A NON-RANDOMIZED, POST MARKETING CLINICAL FOLLOW-UP (PMCF) STUDY OF THE DESyne® X2 NOVOLIMUS ELUTING CORONARY STENT SYSTEM IN THE TREATMENT OF PATIENTS WITH *DE NOVO* NATIVE CORONARY ARTERY LESIONS

"DESyne X2 PMCF Study"

ELX-CL-1705

Revision C

Date: 18 September 2020

DATA MANAGEMENT AND STATISICAL ANALYSIS	Elixir Medical, Milpitas, CA, USA.
STUDY MONITOR	Elixir Medical, Milpitas, CA, USA.
STUDY SPONSOR	Elixir Medical, Milpitas, CA, USA.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

In this amendment the Sponsor is adding into the study the following: the 2.25mm stent in 14, 18, 23, 28, 32, and 38mm lengths, and an update to the inclusion and exclusion criteria to allow enrollment of a broader range of patients. A few minor administrative updates are also included. A Table of Changes for the protocol is provided below. These changes neither affect subjects' rights, safety and welfare, nor the scientific soundness of the study. The Coordinating Investigators and Principal Investigators have been updated on the changes.

Protocol ELX-CL-1705 Rev B	Change to protocol ELX-CL-1705 Rev C	Location in Protocol / Section Number	Rationale
Stent sizing included 2.5 mm – 4.0mm diameters in the 14, 18, 23, 28, 32, and 38 mm lengths	Stent sizing included 2.25 mm – 4.0mm diameters in the 14, 18, 23, 28, 32, and 38 mm lengths	Protocol Summary, Sections 2.2 and 3.5.2	The inclusion of 2.25mm stent in 14, 18, 23, 28, 32 and 38mm lengths will allow enrollment of a broader range of patients
Inclusion/Exclusion Criteria	Changes to inclusion/exclusion criteria	Protocol Summary, Sections 3.1, 3.2, 3.3 and 3.5.2	Inclusion are broadened and exclusion criteria reworded to allow a wider range of patient inclusion. These changes include: • Single site inclusion of up to 40 patients or (40% of the total patients) • No 4. Inclusion of 2.25mm lesions, and inclusion of up to 3 lesions in separate epicardial vessels. • Exclusion criteria: No. 3. clarification of previous stent implantation location (removal of "distal"); • replacement of No. 8 "Lesion involvement of a significant side branch (branch diameter > 2 mm) that would be covered by stenting" with "Bifurcation lesion with planned 2-stent technique"; • rewording of No. 11 MI exclusion to "Patient has a diagnosis of ST elevation myocardial infarction (STEMI) within 72 hours preceding the index procedure, and CK and CK-MB have not returned within normal limits at the time of procedure";

			• rewording of No. 14 “patients participating in another investigational device study that has not completed the primary follow-up phase” to “patient is currently participating in another investigational device study that has not completed the primary follow-up phase, or patients participating in any DAPT or other thrombus/platelet related studies that that has not completed the primary follow-up phase, or enrolled into more than one study on the day of the index procedure.” These changes neither affects subjects’ rights, safety and welfare, nor the scientific soundness of the study.
Time Course enrollment start Q1 2019 and enrollment completion Q3 2019	Time Course enrollment start Q2 2020 and enrollment completion Q1 2021	Protocol Summary	Extension of the Time Course for the study to accommodate the late start of the study enrollment
Bailout Use of non-DESyne X2 Stent in case of bailout	Bailout Include use of DESyne X2 Stent in case of bailout	Section 3.5.3	The DESyne X2 stent maybe used for bailout in cases of dissection, occlusive complication or incomplete lesion coverage requiring additional stent placement.
	Minor administrative changes and spelling/formatting corrections	Throughout Protocol	Minor administrative changes, minor clarifications, spelling and formatting corrections.

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1.0 DESyne X2 PMCF PROTOCOL SUMMARY

Design:	Prospective, non-randomized, multicenter, international Post Marketing Clinical Follow-up (PMCF) study
Enrollment:	Enrollment of up to 100 patients with up to three *de novo* native coronary artery lesions measuring between 2.25 and 4.0 mm in diameter and ≤ 34 mm in length receiving the DESyne X2 Novolimus Eluting Coronary Stent System (CSS).
Clinical Site Locations:	Drawn from up to 10 International Sites
Objective and Rationale:	To confirm the performance of the DESyne X2 Novolimus Eluting Coronary Stent System with regards to the residual risks of lesion access and acute device implantation through visually-assessed angiographic endpoints and physician feedback and demonstrate that these characteristics are not different than the DESyne Novolimus Eluting CSS. A single-arm study comparing the DESyne X2 PMCF data to the historic DESyne acute performance data will confirm that the DESyne X2 delivery system performs similarly to the DESyne delivery system.
Key Endpoints:	Acute Device Success: attainment of final result with < 50% residual stenosis of the target site, using a DESyne X2 stent and standard pre-dilation catheters and post-dilatation catheters (if applicable) Device preparation Lesion access and cross Stent expansion Delivery system removal Stent crossability for post-dilatation as required Device malfunction assessment
Time Course:	Initial Enrollment Q3 2020 Enrollment Complete Q2 2021
Inclusion Criteria:	Candidates for this study must meet all of the following criteria: 1) The patient must be ≥18 years of age. 2) The patient must have stable angina pectoris as defined by the Canadian Cardiovascular Society Classification, documented silent ischemia, acute coronary syndrome, or a positive functional study requiring treatment 3) The patient is considered a candidate for coronary stent implantation and has a planned intervention of up to

	three lesions located in separate major epicardial territories. Each lesion/vessel must meet the following criteria: a. *De novo* lesion b. The target lesion reference site must be visually estimated to be ≥ 2.25 mm and ≤ 4.0 mm in diameter* c. The target vessel must be a major coronary artery or major branch with a visually estimated stenosis of ≥ 50% and < 100%. d. The visually estimated target lesion length must be ≤ 34 mm* e. ≥ TIMI 1 coronary flow *Subject to commercial availability of product sizes in the specific region/country
Exclusion Criteria:	Candidates will be ineligible for enrollment in the study if any of the following conditions apply: 1) The patient has a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, prasugrel or ticagrelor, heparin/bivalirudin, mTOR inhibitor class drugs, cobalt chromium alloy, methacrylate or polylactide polymer, or sensitivity to contrast which cannot be adequately premedicated 2) Women of childbearing potential who have not undergone surgical sterilization or are not post-menopausal (defined as amenorrheic for at least one year) as well as women who are pregnant or nursing 3) Previous placement of a stent within 10 mm of the target lesion 4) Previous placement of a stent proximal to the target lesion 5) Total occlusion or < TIMI 1 coronary flow in the target vessel 6) The proximal target vessel or target lesion is severely calcified by visual assessment 7) Aorto-ostial location, unprotected left main lesion location, or a lesion within 5 mm of the origin of the LAD or LCX 8) Bifurcation lesion with planned 2-stent technique 9) High probability that treatment other than PTCA or stenting will be required for treatment of the same lesion

	10) The target lesion, or the target vessel proximal to the target lesion, contains thrombus 11) Patient has a diagnosis of ST elevation myocardial infarction (STEMI) within 72 hours preceding the index procedure, and CK and CK-MB have not returned within normal limits at the time of procedure 12) The patient is a recipient of a heart transplant 13) The patient has extensive peripheral vascular disease that precludes safe sheath insertion or extreme anti-coagulation 14) The patient is currently participating in another investigational device study that has not completed the primary follow-up phase, or patients participating in any DAPT or other thrombus/platelet related studies that that has not completed the primary follow-up phase, or enrolled into more than one study on the day of the index procedure. 15) Patients who are unable or unwilling to cooperate with study procedures
Clinical and Laboratory Procedures:	It is recommended that the hospital standard testing for coronary stent placement such as an electrocardiogram and cardiac enzymes are completed.
Concomitant Medical Therapy:	It is recommended that all patients receive dual antiplatelet therapy including aspirin and thienopyridine/P2Y12 Inhibitor for at least one year as currently recommended by the AHA/ACC guidelines and hospital standards.

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2.0 INTRODUCTION

2.1 Background and Rationale

Pertinent prior clinical experience with Elixir's DESyne or DESyne BD Novolimus Eluting Coronary Stent System (CSS) includes two randomized studies: the EXCELLA II Randomized Study - Phase 1 and the EXCELLA II Randomized Study – Phase 2.

The EXCELLA II Randomized Clinical Trial - Phase 1 was a single blind, consecutive enrollment, non-inferiority trial which enrolled a total of 210 patients at 21 international sites wherein the Principal Investigator was Professor Patrick W. Serruys, MD, PhD. Co-Principal Investigators included Alexandre Abizaid, MD, PhD, John Ormiston, MD and Stephan Windecker, MD. The study was designed to evaluate the safety and efficacy of the Elixir DESyne Novolimus Eluting Coronary Stent System as compared to the Endeavor Zotarolimus Eluting Coronary Stent System (Medtronic Vascular, Santa Rosa, CA). The primary endpoint for this study was the in-stent late lumen loss assessed by QCA at 9 months. Key secondary endpoints included the device-oriented composite endpoint (DoCE) inclusive of cardiac death, myocardial infarction attributable to the target lesion and clinically-indicated target lesion revascularization evaluated at 30 days, 6, 9, 12 and 24 months. The in-stent percent volume obstruction (%VO) was measured in a sub-group of 65 patients having 9-month intra-vascular ultrasound (IVUS) follow-up.

At 9-months, the in-stent late lumen loss was 0.11 ± 0.32 mm in the DESyne stent arm, as compared to 0.63 ± 0.42 mm in the Endeavor stent arm ($p<0.001$ non-inferiority, $p<0.001$ superiority). In-stent %VO by IVUS was 4.5 ± 5.1% and 20.9 ± 11.3% for the DESyne stent and the Endeavor stent, respectively ($p<0.001$). There was a significant difference between stent groups in the device orientated composite endpoint (DESyne 7.9% vs.

Endeavor 19.7%, p=0.02) indicating superior clinical results driven primarily by the reduction in TLR for the DESyne stent.[1] .

The EXCELLA II Phase 2 Randomized Clinical Trial is a single blind, consecutive enrollment, non-inferiority trial which enrolled a total of 145 patients at 11 international sites. The study was designed to evaluate the safety and efficacy of the Elixir DESyne BD Novolimus Eluting Coronary Stent System with bioabsorbable polymer as compared to the Endeavor Zotarolimus Eluting Coronary Stent System (Medtronic Vascular, Santa Rosa, CA). The primary endpoint for this study is in-stent late lumen loss assessed by QCA at 6 months. Key secondary endpoints include a device-oriented composite endpoint inclusive of cardiac death, myocardial infarction attributable to the target lesion and clinically-indicated target lesion revascularization evaluated at 30 days, 6, 9, and 12 months and annually through 5 years as well as additional angiographic and IVUS endpoints. Patient enrollment into this study is complete with follow-ups ongoing through 5 years.

At 6 months, the primary endpoint of mean in-stent LLL was significantly lower for the DESyne BD Novolimus Eluting CSS compared to the Endeavor Zotarolimus-Eluting CSS, (0.12 ± 0.15 mm vs. 0.67 ± 0.47 mm, non-inferiority $p<0.001$, superiority $p<0.001$. At 60 months, there was no significant difference between study arms in the modified intent to treat (MITT) analysis of the device orientated composite endpoint (DESyne BD Novolimus Eluting CSS 8.0% vs. Endeavor Zotarolimus-Eluting CSS 9.7%, $p = 0.72$) or its individual components of cardiac death, target vessel MI and CI-TLR.

The DESyne Novolimus Eluting Coronary Stent System and the DESyne BD Novolimus Eluting Coronary Stent System have both demonstrated excellent results in clinical studies to date.

2.2 DESyne® X2 Novolimus Eluting Stents Coronary Stent System

The DESyne® X2 Novolimus Eluting Coronary Stent Systems is comprised of four key components including the delivery system, stent, the active drug substance Novolimus, and polymer that controls the release of the drug. The stent, drug substance, drug dose, and polymer of the DESyne X2 NECSS are the same as those used in the DESyne NECSS. The stent, drug substance, and drug dose are the same as those used in the DESyne BD NECSS. The main difference between the DESyne X2 NECSS and the DESyne and DESyne BD NECSS is the delivery system used on the DESyne X2 NECSS. The updated delivery system is used in the same manner and has the same accessory compatibility as the DESyne and DESyne BD delivery systems. The delivery systems have differences with respect to dimensions and materials; however these dimensions and materials similar to other percutaneous balloon delivery systems.

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[1] Iqbal, J, Verheye, S, Abizaid, A, et al., DESyne Novolimus-Eluting Coronary Stent Is Superior to Endeavor Zotarolimus-Eluting Coronary Stent at Five-Year Follow-up: Final Results of the Multicentre EXCELLA II Randomised Controlled Trial. EuroInter. 2016 Dec;12(11):e1336-e1342.

The DESyne X2 delivery system provides a means for carrying the stent through the coronary vasculature to the desired location and expanding the stent through inflation of the balloon. The delivery system is comprised of standard materials with a stainless steel hypotube proximally, a nylon blend shaft distally and nylon blend balloon. The premounted stent is made of cobalt chromium alloy. It is available in diameters of 2.5 mm, 2.75 mm, 3.0 mm, 3.5 mm and 4.0 mm with lengths of 14 mm, 18 mm, 28 mm, 32 mm and 38 mm[2]. The stent has a nominal strut thickness of 0.0032" (0.08 mm) with an 8-crown pattern for the 3.0, 3.5, and 4.0 mm sizes and a 6-crown pattern for the 2.25, 2.5 and 2.75 mm sizes. The DESyne X2 delivery system is substantially similar to the DESyne and DESyne BD delivery systems.

The DESyne X2 Novolimus Eluting Coronary Stent Systems to be evaluated in this study are loaded with approximately 5 mcg of Novolimus per mm of stent length (85 mcg for an 18 mm stent). The DESyne stent is coated with a formulation comprised of Novolimus and a proprietary durable methacrylate polymer which allows sustained release of the drug over a period of 12 weeks. Detailed information on the DESyne X2 Novolimus Eluting CSS can be found in the Instructions for Use.

2.2.1 Novolimus

Novolimus is a metabolite of sirolimus and belongs to the family of compounds of macrocyclic lactones with immunosuppressive and anti-proliferative properties and has a similar mechanism of action to other macrocylic lactones such as rapamycin. Macrocyclic lactones bind to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle. As stated above, this is the same drug used on the DESyne NECSS and the DESyne BD NECSS.

2.2.2 Polymer Coating

The polymer coating is mixed with the drug and applied over the entire surface of the stent. The purpose of either the durable polymer coating is to moderate the delivery of the drug over a period of time. The durable coating is a methacrylate polymer and is similar to polymers that have been used clinically on vascular implants and proven to be safe. The coating and drug provide a thin layer on the stent but do not affect the overall performance of the stent. Note that the amount of polymer applied to the stent is substantially less than other available DES devices using similar polymers. As stated above, this is the same polymer used on the DESyne NECSS.

[2] Not all lengths available in all regions. Subject to commercial availability. Availability is based on regulatory and hospital approvals.

2.3 Risk Assessment

The Elixir DESyne and DESyne BD Novolimus Eluting Coronary Stent Systems have demonstrated excellent clinical safety and efficacy in both the EXCELLA II Randomized Study – Phases 1 and 2. Both of these systems have received CE Mark approval. A post market clinical follow-up study of the DESyne X2 device, which has also received CE Mark approval, is desired to confirm the performance of the DESyne X2 Novolimus Eluting Coronary Stent System with regards to the residual risks of lesion access and acute device implantation through visually-assessed angiographic endpoints and physician feedback and demonstrate that these characteristics are not different than the DESyne Novolimus Eluting CSS. These attributes are most directly related to the performance of the updated delivery system, including stent mounting on the delivery system balloon.

The safety profile and the known mechanism of action of the drug, Novolimus, and the biocompatibility of both the durable methacrylate polymer coating in combination with the scaffolding properties of the DESyne CSS provide a safe and effective method for reducing neointimal hyperplasia. Therefore, the benefits of the acute lesion scaffolding and long-term reduced incidence of restenosis in the treatment of ischemic coronary artery disease have already been demonstrated to outweigh the risks associated with the use of these devices and are applicable to the DESyne X2 NECSS. The use of the DESyne X2 NECSS has the same risk profile as the DESyne NECSS and the DESyne BD NECSS. No differences in risk or the risk/benefit ratio are expected with the use of the updated delivery system of the DESyne X2 NECSS.

2.4 Study Objectives

A single-arm post-market follow-up study (PMCF) comparing the DESyne X2 PMCF data to the historic DESyne acute performance data to confirm the performance of the DESyne X2 Novolimus Eluting Coronary Stent System with regards to the residual risks of lesion access and acute device implantation through visually-assessed angiographic endpoints and physician feedback.

2.5 Summary of Study Design

This PMCF study will enroll up to 100 male and female patients with up to two *de novo* native coronary artery lesions who satisfy all entry criteria. Study endpoints will be summarized.

2.6 Study Endpoints

The endpoints for this post-marketing clinical follow-up study include:

- Acute Device Success: attainment of final result with < 50% residual stenosis of the target site, using a DESyne X2 stent and standard pre-dilation catheters and post-dilatation catheters (if applicable)

Physician feedback will be obtained for the following device characteristics:

- Device preparation
- Lesion access and cross
- Stent expansion
- Delivery system removal
- Stent crossability for post-dilatation as required
- Device malfunction assessment

3.0 MATERIALS AND METHODS

3.1 Selection of Subjects

The study will include up to 100 male and female patients all with *de novo* native coronary artery lesions who meet eligibility criteria and agree to participate in the trial. Sites may enroll up to a maximum of 40 patients per site, or 40% of the total number of enrolled patients.

3.2 Inclusion Criteria

Candidates for this study must meet all of the following criteria:

1) The patient must be ≥18 years of age
2) Patient is able to verbally confirm understanding of risks, benefits and treatment alternatives of receiving the DESyne X2 NECSS and he/she provides written informed consent, as approved by the appropriate Ethics Committee of the respective clinical site, prior to any clinical study related procedure
3) The patient must have stable angina pectoris as defined by the Canadian Cardiovascular Society Classification, documented silent ischemia, acute coronary syndrome, or a positive functional study requiring treatment
4) The patient is considered a candidate for coronary stent implantation and has a planned intervention of up to three lesions located in separate major epicardial territories. Each lesion/vessel must meet the following criteria:
    a. *De novo* lesion
    b. The target lesion reference site must be visually estimated to be ≥ 2.25 mm and ≤ 4.0 mm in diameter*
    c. The target vessel must be a major coronary artery or major branch with a visually estimated stenosis of ≥ 50% and <100%.
    d. The visually estimated target lesion length must be ≤ 34 mm*

    ≥ TIMI 1 coronary flow

    *Subject to commercial availability of product sizes in the specific region/country

3.3 Exclusion Criteria

Candidates will be ineligible for enrollment in the study if any of the following conditions apply:

1) The patient has a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, prasugrel or ticagrelor, heparin/bivalirudin, mTOR inhibitor class drugs, cobalt chromium alloy, methacrylate or polylactide polymer, or sensitivity to contrast which cannot be adequately premedicated
2) Women of childbearing potential who have not undergone surgical sterilization or are not post-menopausal (defined as amenorrheic for at least one year) as well as women who are pregnant or nursing
3) Previous placement of a stent within 10 mm of the target lesion
4) Previous placement of a stent proximal to the target lesion
5) Total occlusion or < TIMI 1 coronary flow in the target vessel
6) The proximal target vessel or target lesion is severely calcified by visual assessment
7) Aorto-ostial location, unprotected left main lesion location, or a lesion within 5 mm of the origin of the LAD or LCX
8) Bifurcation lesion with planned 2-stent technique
9) High probability that treatment other than PTCA or stenting will be required for treatment of the same lesion
10) The target lesion, or the target vessel proximal to the target lesion, contains thrombus
11) Patient has a diagnosis of ST elevation myocardial infarction (STEMI) within 72 hours preceding the index procedure, and CK and CK-MB have not returned within normal limits at the time of procedure
12) The patient is a recipient of a heart transplant
13) The patient has extensive peripheral vascular disease that precludes safe sheath insertion or extreme anti-coagulation
14) The patient is currently participating in another investigational device study that has not completed the primary follow-up phase, or patients participating in any DAPT or other thrombus/platelet related studies that that has not completed the primary follow-up phase, or enrolled into more than one study on the day of the index procedure.
15) Patients who are unable or unwilling to cooperate with study procedures

3.4 Informed Consent

If a patient is potentially eligible for the study, the patient and patient's family if available should be approached. The background of the proposed study and the benefits and risks of the procedures should be explained to the patient. In accordance with the Declaration

of Helsinki (2013), the patient must provide consent prior to enrollment (see Appendix I for an example of the consent form). Failure to obtain signed, informed consent prior to enrollment into the study renders the patient ineligible.

3.5 Conduct of the Study

3.5.1 Screening Procedures and Patient Enrollment Prior to Catheterization

All patients admitted for percutaneous revascularization should be assessed for potential study eligibility.

3.5.2 Catheterization and Stenting Procedure

The stenting procedure will follow standard procedures for balloon angioplasty and shall be in accordance with the Instructions for Use packaged with each DESyne X2 stent. The available stent diameters are 2.25 mm, 2.75 mm, 3.0 mm, 3.5 mm, and 4.0 mm with stent lengths of 14 mm, 18 mm, 23 mm 28 mm, 32 mm, and 38 mm lengths.[3] Pre-dilate the lesion using a balloon that is shorter in length than the planned DESyne X2 stent length. Deploy the stent slowly until the stent is completely expanded. Maintain pressure for 30 seconds. Direct stenting is not recommended.

- Should any resistance be felt at any time during either lesion access or removal of the delivery system post stent implantation, the entire system should be removed as a single unit (See appropriate IFU for further information).
- According to the IFU, stent expansion should not exceed the RBP of 16 atm and the stent should not be expanded beyond 0.5 mm over the nominal diameter.

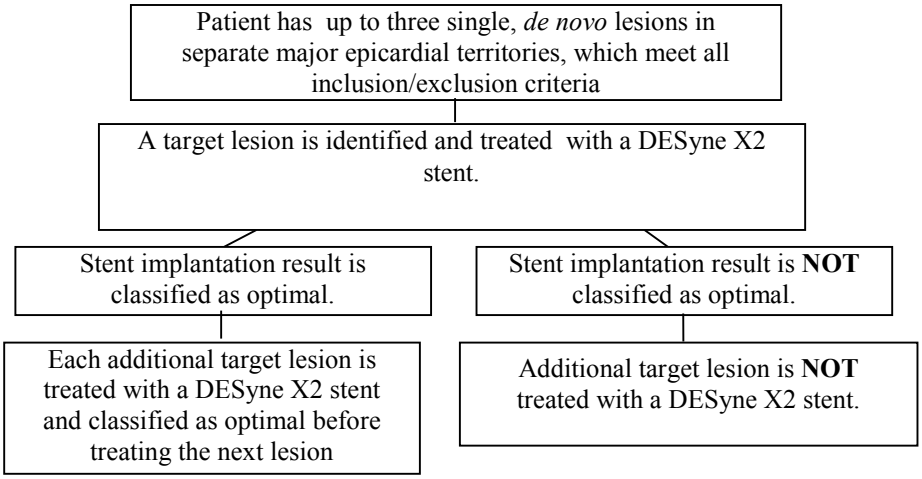
Evaluate the lesion via angiography. If an optimal angiographic result has still not been achieved using the coronary stent system, additional balloon inflations using an appropriately sized, non-compliant balloon may be performed.

The stenting procedure will include a single lesion treatment in a single epicardial vessel or a single lesion treatment in up to three separate major epicardial territories.

Maintain a copy of all of the index procedure angiographic images for possible analysis by an independent angiographic core laboratory.

[3] Not all sizes available in all regions. Subject to commercial availability. Availability is based on regulatory and hospital approvals.

Flowchart for Treatment of Two Lesions in Two Separate Epicardial Territories



Optimal lesion/vessel treatment is defined as:

a. < 20% residual stenosis by visual assessment
b. no evidence of dissection
c. no evidence of thrombus in the target lesion or vessel
d. TIMI 3 flow

3.5.3 Bailout Procedures

In the event that a patient experiences a dissection or an occlusive complication or if there is incomplete lesion coverage, further stenting may be employed as a bailout treatment using a DESyne X2 stent or other commercially available stent of the same metal composition and the same drug family. The stents should overlap by at least 1-2 mm.

3.5.4 Treatment Failures

Failure to implant the DESyne X2 stent at the intended target site will be recorded as a treatment failure on the case report form. In the event of the inability to treat the lesion with the study stent, the physician may treat the patient according to his/her medical judgment with another approved device. These patients should receive standard anti-platelet therapy.

3.5.5 Concomitant Medical Therapy

It is recommended that all patients receive dual antiplatelet therapy including aspirin and aP2Y12 inhibitor for at least one year as currently recommended by the AHA/ACC guidelines and hospital standards.

3.5.6 Clinical and Laboratory Procedures

It is recommended to perform an electrocardiogram and cardiac enzymes be assessed prior to the procedure and post-procedure as per hospital standard.

3.5.7 Other Follow-up Guidelines

There may be situations where an attempt to treat the patient with the DESyne X2 stent is made, but the procedure is stopped prior to the stent being delivered to the target site (i.e., the stent is introduced into the guiding catheter and circulation but patient becomes unstable, power outage, etc.). In these situations, the patient will be deregistered from the study and treated per standard hospital practice.

In the situation where an attempt to treat the patient with the DESyne X2 stent is made but due to a device malfunction or failure to cross the lesion, no DESyne X2 stent is subsequently implanted, the case shall be noted as not meeting the Device Success endpoint. All device failures will be recorded and reported.

4.0 ENDPOINTS

The following endpoints chosen for the post market clinical follow-up evaluation are the recognized professional and industry standards in determining performance of drug eluting stents in interventional cardiology.

- Acute Device Success: attainment of final result with < 50% residual stenosis of the target site, using a DESyne X2 stent and standard pre-dilation catheters and post-dilatation catheters (if applicable)

Physician feedback will be obtained for the following device characteristics:

- Device preparation
- Lesion access and cross
- Stent expansion
- Delivery system removal
- Stent crossability for post-dilatation as required
- Device malfunction assessment

4.1 Lesion, vessel, and stent characteristics

Lesion, vessel, and stent characteristics recorded in the source documentation should include:

- Estimated reference vessel diameter (target lesion)
- Estimated lesion length
- Estimated % DS (target lesion)

- Number of stents used
- Stent brand
- Vessel (LAD, LCX, RCA, Left Main)
- Lesion location (ostial, proximal, mid, distal, branch)
- Stent diameter (mm)
- Stent length (mm)
- Lot number of the DESyne X2 stent
- Success of stent implantation or device malfunction details

Note: Maintain a copy of all of the index procedure angiography for possible analysis by an angiographic core laboratory.

4.2 Device and Drug Related Adverse Events

A list of adverse events which may result from the use of the device, the implant procedure, the drug on the stent, or the use of concomitant procedural drugs are described in the Instructions for Use for each device.

5.0 EARLY WITHDRAWAL FROM THE STUDY

Following the introduction into the body of the intended device, all patients are considered enrolled into the study. Patients will be exempt from only if they withdraw their consent or the physician withdraws them from the study.

6.0 STATISTICAL CONSIDERATIONS

This Post Marketing Clinical Follow-up (PMCF) study is designed to confirm the performance of the DESyne X2 Novolimus Eluting Coronary Stent System with regards to the residual risks of lesion access and acute device implantation through visually-assessed angiographic endpoints and physician feedback and demonstrate that these characteristics are not different than the DESyne Novolimus Eluting CSS. The overall result of this study will be summarized descriptively, and examined relative to the clinical results observed in the EXCELLA II Randomized Study.

Data for all categorical endpoints will be summarized with patient counts, percentages, and exact 95% Clopper-Pearson confidence intervals.

One study population will be examined during the analyses: the modified intent-to-treat population (MITT), which will consist of all patients treated with at least one DESyne X2 stent.

While this post marketing study is not powered to determine extremely rare events, a sample size of 100 patients is sufficient to detect rare, acute device related performance issues.

7.0 DATA MONITORING AND QUALITY CONTROL

7.1 Required Data

All required data for this trial will be collected using Case Report Forms (CRF). Only authorized personnel will be permitted to enter data on the CRFs. The computerized handling of the data by the sponsor and/or designee after receipt of the CRFs may generate additional requests to which the investigator is obliged to respond by confirming or modifying the data questioned.

7.2 Training

The training of appropriate clinical site personnel will be the responsibility of the study sponsor, Elixir Medical, or their appointed designee.

7.3 Logs and Case Report Forms

An authorized signature log, screening log, protocol deviation log, and issues log will be maintained by the investigative site and be available for review by the sponsor when requested. All appropriate CRFs should be completed as soon as possible after enrollment or follow-up contact with the patient. Submission of the CRFs will be coordinated between the investigative site and the data management group. This includes coordination of data discrepancy forms.

7.4 Data Collection, Monitoring, and Tracking

The sponsor and/or designee will monitor the study over its duration according to the pre-specified monitoring plan. The study monitor will utilize an electronic database system to collect completed CRFs and monitor study progress. The study monitor may visit the sites to review investigational data for accuracy and completeness and ensure compliance with the protocol or may require redacted documents to be forwarded by electronic means for off-site examination.

The study monitor may inspect all documents and required records that are maintained by the investigator or investigative site, including medical records (office, clinic or hospital) for the patients in this study. The investigator and site will permit access to such records. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

8.0 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Investigator Responsibilities and Performance

The investigator shall ensure that all work and services shall be conducted in accordance with the highest standards of medical and clinical research practice. The investigator will provide copies of the study protocol to all sub-investigators or other staff responsible for study conduct.

8.1.1 Informed Consent and IRB/Ethics Committee Approval

Institutional Review Board (IRB) or Ethics Committee (EC) written approval for the protocol, protocol amendments, and informed consent form will be obtained by each Investigator prior to initiation of patient enrollment in this study. Until the study is completed, each Investigator will update the IRB/Ethics Committee per institutional requirements.

8.1.2 Source Documentation

Regulations require that investigators maintain information in the study subject's medical records which corroborate the data collected on the case report forms. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history and physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the study including the study sponsor name (Elixir Medical)
- Notes regarding device information and performance and concomitant medications taken during the study
- Study subject's condition upon completion of or withdrawal from the study

8.1.3 Record Retention

Site specific essential documentation of study conduct to be maintained at the site will include: completed CRFs and data correction forms, internal and external correspondence; agreements, logs (authorized signatures, monitoring, screening, protocol deviations, issues), and any other trial-related documents.

The investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). All investigative sites will maintain study records for two years after research has been terminated by the sponsor. They shall take measures to prevent accidental or premature destruction of these documents. The investigator may transfer custody of records to another person/party and document the transfer at the investigation site.

8.1.4 Non-Protocol Research

Elixir Medical has a legal responsibility to comply with regulatory reporting requirements. No investigative procedures during the acute period of treatment and follow-up described in this protocol shall be undertaken on the enrolled patients without the agreement of Elixir Medical.

8.2 Role of the Sponsor - Elixir Medical

As the study sponsor of this PMCF study, Elixir Medical has the overall responsibility for the conduct of the study, including assurance that the study satisfies international regulations and guidelines.[4]

8.2.1 General Duties

The sponsor is responsible for selecting investigators and establishing agreements. The sponsor is also responsible to ensure the study is conducted according to applicable MEDDEV and Good Clinical Practice guidelines (GCPs).[5]

8.2.2 Selection and Monitoring of Clinical Sites and Investigators

Physicians seeking participation should be trained to the hospital procedures for angioplasty and coronary stent implantation, the study protocol, and have clinical study experience.

Elixir Medical will select qualified investigators, obtain signed investigator agreements, and provide the investigators with the information necessary to conduct the study. Ongoing monitoring of each site will be conducted by the sponsor or designee to assure compliance with the protocol.

The sponsor, Elixir Medical, or a designee will monitor the sites either on-site or remotely to ensure the ensure that all investigators and procedures are in compliance with the protocol and that the completed case report forms match the medical records and resolve any differences.

8.2.3 Maintaining Records

Elixir Medical will maintain copies of correspondence, data, adverse device effects and other records related to the clinical trial for a minimum of 2 years following completion of the study. Investigative sites will maintain records related to the study in accordance with local regulations.

8.2.4 Submitting Reports

Elixir Medical will submit the appropriate reports identified by the regulations. This includes unanticipated adverse device effects, annual progress reports, recall information, and final reports.

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[4] MEDDEV 2.12/2 rev2. Guidelines on medical devices. Post market clinical follow-up studies. A guide for manufacturers and notified bodies. January 2012.

[5] ISO 14155:2011, Clinical investigation of medical devices for human subjects - good clinical practice. December 2011.

8.2.5 Patient Confidentiality

The Sponsor will make all efforts to not collect any patient information during this study. To maintain patient confidentiality, the use of alpha-numeric identification of patients will be used on CRFs. Further, any publication of study information will not include any information that would disclose the patient's identity.

8.2.6 Publication Policies

At the conclusion of the DESyne X2 PMCF Study, an abstract reporting the primary results may be prepared and presented in an appropriate international forum. A manuscript may also be prepared for publication in a reputable scientific journal regardless of positive or negative results. The publication of the principal results from any single center experience within the trial is not allowed until both the preparation and publication of the multi-center results as appropriate. All proposed publications and presentations by investigators or their personnel resulting from or relating to the study must be submitted to the sponsor for review and approval at least 60 days prior to the submission for publication or presentation. Elixir Medical will review all materials for proposed publication or presentation for accuracy, confidential information, or patentable inventions and the sponsor may delay any publication or presentation for a reasonable period of time. All information and data relating to the clinical study, Elixir stents, and other study-related data are the sole property of Elixir Medical.

9.0 DEFINITIONS

Acute Success

Acute success will be classified according to the following categories, which serve as comparable "benchmarks" between the similar treatments.

Device success: attainment of final result with < 50% residual stenosis of the target site, using a DESyne X2 stent and standard pre-dilation catheters and post-dilatation catheters (if applicable)

Physician feedback will be obtained summarizing the following device characteristics:

- Device preparation
- Lesion access and cross
- Stent expansion
- Delivery system removal
- Stent crossability for post-dilatation as required
- Device malfunction assessment

Adverse Events and Adverse Device Effects

The following definitions for adverse events are from EN ISO 14155:2011.

- **Adverse Event**

  Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

- **Serious Adverse Event**

  An adverse event that led to death, -OR- led to serious deterioration in the health of the subject, that resulted in a life-threatening illness or injury, or, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical surgical intervention to prevent life-threatening illness or injury, or, a permanent impairment of a body structure or a body function -OR- led to fetal distress, fetal death or a congenital anomaly or birth defect.

- **Adverse Device Effect**

  Adverse event related to the use of the study device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the study device. This definition also includes any event resulting from use error or from intentional misuse of the study device.

- **Serious Adverse Device Effect**

  Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

- **Unanticipated Serious Adverse Device Effect**

  Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Adverse Event Categorization (from EN ISO 14155:2011)

<table>
<tr><th>Adverse Event</th><th>Non-device-related</th><th colspan="2">Device- or procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

Angina Pectoris

- **Canadian Cardiovascular Society Classification of Angina:**

1) Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.
2) Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than 2 blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
3) Marked limitation of ordinary activity; for example, angina occurs walking 1 or 2 blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.
4) Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

Bleeding complications

All transfusions and bleeding complications such as gastrointestinal (GI) bleed, hemoglobin drop of >5 g/dl. Severe bleeding is defined at intracranial bleeding or hemorrhage resulting in hemodynamic compromise. Moderate bleeding is defined as bleeding requiring blood transfusion, but without hemodynamic compromise.

CK and CK-MB

Creatine kinase and creatine kinase - muscle/brain (an isoenzyme of creatine kinase).

***De novo* lesion**

A native coronary artery lesion not previously treated.

Device Related Procedure Complications

- **Abrupt Closure**

  Abrupt (or acute) closure is defined as acute treatment failure in the catheterization laboratory, in which persistent reduced flow requires rescue by another device or emergency surgery in order to prevent myocardial injury. The occurrence of transient closure or "no reflow," in which further stent or balloon use restores normal flow and a patent (<50% residual stenosis) lumen, is occasionally seen and does not represent abrupt closure. Abrupt closure will thus be reserved for the occurrence of reduced flow (TIMI grade 0 or 1), due to mechanical dissection, coronary thrombus, or severe microvascular spasm, that results in: 1) repeat treatment not allowable in the assigned treatment arm, 2) emergent surgery, 3) myocardial infarction, or 4) death.

- **Dissection**

  Dissection is defined as defects that occur during the stent implant procedure that cannot be treated during the procedure to obtain an optimal outcome. Dissection

will be graded according to NHLBI Grades: A: intraluminal radiolucent defect; B: extraluminal cap without staining; C: extraluminal cap with persistence of dye (staining); D: spiral defects; E: persistent filling defect; and F: filling defect with total occlusion.

Optimal treatment of lesion/vessel

Optimal lesion/vessel treatment is defined as:

- < 20% residual stenosis by visual assessment
- no evidence of dissection
- no evidence of thrombus in the target lesion or vessel
- TIMI 3 flow

Ostial lesion

Lesion involving the origin of the coronary artery within the first 3 mm.

Restenotic lesion

A lesion in a vessel segment that has undergone prior percutaneous treatment.

Target Lesion

The target lesion is the treated lesion starting 5 mm proximal of the stented lesion and ending 5 mm distal beyond the stented lesion.

Target Vessel

The target vessel is the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself.

TIMI flow grades

1. No contrast flow through the stenosis.

2. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.

3. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.

4. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

10.0 Appendix I: Sample Patient Informed Consent

A NON-RANDOMIZED, POST MARKETING CLINICAL FOLLOW-UP (PMCF) STUDY OF THE DESyne® X2 NOVOLIMUS ELUTING CORONARY STENT SYSTEM IN THE TREATMENT OF PATIENTS WITH *DE NOVO* NATIVE CORONARY ARTERY LESIONS

"DESyne X2 PMCF Study"

ELX-CL-1705

Background

Your physician has determined that one of your coronary arteries has a significant narrowing that is causing decreased blood flow to your heart muscle. There are two methods commonly used to correct this problem. The first is balloon angioplasty usually followed by the placement of a stent. Balloon angioplasty does not leave a permanent device in the artery after the balloon catheter is removed. Stent placement means that the small metal scaffold (stent), some containing a small amount of drug (drug-eluting stent – DES), is left behind after the balloon is removed and the stent becomes a permanent part of your artery. Stents have been used for many years to treat narrowing in both coronary arteries and bypass grafts (saphenous vein grafts).

Purpose and Procedures

The purpose of this study is to confirm the acute (during the implant procedure) safety and effectiveness of the CE Mark approved DESyne® X2 Novolimus Eluting Coronary Stent System. Patients deemed by their physician to be eligible for this study will be enrolled. Your physician has described the stent procedure to you during which the CE Mark approved and commercially available DESyne X2 stent will be used. This stent system is similar to other market approved stents and is implanted using the same technique. Implantation procedure information will be collected during this study and you will be closely observed by medical staff during your procedure.

The DESyne X2 Stent System incorporates the drug Novolimus and is similar to sirolimus, everolimus and zotarolimus, which are drugs currently approved for use on drug eluting stents. The dose of the drug on the stent is approximately 5.0 mcg of drug per mm of stent length (80 mcg for an 18 mm stent) and similar to or less than the dose on other drug eluting stents. The DESyne X2 stent is covered by a thin coating called a polymer that holds the drug and which allows the release of the drug over a known period of time. The research staff will be able to answer any questions you have concerning the stent system or about the study itself.

As with any stent procedure, you will be required to take routine medications, intended to help prevent your blood from clotting. These routine medications may include clopidogrel, prasugrel, or ticagrelor, and aspirin for at least one year. **Please do not stop taking the medications without first getting approval from your doctor.** It is very important that you take this medication everyday as your doctor has prescribed.

Potential Risks

The drug used on the stent is in such a low dose there is little potential to cause side effects. However, if you experience any signs of an allergic reaction such as rash, itching or swelling, inform your physician immediately. Previous stent implantation studies involving the use of clopidogrel have shown a 1 to 2% chance of blood clotting within the stent. As with any stent implantation procedure, if clotting of the stent does occur, it may lead to repeat catheterization/angioplasty, myocardial infarction (heart attack), urgent bypass surgery, or death.

Furthermore, even with successful initial implantation, there is still a chance of the treated area re-narrowing usually occurring within the first 4 to 9 months. This may require additional therapy, such as repeat angioplasty, stenting, and/or bypass surgery to provide adequate blood flow to the heart muscle jeopardized by the re-narrowing. This treatment may involve some other risks to you, the nature of which is unknown.

Potential Benefits

The use of drug eluting coronary stents has shown the potential to reduce the incidence of re-narrowing in the artery at the treated site.

Confidentiality

Your physician and the study sponsor will maintain your confidentiality during your participation in this study. You will not be identified by name, tax identification number, address, telephone number, or any other direct personal identifier in study records. However, copies of your angiography which may contain your full name, may be sent to an independent reviewer for analysis. When results of a study such as this are reported in medical journals, symposia, or www.clinicaltrials.gov website, the identification of patients is withheld. Medical records of participants are maintained according to current legal requirements and will be made available for review to the appropriate Regulatory Authorities, the study sponsor or its representatives.

Policy Regarding Research-Related Injuries

In the event of injury resulting from your participation in this research there will be no monetary compensation or subsidized medical treatment for this injury provided to you by the study sponsor, (Name of the Institution) or any person involved in this research project.

Pregnancy (risk to fetus)

Pregnant or nursing women as well as women of childbearing potential, or those who do not agree to contraception for at least one year following stent implant, are excluded from this study as there is inadequate information about the long-term effect of this drug on pregnant women. There is no evidence of effect on fertility in males, however the effect of the drug on human sperm is not known.

Alternative Treatment(s)

There are alternative methods available to treat the narrowing in your coronary artery. These include; conventional balloon angioplasty; atherectomy, whereby a cutting device is used to remove

the material causing the narrowing; stent implantation with a different bare metal or drug eluting stent or, coronary artery bypass graft (CABG) surgery.

Problems or Questions

Your doctor has the right to terminate this study or your individual participation at any point. Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research or with regard to any research-related injury, you may contact the Principal Investigator.

Physician Name: _____

Telephone number: _____

Your family physician will be advised of your participation in this trial. You should inform your physician if you sustain any injury during the course of this study or are admitted to a hospital.

It is suggested that you retain a copy of this document for your later reference and personal records.

INFORMED CONSENT

"DESyne X2 PMCF Study"

ELX-CL-1705

You are being invited to take part in a research study involving approximately 100 patients who will be enrolled at this site and others in Europe and other international locations. It is important that you understand several facts that apply to patients participating in clinical studies:

a. Taking part in the study is voluntary;

b. You may or may not receive personal benefits from taking part in the study, but knowledge may be gained from your participation that will benefit others;

c. You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled;

d. Significant new findings discovered during the course of this study, which may affect your willingness to continue participating in this study, will be provided to you.

During your treatment for coronary artery disease, you will receive one or more **DESyne® X2 Novolimus Eluting Coronary Stent.** This stent has CE Mark approval. The purpose of this study is to provide an acute (during the procedure) evaluation of the safety and performance of the stent.

The research staff will have your permission to review your medical records during your hospitalization.

Your physician and the study sponsor will assure that your participation in this study is confidential. You will not be identified by name, social security number, medical record number, or any other direct personal identifier in the study records.

You will not receive additional charges for participation in this study nor will you receive any payment for participation in this study.

You understand that there are no known additional risks involved in your participation in this study which exceed the risks outlined in the consent you have already provided for interventional coronary treatment. **You are urged to discuss any questions you have about this study with staff members.** If you need to talk to someone about your experiences at [hospital name], you can call [research coordinator name] at [phone number] or your doctor at [phone number]. You may also contact the Ethics Committee Chairman at any time during the study if you have questions or concerns at [phone number].

By signing below, I voluntary agree to participate in the study and will comply with the directions provided by the research staff.

Participant's signature: _____ Date _____

Printed name: _____ _____

I have explained and defined in detail the research procedure in which the participant has agreed to participate, and have made a copy of this informed consent form available for the patient.

Consent obtained by: (signature) _____ Date _____

(printed name) _____ Title _____