Sirolimus Eluting Angioplasty Balloon for In-Stent REstenosis (SABRE) Trial Clinical Report[1]

Sponsor:
Caliber Therapeutics, Inc.
150 Union Square Dr.
New Hope, PA 18938

Product: **Virtue® Sirolimus Eluting Balloon**
Regulatory Classification: **Class III combination device**
Study Coordinator (CRO): **genae associates nv**
Justitiestraat 6B
2018 Antwerp
Belgium

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Study Design: **Prospective multicenter study evaluating a Drug Eluting Balloon in patients undergoing percutaneous revascularization of coronary in-stent restenosis.**

[1] Additional detail for this study can be found in Verheye S, Vrolix M, Kumsars I, et al., The SABRE trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis): Angiographic results and 1-year clinical outcomes. *JACC Cardiovasc Interv* 2017; 10(20):2029-2037.

Introduction

Since about 2006, a new class of angioplasty balloons has been under development. These balloons are coated with a drug and are called drug eluting balloons (DEB) or drug-coated balloons (DCB). They consist of typical angioplasty balloons that have been coated with drugs that can prevent restenosis, the process by which arterial tissue regrows after an angioplasty or stent implantation procedure and re-clogs the treated coronary artery. The use of DEBs can thus reduce the high restenosis rate associated with plain old balloon angioplasty (POBA), without the use of a second permanent metal stent. Several DEB products are currently sold, mainly in the European Union (EU), for both coronary and peripheral vessel use, all of which employ the same anti-restenosis drug, paclitaxel (a known anti-tumor and antiproliferation agent). However, another anti-restenosis drug, sirolimus (previously known as rapamycin), is preferred by interventional cardiologists over paclitaxel (nearly 100% in the U.S.) for use with drug eluting stents due to its superior safety profile. Because sirolimus does not function well as a balloon coating, a liquid polymer formulation has been developed that enables sirolimus to be delivered via a porous angioplasty balloon (a balloon with micro holes that allow drug to be pushed out of the balloon and into the local vascular tissue), and to persist in the affected coronary vessel long enough to effectively block restenosis.

Methods

This first-in-human clinical trial was a prospective, single-arm, multicenter study designed to evaluate the Virtue® Sirolimus Eluting Balloon (SEB) in patients undergoing a percutaneous revascularization procedure to treat in-stent restenosis (ISR) in coronary vessels. The Virtue® SEB performs both balloon angioplasty and simultaneously delivers a liquid polymer formulation of sirolimus to the coronary artery restenosis tissue by means of a porous balloon. The target dose density is 12.0µg/mm^2 of vessel or a total dose of approximately 2 – 4 mg of sirolimus. Eligible subjects with in-stent restenotic coronary artery disease were consecutively screened and enrolled if they met both clinical and angiographic inclusion criteria which included (but was not limited to) greater than 18 years of age, willing to provide informed consent, diagnostic evidence of cardiac ischemia, eligibility for coronary intervention and target lesion in a native coronary artery with a prior bare metal or drug eluting stent. Following treatment, patients were followed for up to 3 years. The study allowed up to 50 patients to be enrolled.

It was decided that the success of the treatment would be based on a comparison of late lumen loss at 6 months after treatment (LLL; a measure of regrowth of tissue within the treated stent) with the historical results of 6-month LLL achieved with POBA (plain old balloon angioplasty) from 3 major trials of DEB that were reported in the medical literature. The average LLL in 112 patients in these 3 studies when combined was found to be 0.86 mm. Thus, in order for the Virtue® SEB to be successful, our 6-month LLL result would need to be statistically better than 0.86 mm.

To thoroughly and fairly evaluate the study data, the LLL results were grouped into three different analysis sets: 1) The Full Analysis Set (FAS) which was comprised of all subjects who

meet the study enrollment criteria; 2) a Per-Protocol analysis set (PP) which included all subjects who meet the study enrollment criteria, and had no major protocol violations; and 3) a Revised Per-Protocol analysis set (rPP) which met the same criteria as the PP but was revised, 1) to be representative of the IDE study population by excluding in-stent lesions that had been previously treated with a second stent, and 2) to exclude or include patients that had been previously included or excluded, respectively, from the PP due to differing interpretations of the specific protocol violations.

Secondary endpoints included binary restenosis rate and percent diameter stenosis at 6 months follow-up.

The primary safety endpoint was target lesion failure (TLF) and the components of TLF (cardiac death, target vessel MI and target lesion revascularization) up to 30 days. Other secondary endpoints included Major Adverse Cardiac Events (MACE) which was comprised of death, recurrent non-fatal myocardial infarction, emergent coronary artery by-pass graft (CABG) and/or clinically driven target vessel revascularization (TVR), target lesion revascularization (TLR), and target vessel failure (TVF) during hospitalization for the treatment procedure.

Results

The targeted enrollment of 50 patients was achieved across10 clinical sites in four countries (Belgium, Denmark, Netherlands, Latvia). Forty-seven patients completed the 6-month follow-up (which included a clinical work-up and a repeat angiographic procedure), 49 patients completed 1- and 2-year follow-up and 48 patients completed 3-year follow-up (1, 2, and 3 year follow-up occurred by telephone contact). The trial closed after the 3-year follow-up as planned. Enrollment was completed January 2015 and primary endpoints were completed in July of 2015.

The primary performance endpoint of late lumen loss (LLL) with the Virtue® SEM at 6 months was 0.32mm ±0.52 (mean ± SD), n=47 (Table 1). A statistical comparison of Virtue® SEB to a combined weighted-average for LLL obtained from the three prior POBA studies (0.86mm) showed Virtue® SEB to be superior ($p < 0.0001$). In the 35 patient PP population, LLL was 0.25mm ± 0.47 at 6 months ($p<0.0001$ when compared with the weighted-average POBA LLL of 0.86 mm) while in the rPP, LLL was 0.12mm ± 0.33mm ($p<0.0001$ vs POBA).

Table 1. Late Lumen Loss (LLL) Results in the Three Analysis Groups.

Population	N	LLL Mean (mm)	±SD	p-value
FAS Population	47	0.32	0.52	< 0.0001
PP Population	35	0.25	0.47	< 0.0001
rPP Population	36	0.12	0.33	< 0.0001

Secondary 6-month endpoints in the FAS population include binary restenosis (19.1%), diameter stenosis (30.3 ± 19.9%), and major adverse cardiac events (MACE) (10.2%, n=49). Restenosis rate in the PP and rPP populations was 11.4% and 2.8%, respectively.

Table 2 provides the major safety findings of this study. Procedural success (delivery of a dose of the sirolimus formulation to the target vessel with the Virtue® SEB) in the Full Analysis Set population (FAS; all treated patients) was 100%. The primary safety endpoint was target lesion failure (TLF – cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization) assessed at 30 days (0%, n=50, Table 2). Procedural complications occurred only rarely and are provided in Table 3.

Table 2. MACE Rates for FAS, PP and rPP from In-Hospital through 3 Years

ITT (Intent to Treat Analysis)							PP (Per Protocol Analysis)					
	in Hospital	30 Day	6 months	1 yr	2 yr	3 yr	in Hospital	30 Day	6 months	1 yr	2 yr	3 yr
N	**50**	**50**	**49**	**49**	**49**	**49**	**36**	**36**	**36**	**36**	**36**	**36**
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
MI	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CABG	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	0 (0.0%)	0 (0.0%)	4 (8.2%)	6 (12.2%)	6 (12.2%)	6 (12.2%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	4 (11.1%)	4 (11.1%)	4 (11.1%)
TLF	0 (0.0%)	0 (0.0%)	4 (8.2%)	6 (12.2%)	7 (14.3%)	7 (14.3%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	4 (11.1%)	5 (13.9%)	5 (13.9%)
MACE	0 (0.0%)	0 (0.0%)	5 (10.2%)	7 (14.3%)	8 (16.3%)	8 (16.3%)	0 (0.0%)	0 (0.0%)	2 (5.6%)	4 (11.1%)	5 (13.9%)	5 (13.9%)
3 non flow limiting procedural dissections not included in statistics							**2 non flow limiting procedural dissections not included in statistics**					
MACE per patient -death, MI, CABG and TLR							**MACE per patient -death, MI, CABG and TLR**					
TLF per patient - cardiac death, TV-MI, TLR							**TLF per patient - cardiac death, TV-MI, TLR**					
03-03 has MI and TLR												

rPP (Revised Per Protocol Analysis)						
	in Hospital	30 Day	6 months	1 yr	2 yr	3 yr
N	**36**	**36**	**36**	**36**	**36**	**36**
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CABG	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	2 (5.6%)
TLF	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	2 (5.6%)
MACE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	2 (5.6%)	2 (5.6%)
MACE per patient -death, MI, CABG and TLR						
TLF per patient - cardiac death, TV-MI, TLR						

Table 3. Device and Procedural Complications

Total	Dissection	Inter-procedural thrombus	Arrhythmia - Bradycardia	Balloon Slipping During Delivery	Second Device Delivered due to Plaque Shift
50	3	1	1	1	1

Values are number of patients

Conclusions

The data presented in this report show that the Virtue® SEB met the criteria for performance and safety. The primary safety endpoint for the SABRE trial, TLF at 30 days (0%), was successful, and composite safety endpoints at 12-month clinical follow-up (TLF 12.2% and MACE 14.3%) and angiographic performance (LLL 0.32 ± 0.52mm at 6 months) are within the ranges established by recent randomized ISR trials. Additionally, both the PP and rPP populations showed acceptable safety and effectiveness. This multicenter study has demonstrated that the use of the Virtue® SEB microporous balloon for delivery of sirolimus nanoparticles to the vessel wall during angioplasty for the treatment of in-stent restenosis is both feasible and safe.

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