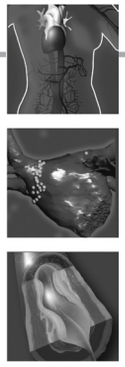

Novolimus™-eluting coronary stent system

Owing to their marked efficacy in reducing restenosis, drug-eluting stents currently represent the predominant strategy for percutaneous coronary intervention in the majority of cathertization laboratories. However, safety issues, mainly related to the presence and amount of durable polymers and/or antiproliferative drugs in the first-generation systems, may have resulted in increased rates of late and very-late stent thrombosis following implantation. The Elixir DESyne Novolimus™-eluting coronary stent system (Elixir Medical, CA, USA) comprised of a thin cobalt–chromium stent platform and the novel antiproliferative agent Novolimus, a sirolimus metabolite, released from either a durable methacrylate polymer, or bioabsorbable polylactide polymer, has recently been developed and tested as a possible safer alternative to first-generation systems. In this article, we describe the components of this novel device presenting some preliminary preclinical and clinical data of Elixir's research program.

KEYWORDS: biodegradable polymer ■ drug-eluting stent ■ Novolimus™

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Since the introduction of percutaneous coronary intervention as an alternative approach to treat coronary atherosclerotic disease, restenosis has been the major drawback of this technique. Its occurrence varies from 15 to 70%, depending on the clinical and angiographic complexity of the treated cases as well as the device used (e.g., balloon catheter only, bare-metal stents) [1–5].

Approximately 10 years ago, drug-eluting stents (DES) were introduced to overcome this major limitation of percutaneous coronary intervention. Combining a metallic platform with an antiproliferative drug locally delivered through a polymer that also controls the drug-release kinetics, these novel devices were able to reduce restenosis in more than 60% of cases, bringing the rates of this adverse event to less than 10% in most scenarios [6–10].

Nonetheless, the rise in efficacy obtained with first-generation DES Cypher® sirolimus-eluting coronary stent system (Cordis, Warren, NJ, USA) and Taxus® paclitaxel-eluting coronary stent system (Boston Scientific, Natick, MA, USA) was accompanied by an infrequent but important downside, the increase in the occurrence of late and very-late stent thrombosis motivated in part by local inflammatory reactions following the deployment of those devices [11–14]. Among the various possible reasons to explain these untoward events, the amount and type of antiproliferative agent as well as the type of polymer present in those systems seem to play a central role in the process [15,16].

Based on these assumptions, the recent focus of interventional cardiology research has been shifted to the development of next-generation DESs with at least similar efficacy profiles to first-generation DESs but with an improved safety profile.

Recently developed, the Elixir Novolimus™-eluting coronary stent systems (Elixir Medical Corporation, Sunnyvale, CA, USA) are comprised of a thin cobalt–chromium stent platform and the novel antiproliferative agent Novolimus, a sirolimus metabolite, released from either a durable methacrylate polymer, or bioabsorbable polylactide polymer; both systems have shown great promise.

The details on both Elixir DES systems and the most relevant preclinical data together with the results from the ongoing clinical programs are presented below.

Elixir Novolimus-eluting coronary stent system

■ Stent & delivery system platform

The stent delivery system platform is comprised of the Elixir core coronary stent system, which has received the CE approval mark in the EU. The premounted balloon-expandable stent is fabricated from a cobalt–chromium (L605) alloy, which maintains radiopacity, allowing

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both flexibility and trackability despite having thinner struts. The stent is available in diameters ranging from 2.5 to 3.5 mm and lengths that vary from 14 to 28 mm and it has a nominal strut thickness of 0.08 mm with an eight-crown pattern for the 3.0 and 3.5 mm sizes and a six-crown pattern for the 2.5 mm sizes. Previous studies have correlated thicker struts with higher rates of restenosis, possibly due to increased local inflammatory response.

■ Polymers

Elixir has developed and evaluated two different types of polymers for use in DES systems.

The durable polymer is poly-*N*-butyl methacrylate, which is similar to those currently in clinical use on other DES systems such as the Cypher sirolimus eluting coronary stent system, the Xience™ V (Abbott Vascular, Santa Clara, CA, USA) and Promus™ (Boston Scientific) everolimus-eluting coronary stent systems and the Resolute® zotarolimus-eluting coronary stent system (Medtronic Vascular, Santa Rosa, CA, USA) [17–20]. Of note, the polymer undergoes a purification process resulting in an important reduction in the overall monomer content. This polymer allows the release of 80% of Novolimus over 12 weeks.

Elixir has also tested a bioabsorbable polylactide polymer, which allows the release of approximately 95% of Novolimus over 12 weeks and which bioerodes over a period of 6–9 months.

Both polymers are applied to the surface of the stent without the use of a primer coating, using a proprietary application process that results in a coating thickness of less than 3 µm, which is thinner than that found on second-generation DES such as Endeavor Resolute zotarolimus-eluting coronary stent system (5.6 µm) or Xience V/Promus everolimus-eluting stent system (7.8 µm) [21].

■ Antiproliferative drug

Novolimus belongs to the family of compounds of macrocyclic lactones with immunosuppressive and antiproliferative properties and has a similar mechanism of action to other macrocylic lactones. Novolimus is developed by the removal of a methyl group from carbon C16 [Data on file at Elixir Medical] from the macrocyclic lactone ring. Of note, this differs from other macrocyclic lactones used for DES systems, which have all been developed through modifications on the carbon C40 ring [22].

The macrocyclic lactone Novolimus binds to and inhibits the activation of mTOR, a key regulatory kinase to generate an immunosuppressive complex. This inhibition suppresses cytokine-driven cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle. Novolimus has been shown through *in vitro* studies to have a high potency to inhibit human smooth muscle cells with an IC_{50} of 0.5 nM, which is comparable with the IC_{50} of sirolimus in the same study and to values reported in the literature [23].

The dose of Novolimus in the Elixir DES systems with both the durable and bioabsorbable polymer is 5 µg/mm of stent length (compared with 10 µg/mm for the Endeavor DES, >8 µg/mm

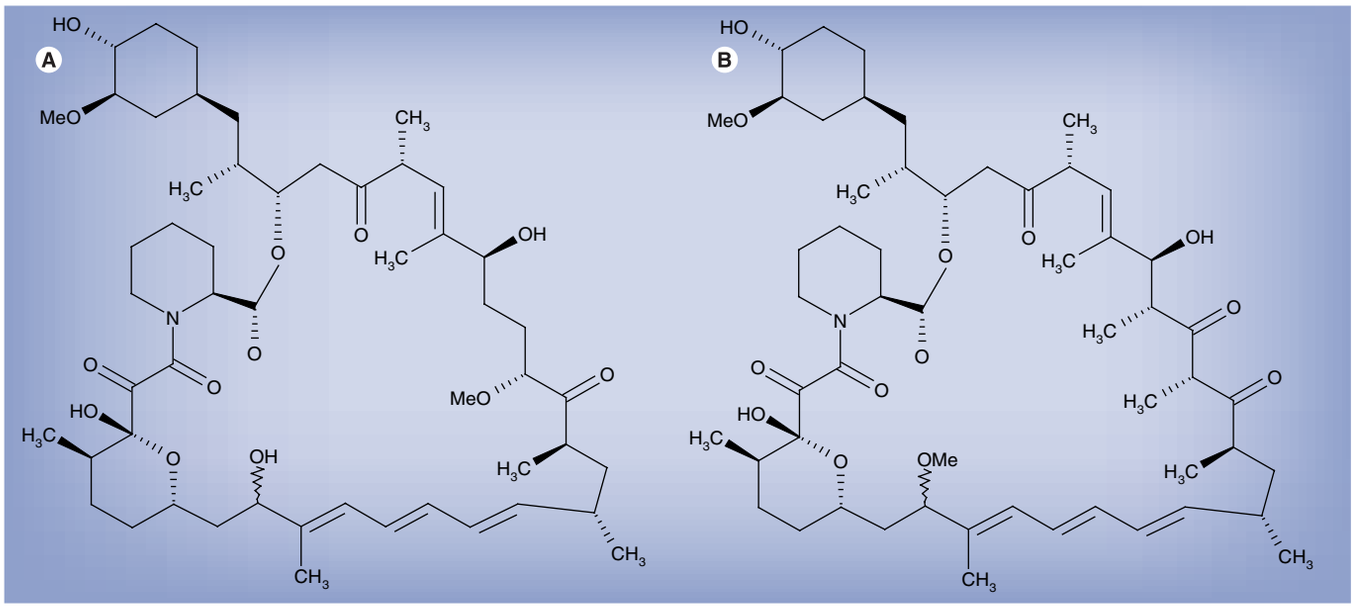

Figure 1. (A) Novolimus™ and (B) sirolimus.

Table 1. *In vivo* test results.

	Elixir DES with durable polymer (n = 6)	Elixir DES with bioabsorbable polymer (n = 7)	Cypher® DES (n = 3)
Histology			
Area stenosis (%)	25.7 ± 9.0	24.9 ± 7.1	27.7 ± 9.7
Pathology			
Inflammation score	0.37 ± 0.21	0.29 ± 0.06	0.41 ± 0.19
Endothelialization (mm)	2.95 ± 0.13	3.00 ± 0.00	2.56 ± 0.51

DES: Drug-eluting stent.

for the Cypher DES and 100 µg/cm^2 Xience V/Promus DES). The chemical structures of Novolimus and sirolimus are presented in (Figure 1).

Preclinical studies

The Elixir Novolimus-eluting coronary stent system with durable polymer was compared with the Cypher stent in the preclinical setting using a porcine model. At 28 days, histomorphometric and histopathologic results from concurrent studies demonstrated that there were no differences between the two stents in percentage area stenosis, inflammation or endothelialization scores. Similar comparison with porcine model testing was carried out between the Elixir Novolimus-eluting coronary stent system with bioabsorbable polymer and the Cypher stent with equivalent results achieved, pointing to no difference between the systems regarding both efficacy and safety. Preclinical data are presented in Table 1.

Pharmacokinetics (PK) testing to evaluate the elution profile of Novolimus was conducted by extracting the drug from the stent and surrounding tissue and measuring it at various time points using standard bioanalytical techniques. The PK testing of the Elixir Novolimus-eluting coronary stent system with durable polymer loaded with 85 µg of Novolimus demonstrated that the majority of the drug was released from the stent in over 12 weeks (Figure 2). The release kinetics from the Elixir DES were similar to published Cypher DES and Endeavor Resolute PK data, wherein the majority of the drug is released from the stent at approximately 28 days (Cypher 80% at 28 days [6], Elixir DES 60–70% at 28 days and Endeavor Resolute 85% at 60 days) [24]. The PK testing of the Elixir Novolimus-eluting coronary stent system with bioabsorbable polymer loaded with 85 µg of Novolimus demonstrated faster release kinetics than with the durable polymer with 95% of the drug released from the stent in 12 weeks (Figure 2). Therapeutic amounts of drug were measured in tissue surrounding the stented area at 28 days for both Elixir DES systems.

Clinical studies

A first-in-man assessment (EXCELLA I trial) of the Elixir Novolimus-eluting coronary stent system with durable polymer was conducted in our center in Brazil enrolling 15 patients with single, *de novo* lesions in native coronaries of 3.0–3.5 mm in diameter and up to 14 mm in length. All patients underwent invasive follow-up with quantitative coronary angiography and intravascular ultrasound (IVUS) at two different time points. The study showed an in-stent late lumen loss of 0.15 ± 0.29 mm and 0.31 ± 0.25 mm at 4 and 8 months, respectively. By IVUS, the in-stent percentage (%) neointimal volume obstruction was 2.6 ± 2.6% and 6.0 ± 4.4% at 4 and 8 months, respectively [19], together with no major adverse cardiac events (MACEs) through 12 months and a single MACE through 2 years, which was a death in a patient with aortic valve replacement and multiple comorbidities [25,26].

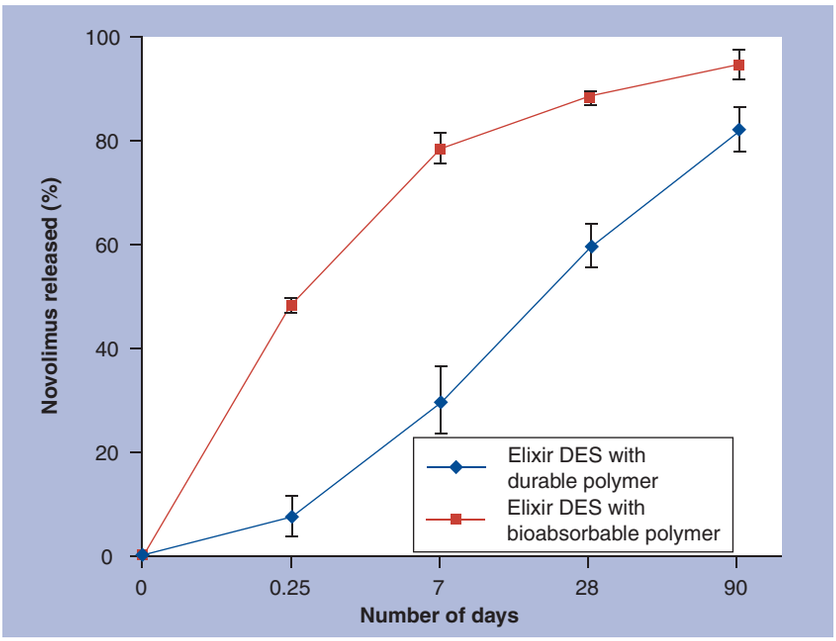

Figure 2. Release kinetics of Novolimus™ via a durable and bioabsorbable polymer.
DES: Drug-eluting stent.

Following that preliminary feasibility study, a larger, multicenter, randomized trial (EXCELLA II) was conducted comparing in a 2:1 fashion the Elixir Novolimus DES (n = 139) to the Endeavor zotatolimus-eluting coronary stent system (n = 71). The primary end point for this comparison was in-stent late lumen loss at 9 months. For the second end point, IVUS and clinical parameters were also compared. Notably, the Elixir Novolimus-eluting coronary stent system with durable polymer was shown to be not only noninferior, but also superior to the Endeavor stent in terms of in-stent late lumen loss reduction at 9 months (0.11 ± 0.32 vs 0.63 ± 0.42 mm; $p < 0.001$ for both noninferiority and superiority). By IVUS, similar results were found with a significant suppression of neointimal tissue formation observed in the Elixir cohort (percentage of neointimal volume obstruction of 4.5 ± 5.1 vs 20.9 ± 11.3%; $p < 0.001$). Regarding clinical outcomes, combined device-oriented composite end points (including cardiac death, myocardial infarction and clinically driven target-lesion revascularization) was comparable between the two groups (2.9% for the Elixir DES vs 5.6% for the Endeavor DES; $p = 0.45$) with no differences in the individual components (e.g., death, myocardial infarction and target-lesion revascularization) up to 9 months [22].

Preliminary clinical data from the first-in-man study, reported an angiographic in-stent late loss of 0.16 ± 0.23 mm and percentage volume obstruction by IVUS of 1.6 ± 0.9% at 6 months with no MACEs at 9 months [27]. Larger clinical studies with this device are planned to commence in the near future.

Future perspective

After demonstrating the feasibility of the Elixir Novolimus-eluting coronary stent system with durable polymer including subsequent superiority over the Endeavor zotarolimus-eluting stent in terms of surrogate efficacy end points, Elixir will consider clinical study designs based on clinical end points with broader inclusion criteria. In parallel, a larger study with the Elixir Novolimus-eluting coronary stent system with bioabsorbable polymer is warranted to validate the first-in-man results. As a next step, the company has also been working on a fully bioresorbable DES system [28].

Executive summary

Stent & delivery system platform

- Balloon-expandable cobalt–chromium (L605) stent.
- Available in diameters from 2.5 to 3.5 mm and lengths from 14 to 28 mm.

Polymers

- Two different polymers are being tested.
- The durable polymer is poly-*n*-butyl methacrylate.
- The bioabsorbable polymer is made of polylactide and erodes over a period of 6–9 months.
- Both polymers are applied to the surface of the stent without the use of a primer coating.

Antiproliferative drug

- Novolimus™ belongs to the family of macrocyclic lactones with immunosuppressive and antiproliferative properties and has a similar mechanism of action to other macrocylic lactones such as sirolimus.
- The dose of Novolimus on the Elixir drug-eluting stent systems with both the durable and bioabsorbable polymer is 5 µg/mm of stent length.

Pharmacokinetic properties

- Between 60 and 70% of Novolimus is released within 28 days into the system with durable polymer and approximately 100% up to 12 weeks.
- A total of 95% of the Novolimus is released with 12 weeks into the system with biodegradable polymer.

Clinical studies

- First-in-man trial of the Elixir Novolimus-eluting coronary stent system with durable polymer was conducted in 15 patients and demonstrated an in-stent late lumen loss of 0.15 ± 0.29 mm and 0.31 ± 0.25 mm at 4 and 8 months, respectively.
- By intravascular ultrasound, the in-stent percent (%) neointimal volume obstruction was 2.6 ± 2.6% and 6.0 ± 4.4% at 4 and 8 months, respectively.
- The EXCELLA 2 trial compared in a random fashion (2:1) the Elixir Novolimus-eluting coronary stent system with durable polymer to the Endeavor stent.
- At 9 months, the Elixir Novolimus-eluting coronary stent system with durable polymer was shown to be not only noninferior but also superior to the Endeavor stent in terms of in-stent late lumen loss reduction at 9 months (0.11 ± 0.32 vs 0.63 ± 0.42 mm; $p < 0.001$ for both noninferiority and superiority).
- First-in-man trial of the Elixir Novolimus-eluting coronary stent system with absorbable polymer showed an angiographic in-stent late loss of 0.16 ± 0.23 mm and percentage volume obstruction by intravascular ultrasound of 1.6 ± 0.9% at 6 months with no major adverse cardiac events through 9 months.

Financial & competing interests disclosure

Alexandre Abizaid currently serves as a consultant for Elixir and Dante Pazzanese has received a research grant to conduct Elixir studies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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