endpoints are the time to confirmed occurrence of:

1) All cause mortality

2) CV-related death
3) Fatal or nonfatal myocardial infarction
4) Fatal or nonfatal stroke
5) Hospitalization for acute coronary syndrome (ACS)
6) Hospitalization for congestive heart failure (CHF)

Details of the testing strategy of the secondary efficacy endpoints will be provided in the Statistical Analysis Plan (SAP).

9.7 Analysis Populations

The three predefined analysis populations are:

1) The Intent to Treat (ITT) Population
2) The Per Protocol Population
3) The Safety Population

9.7.1 Intent-To-Treat Population

The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the Trial Termination Visit date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the Trial Termination Visit date. Every effort will be made to collect CV events until the Trial Termination Visit date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.

9.7.1.1 On-Treatment Analysis

An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred through the last dose of study medication or the Trial Termination Visit date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized. The on-treatment censoring scheme will also be applied for analysis for on-treatment + n days, where n=7, 30, and 70.

9.7.2 Per-Protocol Population

The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or the Trial Termination Visit date, whichever occurs first), such as:

- Initiation of an open-label prohibited medication, i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication.
- Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the Trial Termination Visit date, whichever occurs first.
- Taking incorrect study medication for more than three months.

All protocol violations will be specified in the statistical analysis plan prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. Patients will be analyzed as randomized.

The primary safety and primary efficacy analyses will be repeated with the per-protocol population as sensitivity analyses.

9.7.3 Safety Population

The safety population consists of all randomized patients who received at least 1 dose of study therapy; in addition, if a patient is found to have taken a study therapy for the entire duration of the study, different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 70 days after the last dose of study medication, will be summarized. For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

9.8 Safety Data Analysis

Safety parameters will be summarized and presented in tables for the safety population. Serious adverse events will be listed as described in the SAP.

9.9 Subgroup Analyses

Subgroup analyses for the primary CV composite endpoint will be performed on the ITT population in order to explore whether the treatment effect on the risk of developing CV events is consistent across subgroups. The following subgroups will be assessed:

- Class of AHA therapy at entry (mono or combination)
- Race (Indian [American] or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Hispanic, Other)
- Geographic region (North America, Latin America, Europe and Asia Pacific)
- Gender (Male, Female)
- Age (<65 or ≥65)
- Baseline HbA_{1c} (<8.0% or ≥8/0%)
- Baseline BMI (<30 or ≥30 kg/m^2)
- Duration of diabetes (<5, 5-14, ≥15 years)
- eGFR groups (in mL/min/1.73 m^2)
  - (<60 or ≥60)
  - Stage 1: 90+, Stage 2: 60-89, Stage 3: 30-59, Stage 3a: 45-59, Stage 3b: 30-44, Stage 4: 15-29, Stage 5: <15
- History of previous cardiovascular event (e.g., previous MI or stroke)

The hazard ratios, 95% CIs, and appropriate summary statistics for each of the subgroups (by treatment group) will be provided and the hazard ratios examined for interaction effects. The

interaction effect would be treatment × stratified variable, in additive format with treatment + stratified variable. For example, the stratified variable means the categorical variable 'Region'.

9.10 Interim Analyses

The DSMB will undertake safety reviews of all available data every 6 months or more frequently if the committee deems it appropriate.

Two formal interim efficacy analyses are planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the targeted 1360 primary composite CV events. The analyses will test for superiority using a Haybittle-Peto spending function where the study termination guideline for overwhelming superiority will be p-value < 0.0001 for the first interim analysis and p-value <0.001 for the second interim analysis. This will ensure a significance level of 0.0499 for the final analysis.

If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons.

The interim analyses will be performed by an independent statistical group. Further details of the interim analyses are provided in the DSMB Charter.

9.11 Economic Analysis

The primary objective of the economic analysis is to collect sufficient data from the trial participants on resource use and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in the study. Resource use data on hospitalizations, visits and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study. Quality of life data from the EQ-5D will be combined with survival data to calculate quality adjusted time in the trial per patient.

Cost-effectiveness analyses will report the incremental cost per major CV outcome averted, CV-related death averted, life-year gained and quality-adjusted life year gained, of including EQW in addition to usual care *vs.* usual care without EQW. Analyses will be conducted within trial and using a lifetime perspective, with lifetime extrapolation performed using the UKPDS Outcomes Model or all patients still alive at the end of the study, using risk factor characteristics from the last available visit. A full analysis plan for the economic analysis will be prepared and reported separately from this protocol.

For the main clinical study report (CSR), the quality of life data will be summarized descriptively for baseline and changes from baseline by treatment.

10 SAFETY ASSESSMENTS

10.1 Definitions

Adverse Event (AE)

An adverse event is defined as any unfavorable and unintended sign, symptom, disease or change in the structure, function, or chemistry of the body temporally associated with the use of the investigational product, whether or not considered related to the use of the product. Any

worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the investigational product, is also an adverse event. Adverse events include those reported spontaneously by the patient or as the result of non-directed questioning from study site personnel. Changes as a result of normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse events (e.g. the onset of menopause occurring at a physiologically appropriate time).

Serious Adverse Event (SAE)

This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose:

- Results in death
- Is life-threatening
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is defined as a serious adverse event, the nature or severity of which is not consistent with the known study treatment information.

10.2 Adverse Event Assessment

Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post-trial medication follow-up period. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded in the eCRF, with the exception of events noted in Section 10.3.

10.3 Recording and Reporting Adverse Events

10.3.1 Recording Adverse Events

SAEs will be recorded in the **Clinical Events or SAE eCRF** modules as appropriate (see Table 1) throughout the trial (including the 70 day safety wash-out period after last dose of study medication). Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the **Clinical Events eCRF** module include SAEs that are: (1) Obvious

trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.

In addition, non-serious adverse events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminurea, hyperlipidemia/dyslipidemia, hypertension, or gout also will be recorded in the **Clinical Events eCRF** module (see Appendix 1).

Any SAE which is not included among the expected events on the Clinical Events List will be recorded in the **SAE eCRF** module.

Events of neoplasia and pancreatitis should be reported on the **SAE eCRF** even if the event does not meet seriousness criteria.

Note: The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR via the **SAE eCRF** as long as it is not any of the **possible trial endpoints** listed in Appendix 1, Section I).

Table 1:	**List of events to be recorded in each eCRF reporting module***
eCRF reporting module to be used	**List of events to be recorded in this eCRF reporting module:**
Clinical Event eCRF	- Clinical Events that meet the criteria of an SAE (i.e. serious adverse event) and are listed in Appendix 1 - All **non-serious** (or serious) events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, macroalbuminuria, hyperlipidemia/dyslipidemia, hypertension, or gout - All neoplasia events - All pancreatitis events
SAE eCRF	- Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are **not** listed in Appendix 1 - All episodes of pancreatitis - All episodes of any type of neoplasia/cancer - Any AE or SAE resulting from an overdose of study drug - Any event that is recorded in the Clinical Event eCRF, that the investigator considers a SUSAR, with the exception of possible Primary or Secondary trial endpoints (i.e. all events listed in Appendix 1, Section I)
*** Trial sites will be provided with an 'EXSCEL Event Reporting' flow chart that can be referenced to help identify which events should be reported in which eCRF reporting module.**	

The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAEs should be

reviewed for all patients randomized regardless of whether the patient is currently on trial medication.

10.3.2 Safety Reporting

The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAEs recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAEs recorded as Clinical Events, including death related to an event in the Clinical Events List, ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial medication*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. This will be applicable throughout the duration of trial including the 70 day wash-out period. There will be no switch to collecting and reporting Clinical Events as SAEs. Thus, the exemption from routine SAE reporting of events listed in Protocol Appendix 1 will remain for the entire trial duration, including the safety wash-out phase. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.3). **All SUSARS** will be reported in an expedited manner with the exception of possible trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events.

Note that pancreatitis and pancreatic neoplasms / malignancies are events of special interest for GLP-1 based therapies, such as exenatide. As described above, all events of pancreatitis and all neoplasms (including pancreatic cancer) are to be reported on both the Clinical Events eCRF and the SAE eCRF, even if the event does not meet seriousness criteria. These events are reviewed by the DSMB and adjudicated by the CEC.

Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.

10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events

The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. SAEs that are not recorded as Clinical Events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

10.4 Calcitonin Monitoring

Studies in rodents have indicated an increased incidence of thyroid C-cell tumors (adenomas, carcinomas) with EQW treatment. The relevance of these findings to human safety is currently unknown and is being investigated. In clinical studies, there was no difference between exenatide (BID or once weekly) and comparators with respect to thyroid neoplasms. A detailed summary of findings in rodents and clinical studies is available in the Exenatide Investigator Brochure. Measurement of calcitonin has been added to newly initiating clinical trials of EQW to characterize any effects of exenatide or comparator treatment on calcitonin levels over time to better assess evidence of a biologic effect on c-cells. In clinical trials, no difference in calcitonin was observed between exenatide and comparators.

Calcitonin concentrations will be monitored at baseline, annually and at the Trial Termination visit. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 40 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and they should call the Trial Hotline for advice, where they will be instructed to alert the usual care provider and permanently discontinue study medication. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.

10.5 Overdose

10.5.1 Definition of an Overdose for This Protocol

An overdose is defined as a patient taking more than 1 dose of study medication in the same day. In the event of an overdose, medical treatment may be needed since severe nausea and vomiting are possible. The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose.

10.5.2 Reporting of Overdose

If an adverse experience(s) is associated with ("results from") the overdose of study medication, the adverse experience(s) is collected as a serious adverse experience, even if no other criteria for seriousness are met.

If a dose of study drug meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as an Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 1 day of the site's knowledge of the event.

10.6 Reporting of Pregnancy

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 70 days of completing the trial. All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. All occurrences of pregnancy must be reported via the Pregnancy Surveillance Form. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

10.7 Unblinding

Breaking the blind is strongly discouraged and should only be requested if it is deemed necessary for the wellbeing or safety of the patient. Any Investigator requesting the unblinding of a patient will be asked to contact the trial hotline physician, available 24hrs/day to discuss the case and determine the course of action; however, it is the prerogative of the treating physician to insist that their patient should be unblinded. Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.

11 ETHICAL AND LEGAL ASPECTS

11.1 General Informed Consent

The investigator must obtain written documented consent to participate in the trial from each potential patient in his/her native language. Consent must be documented by the patient's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., trial staff personnel). A copy of the signed and dated consent form should be given to the patient.

The initial informed consent form, any subsequent revised written informed consent forms, and any written information provided to the patient must receive the IRB/IECs approval/ favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient’s willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form.

The informed consent form will describe the regular two-way exchange of information that is expected to occur between trial physicians and the usual care physicians. The informed consent form will also include a request that the patient provide permission for the collection of medical records and copies of relevant reports necessary for complete data collection even if trial medication is discontinued beforehand.

11.2 Consent and Collection of Specimens for Genetic and Genomic Analysis

Patients providing informed consent will have a whole blood specimen collected for potential future genetic research. This is an optional activity, and only those patients who have consented to having this genetic sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.3 Consent and Collection of Biomarker Specimens

Patients providing informed consent will have blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), Year 1, and at the Trial Termination visit. Biomarker samples will be stored in at least two aliquots for potential future proteomic and/or metabolomic analysis. This is an optional activity, and only those patients who have consented to having this biomarker sample collected may have this blood sample drawn. The approval of the consent form for analysis and the associated protocol procedures (e.g., collection of a blood sample) may, in some cases, proceed independently through Institutional Review Boards, Ethical Review Boards, Independent Ethical Review Committees (ERCs), Privacy Committees, etc., from the associated clinical trial.

11.4 Ethics Committee or Institutional Review Board

Documented approval from appropriate Ethics Committee(s) or Institutional Review Board(s) must be obtained for all participating centers prior to study start, according to Good Clinical Practice (GCP), local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must also be obtained. Ethics Committees, upon request, may be required to provide a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations. Modifications to the study protocol will not be implemented without the agreement of the Executive Committee and appropriate ethical approval.

11.5 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives. The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor.

All potential serious breaches must be reported to the sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

11.6 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

11.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The patient will be identified only by a unique patient ID number on the eCRF. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act.

Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, Ethical Committees, Institutional Review Boards or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

When the results of the study are published, the patient's identity will remain confidential. The investigator will maintain a list to enable patients' records to be identified.

11.8 Records

11.8.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study.

The sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

11.8.2 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and

reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet training requirements and must only access the electronic data capture tool using their unique user account. User accounts are not to be shared or reassigned to other individuals.

12 TRIAL MANAGEMENT/GOVERNANCE COMMITTEES

12.1 Executive Committee (EC)

The EC will be responsible for overall management and oversight of the trial. The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired PPD An EC charter will outline the committee membership and structure and delineate operating procedures.

The Executive Committee is the main decision-making body for the EXSCEL trial and is charged with the overall scientific, professional, and operational conduct of the trial.

The primary functions of the Executive Committee are to:

1. Review and approve the trial protocol and all protocol amendments.
2. Supervise the conduct of the trial in accordance with its responsibilities described in the trial protocol and committee charter.
3. Review and approve the Statistical Analysis Plan.
4. Oversee all trial subcommittees, including but not limited to:

- Clinical Endpoint Committee
- Data Safety Monitoring Board
- Operations Committee
- Strategic Advisory Committee

5. Review and consider recommendations from the Data Safety Monitoring Board (DSMB).
6. The Executive Committee will determine the time to terminate the trial, based on recommendations from the DSMB and other available information. The Executive Committee may also find it necessary to terminate the trial under certain circumstances, including but not limited to the following reasons:

- Animal, human or toxicological test results, in the reasonable determination of the Executive Committee, support termination of the trial
- Ethical or patient safety issues occur that the Executive Committee feels support termination of the trial
- Extraordinary scientific, regulatory or other events that negatively impact the rationale for the trial such that the Executive Committee agrees it is appropriate to terminate the trial

7. Review all sub-study requests and approve where appropriate.

8. Consider, authorize as appropriate and prioritize requests for access to trial data and/or genetic and biomarker samples for academic or other collaborations. After the Executive Committee disbands, DCRI, DTU and the sponsor will assume this responsibility.

9. Approve the communication strategy on how to best communicate information about the progress of the trial.

10. Ensure accurate, uniform, timely, and high quality reporting of the main trial and all approved sub-studies.

11. Serve as the writing group who will prepare and submit for publication the primary manuscript describing the main trial results. All members of the Executive Committee will have access, in confidence to the draft manuscript describing the primary results paper.

12. Assume the role of publications committee and review, authorize and prioritize proposals for publications which require trial or sub study data, samples, or genetic material and assign writing groups.

13. Review and comment on any independent publications reporting results from the trial following the primary publication.

12.2 Operations Committee (OC)

The Operations Committee (OC) is composed of Country Leads selected by the Executive Committee from investigators in each country with appropriate clinical trial experience. The OC will be co-chaired by the clinical coordinators from the Duke Clinical Research Institute (DCRI) and the Diabetes Trials Unit (DTU). Balance will be sought between cardiologists and endocrinologists. The primary role of the OC is to serve as the interface between the EC and the trial sites, and to assist in the progress of the trial at the regional level. Committee members will be instrumental in serving as ambassadors of the trial to encourage recruitment as well as ensure trial compliance by working with study personnel and mediating in country-specific issues. The committee will provide a means of transmitting any identified needs, concerns, or suggestions from the sites to the EC and assist in disseminating clinical or operational information to the sites. The functions and operating procedures of the OC are delineated in a charter.

12.2.1 Remit of Operations Committee

Specific functions of the OC will include the following:

1. All members will serve as regional leaders for site investigators.
2. All members will serve as advocates for the trial.
3. Country Leads will:

a) Communicate with investigators in the Lead's country to review country specific progress reports, including but not limited to recruitment/retention of patients, event reporting and data collection, and communication between sites and usual care providers.
b) Liaise with the academic coordinating centers and global Contract Research Organizations (CROs) to review and attempt to resolve any operational issues raised within a region.
c) Support regulatory submissions, as needed in collaboration with the Sponsor's Regulatory Affairs Department.

4. Committee Co-Chairs will:
   a) Compile country-specific performance metrics for presentation to the Executive Committee.
   b) Liaise with Country Leads, academic coordinating centers (DCRI and DTU project teams), sponsors and global AROs/CROs to implement trial policies.

12.3 Data Safety Monitoring Board (DSMB)

The DSMB will be composed of six senior academic individuals, including the DSMB Chair. There will be at least one member with high-level expertise for each of cardiology, endocrinology, and statistics. An Independent Statistician (not affiliated with the DCRI, DTU, or the Sponsor) will also be in attendance. All of these individuals will have long-standing experience in the operational, medical, and biostatistical aspects of international clinical trials. The DTU senior statistician assigned to the trial will oversee the provision of interim masked data sets for use by the DSMB and the DCRI/DTU trial coordinating centers. DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the IVRS vendor. During the Open Session of the DSMB meetings, representatives of the Executive Committee may present updates on the trial status or the safety profile of exenatide, but will not be privy to discussions of the unmasked data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake regular reviews of the safety data. The DSMB will have access to an agreed subset of the trial data as listed in the DSMB charter (updated as necessary during the trial) in an unblinded fashion throughout the trial duration. In addition, the DSMB will evaluate two interim analyses after approximately one-third and two-thirds of the total targeted number of primary composite CV events (see Sec 9.10 for details).

If the DSMB finds it necessary to recommend actions regarding interruption of the trial or changes to the protocol based on medical rationale that would make it unethical to continue the trial in its present form, those recommendations will be forwarded to the EC. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

12.4 Clinical Events Committee (CEC)

The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, pancreatitis, neoplasm, ventricular fibrillation/tachycardia, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions. The CEC will be blinded to the assigned trial medication. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.

12.5 Strategic Advisory Committee

The Strategic Advisory Committee will provide oversight for the operational conduct of the study across all participating institutions. It will be composed of senior management from the Sponsors, AROs and contracted CROs, who are experts in the operational aspects of the conduct of clinical trials and the EXSCEL Clinical Leads.

13 DISCLOSURE OF DATA, PUBLICATIONS, AND CLINICAL STUDY REPORT

During the Trial all data derived from the Trial will be held by the AROs but with access for Sponsor to any data required for safety and regulatory purposes. At the time database lock occurs, the IVRS provider will provide the AROs with an electronic file containing the full randomization codes for upload to the electronic database. The ARO will undertake the planned analyses and prepare and submit manuscripts for publication and presentation to academic meetings agreed by the Executive Committee. The Sponsor will have the right to comment on these but the final editorial control remains with the Executive Committee. The Executive Committee will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.

In addition, a CSR will be prepared for regulatory purposes. The Signatory Investigator responsible for signing the CSR will be selected by the Sponsor in conjunction with the Executive Committee.

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APPENDIX 1 CLINICAL EVENTS LIST

Any clinical event listed in this appendix that meets the criteria of an SAE (unless indicated otherwise below) must be reported in the Clinical Event eCRF reporting module.

I. Obvious Trial Endpoints

(These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter)

Death

- Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI] / cerebrovascular accident [CVA] / congestive heart failure [CHF] / arrhythmia, cardiac arrest, death following CV intervention)
- Non-CV Death

Nonfatal MI

Acute coronary syndrome

Nonfatal CVA

CHF requiring hospitalization

II. Cardiovascular Events of Interest

(Some of these events will result in prompts to answer additional questions in the eCRF – these questions will be designed to determine whether or not a primary or secondary outcome of interest has occurred)

Atrial fibrillation/Atrial flutter

Ventricular fibrillation/tachycardia requiring intervention

Deep Vein Thrombosis (DVT)

Pulmonary embolism

Percutaneous Coronary Intervention (PCI) – (including non-serious events)

Coronary Artery Bypass Graft (CABG)

Coronary catheterization

Stress test (including non-serious events)

Abdominal aortic aneurysm/repair

Carotid endarterectomy/Carotid angioplasty and/or stenting

Any hospitalization due to cardiovascular events (i.e., whether or not the hospitalization was for an obvious trial endpoint)

Shock/hypotension

Accelerated or malignant hypertension/hypertensive urgency

Transient Ischemic Attack (TIA)

Syncope

Renal artery angioplasty and/or stenting

Other arterial angioplasty and/or stenting

III. Expected Events and Diabetic Complications

(Subcategories indicate potential additional information to be captured, usually as an indication of severity)

A. Peripheral Vascular Disease (PVD)

- Limb PCI
- Vascular surgery

- Amputation
- Surgical debridement of ulcer

B. Gangrene

C. Severe hypoglycemia (including non-serious events) / Hyperglycemia / Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma

D. Diabetic eye disease (including non-serious events)

- Photocoagulation or other laser therapy
- Cataract extraction
- Blindness
- Enucleation
- Steroid/Avastin injection
- Scleral buckling or other retinal fixation procedure

E. Diabetic neuropathy (including distal sensorimotor, focal/multifocal, or autonomic) (including non-serious events)

- Foot ulcer

F. Diabetic nephropathy (including non-serious events)

- Microalbuminuria
- Macroalbuminuria

G. Renal failure

- Acute renal failure, requiring or associated with hospitalization
- Chronic renal failure, requiring peritoneal or hemodialysis, including creation of fistula or other vascular access for hemodialysis
- Renal transplant

H. Any hospitalization due to complications of DM

I. Infections

- Osteomyelitis
  - IV antibiotic therapy vs. debridement
- Cellulitis
  - Oral vs. IV antibiotic therapy
- Mucormycosis
- Pneumonia
  - Community acquired vs. hospital acquired
  - Oral vs. IV antibiotic therapy
- Bacteremia
- Sepsis
- Infected joints
  - Prosthetic joint
- Complicated or serious urinary tract infection (UTI) / Pyelonephritis
  - Requiring hospitalization
- Malignant external otitis

J. Gastrointestinal (GI) conditions

- Abdominal pain
- Nausea / vomiting
- Diarrhea
- Fatty liver disease / Nonalcoholic steatohepatitis (NASH)
- Cholecystitis / cholelithiasis
- Elevated liver enzymes

K. Metabolic Conditions Associated with Diabetes (including non-serious events)

- Hyperlipidemia / dyslipidemia
- Hypertension
- Gout

APPENDIX 2 TRIAL PLAN (PROTOCOL BCB109)

Table 1: Trial Plan								
		Treatment Initiation		Follow-up [4]		Drug or Study Termination		
Evaluation	**Screening Day -1**	**Randomization Day 0 Visit 1 [1]**	**Week 1 and Month 2 Visit 2 and 3**	**Semi-Annual**	**Annual**	**Drug Termination [5]**	**Trial Termination [8]**	**Post-Treatment Follow-up Contact [9]**
Informed Consent/HIPAA [2] and Stored Blood Sample Authorization	X							
Medical History	X							
Physical Examination	X							
Height	X							
Blood Pressure, Heart Rate and Body Weight	X	X		X	X	X	X	
Calcitonin Blood Sample		X			X		X	
Collect and review available information including most recent HbA_{1c}, serum creatinine and lipid profile	X [6]			X	X	X	X	
Randomization		X						
If consent obtained, collect blood sample for genetic and genomic analysis		X [7]						
If consent obtained, blood sample (serum and plasma) and urine sample for archive		X			Year 1 only		X	
Drug Dispensation		X		X	X			
Used/Unused Vial Assessment				X	X	X	X	
Clinical and SAE Event Assessment		X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	
Confirm competency with injections [3]			X					
EQ-5D Completion		X		Month 6 only	X		X	

[1] Wherever possible the screening and randomization visit should be combined.

[2] Informed Consent Form and if applicable, authorization to use and disclose protected health information.

[3] Patients will return approximately 1 week (±3 days) as well as 2 months (± 2 weeks) after Day 0 to perform a self-injection under the observation of the clinical site to confirm competency with injection. An additional visit can be considered at ~1 month if the patient is not able to adequately inject themselves.

[4] Semi-annual (±1 month) and Annual Follow-up (±1 month) Visits will occur in reference to Visit 1 Day 0 for the duration of participation in the trial.

[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.

[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).

[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.

[8] For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up.

[9] Patients will be contacted by telephone to check for any Clinical Events, serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. (see Section 10.3.1).

APPENDIX 3 PROTOCOL AMENDMENT 01: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **01**

Amendment Purpose: **Date: 11 November 2010**

The purpose of Amendment 1 is to add annual and study termination calcitonin assessments and monitoring to the conduct of the trial. Additional clarifications and edits are included. Notable changes are detailed in the table below.

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
Title Page	Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US. For investigative sites outside of the US and Puerto Rico, Lilly will serve as the study sponsor.	Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and will serve as the sponsor for the Clinical Trial Application in Canada. Amylin Pharmaceuticals, Inc. transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US, Puerto Rico and Canada. For investigative sites outside of the US, Puerto Rico and Canada, Lilly will serve as the study sponsor.
4.1 Design Description	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA_{1c}) ≥7.0 % and ≤10.0 % on stable doses of up to three oral antihyperglycemic agents (AHAs) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months.	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months.
5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. *A patients whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three (i.e. 0-3) oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. Concomitant use of DPP-4 inhibitors is permitted. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*
5.1 Inclusion Criteria	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that 40% will not have had a prior CV event and 60% will have	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that approximately 40% will not have had a prior CV event and 60% will have had

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
	had a prior CV event defined as at least one of the following:	a prior CV event defined as at least one of the following:
6.1 Trial Procedures	*Study Design Figure*	The study design figure has been updated
6.3 Method of Assigning Patients to Treatment Groups (Visit 1)	This automated system will assign a unique allocation number to eligible patients and dispense double-blind trial medication.	This automated system will randomize eligible patients and dispense double-blind trial medication.
6.8 Calcitonin Sample Collection	(*this is a new subsection; subsequent subsections have been renumbered accordingly*)	Serum calcitonin concentrations will be monitored throughout the patient's participation in the trial. Samples will be collected at baseline, annually and trial/early termination.
6.9 Genetic and Biomarker Sample Collection (*previously Section 6.8*)	These fasting specimens will be obtained at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year).	These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination.
6.12 Early Discontinuation of Trial Medication (*previously Section 6.11*)	Unless consent to follow the patient is specifically withdrawn, patients should continue to be followed as outlined in Section 6.14 until the end of the trial. When a patient withdraws consent prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time.	Unless consent to follow the patient is specifically withdrawn, patients should continue with their regular visit schedule as outlined in Section 6.15 until the end of the trial. When a patient withdraws consent prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time.
7.2 Formulation, Packaging, and Storage	The Microsphere Diluent must be stored between 2°C and 27°C (36°F and 81°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Directions For Use (DFU).	The Microsphere Diluent must be stored between 2°C and 25°C (36°F and 77°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the injection will be provided in the Patient Instructions For Use (PIU).
7.3 Dispensing of Trial Medication	Study materials will be provided to subjects by the investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than subjects participating in the study.	Study materials will be provided to subjects by the investigator, medically qualified subinvestigator or other qualified study-site personnel. Under no circumstance will the investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than subjects participating in the study.

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
7.4 Dose Administration Procedure, Route and Schedule	Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly.	Doses of EQW or matching placebo are to be injected into subcutaneous (SC) tissue of the abdomen, thigh or back of the upper arm. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly. The same anatomical region can be used for the injection but the site should be rotated (e.g. different quadrants of the abdomen can be used in a weekly rotation).
7.4 Dose Administration Procedure, Route and Schedule	Subjects will be seen one week as well as one month after randomization to confirm competency with study medication.	Subjects will be seen one week as well as two months after randomization to confirm competency with study medication.
7.5 Randomization Schedule and Blinding Procedures	The study-site personnel must call the IVRS at all subsequent visits (except Study Termination) to record the visit and confirm the kit assignment.	The study-site personnel must call the IVRS at all subsequent visits (except Visits 2, 3 and Study Termination) to record the visit and confirm the kit assignment
7.6 Drug Accountability	Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. The study-site personnel should make a copy of the shipping form for the site's file, and return the original completed form to the sponsor (or designee). In addition, the study-site personnel will contact IVRS to verify receipt of study medication.	Drug accountability will be the responsibility of the study-site personnel. Upon receipt of study medication, study site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. In addition, the study-site personnel will contact IVRS to verify receipt of study medication.
9.8.3 Safety Population	Serious AEs and AEs leading to discontinuation of study medication, any of which occurred within 90 days after the last dose of study medication, will be collected.	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 90 days after the last dose of study medication, will be collected.
10.1 Definitions	• Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)	• Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)
10.3 Classification and Reporting of Adverse Events	Table 1. (*additional footnote included to clarify collection of pancreatitis and neoplasia*)	** All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events.
10.3 Classification and Reporting of Adverse Events	As described in Section 10.1.1 all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module within 1 day of a trial site becoming aware of the event. Brief	As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within 1 day of a trial site

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
	information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. Episodes of pancreatitis, diagnoses of thyroid carcinoma and pancreatic cancer will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.	becoming aware of the event. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). **Note**: Events which meet the criteria to be classified as an Ancillary Event which result in death and are deemed to be possibly related to study drug will be collected and reported as Ancillary Events. Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly. All patients with serious adverse events must be followed to assess outcome until resolution or until designated permanent.
10.4 Calcitonin Monitoring	(*this is a new subsection; subsequent subsections have been renumbered accordingly*)	Studies in rodents have indicated an increased incidence of thyroid C-cell tumors (adenomas, carcinomas) with EQW treatment. The relevance of these findings to human safety is currently unknown and is being investigated. In clinical studies, there was no difference between exenatide (BID or once weekly) and comparators with respect to thyroid neoplasms. A detailed summary of findings in rodents and clinical studies is available in the Exenatide Investigator Brochure. Measurement of calcitonin has recently been added to newly initiating clinical trials of EQW to characterize any effects of exenatide or comparator treatment on calcitonin levels over time to better assess evidence of a biologic effect on c-cells. In clinical trials, no difference in calcitonin was observed between exenatide and comparators. Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 100 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value is identified during trial follow-up, the site investigator will

SECTION	ORIGINAL PROTOCOL TEXT	AMENDMENT 01 TEXT
		be notified and will alert the usual care physician. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.
10.5.2 Reporting of Overdose (previously section 10.4.2)	If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for seriousness are met.	If an adverse experience(s) is associated with ("results from") the overdose of study medication, the adverse experience(s) is collected as a serious adverse experience, even if no other criteria for seriousness are met.
10.6 Reporting of Pregnancy (previously Section 10.5)	All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported.	All patients who become pregnant must stop taking blinded trial medication and be followed to the completion/termination of the pregnancy. All occurrences of pregnancy must be reported via the Lilly Pregnancy/Breastfeeding Exposure Form. If the pregnancy continues to term, the outcome (health of infant) must also be reported.
11.3 Consent and Collection of Biomarker Specimens	Patients providing informed consent will have a fasting blood sample collected at baseline (prior to drug exposure), and either at one year of treatment or at the time of drug discontinuation (if occurring within the first year).	Patients providing informed consent will have a blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), annually, and at the time of trial termination.
12.3 Data Safety Monitoring Board (DSMB)	The DSMB will be composed of five senior academic individuals, including the DSMB Chair.	The DSMB will be composed of six senior academic individuals, including the DSMB Chair.
12.5 Strategic Advisory Committee	(*this is a new subsection*)	The Strategic Advisory Committee will provide oversight for the operational conduct of the study across all participating institutions. It will be composed of senior management from the Sponsors, AROs and the contracted CRO, who are experts in the operational aspects of the conduct of clinical trials and the EXSCEL Clinical Leads.
Appendix 2 Trial Plan (Protocol BCB109)	Please refer to Appendix 2 for specific changes.	Please refer to Appendix 2 for specific changes. Significant changes are summarized below: • Calcitonin samples will be collected annually and at trial/early termination visits. • Heart rate will be measured at randomization, all six-monthly visits (e.g. semi-annual and annual), and drug or trial/early termination visits. • Clarification that consent is required for the biomarker assessment • Samples for future biomarker assessments will now be collected annually trial/early termination rather than at one year only.

APPENDIX 4 PROTOCOL AMENDMENT 02: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **02**

Amendment Purpose: **Date: 10 May 2011**

The purpose of Amendment 02 is to allow insulin use prior to randomization, lower the calcitonin exclusion threshold to >40 ng/L, define the calcitonin exit threshold to be ≥50 ng/L, and clarify reporting of Clinical Events, Serious Adverse Events, and deaths. Additional clarifications and edits are included. Notable changes are detailed in the table below.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Title Page		IND Number added
1.2 Rationale for Conduct of the Study	Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials (9) showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies.	Exenatide, a GLP-1 receptor agonist, has been shown in randomized clinical trials to improve glycemic control, augment endogenous insulin secretion, to reduce blood pressure and promote weight loss with a meta-analysis of exenatide twice-daily (BYETTA) trials (9) showing a trend to lower relative risk for CV events versus pooled comparators of 0.70 (95% confidence interval 0.38 - 1.31). BYETTA (exenatide) injection is currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies. The addition of BYETTA to titrated basal insulin therapy (not currently an approved indication) has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13).

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
4.1 Design Description	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0% and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event.	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic clinical trial. Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA1c) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months i.e. no oral AHA adjustments in the past 3 months. A stable dose of insulin (±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event.
5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% on stable doses of up to three (i.e. 0-3) oral AHAs for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. Concomitant use of DPP-4 inhibitors is permitted. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is > 10.0% may, at the discretion of the investigator, have their oral AHA therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤ 10.0% • A stable dose of up to three (i.e. 0-3) oral AHAs for at least 3 months will be allowed (i.e. no oral AHA adjustments in the past 3 months). o Concomitant use of DPP-4 inhibitors is permitted. o A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months. *HbA1c values must be from within the 3 months prior to randomization. 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 (≥ 7.0 % and ≤ 10.0%) following a 3-month period on stable AHA doses.*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
5.2 Exclusion Criteria	b. Patient has taken insulin within 2 weeks of screening visit or for greater than 1 week within 3 months of screening visit.	b. Patient has a history (≥ 2 episodes) of severe hypoglycemia within 12 months of enrollment.
	l. Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level of 100 ng/L or greater.	l. Personal or family history of medullary thyroid cancer or MEN2 (Multiple Endocrine Neoplasia Type 2) or calcitonin level > 40 ng/L at baseline.
	o. *No original protocol text; new to this version*	o. Is an employee of Eli Lilly and Company or Amylin Pharmaceuticals

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
6.5 Concomitant Therapy	During the double-blind treatment period, trial investigators are expected to monitor patients' AHA regimens and communicate with usual care physicians, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication. In addition, the degree of locally-appropriate HbA_{1c} goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly. Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA1c levels begin reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA1c goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial drug following initiation of insulin.	During the double-blind treatment period, trial investigators are expected to monitor patients' AHA regimens and communicate with usual care physicians, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA_{1c} goals. The Executive Committee (EC) and Operations Committee (OC) will provide a brief list of guidelines for usual care based on clinical care practice guidelines published by national and international societies that will be updated as knowledge about T2DM evolves over the course of the trial. These goals will be individualized, with the understanding that currently applicable glycemic guidelines may vary among different geographic regions. With adherence to local custom and laws (including privacy regulations such as HIPAA), types of communication may be informal *e.g.* email or telephone exchanges, to enhance frequency and ease of two-way communication. In addition, the degree of locally-appropriate HbA_{1c} goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly. Usual care providers should be notified that adjustments to the AHA regimen are not recommended until HbA1c levels begin reflect the effect of randomized therapy. Any AHA agent, with the exception of GLP-1 receptor agonists, is acceptable. If HbA1c goals are not met following adjustment with oral AHAs in patients not receiving insulin, an insulin regimen may be initiated, preferably without discontinuing or down-titrating some or all of the existing AHAs, as clinically appropriate. Patients already receiving insulin therapy may up-titrate insulin during the trial if necessary. Ideally, patients should generally remain on the baseline AHA therapies throughout the course of the trial, unless the baseline AHA is no longer clinically appropriate. However, this should be at the discretion of the usual care provider. In addition, patients should be reminded to keep taking their blinded trial drug following initiation of insulin.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
6.9 Genetic and Biomarker Sample Collection	In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient. Patients enrolled in the trial will be asked to consent separately to provide two blood and two urine samples for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination.	In a subset of sites, patients enrolled in the trial will be asked to consent separately to provide a whole blood sample for future pharmacogenomic analyses. The objective of collecting blood samples from which genetic analyses can be performed is to investigate the relationships between genetic make-up and clinical events. These samples will be drawn at baseline, or at any point in the trial at which consent is obtained from the patient. Patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination. All samples will be divided and stored in 2 aliquots at the Laboratory Corporation of America facility in Kannapolis, North Carolina, USA.
6.11 End of Trial Visit and Post Trial Telephone Contact	**NOTE:** ***All patients should have an End of Trial Visit. (Patients who have discontinued trial drug must, at minimum, have an End of Trial telephone contact visit.)***	**NOTE:** ***All patients should have an End of Trial Visit. (Patients who have discontinued trial drug prior to the end of the trial must, at minimum, have an End of Trial telephone contact visit.)***
6.12 Early Discontinuation of Trial Medication	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for protocol-specified reasons (Section 6.14), due to the judgment of the primary investigator or because the patient withdraws consent. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial drug (Section 6.17).	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for protocol-specified reasons (Section 6.14), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial drug (Section 6.17).
6.14 Permanent Discontinuation of Trial Drug Per Protocol	*No original text*	e) Annual calcitonin measurement ≥ 50 ng/L

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
7.6 Drug Accountability	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment. The study site personnel must maintain documentation of any missing or unreturned study medication.	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee). A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment; however, if the site manager/CRA approves, the site can destroy the material instead of returning the used and unused study drug. The study site personnel must maintain documentation of any missing or unreturned study medication.
10.1 Definitions	Events meeting the above definition as SAEs and will be recorded in the safety trial database as either Clinical or Ancillary Events (definitions and criteria are summarized in Table 1). Serious Adverse Event (SAE) This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose: • Results in death • Is life-threatening • Results in persistent or significant or disability/incapacity • Requires in-patient hospitalization or prolongs existing hospitalization • Results in a congenital anomaly or birth defect • Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)	*Text removed* Serious Adverse Event (SAE) This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose: • Results in death • Is life-threatening • Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • Requires in-patient hospitalization or prolongs existing hospitalization • Results in a congenital anomaly or birth defect • Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses of study medication whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.2 Adverse Events Assessment	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the subject's participation, including the 90 day post-trial drug follow-up period or withdrawal. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded.	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the subject's participation, including the 90 day post-trial drug follow-up period or withdrawal. Adverse events reported by the patient will be evaluated by the investigator to determine if a given event meets the criteria for a serious event (described in Section 10.1). Any adverse event that does not meet the definition of a serious event will be considered non-serious and will not be recorded in the eCRF, with the exception of events noted in Section 10.3.
10.3 Recording and Reporting Adverse Events	Original section structure 10.3 Classification and Reporting Adverse Events 10.3.1 Sponsor Responsibility for Reporting Serious Adverse Events	New section structure 10.3 Recording and Reporting Adverse Events 10.3.1 Recording Adverse Events 10.3.2 Safety Reporting 10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.1 Recording Adverse Events	The classification of an SAE as a Clinical or Ancillary event is dependent on if the SAE is included in the Clinical Events List (Appendix 1). The Clinical Events List is inclusive of SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes; (5) expected events based on information noted in the exenatide investigator brochure. SAE which meet these criteria will be reported in the **Clinical Events eCRF module**. SAE which are not included on the Clinical Events List will be considered Ancillary events and will be reported in the **Ancillary Events eCRF module**. The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAE should be reviewed for all patients randomized regardless of whether the patient is currently on trial medication.	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the **Clinical Events eCRF** module include SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes (Table 1). These events represent trial outcomes and expected events for this population. In addition, non-serious adverse events of stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminurea, proteinuria, hyperlipidemia / dyslipidemia, hypertension, and gout also will be recorded in the **Clinical Events eCRF** module (see Appendix I). Any SAE which is not included among the expected events on the Clinical Events List will be recorded in the **SAE eCRF** module. Events of neoplasia and pancreatitis should be reported on the **SAE eCRF** even if the event does not meet serious criteria. Note: The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, <u>including those events with an outcome of death</u>. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR as long as it does not require adjudication. If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event. The Clinical Events List will be reviewed and the eCRF will be completed during every visit to determine if a patient has experienced one or more of the listed events. SAE should be reviewed for all patients randomized regardless of whether the patient is currently on trial medication.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.2 Safety Reporting	*(Formerly Section 10.3)* SAE recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication, expected sequelae of T2DM, or are expected based on information provided in the exenatide investigator brochure. Clinical events will be monitored by the DSMB and **will not** require expedited reporting to the sponsor even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. ***Regardless of relationship to trial drug, Clinical Events will not be reported by the sponsor to regulatory agencies or ethics committees in an expedited manner, nor in the format of a line listing as part of an Annual Safety Report.*** Events reported via this module will be regularly monitored by the DSMB and those which may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator as Ancillary Events. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **1 day** of a trial site becoming aware of the event. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported as Ancillary Events. All Ancillary Events will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.1). **Note:** Events which meet the criteria to be classified as an Ancillary Event which result in death and are deemed to be possibly related to study drug will be collected and reported as Ancillary Events.	The DSMB will monitor the totality of collected safety data (i.e. events recorded on both the Clinical Events and SAE eCRFs) on a semi-annual basis regardless of event classification. SAE recorded on the Clinical Events eCRF represent those events which are components of the composite CV endpoint, other trial endpoints, potential components of the CV endpoint that require adjudication or are expected sequelae of T2DM. SAE recorded as Clinical Events, including death related to an event in the Clinical Events List, and ***will not be reported to the Sponsor, regulatory agencies or ethics committees, regardless of relationship to trial drug*** even though they may be considered possibly, probably or definitely drug-related and meet SAE criteria. In addition to the un-blinded review by the DSMB, events reported via this module that may be associated with a trial endpoint will be adjudicated by the CEC. As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module. These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **1 day** of a trial site becoming aware of the event. Any SAEs meeting the definition of a SUSAR will be subject to expedited reporting as per current legislation. Brief information on the clinical course of the event, treatment, and relevant diagnostic, laboratory or other investigations will be collected on the eCRF. All episodes of pancreatitis and neoplasia will be treated as SAEs and will be collected and reported in the SAE eCRF module. All events recorded in the SAE eCRF module will be reported to the appropriate regulatory agencies in a manner and timeframe consistent with all applicable laws and regulations (Section 10.3.2). **All SUSARS** will be reported in an expedited manner with the exception of those fulfilling the criterion of an efficacy endpoint (as detailed in Section 1 of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
10.3.3 Sponsor Responsibility for Reporting Serious Adverse Events	(*Formerly Section 10.3.1)* The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. All Ancillary SAE will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.	The Sponsor will ensure that all appropriate regulatory agencies confirm that the approach for monitoring Clinical Events, described in the Safety Assessments Section is acceptable to them. SAE that are not recorded as Clinical Events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.
10.4 Calcitonin Monitoring	Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 100 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.	Calcitonin concentrations will be monitored at baseline, annually and at trial/early termination. Investigators and participants will be blinded to calcitonin values. If the baseline value exceeds 40 ng/L, the site will be informed and directed to have the patient terminate study medication. If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician and study medication will be discontinued. Calcitonin concentrations will be monitored by the DSMB, which will include a thyroid expert.
10.7 Un-blinding	*No original text*	Breaking the blind is strongly discouraged and should only be requested if it is deemed necessary for the wellbeing or safety of the patient. Any Investigator requesting the unblinding of a patient will be asked to contact the trial hotline physician, available 24hrs/day to discuss the case and determine the course of action; however, it is the prerogative of the treating physician to insist that their patient should be unblinded.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
12.4 Clinical Events Committee (CEC)	The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions for the diagnoses of MI, stroke, acute coronary syndrome, and CHF requiring hospitalization. The CEC will be blinded to the assigned trial drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.	The events which constitute the principal endpoints of this trial will be adjudicated by the Clinical Events Classification Committee (CEC), coordinated through the Duke Clinical Research Institute (DCRI), which will be comprised of approximately 5-7 physicians and a coordinator. The specific endpoints to be adjudicated include: cause of death (cardiovascular-related vs. non-cardiovascular), MI, stroke, acute coronary syndrome, pancreatitis, neoplasm, ventricular fibrillation/tachycardia, and CHF requiring hospitalization. Clinical reviewers will be board certified or board eligible endocrinologists, cardiologists, neurologists, gastroenterologists, or physicians with clinical expertise and prior clinical event classification experience. The CEC will review clinical data and adjudicate safety and efficacy endpoints. The CEC will adjudicate clinical events using pre-specified criteria and definitions. The CEC will be blinded to the assigned trial drug. Sites will provide clinical information via the eCRF and also provide supplemental information from medical records, when needed. The CEC operations and endpoint criteria will be described in a separate charter.
References	*No original text*	13. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154(2):103-112.
Appendix 1	**CLINICAL EVENTS LIST (TO BE INCORPORATED INTO ECRF)** The following list of events would be recorded in the eCRF at the time of the trial visit, *but not reported to the Sponsor or regulatory agencies urgently* regardless of relationship to trial drug. Included are trial endpoints as well as events that are expected to occur in this trial population.	**CLINICAL EVENTS LIST (TO BE RECORDED IN THE CLINICAL EVENTS eCRF)** *Deleted existing text*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Appendix 1	**I. A. Obvious trial endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter) Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention) • Non-CV Death	**I.A. Obvious trial endpoints** (These events will prompt the investigator to complete an endpoint package which will then be adjudicated according to the Clinical Events Classification [CEC] charter) Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention) • *Deleted existing text*
Appendix 1	**Section II. C.** Hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma	**Section II. C.** Severe hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma
Appendix 1	*No original text*	Added the term "(including non-serious events)" to the existing events: -stress test -diabetic eye disease -diabetic neuropathy -diabetic nephropathy -metabolic conditions associated with diabetes

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Appendix 1	III. Terms listed in the exenatide Investigator Brochure A. Allergic/Hypersensitivity Reactions • Injection site reactions • Pruritis and/or urticaria • Rash • Angioedema • Anaphylactic reaction B. Gastrointestinal reactions • Nausea • Vomiting and/or diarrhea resulting in dehydration • Abdominal distension or pain • Eructation • Constipation • Flatulence • Diarrhea C. Renal and Urinary Disorders • Altered renal function, including acute or worsened chronic renal failure • Renal impairment • Increased serum creatinine D. Development of antibodies to exenatide E. For all other terms please refer to the current Investigator Brochure	*Deleted Section III.*

APPENDIX 5 PROTOCOL AMENDMENT 03: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **03**

Amendment Purpose: **Date: 23 April 2012**

The purpose of Amendment 03 is to alter inclusion criteria to allow patients with an HbA1c ≥6.5% and using insulin, alone or in combination with oral antihyperglycemic medications, to be eligible to enroll in the study. In addition, the requirement for patients to have been on a stable dose of oral antihyperglycemic medication has been removed. Additional safety language regarding hypoglycemia has been included for patients using concomitant insulin and/or sulfonylurea. In addition, patients discontinued due to pregnancy can resume study medication following completion of the pregnancy and cessation of breastfeeding (if applicable). Finally, clarifications regarding events requiring adjudications were added. Minor editorial changes have also been included to improve clarity and consistency. Notable changes are detailed in the table below.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Title Page	PPD **Amylin Pharmaceuticals, Inc.**	PPD PPD **Amylin Pharmaceuticals, Inc.**
List of Abbreviations	*None*	CRO Contract Research Organization HLGT High level group term IFU Instructions for use ITT Intent-to-Treat PCI Percutaneous coronary intervention TC Total cholesterol TG Triglycerides TIA Transient ischemic attack
List of Abbreviations	EDC Electronic Data Collection	EDC Electronic Data Capture ~~Collection~~

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 1.2 Rationale for Conduct of the Study	The addition of BYETTA to titrated basal insulin therapy (not currently an approved indication) has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13). Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, is under development and currently being reviewed by the US FDA.	The addition of BYETTA to titrated basal insulin therapy ~~(not currently an approved indication)~~ has also been demonstrated to improve glycemic control without an increased risk of hypoglycemia in patients receiving concomitant diet/exercise, metformin, or metformin+pioglitazone therapy (exenatide enhances insulin secretion in a glucose-dependent manner, thus minimizing the risk of hypoglycemia in the absence of an insulin secretagogue) (13). Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control. ~~is under development and currently being reviewed by the US FDA~~.
Section 2.2 Secondary Objectives	(4) Hospitalization for heart failure (CHF)	(4) Hospitalization for congestive heart failure (CHF)
Section 3 Trial Governance	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two Alliance representatives.	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two ~~Alliance~~ sponsor representatives.
Figure 1		*Figure updated to clarify groups involved*
Section 4.1 Design Description	Eligible patients will have type 2 diabetes with a glycated hemoglobin (HbA_{1c}) ≥7.0 % and ≤10.0 % on stable doses of up to three (i.e. 0-3) oral antihyperglycemic agents (AHAs) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. A stable dose of insulin (±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted.	Eligible patients will have type 2 diabetes with ~~a glycated hemoglobin (HbA_{1c}) ≥7.0 %~~ an HbA_{1c} ≥6.5% and ≤10.0 % on ~~stable doses of~~ up to three (i.e., 0-3) oral ~~antihyperglycemic agents (~~AHAs~~) for at least 3 months *i.e.* no oral AHA adjustments in the past 3 months. A stable dose of~~ or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. ~~(±20% of the scheduled total daily insulin dose), either alone or in combination with a stable dose of metformin for at least 3 months, will also be permitted.~~
Section 4.1 Design Description	Per usual care, HbA_{1c} values should be measured locally using a NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay (12).	Per usual care, HbA_{1c} values should be measured locally. ~~using a~~ An NGSP (National Glycohemoglobin Standardization Program) certified HbA_{1c} assay should be used if available (12).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 4.2 Trial Duration	All patients that cease study medication will be followed up, if at all possible, for the full study period. All patients that withdraw from the trial will have their vital status ascertained, if at all possible, at the end of the trial.	All patients that discontinue ~~cease~~ study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period ~~All patients that withdraw from the trial~~ and will have their vital status ascertained, if possible, at the end of the trial.
Section 5.1 Inclusion Criteria	c. Patient has an HbA_{1c} of ≥ 7.0 % and ≤10.0% • A stable dose of up to three (i.e., 0-3) oral AHAs for at least 3 months will be allowed (*i.e.* no oral AHA adjustments in the past 3 months). ○ Concomitant use of DPP-4 inhibitors is permitted. ○ A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months. *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is>10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥7.0 % and ≤10.0%) following a 3-month period on stable AHA doses.*	c. Patient has an HbA_{1c} of ≥6.5 % ~~≥ 7.0 %~~ 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 (ie., 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 the time of enrollment.* ~~• A stable dose of up to three (i.e., 0-3) oral AHAs for at least 3 months will be allowed (*i.e.* no oral AHA adjustments in the past 3 months).~~ ~~○ Concomitant use of DPP-4 inhibitors is permitted.~~ ~~○ A stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months is permitted. The use of basal and prandial insulins is permitted in any combination of individual or premixed insulins. If the prescribed insulin regimen includes adjustments, the total dose should not vary by more than 20% from day to day over the preceding 3 months.~~ *HbA1c values must be from within the 3 months prior to randomization. If multiple values are available, the most recent reported value should be used. A patient whose HbA_{1c} is>10.0% may, at the discretion of the investigator, have their oral AHA or insulin therapy adjusted and be re-screened once for HbA_{1c} randomization eligibility (≥6.5 % ~~≥7.0 %~~ and ≤10.0%). ~~following a 3-month period on stable AHA doses~~*

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 5.1 Inclusion Criteria	○ History of ischemic stroke. Strokes not known to be hemorrhagic will be allowed as part of this criterion;	○ History of ischemic stroke; strokes not known to be hemorrhagic will be allowed as part of this criterion; transient ischemic attacks (TIAs) are not included
Section 5.2 Exclusion Criteria	*None*	Each patient meeting any of the following criteria will be excluded from this trial.
Section 5.2 Exclusion Criteria	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 <30 mL/min/1.73 m^2.	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 <30 mL/min/1.73 m^2 (see Appendix 2).
Section 5.2 Exclusion Criteria	**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 for vital status and be part of the intention to treat analysis.	**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 ~~intention to treat~~ analysis.
Section 6.1 Trial Procedures	At baseline (Visit 1) patients will be provided with the patients' instruction brochure and be trained by study personnel to administer the study medication injection.	At randomization ~~baseline~~ (Visit 1) patients will be provided with the patients' instruction for use (IFU) ~~brochure~~ and be trained by study personnel to administer the study medication injection.
Section 6.1 Trial Procedures	At semi-annual and annual visits, additional procedures will include blood pressure, body weight, review of routine laboratory values and dispensing of study drug as described in Appendix 2.	At semi-annual and annual visits, additional procedures will include blood pressure, body weight, heart rate, review of laboratory values and dispensing of study drug as described in Appendix 2.
Section 6.2 Pre-Enrollment and Enrollment Procedures	Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1.	Patients may qualify for enrollment based on recent laboratory data *e.g.* HbA_{1c} within the last 3 months, obtained as part of usual care prior to Visit 1 (recommended guidance for management of serum creatinine values will be provided to each site).
Section 6.4 Treatments Administered	As part of standard of care, serum creatinine should be among labs drawn annually.	As part of standard of care, serum creatinine should be, at minimum, among labs drawn annually.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.4 Treatments Administered	If the need for drug discontinuation is confirmed, the patient will be invited back to the trial site for an unscheduled visit to explain the situation, to stop the study drug and to encourage the patient to continue follow up off study drug until the end of the trial.	If the need for drug discontinuation is confirmed, the situation will be explained to the patient and the patient will be asked to stop the study drug and encouraged ~~the patient will be invited back to the trial site for an unscheduled visit to explain the situation, to stop the study drug and to encourage the patient~~ to continue follow up off study drug until the end of the trial. If deemed necessary by the investigator, an unscheduled visit can be performed to discuss study drug discontinuation and the importance of subsequent follow up.
Section 6.6 Precautions to Minimize Rates of Hypoglycemia	At the screening/enrollment visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with participants.	At the screening/randomization ~~enrollment~~ visit and all subsequent visits, the symptoms and appropriate management of hypoglycemia will be reviewed with patients. ~~participants~~
Section 6.6 Precautions to Minimize Rates of Hypoglycemia	*None*	Combination therapies with insulin and sulfonylurea have an increased risk of hypoglycemia. To minimize this risk, patients whose diabetes is well controlled may require a reduction in the insulin or sulfonylurea dose when allocated study medication. EXSCEL will employ both patient- and investigator-directed education to minimize the risk of hypoglycemia. Patients receiving sulfonylurea/insulin combinations will be explicitly reminded of the symptoms and proper management of hypoglycemia before starting study drug. The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.
Section 6.7 Laboratory and Anthropometric Measurements	Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in the flow chart.	Blood pressure, heart rate, height, and body weight will be collected by study personnel as indicated in Appendix 2. ~~in the flow chart~~
Section 6.10 Resource Utilization Quality of Life Data for Economic Evaluation	This instrument will be administered at baseline, at 6 months and annually thereafter.	This instrument will be administered at baseline, at 6 months, at subsequent annual visits, and at the trial/early termination visit. ~~and annually thereafter~~
Section 6.11 Trial/Early Termination Visit and Post Trial Telephone Contact	Section 6.11 End of Trial Visit and Post Trial Telephone Contact	Section 6.11 ~~End of Trial~~ Trial/Early Termination Visit and Post Trial Telephone Contact

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.11 Trial/Early Termination Visit and Post Trial Telephone Contact	End of Trial Visit	~~End of Trial~~ Trial/Early Termination Visit
Section 6.12 Temporary Discontinuation of Trial Medication	Section 6.12 Early Discontinuation of Trial Medication	Section 6.12 ~~Early~~ Temporary Discontinuation of Trial Medication
Section 6.12 Temporary Discontinuation of Trial Medication	Unless resumption of trial medication is considered unsafe or is refused by the participant, the patient will be expected to resume regular use of the blinded trial medication. Should a participant stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit (as described in Section 6.13) as soon as possible after stopping the trial drug.	Unless resumption of trial medication is considered unsafe or is refused by the patient, ~~participant~~ the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient ~~participant~~ stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a drug termination ~~medication discontinuation~~ visit (as described in Section 6.13) as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). ~~as soon as possible after stopping the trial drug.~~
Section 6.12 Early Discontinuation of Trial Medication	*None*	**NOTE:** After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 6.13 Permanent Discontinuation of Trial Medication Visit Procedures	All randomized patients who permanently discontinue trial medication should have a medication discontinuation visit as soon as possible after stopping the trial drug. Necessary procedures are indicated in the Flow Chart. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Patients will be asked to continue with all other trial follow up until the completion of the trial, including annual in-person visits and telephone calls, as well as the annual calcitonin measurement. IVRS should be contacted to register the patient as discontinued only after all efforts have been exhausted to get patients back on trial drug if appropriate.	All randomized patients who permanently discontinue trial medication should have a drug termination ~~medication discontinuation~~ visit as part of their next scheduled visit (unless a separate drug termination visit is deemed necessary by the investigator). ~~soon as possible after stopping the trial drug.~~ Necessary procedures are indicated in Appendix 2. ~~the Flow Chart.~~ All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit. Patients will be asked to continue with all other trial follow up until the completion of the trial, including semi-annual in-person visits and/or telephone calls, as well as the annual calcitonin measurement. IVRS should be contacted to register the patient as having discontinued study medication only after all efforts have been exhausted to get patients back on trial medication ~~drug~~ if appropriate.
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	b) Pregnancy, as confirmed by serum pregnancy test. Patient must stop taking blinded trial medication, and be followed if she becomes pregnant during the trial (Section 10.6)	*Deleted; remaining items in list renumbered*
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	*The usual care provider will be provided with standard guidance on down-titrating AHAs in the presence of hypoglycemia.*	*The usual care provider will be provided with standard guidance by the trial investigator on down-titrating AHAs in the presence of hypoglycemia.*
Section 6.14 Permanent Discontinuation of Trial Medication Per Protocol	d) Severe, irreversible renal dysfunction (eGFR <30 ml/min/1.73m^2) or renal replacement therapy.	c) Severe, irreversible renal dysfunction (confirmed by two consecutive eGFR <30 ml/min/1.73m^2) or renal replacement therapy.
Section 6.15 Follow-up for Patients who Permanently Discontinue Trial Medication	End of Trial Visit	~~End of Trial~~ Trial/Early Termination Visit
Section 7.2 Formulation, Packaging, and Storage	Specific instructions for dose preparation of the injection will be provided in the Patient Instructions for Use (PIU).	Specific instructions for dose preparation of the injection will be provided in the ~~Patient~~ Instructions for Use (IFU ~~PIU~~).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 7.4 Dose Administration Procedures, Route, and Schedule	Subjects who terminate study medication will be followed for the remainder of the study for the assessment of clinical events unless the subject opts to withdraw consent.	Patients ~~Subjects~~ who terminate study medication will be followed up, per the protocol, for the remainder of the study unless the patient ~~subject~~ opts to withdraw consent.
Section 7.6 Drug Accountability	A drug disposition form will be provided to record all study medication dispensed to or returned from each subject. Upon completion of the study, all used and unused remaining EQW or matching placebo, empty containers, and copies of completed drug disposition forms should be returned to the sponsor (or designee).	A drug accountability log ~~disposition form~~ will be provided to record all study medication dispensed to or returned from each patient ~~subject~~. Upon completion of the study, all used and unused EQW or matching placebo vials ~~empty containers,~~ and copies of completed drug accountability logs ~~disposition forms~~ should be returned to the sponsor (or designee).
Section 9.7 Secondary Analyses	5. Hospitalization for heart failure (CHF)	5. Hospitalization for congestive heart failure (CHF)
Section 9.8.1 Intent-To-Treat Population	Every effort will be made to collect CV events to study termination even in those who have discontinued the study.	Every effort will be made to collect CV events to study termination even in those who have discontinued study medication or the study.
Section 9.8.2 Per Protocol Population	If a patient is found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized then the patient is counted in the treatment group of the drug he/she actually received.	If a patient is found to have taken a study medication for any ~~the entire~~ duration of the study that is different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received.
Section 9.10 Subgroup Analyses	• Region (North/South America or Canada, Europe or South Africa, ROW)	• Region (North/South America or Canada, Europe or South Africa, Rest of world ~~ROW~~)
Section 10.3.1 Recording Adverse Events	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules.	SAEs will be recorded in the **Clinical Events or SAE eCRF** modules as appropriate (see Table 1).
Section 10.3.1 Recording Adverse Events	In addition, non-serious adverse events of stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminurea, proteinuria, hyperlipidemia/dyslipidemia, hypertension, and gout also will be recorded in the **Clinical Events eCRF** module (see Appendix I).	In addition, non-serious adverse events of percutaneous coronary intervention (PCI), stress tests, severe hypoglycemia, diabetic eye disease, foot ulcer, microalbuminuria, ~~proteinuria,~~ macroalbuminuria, hyperlipidemia/ dyslipidemia, hypertension, or ~~and~~ gout also will be recorded in the **Clinical Events eCRF** module (see Appendix 1).

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Section 10.3.1 Recording Adverse Events	**Note:** The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR as long as it does not require adjudication. If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event.	**Note:** The events listed in Appendix 1 are Clinical Events that are trial endpoints or expected events for this population, and do not generally fit the definition of a SUSAR, including those events with an outcome of death. However, if the investigator's assessment of an event is that it meets SUSAR criteria despite being listed as a Clinical Event, the event may be reported as a SUSAR via the **SAE eCRF** as long as it is not a **possible Primary or Secondary trial endpoint** (i.e. all events listed in Appendix 1 Section I). ~~If the investigator feels that a Clinical Event meets SUSAR criteria the **SAE eCRF** should be used to report the event.~~
Table 1		***Table format updated for clarity***
Section 10.3.2 Safety Reporting	**All SUSARS** will be reported in an expedited manner with the exception of those fulfilling the criterion of an efficacy endpoint (as detailed in Section I of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.	**All SUSARS** will be reported in an expedited manner with the exception of Primary and Secondary trial endpoints as detailed in Section I of Appendix 1, which will be handled as Clinical Events. ~~fulfilling the criterion of an efficacy endpoint (as detailed in Section I of Appendix 1: Primary or Secondary Trial Endpoints) which will be handled as Clinical Events.~~
Section 10.4 Calcitonin Monitoring	If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and will alert the usual care physician and study medication will be discontinued.	If a concerning calcitonin value (≥50 ng/L) is identified during trial follow-up, the site investigator will be notified and they should call the Trial Hotline for advice, where they will be instructed to alert the usual care provider and permanently discontinue study medication. ~~and will alert the usual care physician and study medication will be discontinued.~~
Section 10.5.1 Definition of an Overdose for This Protocol	The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose 1 day of the trial site becoming aware of the event.	The patient should be instructed to contact the investigational site, and/or healthcare provider in the event of an overdose ~~1 day of the trial site becoming aware of the event~~.
Section 13 Disclosure of Data and Publications	The Executive Committee, which includes principal investigators, Sponsor representatives, academic cardiologists and academic endocrinologists, will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.	The Executive Committee~~, which includes principal investigators, Sponsor representatives, academic cardiologists and academic endocrinologists,~~ will draft the manuscript describing the main study results, and oversee publications requiring trial data, samples, or genetic material.
Appendix 1	**CLINICAL EVENTS LIST (TO BE RECORDED IN THE CLINICAL EVENTS eCRF)**	**CLINICAL EVENTS LIST ~~(TO BE RECORDED IN THE CLINICAL EVENTS eCRF)~~** Any clinical event listed in this appendix that meets the criteria of an SAE (unless indicated otherwise below) must be reported in the Clinical Event eCRF reporting module.

SECTION	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
Appendix 1	Percutaneous Coronary Intervention (PCI)	Percutaneous Coronary Intervention (PCI) – including non-serious events
Appendix 1	C. Severe hypoglycemia / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma	C. Severe hypoglycemia (including non-serious events) / Hyperglycemia /Diabetic ketoacidosis / Hyperosmolar hyperglycemic nonketotic coma
Appendix 1	F. Diabetic nephropathy (including non-serious events) • Microalbuminuria • Proteinuria	F. Diabetic nephropathy (including non-serious events) • Microalbuminuria • Macroalbuminuria ~~Proteinuria~~
Appendix 1	G. Renal failure/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)	G. Renal failure~~/peritoneal or hemodialysis/renal transplant (including creation of fistula or other vascular access for hemodialysis)~~ • Acute renal failure, requiring or associated with hospitalization • Chronic renal failure, requiring peritoneal hemodialysis, including creation of fistula or other vascular access for hemodialysis • Renal transplant
Appendix 2	[5] Patients who terminate study medication are required to have a Drug Termination Visit as soon as possible following the cessation of study medication. Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.	[5] Patients who terminate study medication are required to have a Drug Termination Visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). ~~as soon as possible following the cessation of study medication.~~ Patients will continue to be observed following the Drug Termination visit according to their planned visit schedule for the remainder of the trial. All procedures for remaining Semi-annual and Annual Visits are to be followed with the exception of Drug Dispensation.
Appendix 2	*None*	[6] It is recommended that serum creatinine value draw dates be within 3 months of randomization but up to 12 months is acceptable (however, if > 6 months old and value is between 30-40mL/min/1.73m^2 it is recommended that a new serum creatinine value is obtained as part of usual care).
Appendix 2	*None*	[7] Blood sample for genetic and genomic analysis may be collected at any time during the trial after consent is obtained.
Appendix 4	*None*	*Added Protocol Amendment 02 Summary of Changes*

APPENDIX 6 PROTOCOL AMENDMENT 04: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **04**

Amendment Purpose: **Date: 12 September 2012**

The purpose of Amendment 04 is to change the sponsorship to include only Amylin Pharmaceuticals, LLC. In addition, minor changes have been included in the safety section to clarify reporting of serious adverse events, given the change in sponsorship. Notable changes are detailed in the table below.

SECTION	AMENDMENT 03 TEXT	AMENDMENT 04 TEXT
Global Change	Amylin Pharmaceuticals, Inc.	Amylin Pharmaceuticals, LLC
Title Page	Eli Lilly and Company	
Title Page	Throughout this protocol, unless otherwise specified, the term "Lilly" is used to refer to Eli Lilly and Company and its affiliates, acting as a representative of Amylin Pharmaceuticals, Inc. Amylin Pharmaceuticals, Inc. sponsors the Investigational New Drug Application in the US and Puerto Rico and will serve as the sponsor for the Clinical Trial Application in Canada. Amylin Pharmaceuticals, Inc. transfers the clinical sponsor obligations to Lilly for the conduct of this study outside the US, Puerto Rico and Canada. For investigative sites outside of the US, Puerto Rico and Canada, Lilly will serve as the study sponsor. The applicable party will hereinafter be referred to as the "sponsor".	Amylin Pharmaceuticals, LLC sponsors the Investigational New Drug Application.
List of Abbreviations	Alliance Amylin/Lilly exenatide consortium Amylin Amylin Pharmaceuticals, Inc.	Amylin Amylin Pharmaceuticals, LLC
Section 3 Trial Governance	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two sponsor representatives.	The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and sponsor representatives.
Section 3 Trial Governance	EXSCEL will be Co-Chaire PPD ut sponsored and funded by Amylin on behalf of the Alliance (Amylin & Eli Lilly).	EXSCEL will be Co-Chaired PPD ut sponsored and funded by Amylin.
Section 5.2 Exclusion Criteria	o. Is an employee of Eli Lilly and Company or Amylin Pharmaceuticals	o. Is an employee of Amylin Pharmaceuticals, LLC

SECTION	AMENDMENT 03 TEXT	AMENDMENT 04 TEXT
Section 10.3.2 Safety Reporting	These events must be recorded in this module (or faxed to Lilly if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event.	These events must be recorded in this module (or faxed to the number provided on the SAE report form if EDC is unavailable) within **24 hours** of a trial site becoming aware of the event.
Section 10.3.2 Safety Reporting	Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline to Amylin/Eli Lilly.	Additionally, any SAE considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator after study closeout must be reported within the above timeline.
Section 10.6 Reporting of Pregnancy	All occurrences of pregnancy must be reported via the Lilly Pregnancy/Breastfeeding Exposure Form.	All occurrences of pregnancy must be reported via the Pregnancy/Breastfeeding Exposure Form.
Appendix 5	*None*	*Added Protocol Amendment 03 Summary of Changes*

APPENDIX 7 PROTOCOL AMENDMENT 05: SUMMARY OF CHANGES

Exenatide QW Clinical Study Protocol BCB109

PROTOCOL TITLE: A RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIAL TO EVALUATE CARDIOVASCULAR OUTCOMES AFTER TREATMENT WITH EXENATIDE ONCE WEEKLY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Protocol Number: **BCB109**

Amendment Number: **05**

Amendment Purpose: **Date: 25 October 2013**

Based on blinded review of accrued data, the event rate for the primary composite CV endpoint is approximately 2.2 per 100 patient-year, which is less than the anticipated rate of 3.8 per 100 patient-year. To achieve completion of the study within the commitment date of the FDA Post-Marketing Request, a number of measures will be taken in protocol amendment 05:

1. The power of the study to achieve the primary objective of superiority of exenatide once weekly versus placebo with regard to the primary composite CV endpoint has been reduced from 90% to 85% resulting in a reduction of the targeted number of events from 1591 to 1360.

2. The total number of patients to be enrolled in order to achieve the targeted number of events is being increased from 9500 to 14000.

3. The proportion of patients enrolled with a prior history of a CV event is being increased from 60% to 80% (for newly enrolled patients). Since more than 7000 patients have been enrolled under the 60:40 scheme, it is anticipated that the ratio of patients with prior history of CV event to those with no prior CV event will be approximately 70:30 at study end. It is anticipated that more than 4000 patients (around 30%) without any prior CV history will be enrolled in the study.

In addition, the following changes are being made throughout this protocol amendment:

4. The secondary hypothesis of non-inferiority of exenatide once weekly compared with placebo with regard to the primary composite CV endpoint is updated to a primary safety hypothesis.

5. The end of study procedures have been clarified.

6. Clarifications have been made to the specifications around withdrawal of consent, lost-to-follow-up procedures, and the follow-up phone call for safety purposes after end-of-study discontinuation of study treatment.

7. Update to planned interim analyses as specified in the DSMB charter.

8. Administrative changes, such as, requirements for reporting of a potential serious breach of GCP, record retention, source documentation, case report form completion and the Clinical Study Report have been made.

Notable changes are detailed in the table below.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
Throughout	Trial / Early Termination Visit	Trial Termination Visit
1.2 Rationale for Conduct of the Study	Exenatide once weekly (EQW), a new formulation of exenatide that is administered once weekly rather than twice daily, has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.	Exenatide once weekly (EQW; BYDUREON), is an extended release formulation of exenatide that is administered once weekly rather than twice daily. EQW has been approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and in the European Union as an adjunct to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and SU, or a combination of metformin and TZD therapy to improve glycemic control in adult patients with type 2 diabetes mellitus.
2.1 Primary Objective	The primary objective of EXSCEL will be to evaluate the effect of EQW, used in conjunction with the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes. Objective: To compare the impact of including EQW as part of usual care vs. usual care without exenatide on major CV outcomes as measured by the primary CV composite endpoint of CV related death, nonfatal myocardial infarction (MI), or nonfatal stroke. Hypothesis: EQW, when used as part of usual care, is superior to usual care without exenatide with regard to the risk of developing a confirmed event in the primary CV composite endpoint.	The primary objective of EXSCEL will be to evaluate the effect of EQW, used in addition to the current usual care for glycemic control, on major macrovascular events when administered to patients with type 2 diabetes. Objective: To compare the impact of including EQW in addition to usual care vs. usual care without EQW on major CV outcomes as measured by the primary CV composite endpoint of CV related death, nonfatal myocardial infarction (MI), or nonfatal stroke. Hypotheses: Efficacy: EQW, when used in addition to usual care, is superior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint. Safety: EQW, when used in addition to usual care, is non-inferior to usual care without EQW with regard to the risk of developing a confirmed event in the primary CV composite endpoint.
2.2 Secondary Objectives	The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:	The secondary objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:
2.3 Additional Objectives	Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in conjunction with the current usual care for glycemic control on:	Additional objectives of EXSCEL are to evaluate the effect of EQW treatment used in addition to the current usual care for glycemic control on:

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
3 Trial Governance	EXSCEL is a multinational pragmatic trial that will be conducted in approximately 500 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin). EXSCEL will be Co Chaire PPD but sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of approximately eleven individuals, comprising nine senior independent academic representatives who are experts in their field and two sponsor representatives. It will be Co-Chaired PPD with other academic members comprising four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus.	EXSCEL is a multinational pragmatic trial that will be conducted in approximately 800 sites worldwide. It will be run jointly by the Duke Clinical Research Institute (DCRI) and the University of Oxford Diabetes Trials Unit (DTU) Academic Research Organizations (AROs), in an academic collaboration with Amylin Pharmaceuticals, LLC (Amylin), a wholly owned subsidiary of Bristol-Myers Squibb. EXSCEL will be Co Chaire P P D and sponsored and funded by Amylin. The EXSCEL Executive Committee (EC) will have overall responsibility for the oversight and management of the trial (Figure 1). The EC will consist of senior independent academic representatives who are experts in their field and sponsor representatives. It will be Co-Chaired PPD (see Section 12.1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
4.1 Design Description	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral AHAs or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 60% having had a prior CV event. Approximately 9500 patients meeting all enrollment criteria will be recruited in to the trial over an approximately three year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed up for a minimum of four years. The trial will continue until adjudicated 1591 primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments. Approximately one-third of patients will be enrolled in the Americas (North/South America & Canada), one-third in Europe and one-third in the Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period, which is expected to provide an average 5.5 patient years of follow up.	EXSCEL will be a multinational, placebo-controlled, double-blind, randomized, parallel group pragmatic clinical trial. Eligible patients will have type 2 diabetes with an HbA1c ≥6.5% and ≤10.0 % on up to three (i.e., 0-3) oral antihyperglycemic agents (AHAs) or insulin either alone or in combination with up to 2 (i.e., 0-2) oral AHAs. Patients enrolled will be at a wide range of CV risk with approximately 70% having had a prior CV event (see Section 6.3). Approximately 14,000 patients meeting all enrollment criteria will be recruited in to the trial over approximately a five year period, randomly allocated to treatment with either EQW 2 mg or matching placebo subcutaneous injections once weekly in a 1:1 ratio, and followed until the requisite number of primary endpoint events have been reported. The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued, or until the independent Data Safety Monitoring Board (DSMB) advises otherwise. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued); all patients will be expected to have follow-up through this date (Section 6). The trial will assess the impact of EQW therapy upon CV outcomes in a large population from a heterogeneous group of countries and practice environments; patients will be enrolled in the Americas (North/South America), Europe and Asia/Australasia. Given that this population will be at elevated CV risk, it is anticipated that patients will see their usual care provider at least twice per year for routine care. Trial follow up will consist of a blend of trial visits and phone calls during the double-blind placebo-controlled treatment period.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
4.2 Trial Duration	Minimum follow up for the last patient randomized will be 4 years unless the trial is terminated earlier. All patients that discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up if possible, for the full study period and will have their vital status ascertained, if possible, at the end of the trial.	It is anticipated that enrollment will occur over approximately a five year period, and that an additional 2 to 3 years may be required to accumulate the requisite number of patients with positively adjudicated primary endpoint events, for a total duration of up to approximately 7.5 years, unless the trial is terminated earlier. All patients who discontinue study medication, but have not withdrawn consent to participate in the study, will be followed up, if possible, for the full study period and will have their vital status ascertained, if possible, as of the data cut-off date for primary endpoint events.
4.3 Post Trial Access to Therapy	New Section in Amendment 05	At the end of the trial, the sponsor will not continue to supply study drug to patients/investigators. The investigator should ensure that the patient receives appropriate standard of care to treat the condition under study according to national treatment guidelines.
5.1 Inclusion Criteria	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained such that approximately 40% will not have had a prior CV event and 60% will have had a prior CV event	d. Patients with any level of CV risk and meeting all other inclusion criteria may be enrolled. Recruitment will be constrained (see Section 6.3) such that approximately 30% will not have had a prior CV event and 70% will have had a prior CV event
5.2 Exclusion Criteria	c. Patient has ever been treated with an approved or investigational GLP-1 receptor agonist e.g., BYETTA (exenatide), EQW, VICTOZA (liraglutide),or taspoglutide o. Is an employee of Amylin Pharmaceuticals, LLC.	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 o. Is an employee of Amylin Pharmaceuticals, LLC, Bristol-Myers Squibb Company, or AstraZeneca
5 Trial Population	New addition in Amendment 05	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.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.1 Trial Procedures - Overview	New addition in Amendment 05	The trial is planned to continue until 1360 patients with positively adjudicated primary endpoint events have been accrued. It is anticipated that the EXSCEL Executive Committee will monitor the accrual of the aggregate number of adjudicated primary endpoint events and will determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued; all patients will be expected to have follow-up through this date). Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visit will be established. NOTE: Patients who have temporarily or permanently discontinued trial medication should continue with their regular visit schedule. ALL patients should have a Trial Termination Visit (including patients who have previously discontinued trial medication). After the Trial Termination Visit patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. Patients who have discontinued trial medication 70 or more days prior to the Trial Termination Visit will not need to have the telephone contact visit performed. These patients will have their final assessment of serious adverse experiences and hospitalizations completed at the Trial Termination Visit. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).
6.3 Method of Assigning Patients to Treatment Groups (Visit 1)	New addition in Amendment 05	The IVRS will be programmed to ensure the expected overall proportion of randomized patients with a prior CV event is approximately 70%. With transition to Amylin-labeled trial medication (beginning in 2013), the IVRS was programmed to ensure at least 80% of newly randomized patients have a history of a prior CV event (previously was programmed to ensure approximately 60% of patients had a prior CV event).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.5 Concomitant Therapy	During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA1c goals. The Executive Committee (EC) and Operations Committee (OC) will provide a brief list of guidelines for usual care based on clinical care practice guidelines published by national and international societies that will be updated as knowledge about T2DM evolves over the course of the trial.	During the double-blind treatment period, investigators are expected to monitor patients' AHA regimens and communicate with usual care providers, who will be responsible for adjusting the AHA regimen in order to achieve locally-appropriate HbA1c goals based on clinical care practice guidelines published by national and international societies.
6.5 Concomitant Therapy	In addition, the degree of locally-appropriate HbA1c goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly.	~~In addition, the degree of locally-appropriate HbA1c goal-attainment at each site will be monitored centrally and sites with unusually low goal attainment will be advised accordingly.~~
6.6 Precautions to Minimize Rates of Hypoglycemia	The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.	~~The EXSCEL study team will also provide investigators with training materials to demonstrate best practice for minimizing hypoglycemia risk in these patients.~~
6.9 Genetic and Biomarker Sample Collection	Patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), annually and trial/early termination. All samples will be divided and stored in 2 aliquots at the Laboratory Corporation of America facility in Kannapolis, North Carolina, USA.	In addition, a subset of patients enrolled in the trial will be asked to consent separately to provide one serum sample, one plasma sample, and one urine sample for future biomarker analyses. These specimens (preferably fasting) will be obtained at baseline (prior to drug exposure), year 1 and at the Trial Termination visit.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.11 Temporary or Permanent Discontinuation of Trial Medication	Amendment 04 Section 6.12 Temporary Discontinuation of Trial Medication, Section 6.13 Permanent Discontinuation of Trial Medication Visit Procedures, and Section 6.15 Follow-up for Patients who Permanently Discontinue Trial Medication, were combined in Amendment 05 Section 6.11	Following randomization, it is expected that patients will remain on study medication for the duration of trial participation. However, it is recognized that patients may need to discontinue trial medication, in some cases permanently, for when protocol-specified reasons apply (Section 6.12), due to the judgment of the primary investigator or the decision of the patient. The Trial Hotline should be contacted whenever a site is considering interrupting or discontinuing trial medication (Section 6.18). Unless resumption of trial medication is considered unsafe or is refused by the patient, the patient will be expected to resume regular use of the blinded trial medication after a period of temporary discontinuation. Should a patient stop taking trial medication, either permanently or temporarily, the reasons for discontinuation and length of time the patient stopped taking trial medication will be assessed and recorded. All randomized patients who permanently discontinue trial medication should have a drug termination visit as part of their next scheduled study visit (unless a separate drug termination visit at that point is deemed necessary by the investigator). Necessary procedures are indicated in Appendix 2. All efforts should be made to reinforce with patients that this would be a medication discontinuation visit, not a trial discontinuation visit; patients should continue with their regular visit schedule until the end of the trial, including semi-annual in-person visits, as well as the annual calcitonin measurement. If patients cannot attend visits in person, they will be followed via telephone contact for all subsequent visits. NOTE: After trial medication is discontinued due to pregnancy, re-initiation of study medication can be considered following completion of the pregnancy and breastfeeding (if applicable).
6.12 Permanent Discontinuation of Trial Medication Per Protocol	Note: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia. The usual care provider will be provided with standard guidance by the trial investigator on down-titrating AHAs in the presence of hypoglycemia.	Note: The patient and the Investigator will notify the usual care provider of severe hypoglycemic events. The usual care provider should make a thorough attempt to down-titrate and/or modify co-interventional and baseline therapies that may contribute to hypoglycemia before discontinuing blinded trial medication for hypoglycemia.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.13 Trial Termination Visit 6.14 Post-Treatment Telephone Contact	Amendment 04 Section 6.11 Trial/Early Termination Visit and Post-Trial Telephone Contact was separated into sections 6.13 and 6.14 in Amendment 05. In addition, the timing of the post-treatment telephone contact was modified from 90 days to 70 days after the administration of the last dose of trial medication, if applicable.	6.13 Trial Termination Visit Investigators will be informed by the DCRI and DTU Coordinating Centers as to when the Trial Termination Visit is to be completed, and will schedule all patients for the Trial Termination Visit. Based on the primary endpoint event cut-off date, a window of time for conduct of the Trial Termination Visits will be established; this window will be a period of time following the primary endpoint event cut-off date. At the Trial Termination Visit, all patients must be discontinued from trial medication; the investigator should ensure that the patient receives appropriate standard of care. For procedural details of the Trial Termination Visit, refer to Appendix 2. NOTE: All patients should have a Trial Termination Visit. (Patients who have discontinued trial medication prior to the end of the trial must, at minimum, have a Trial Termination telephone contact.) If a patient fails to return or otherwise becomes difficult to contact, it is the investigator's responsibility to make every effort to maintain contact so that at the end of the trial the patient can be located to determine status and to obtain necessary information for serious adverse experience reporting and/or endpoint adjudication as of the primary endpoint event cut-off date. 6.14 Post-Treatment Telephone Contact After the Trial Termination Visit, patients will be contacted by telephone to check for any serious adverse experiences and hospitalizations that occurred within 70 days after the administration of the last dose of trial medication. For patients who have been discontinued from trial medication for more than 70 days as of the Trial Termination Visit, the Trial Termination Visit will be the final study follow-up. Note that all serious adverse experiences, hospitalizations, and reportable study events with an onset date after the primary endpoint event cut-off date established by the study Executive Committee will be managed as serious adverse experiences (see Section 10.3.1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.15 Withdrawal of Consent	New Section in Amendment 05	Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient explicitly withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law. When a patient withdraws consent from future follow-up prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at that time (Section 6.13).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
6.16 Lost to Follow-Up	New Section in Amendment 05	All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above as well as the usual care provider. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If an investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. Where specific consent has been obtained from the participant, the site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.
6.17 Breaking the Blind AND 10.7 Unblinding	New addition in Amendment 05	Patients whose treatment has been unblinded can continue to receive trial medication and can continue to be followed in the trial as described in this protocol.
8 Efficacy Assessments	Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. These definitions will be provided in a separate document, along with the description of the Clinical Events Classification Committee (CEC). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.	Trial endpoints will be defined based on clinical standards, regulatory precedent, and historical trials. The definitions of the events to be adjudicated by the Clinical Events Classification Committee (CEC) and the committee procedures will be included in the CEC Charter (Section 12.4). Patients will be asked at each trial visit about procedures and hospitalizations which have taken place since they were last seen.
8.2 Secondary Efficacy Endpoints	Time to first confirmed CV event for each component of the primary composite endpoint Defined as time from randomization to a confirmed CV-related death, nonfatal MI or nonfatal stroke.	Time to first confirmed CV event for each component of the primary composite endpoint Defined as time from randomization to a confirmed CV-related death, fatal or nonfatal MI, or fatal or nonfatal stroke.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
8.2 Secondary Efficacy Endpoints	Time to hospitalization for heart failure Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy.	Time to hospitalization for heart failure Defined as time from randomization to hospital admission for congestive heart failure requiring treatment with increased oral or intravenous diuretics, inotropes, or vasodilator therapy.
9.2 Sample Size	The planned sample size for this study is 9500 patients, randomized 1:1 to each of the two treatment arms assuming: • An annual composite cardiovascular primary endpoint event rate estimated to be 3.8% per year for the population to be enrolled. • A planned accrual period of 3 years • A minimum treatment period of 4 years • An estimated annual lost-to-follow up rate of 1% • An anticipated treatment discontinuation rate of 5% per year The number of cardiovascular primary endpoint events required is commensurate with a 90% power to detect a 15% relative risk decrease in the EQW group, i.e. a true hazard ratio of 0.85 relative to placebo, with a two-sided alpha=0.05. For an exponential maximum likelihood test of equality of survival curves, a total of 1591 composite cardiovascular events were calculated to be required using nQuery.	The primary endpoint is the time from randomization to the first confirmed CV event defined as a CV-related death, nonfatal MI or nonfatal stroke. The study is designed to assess the primary efficacy objective of superiority of EQW to placebo through the following hypothesis: H0: upper limit of the 95% CI of the HR [exenatide:placebo] ≥ 1 versus H1: upper limit of the 95% CI of the HR [exenatide:placebo] < 1 In order to test the above hypothesis with 85% power and 2-sided α=0.05, a total number of 1360 composite CV events are required assuming a risk reduction of 15% on EQW compared with placebo. With this number of events, the power will be much larger than 90% to assess the primary safety objective of non-inferiority of EQW compared with placebo. In addition, with the following assumptions made for this study, • An annual composite cardiovascular primary endpoint event rate estimated to be around 2.2% per year for the population to be enrolled • A planned accrual period of 5-6 years • An estimated annual lost-to-follow up rate of 1% • An anticipated treatment discontinuation rate of 5% per year it is expected that a total of 14000 patients need to be randomized in a 1:1 ratio into EQW and placebo to achieve the targeted 1360 confirmed composite CV events.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.4 Primary Hypothesis	The primary hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular outcome, with the participants analyzed according to their allocated treatment (intention to treat).	The primary efficacy hypothesis is that EQW will be superior to placebo with respect to the primary composite cardiovascular endpoint, defined as the time from randomization to the first confirmed CV-related death, nonfatal MI or nonfatal stroke with the patients analyzed as randomized. The primary safety hypothesis is that EQW will be non-inferior to placebo with respect to the primary composite cardiovascular endpoint, with patients analyzed as randomized.
Secondary Hypothesis	This section (9.5) from Amendment 04 was deleted	Not applicable

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.5 Primary Analysis	Statistical analyses will be based upon adjudicated outcomes with patients who discontinue prematurely from treatment followed until the end of the study, i.e. until the requisite number of primary composite events has been accrued. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with participants analyzed according to their allocated treatment (intention to treat). A log rank test will be performed first, with Kaplan-Meier curves for time to event used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time of occurrence of the composite endpoint for the EQW and placebo treated groups and its 95% confidence interval will then be estimated using a Cox proportional hazards model without covariate adjustment. Secondary Cox proportional hazards model analyses using covariate adjustments will also be performed as detailed in the SAP.	The primary statistical analysis will be based upon adjudicated CV events with patients who discontinue prematurely from treatment followed until the end of the study, i.e. until the requisite number of primary composite events has been accrued. It is anticipated that the Executive Committee will monitor the accrual of the aggregate number of primary composite CV events to determine the primary endpoint event cut-off date (i.e., the date at which the anticipated number of events is expected to have accrued). All patients will be expected to have follow-up through this date. Analysis of the primary composite cardiovascular outcome will be based on the time from randomization to the occurrence of the first event, with patients analyzed according to their randomized treatment. The primary analysis will include all adjudicated CV events with onset dates up to and including the primary endpoint event cut-off date. Kaplan-Meier curves for time to the first occurrence of a primary composite endpoint event will be used to depict the accumulation of events over time for the EQW and placebo treatment groups. The hazard ratio for the time to first occurrence of the primary composite endpoint event for the EQW treated group to that of the placebo treated group and its 95% confidence interval will then be estimated using a Cox proportional hazards model stratified by baseline CV risk group (prior CV event or no prior CV event) and using treatment group as covariate. The primary safety hypothesis will be assessed by a non-inferiority analysis with the non-inferiority margin of 1.30, i.e., non-inferiority will be concluded if the upper limit of the confidence interval is less than 1.30. The primary efficacy hypothesis of superiority will be then assessed by the 95% confidence interval for the hazard ratio of EQW to placebo, i.e., superiority will be concluded if the 95% confidence interval does not include 1 (upper limit of 95% confidence interval < 1).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.6 Secondary Efficacy Analyses	Secondary analyses will be conducted with participants analyzed according to their allocated treatment (intention to treat) with a Hochberg adjustment for multiple testing. These analyses will examine: 1. All cause mortality 2. Fatal or nonfatal myocardial infarction 3. Fatal or nonfatal stroke 4. Hospitalization for acute coronary syndrome (ACS) 5. Hospitalization for congestive heart failure (CHF)	The secondary efficacy endpoints are the time to confirmed occurrence of: 1. All cause mortality 2. CV-related death 3. Fatal or nonfatal myocardial infarction 4. Fatal or nonfatal stroke 5. Hospitalization for acute coronary syndrome (ACS) 6. Hospitalization for congestive heart failure (CHF) Details of the testing strategy of the secondary efficacy endpoints will be provided in the Statistical Analysis Plan (SAP).
9.7.1 Intent-To-Treat Population	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the date of final post-study telephone contact, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the date of their final post-study telephone contact. Every effort will be made to collect CV events to study termination even in those who have discontinued study medication or the study. For the ITT population, any patient found to have taken a study medication for the entire duration of the study that is different from that to which he/she was randomized will be counted in the treatment group of the drug to which he/she was randomized.	The ITT population consists of all randomized patients. Evaluation will include all events which occurred from randomization to the primary endpoint event cut-off date, regardless of the time interval between patient discontinuation of study drug and final contact. Patients who do not have any events during the study will be censored at the primary endpoint event cut-off date. Every effort will be made to collect CV events through the primary endpoint event cut-off date even in those who have discontinued study medication or the study. For the ITT population, patients will be analyzed as randomized.
9.7.1.1 On-Treatment Analysis	New addition in Amendment 05	An on-treatment analysis using the ITT population will be performed for the primary and secondary analyses as sensitivity analyses. This analysis will include only those events that occurred within 70 days of the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. The patients will be analyzed according to the treatment group to which they were randomized.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.7.2 Per-Protocol Population	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations such as: • Initiation of an open-label prohibited medication i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Discontinuation from study medication. Evaluation will include events which occurred from randomization to 90 days after the last dose of study medication. • Taking incorrect study medication for more than three months. All such protocol violations will be identified prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. If a patient is found to have taken a study medication for any duration of the study that is different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received. Patients who do not have any events during the study will be censored 90 days after the last dose of study medication.	The Per-Protocol population consists of all randomized patients who have taken at least one dose of study medication and will include in their analysis all data collected prior to any major protocol violations (or primary endpoint event cut-off date, whichever occurs first), such as: • Initiation of an open-label prohibited medication i.e. a GLP-1 receptor agonist. Evaluation will include all data up to the day of the initiation of the prohibited medication. • Early discontinuation from study medication. Evaluation will include events which occurred from randomization to 70 days after the last dose of study medication or the primary endpoint event cut-off date, whichever occurs first. • Taking incorrect study medication for more than three months. All protocol violations will be specified in the statistical analysis plan prior to unblinding of the data. Events that occurred after protocol violation will be excluded from the analysis. Patients will be analyzed as randomized. The primary safety and primary efficacy analyses will be repeated with the per-protocol population as sensitivity analyses.
9.7.3 Safety Population	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 90 days after the last dose of study medication, will be collected.	Serious AEs, including those which lead to discontinuation of study medication, occurring between randomization and 70 days after the last dose of study medication, will be summarized.
9.9 Subgroup Analyses	The subgroups will be divided by categories or by the tertiles for continuous variables.	~~The subgroups will be divided by categories or by the tertiles for continuous variables.~~

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
9.10 Interim Analyses	The DSMB will review available data every 6 months or more frequently if the committee deems it appropriate as outlined in the DSMB Charter. Stopping guidelines will be detailed in the DSMB Charter. The overall alpha=0.05 will be preserved by limiting the number of interim superiority analyses conducted as detailed in the DSMB Charter. The DSMB may, however, advise stopping the study before the minimum follow-up of 4 years has been achieved on ethical or safety grounds.	The DSMB will undertake safety reviews of all available data every 6 months or more frequently if the committee deems it appropriate. Two formal interim efficacy analyses are planned after approximately 453 and 906 primary composite CV events are adjudicated, corresponding to one-third and two-thirds, respectively, of the targeted 1360 primary composite CV events. The analyses will test for superiority using a Haybittle-Peto spending function where the study termination guideline for overwhelming superiority will be p-value < 0.0001 for the first interim analysis and p-value <0.001 for the second interim analysis. This will ensure a significance level of 0.0499 for the final analysis. If the stopping boundary for efficacy is met at either of the interim analyses, the DSMB may recommend terminating the study earlier than planned. The DSMB may, however, also advise terminating the study early for safety or ethical reasons. The interim analyses will be performed by an independent statistical group. Further details of the interim analyses are provided in the DSMB Charter.
10.2 Adverse Event Assessment	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 90 day post trial medication follow-up period or withdrawal.	Adverse events will be monitored over the course of the trial, starting from the time of randomization and through the duration of the patient's participation, including the 70 day post trial medication follow-up period.
10.3.1 Recording Adverse Events	SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1). Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) components of the primary or secondary composite cardiovascular endpoints, (2) other trial endpoints, (3) potential components of the CV endpoint that are included among terms sent for review by the CEC; (4) expected sequelae of type 2 diabetes (Table 1). These events represent trial outcomes and expected events for this population.	SAEs will be recorded in the Clinical Events or SAE eCRF modules as appropriate (see Table 1) through the primary endpoint event cut-off date; ALL SAEs with onset dates AFTER the primary endpoint event cut-off date will be recorded in the SAE eCRF module. Guidelines for events which qualify as Clinical Events are provided in Appendix 1. Events to be recorded in the Clinical Events eCRF module include SAEs that are: (1) Obvious trial endpoints, (2) Cardiovascular Events of Interest, (3) Expected Events and Diabetic Complications.
Table 1: List of events to be recorded in each eCRF reporting module	SAE eCRF: Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are not listed in Appendix 1	SAE eCRF: Any event meeting the criteria of an SAE (see Section 10.1 for definition of SAE) that are not listed in Appendix 1 and all events above with an onset date after the primary endpoint event cut-off date

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
10.3.2 Safety Reporting	As described above, all SAEs that are not included in the Clinical Events List will be recorded by the investigator in the SAE eCRF module.	As described above, all SAEs that are not included in the Clinical Events List and "Clinical Events" with onset dates after the primary endpoint event cut-off date will be recorded by the investigator in the SAE eCRF module.
10.3.2 Safety Reporting	New addition in Amendment 05	Note that pancreatitis and pancreatic neoplasms / malignancies are events of special interest for GLP-1 based therapies, such as exenatide. As described above, all events of pancreatitis and all neoplasms (including pancreatic cancer) are to be reported on both the Clinical Events eCRF and the SAE eCRF, even if the event does not meet seriousness criteria. These events are reviewed by the DSMB and adjudicated by the CEC.
10.6 Reporting of Pregnancy	Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 90 days of completing the trial.	Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the trial or within 70 days of completing the trial.
11.3 Consent and Collection of Biomarker Specimens	Patients providing informed consent will have a blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), annually, and at the time of trial termination.	Patients providing informed consent will have blood and urine samples, preferably fasting, collected at baseline (prior to drug exposure), Year 1, and at the Trial Termination visit.
11.5 Ethical Conduct of the Study	New addition in Amendment 05	The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor. All potential serious breaches must be reported to the sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study. Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
11.8 Records	New Section in Amendment 05	11.8.1 Records Retention The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study. The sponsor will notify the investigator when the study records are no longer needed. If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor. 11.8.2 Case Report Forms An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study. The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing electronic CRFs must meet training requirements and must only access the electronic data capture tool using their unique user account. User accounts are not to be shared or reassigned to other individuals.

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
12.1 Executive Committee (EC)	The EC will be composed of approximately eleven individuals consisting of nine senior independent academic representatives who are experts in their field and two representatives from the Alliance. The Committee will be co-chaired PPD The other academic members will comprise four further diabetologists and three further cardiologists. Geographical balance will be sought. Decision making will be by consensus. An EC charter will delineate operating procedures. The Executive Committee is the main decision-making body for EQW and is charged with the overall scientific, professional, and operational conduct of the trial.	The EC will be composed of senior independent academic representatives who are experts in their field and representatives from the sponsor. The Committee will be co-chaired PPD An EC charter will outline the committee membership and structure and delineate operating procedures. The Executive Committee is the main decision-making body for the EXSCEL trial and is charged with the overall scientific, professional, and operational conduct of the trial.
12.3 Data Safety Monitoring Board (DSMB)	DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the Sponsor. In addition, the DSMB will evaluate interim analyses of the data every six months (or on an ad hoc basis if needed) to determine if it believes either the trial should be terminated early because the exenatide arm (with respect to the placebo arm) demonstrates (a) clear inferiority, i.e., it is not in patient's best interest to continue taking blinded therapy; or (b) clear superiority, i.e., it is not in patient's best interest to continue taking blinded placebo.	DTU will transfer pre-agreed masked datasets to the Independent Statistician who will then prepare unmasked confidential reports for the DSMB, using treatment codes provided in advance by the IVRS vendor. In addition, the DSMB will evaluate two interim analyses after approximately one-third and two-thirds of the total targeted number of primary composite CV events (see Sec 9.10 for details).
13 Disclosure of Data, Publications, and Clinical Study Report	Following submission for publication of the main trial results, a copy of the database will be transferred to the Sponsor. New addition in Amendment 05:	~~Following submission for publication of the main trial results, a copy of the database will be transferred to the Sponsor.~~ In addition, a Clinical Study Report (CSR) will be prepared for regulatory purposes. The Signatory Investigator responsible for signing the CSR will be selected by the Sponsor in conjunction with the Executive Committee.
Appendix 1: Clinical Events List	List re-organized from: I. Primary or Secondary Trial Endpoints A. Obvious Trial Endpoints B. Cardiovascular Events of Interest II. Expected Events and Diabetic Complications	I. Obvious Trial Endpoints II. Cardiovascular Events of Interest III. Expected Events and Diabetic Complications

SECTION	AMENDMENT 04 TEXT	AMENDMENT 05 TEXT
Appendix 1: Clinical Events List (Obvious Trial Endpoints)	Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI]/cerebrovascular accident [CVA]/ congestive heart failure [CHF]/arrhythmia, cardiac arrest, death following CV intervention)	Death • Cardiovascular (CV) Death (i.e., fatal myocardial infarction [MI] /cerebrovascular accident [CVA] / congestive heart failure [CHF] / arrhythmia, cardiac arrest, death following CV intervention) • Non-CV Death
Appendix 1: Clinical Events List (Expected Events and Diabetic Complications)	G. Renal Failure • Chronic renal failure, requiring peritoneal hemodialysis, including creation of fistula or other vascular access for hemodialysis	G. Renal Failure • Chronic renal failure, requiring peritoneal ***or*** hemodialysis, including creation of fistula or other vascular access for hemodialysis
Appendix 2: Trial Plan	New addition in Amendment 05	Added "Post-Treatment Follow-up Contact"
Appendix 2: Trial Plan	Blood sample (serum and plasma) and urine sample for archive - specimens obtained at baseline (prior to drug exposure), annually and trial/early termination.	Blood sample (serum and plasma) and urine sample for archive - specimens obtained at baseline (prior to drug exposure), Year 1 and at the Trial Termination visit.
Appendix 2: Trial Plan	EQ-5D Completion listed for "Drug Termination Visit"	EQ-5D Completion removed from "Drug Termination Visit" consistent with Section 6.10
Appendix 6	None	Added Protocol Amendment 04 Summary of Changes