Prospective, Multicenter and Randomized Controlled Study on Evaluation of Safety and Effectiveness of Vesselin Drug Coated Coronary Balloon Catheter in the Treatment of In-stent Restenoses

Clinical Trial Report

Name of the medical device for trial: Intravascular Drug (Paclitaxel) Eluting Balloon Catheter (Coronary Artery)

Specification and model: See the text of the report

Management category of the medical device for trial: Class III

Class III medical device requiring clinical trial approval Yes ☐ No ☑

Similar products in China Yes ☑ No ☐

Clinical trial institution: Peking University First Hospital

Start time: March 2016

End time: May 2019

Peking University First Hospital National Clinical Trial Institution for Drugs

Protocol number: None

Protocol version number and date: V2.0/March 4, 2016

Investigator: Professor Huo Yong

Sponsor: Lepu Medical Technology (Beijing) Co., Ltd.

Agent: None

Lepu Medical Technology (Beijing) Co., Ltd.

May 31, 2019

Completion instructions:

1. Clinical trial institutions and investigators should take a serious and responsible attitude to implement clinical trials in strict accordance with the clinical trial protocol, and prepare clinical trial reports fairly and objectively.

2. Clinical trial institutions and investigators should be responsible for the authenticity and scientificity of the trial reports.

3. This report should be signed and dated by the investigator. In addition, it should also be commented, signed and dated by the clinical trial management department of the clinical trial institution.

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I. General information

Sponsor	Lepu Medical Technology (Beijing) Co., Ltd.
Registered address	No. 37 Chaoqian Road, Science and Technology Park, Changping District, Beijing
Contact number	010-80120666
Protocol name	Prospective, Multicenter and Randomized Controlled Study on Evaluation of Safety and Effectiveness of Vesselin Drug Coated Coronary Balloon Catheter in the Treatment of In-stent Restenoses
Protocol version number and date	V2.0/March 4, 2016
Primary Investigator (PI) of the trial	Peking University First Hospital / Professor Huo Yong
Trial institutions/investigators	Peking University First Hospital / Chen Ming People's Hospital of Tianjin / Yao Zhuhua The Central Hospital of Wuhan / Chen Manhua The Second Hospital of Jilin University / Liu Bin Emergency General Hospital / Wu Di Beijing Friendship Hospital, Capital Medical University / Chen Hui The Third Medial Center of PLA General Hospital / Ma Dongxing Central Hospital of Zibo / Wang Jun The First Affiliated Hospital of Bengbu Medical College / Zhang Heng Wuhan No.5 Hospital / Hong Lifeng Fujian Provincial Hospital / Guo Yansong Beijing Luhe Hospital, Capital Medical University / Guo Jincheng
Trial design	Randomized controlled study Trial product: Intravascular Drug (Paclitaxel) Eluting Balloon Catheter (Coronary Artery) Reference product: Drug (Paclitaxel) Eluting Balloon Catheter (Coronary Artery) (trade name: SeQuent Please)

II. Abstract

(I) Purpose

To verify the safety and effectiveness of Vesselin Drug Coated Coronary Balloon Catheter in the treatment of in-stent restenoses.

(II) Content

This study is a prospective, multicenter and randomized controlled trial. A total of 224 cases (112 cases respectively in the Trial Group and the Control Group) were randomly selected at the ratio of 1:1. Vesselin Drug Coated Coronary Balloon Catheter of Lepu Medical Technology (Beijing) Co., Ltd. were used for the Trial Group, while coronary artery balloon catheters for paclitaxel release (trade name: SeQuent Please) of Braun were used for the Control Group. Subjects were followed up clinically at 30 days, 6 months, 9 months and 1 year after PTCA and followed up by angiography at 9 months after PTCA. The effectiveness of the device was evaluated with the intrasegmental late lumen loss at 9 months after surgery as the main research endpoint. All subjects were followed up within one year for observation of the occurrence of adverse events in order to make an accurate and reliable evaluation of the safety of Vesselin Drug Coated Coronary Balloon Catheter.

In this trial, an independent data management and statistics center collected, collated and statistically analyzed all relevant clinical data.

(III) Results

A total of 13 centers participated in this trial, and 239 subjects were selected, including 121 in the Trial Group and 118 in the Control Group. The analysis on the trial results shows that:

Primary endpoint:

Patient level: There were 239 subjects (121 in the Trial Group and 118 in the Control Group) in the FAS population and 165 subjects (83 in the Trial Group and 82 in the Control Group) in the PPS population. In the FAS population, the intrasegmental late lumen loss at 9 months after surgery was 0.39 mm vs 0.34 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.19), and the upper limit was 0.19, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. In the PPS population, the intrasegmental late lumen loss at 9 months after surgery was 0.40 mm vs 0.35 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.19), and the upper limit was 0.19, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group.

Lesion level: In the FAS population, the intrasegmental late lumen loss at 9 months after surgery was 0.38 mm vs 0.34 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.19), and the upper limit was 0.19, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. In the PPS population, the intrasegmental late lumen loss at 9 months after surgery was 0.39 mm vs 0.35 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.18), and the upper limit was 0.18, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group.

Secondary endpoint:

(1) The success rate of the device was 98.6% vs 96.3% (p=0.275) respectively in the Trial Group and the Control Group, which had no statistical difference. The success rate for lesions was 98.6% vs 97.8% (p=0.680) respectively, which had no statistical difference. The clinical success rate was 98.3% vs 96.6% (p=0.442), which had no statistical difference.

(2) FAS population: The restenosis rate of the target lesion was 12.8% vs 13.4% (p=0.886) respectively in the Trial Group and the Control Group, which had no statistical difference. PPS population: The restenosis rate of the target lesion was 18.5% vs 19.8% (p=0.827) respectively in the Trial Group and the Control Group, which had no statistical difference.

(3) The target lesion failure rate at 30 days after surgery was 0% vs 1.7% (p=0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 2.5% vs 3.4% (p=0.720) respectively, which had no statistical difference. That at 9 months was 8.3% vs 11.1% (p=0.471) respectively, which had no statistical difference. That at 1 year after surgery was 12.4% vs

12.7% (p=0.941) respectively, which had no statistical difference.

(4) The POCE at 30 days after surgery was 0% vs 1.7% (p=0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 2.5% vs 3.4% (p=0.720) respectively, which had no statistical difference. That at 9 months was 14.9% vs 18.6 (p=0.435) respectively, which had no statistical difference. That at 1 year after surgery was 19.8% vs 20.3% (p=0.922) respectively, which had no statistical difference.

(5) Thrombotic events

No thrombotic events occurred in the Trial Group and the Control Group at 30 days, 6 months and 9 months after surgery. One thrombotic event occurred at one year after surgery in the Trial Group, while no thrombotic event occurred in the Control Group. The occurrence rate of thrombotic events was 0.8% vs 0% (P = 1.000) respectively in the Trial Group and the Control Group, which had no statistical difference.

Performance of balloon catheters:

(1) There was no statistical difference between the balloons in the two groups in terms of the evaluation of the pushability, patency, visibility, adaptability of the balloon to the blood vessel shape and retraction ability (P>0.05).

Safety evaluation:

(1) All-cause mortality and myocardial infarction

There was no death in the Trial Group and the Control Group at 30 days after surgery. The death rate at 6 months was 0.8% vs 0% (p=1.000) respectively, which had no statistical difference. That at 9 months and 1 year after surgery was 2.5% vs 0.8% (p=0.622) respectively, which had no statistical difference.

The occurrence rate of myocardial infarction at 30 days after surgery was 0% vs 1.7% (p=0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 1.7% vs 1.7% (p=1.000) respectively, which had no statistical difference. That at 9 months was 1.7% vs 2.5% (p=0.681) respectively, which had no statistical difference. That at 1 year after surgery was 2.5% vs 2.5% (p=1.000), which had no statistical difference.

(2) Occurrence of thrombotic events

No thrombotic events occurred in the Trial Group and the Control Group at 30 days, 6 months and 9 months after surgery. One thrombotic event occurred at one year after surgery in the Trial Group, while no thrombotic event occurred in the Control Group. The occurrence rate of thrombotic events was 0.8% vs 0% (P = 1.000) respectively in the Trial Group and the Control Group, which had no statistical difference.

(3) Occurrence of adverse events

A total of 165 cases and 433 times of adverse events were reported in this study (83 cases and 194 times in the Trial Group and 82 cases and 239 times in the Control Group), including 91 cases and 149 times of serious adverse events (45 cases and 66 times in the Trial Group and 46 cases and 83 times in the Control Group). There was no statistical difference in the occurrence rate of adverse events and serious adverse events in the two groups (P > 0.05).

Results of the effectiveness endpoint indicators above - intrasegmental late lumen loss, success rate of surgery, restenosis rate, TLF, POCE and thrombotic events showed that there was no statistical difference between the Trial Group and the Control Group. The catheter performance - pushability, patency, visibility, adaptability of the balloon to the blood vessel shape and retraction ability had no statistical difference between the Trial Group and the Control Group. Safety indicators - all-cause mortality, myocardial infarction and thrombotic and adverse events had no statistical difference between the Trial Group and the Control Group.

(IV) Clinical trial conclusions

The results of follow-up at 1 year after surgery in this trial came from 239 patients with coronary heart diseases and in-stent restenoses in 13 centers. The results showed that for in-stent restenoses, the intrasegmental late lumen loss at 9 months after surgery of Vesselin Drug Coated Coronary Balloon Catheter produced by Lepu Medical Technology (Beijing) Co., Ltd. was not inferior to that of coronary artery balloon catheters for paclitaxel release (trade name: SeQuent Please) produced by Braun. The clinical follow-up results at 30 days, 6 months, 9 months and 1 year after surgery showed that there was no significant difference in the occurrence rate of clinical events between the Trial Group and the Control Group, indicating similar safety and effectiveness of Vesselin Drug Coated Coronary Balloon Catheter

produced by Lepu and SeQuent Please drug balloon catheters.

III. Introduction

Percutaneous coronary intervention (PCI) is the most important means to treat acute coronary syndrome at present. Its development has experienced the initial balloon dilatation, bare metal stent (BMS), the first generation of drug eluting stent (DES) and the current second generation of DES and biodegradable DES. For a long time, restenosis has been a major problem troubling the efficacy of PCI. The occurrence rate of ISR was as high as 50% in the era of simple balloon dilatation, which decreased to 20% ~ 40% after entry into the BMS era. DES further reduced it to 5% ~10% today. Even so, ISR is still a problem demanding prompt solution in the current PCI treatment field. In addition, some studies have found in recent years that there is a "late catch-up phenomenon" after DES implantation. Therefore, DES-ISR has attracted more and more attention from academic circles.

ISR can be divided into imaging restenosis and clinical restenosis. The former means that coronary angiography confirms that the lumen loss in the stent implantation segment is ≥50%. According to the length of the stenosis and the relationship with the stent, it can be further divided into four types: type I focal, with the stenosis length less than 10 mm, which can be located in the stent, at the junction and on the edge, or distributed multifocally; type II diffose, with the stenosis length greater than 10 mm, located in the stent; type III proliferative, with the stenosis length more than 10 mm and the edge extending out of the stent; type IV total occlusion, with total occlusion at the stenosis and TIMI blood flow Grade 0. Clinical restenosis is defined as follows: revascularization of target lesions caused by lumen loss ≥70%, with or without ischemic symptoms and signs; or lumen loss ≥50% and presence of one of the following clinical conditions: recurrent angina pectoris, which is presumed to be related to the target vessel; objective evidence of myocardial ischemia, which is presumed to be related to the target vessel; positive findings in vascular functional evaluation, such as FFR and IVUS.

The risk factors of ISR can be summarized in the following five aspects. (1) Clinical factors: Diabetes and the history of ISR are considered to be strong risk factors for the recurrence of ISR, while male, old age and hypertension are also considered to be positively correlated with ISR, but their effects are weak. Although smoking is a strong risk factor for diseases such as coronary heart diseases and myocardial infarction, it is a protective factor for ISR; (2) Biological factors: Inflammatory response is an essential part of ISR. Therefore, scholars have discussed the relationship between some inflammation indexes and ISR and found that CRP is positively correlated with BMS-ISR but unrelated with DES-ISR. Tumor necrosis factor (TNF) is an important mediator of inflammatory response, which has also been found to be related to ISR. Its gene polymorphism is also significantly related to ISR. Other substances involved in vascular remodeling and function are also related to ISR, such as matrix metalloproteinase (MMP) and nitric oxide synthase. (3) Genetic factors: The gene polymorphism of some molecules, including IL-10 and platelet glycoprotein (ITGB3) besides TNF and NOS mentioned above, is significantly related to ISR; (4) Plaque-related factors: Plaque-related factors that will lead to ISR increase include chronic total occlusion lesion, restenosis lesion, vascular curvature, long lesion, ACC/AHAC lesion, small vessel lesion and calcification lesion; (5) Operation-related factors: As mentioned earlier, the occurrence rate of ISR in simple balloon dilatation or BMS implantation is significantly higher than that in DES implantation. Multiple-stent implantation, stent breakage and excessively small inner diameter of the lumen after PCI will also lead to a significant increase in the occurrence rate of ISR, while the use of IVUS to guide PCI strategy can significantly reduce the rate.

At present, many research results have shown that drug balloon (DCB) is very effective in the treatment of stenosis in bare metal stents (BMS-ISR). The European Society of Cardiology listed drug balloon as Class IIa recommendation and Class b evidence for the treatment of restenosis in bare metal stents based on the data of three 5 to 7-year clinical researches, Paccochisiri, PACCOCACH ISR II and PEPCAD in 2010.

Research results of Japanese doctor Habara et al. and the results of two clinical researches PEPCAD-DES and ISAR-DESIRE3 showed that paclitaxel drug balloons (PCB) are very effective in treating restenosis in drug stents (DES-ISR). Compared with common balloons, drug balloons can significantly reduce the late lumen loss (LLL) and the probability of major myocardial adverse events in the treatment of restenosis in drug stents. The late lumen loss (LLL) and the probability of major adverse cardiac events in the treatment of restenosis in drug stents with drug balloons are not inferior to those with paclitaxel drug stents. It is based on the data of the two clinical researches PEPC CAD-DES and ISAR-DESIRE3 that drug balloons were listed as Class I recommendation and Class a evidence for the treatment of restenosis in bare metal stents in 2013. Therefore, drug balloons have become the first

choice for the treatment of in-stent restenoses.

Vesselin Drug Coated Coronary Balloon Catheter developed by Lepu Medical Technology (Beijing) Co., Ltd. (hereinafter referred to as Lepu) have had the type inspection (report No.: 2015040909) completed in Jinan Medical Device Quality Supervision and Inspection Center, China Food and Drug Administration. All the items are conforming. All the conditions for clinical trials stipulated by the National Medical Products Administration have been met.

IV. Purpose

To verify the safety and effectiveness of Vesselin Drug Coated Coronary Balloon Catheter in the treatment of in-stent restenoses.

V. Method

This study is a prospective, multicenter and randomized controlled clinical trial.

VI. Content

This study is a prospective, multicenter and randomized controlled trial. A total of 224 cases (112 cases respectively in the Trial Group and the Control Group) were randomly selected at the ratio of 1:1. Vesselin Drug Coated Coronary Balloon Catheter of Lepu were used for the Trial Group, while coronary artery balloon catheters for paclitaxel release (trade name: SeQuent Please) of Braun were used for the Control Group. Subjects were followed up clinically at 30 days, 6 months, 9 months and 1 year after PTCA and followed up by angiography at 9 months after PTCA. The effectiveness of the device was evaluated with the intrasegmental late lumen loss at 9 months after surgery as the main research endpoint. All subjects were followed up within one year for observation of the occurrence of adverse events in order to make an accurate and reliable evaluation of the safety of Vesselin Drug Coated Coronary Balloon Catheter.

In this trial, an independent data management and statistics center collected, collated and statistically analyzed all relevant clinical data.

VII. General clinical information

(I) Trial scope

In this study, a total of 224 cases (112 cases respectively in the Trial Group and the Control Group) with coronary artery in-stent restenosis will be selected, with the reference lesion diameter of 2.5 mm - 4.0 mm (visual inspection) and the lesion length less than or equal to 30 mm (visual inspection). Patients must meet the selection criteria.

(II) Case selection

1. Selection criteria

(1) Age at 18 and above and 80 and below and no gender limitation;

(2) Patients with stable angina, unstable angina, old myocardial infarction or silent myocardial ischemia;

(3) Patients with the first in-stent restenosis of type I focal/type II diffuse/type III proliferative;

(4) The reference vessel diameter is 2.5 mm - 4.0 mm; the lesion length is less than or equal to ≤30mm; the diameter stenosis degree is more than or equal to 70% or 50% (visual inspection) accompanied by the evidence of ischemia; and TIMI blood flow is greater than or equal to Grade I;

(5) The distance between other lesions requiring interventional therapy and the target lesion must be more than 10 mm;

(6) Patients can receive any type of coronary revascularization (including balloon angioplasty, stent implantation or coronary artery bypass grafting);

(7) Patients who can understand the purpose of the trial, participate in the trial voluntarily and sign the informed consent form and are willing to receive clinical and angiography follow-up at 9 months after surgery.

2. Exclusion criteria

(1) Any myocardial infarction within one week;

(2) Bifurcation lesions with the distance from the ostial lesion to the left main artery less than or equal to 2 mm and the diameter of branch vessels more than or equal to 2.5 mm;

(3) Evidence shows that the target blood vessel has a large number of thrombi;

(4) Severe heart failure (NYHAIV);

(5) Patients with severe renal failure ((glomerular filtration rate (GFR) <30 ml/min) or undergoing hemodialysis;

(6) Patients with restenosis of vein grafts after bypass or severe heart valve diseases;

(7) Female patients during pregnancy or lactation;

(8) Patients with life expectancy less than 12 months;

(9) Patients with bleeding tendency, history of active digestive tract ulcers, stroke during 6 months before surgery and contraindications of antiplatelet agents and anticoagulants, who cannot be treated with anticoagulation;

(10) Patients who participated in clinical trials of other drugs or medical devices before being selected but did not reach the main endpoint time limit;

(11) Patients with heart transplantation;

(12) People who are allergic to aspirin, clopidogrel, heparin, contrast agent and paclitaxel;

(13) Patients with poor compliance who cannot complete the study as required, as judged by the investigator.

3. Withdrawal and elimination criteria

(1) The subject withdraws from the trial for any reason;

(2) The subject, Principal Investigator (PI), Ethics Committee, supervisors or/and the head of the clinical pharmacology base and the head of national or local food and drug administrations consider suspending the study from the perspective of ethics due to adverse events, especially serious adverse reactions.

(3) The investigator considers it necessary for the subject to terminate the study from a medical viewpoint;

(4) The study runs counter to the trial protocol;

(5) The subject had a loss of follow-up due to changes in work and living environment or accidents. However, subjects having accidents such as traffic accidents, deaths and fractures should be followed up in time to determine the causal relationship with the investigational devices;

(6) The informed consent is incomplete or absent;

(7) Those who need to suspend the trial for other reasons.

(III) Calculation of sample size

This study is a non-inferiority design, with the intrasegmental late lumen loss (LLL) at 9 months after surgery as the main indicator. According to the clinical research data of PEPCAD China ISR for SeQuent Please paclitaxel coronary balloons from Braun, it is assumed that the standard deviation of the two groups is 0.51mm, the non-inferiority cut-off level is 0.23 mm, and the LLL of both groups is expected to be 0.46 mm at 9 months after balloon operation. When the inspection level is 0.025 (one-sided) and the power of test is 80%, the sample size is calculated as below:

$$N=2\ (\mu_{1-\alpha}+\mu_{1-\beta})^2\sigma^2\ /(\Delta-(\chi_T-\chi_C))^2$$

σ^2= Pooled variance of the Trial Group and the Control Group

Δ= Cut-off level of non-inferiority test

χ_T= Expected LLL at 9 months after surgery in the Trial Group

χ_C= Expected LLL at 9 months after surgery in the Control Group

Test efficiency 1 -β= 0.80

Significance level α=0.025 (one-sided)

The calculation requires 156 cases (78 cases respectively in the Trial Group and the Control Group). Assuming that the failure rate is 30%, the total number of cases required is 224 (112 cases respectively in the Trial Group and the Control Group).

(IV) Number of cases

Inclusion: 239 cases were included in total, including 121 in the Trial Group and 118 in the Control Group. The distribution of cases is shown in Table 1:

Table 1 Case distribution

S/N	Name of research center	Number of selected cases	
		Trial Group	Control Group
1	Peking University First Hospital	13	12
2	People's Hospital of Tianjin	13	16
3	The Central Hospital of Wuhan	21	18
4	The Second Hospital of Jilin University	20	20
5	Emergency General Hospital	6	6
6	Beijing Friendship Hospital, Capital Medical University	6	6
7	The Third Medical Center, Chinese PLA General Hospital	20	19
8	Central Hospital of Zibo	3	3
9	The First Affiliated Hospital of Bengbu Medical College	6	6
10	Wuhan No.5 Hospital	4	4
11	Fujian Provincial Hospital	3	2
12	Beijing Luhe Hospital, Capital Medical University	1	2
13	Central Hospital of Xiangtan	5	4
Total		121	118

Principal Investigator: Huo Yong from Peking University First Hospital

Core medical imaging laboratory: Fuwai Hospital, National Center for Cardiovascular Diseases

Data management and statistical analysis: GCP ClinPlus (Beijing) Medical Technology Development Co., Ltd.

VIII. Medical devices for trial and control

(I) Medical device for trial

Intravascular Drug (Paclitaxel) Eluting Balloon Catheter (Coronary Artery)

Diameter (mm)	Length (mm)			
2.5	14	20	28	35
2.75	14	20	28	35
3.0	14	20	28	35
3.5	14	20	28	35
4.0	14	20	28	35

(II) Medical device for control

Drug (Paclitaxel) Eluting Balloon Catheter (Coronary Artery) (trade name: SeQuent Please)

Diameter (mm)	Length (mm)					
2.5	10	15	17	20	26	30
2.75	/	15	17	20	26	/

3.0	10	15	17	20	26	30
3.5	10	15	17	20	26	30
4.0	10	15	17	20	/	/

IX. Statistical and evaluation methods

(I) Statistical analysis method

1. Population under analysis

Full analysis set (FAS): the set of subjects under the principle of Intention To Treat: the data set composed of all subjects participating in the treatment and having baseline efficacy evaluation. For subjects without observations of all the efficacy evaluations, the principle of LOCF (Last Observation Carry Forward) will be adopted for data conversion.

Per protocol set (PPS): the group of patients subject to treatment who have completed the trial, in which those in serious violation of the protocol (i.e. the violation of research objects against inclusion or exclusion criteria) have been excluded.

Safety set (SS): the set of all subjects grouped randomly and with the test device used and with at least one baseline safety evaluation.

The curative effect analysis will be carried out based on FAS and PPS; all baseline demographic data analyses will be conducted based on FAS, and the safety evaluation based on SS.

2. Statistical analysis method

The statistical analysis software of SAS® 9.2 or above will be used for statistical analysis.

All statistical tests will be double-sided. The difference will be considered statistically significant if the P value is less than or equal to 0.05 unless otherwise specified.

For the description of quantitative indicators, the total number of cases, the number of missing cases, mean, standard deviation, median, quartile interval, minimum value and maximum value will be calculated.

For the description of classification indicators, the number and percentage of cases in each category will be calculated.

(II) Statistical evaluation method

1. Baseline evaluation

A between-group comparison of enumeration data will be made. The precise probability method Fisher will be adopted when the theoretical frequency in the four-fold table is less than 5. Group t test or Wilcoxon rank sum test will be used for the between-group comparison of measurement data.

2. Therapeutic evaluation method

The two groups will be compared with the covariance analysis (ANCOVA) model in terms of the intrasegmental late lumen loss at 9 months after surgery. In the model, the preoperative diameter stenosis (%) will be taken as the covariate, and the role of the center and groups will be considered.

Pre-test of interaction items: The main analysis model also includes interaction terms of the center and groups. The interaction term entered into the model will be used to analyze the statistical significance of interaction at the test level of α=0.10. The interaction term will be eliminated in the final analysis model if the interaction is not statistically significant.

If the interaction term of the center and groups is statistically significant, the mean square of the interaction term (MS center * groups) will be used as the error term to evaluate the therapeutic effect. Besides, the therapeutic effect will be evaluated by center when the interactive term is statistically significant.

Calculation of confidence interval (CI) and determination of non-inferiority: The LSMean of variation differences (μA-μB) of the two groups and its 95% CI will be calculated according to the model. It will be judged whether the non-inferiority standard is met according to the upper limit of the confidence interval. The conclusion will be non-inferiority if the upper limit of 95% CI is less than 0.23.

The occurrence time and rate of target lesion failure (TLF) rate, target lesion reconstruction (TLR) rate, death, myocardial infarction and thrombosis will be statistically described by means of survival analysis.

The success rate of operation will be statistically described.

3. Safety evaluation method

Statistics will be made for the number, times and occurrence rate of all adverse events and serious adverse events in the two groups. Cases with the study suspended due to adverse events and those with serious adverse events will be given in the form of a list.

For laboratory examination and other items, all completed examination items and descriptive statistics will be listed in the form of a cross table of information before and after treatment (according to the investigator' judgment of clinical significance). Inspection items with abnormal values and clinical significance should be listed.

X. Clinical evaluation criteria

(I) Clinical performance evaluation criteria

1. Success rate of surgery (including device success, lesion success and clinical success)

- Criteria for device success: The residual diameter stenosis degree of the target lesion is less than 50% upon visual inspection and the TIMI blood flow is of grade 3 after successful delivery of the device specified in the study and successful dilation without the application of other extra interventional therapeutic methods.
- Criteria for lesion success: The final residual stenosis degree of the target lesion is less than 20% upon visual inspection, the TIMI blood flow is of grade 3 and there is no residual dissection or thrombus after application of any interventional therapeutic method.
- Criteria for clinical success: No major adverse cardiac events caused by ischemia occurred during the hospitalization period (up to 7 days after surgery) on the basis of lesion success.

2. Evaluation of operating performance of balloon catheters, including the pushability, patency, visibility, adaptability of the balloon to the blood vessel shape, retraction ability and sealing performance (excellent, good, fair, poor).

(II) Effectiveness evaluation criteria

1. Main indicators:

- Intrasegmental late lumen loss: the difference between the minimum intrasegmental lumen diameter in the target lesion immediately after PTCA and that during contrast reexamination at 9 months after surgery.

2. Secondary indicators:

- Restenosis rate of the target lesion: The stenosis of the target lesion is more than or equal to 50% (QCA) according to contrast reexamination at 9 months after surgery.
- Target lesion failure (TLF), including cardiac death, target vessel-related myocardial infarction (TV-MI) and target lesion revascularization caused by ischemia (iTLR).

Target lesion revascularization caused by ischemia (iTLR) is defined as below: The diameter stenosis is greater than or equal to 50% (determined by the core medical imaging laboratory) during coronary angiography in the follow-up period after surgery, and at least one of the following criteria is met:

(1) History of recurrent angina that may be related to the target lesion;

(2) Objective ischemic indications (ECG changes) related to the target lesion during rest or exercise test (or equivalent);

(3) Abnormal results in any invasive diagnostic examination, such as Doppler flow reserve analysis and intracoronary flow reserve;

(4) The diameter stenosis is greater than or equal to 70% (determined by the core medical imaging laboratory) when there are no signs or symptoms of ischemia mentioned above.

- Related cardiovascular clinical composite endpoints (POCE) of patients, including all-cause mortality,

all myocardial infarction and any revascularization.

(III) Safety evaluation criteria

1. The occurrence rate of all-cause mortality (including cardiac death and non-cardiac death) and all myocardial infarction (including Q wave and non-Q wave) at 30 days, 6 months, 9 months and 1 year after surgery.

2. Occurrence rate of thrombotic events:

Definite thrombotic events: occlusion of the target lesion caused by thrombus confirmed by angiography or pathology, accompanied by any of the following criteria: (1) symptoms of acute myocardial ischemia; (2) ischemic ECG changes; and (3) increased myocardial enzymes. Probable thrombotic events: any unexplained death within 30 days; any myocardial infarction related to acute ischemia in the target vascular area, but without thrombus confirmed by angiography, or without any other definite cause.

Thrombotic events can be divided into acute, subacute, late and late-onset ones according to the occurrence time. Acute thrombosis is defined as thrombosis within 24 hours after surgery, subacute thrombosis as thrombosis within 30 days after surgery, late thrombosis as thrombosis within 30 days to one year after surgery, and late-onset thrombosis as thrombosis within one year after surgery.

3. Adverse events: Adverse events will be observed and recorded during the trial. Adverse events refer to adverse medical events that occur after subjects receive the test product, but that are not necessarily related to the test product.

XI. Organization of clinical trial

Sponsor	Lepu Medical Technology (Beijing) Co., Ltd.
Clinical trial institutions	Peking University First Hospital People's Hospital of Tianjin The Central Hospital of Wuhan The Second Hospital of Jilin University Emergency General Hospital Beijing Friendship Hospital, Capital Medical University The Third Medical Center, Chinese PLA General Hospital Central Hospital of Zibo The First Affiliated Hospital of Bengbu Medical College Wuhan No.5 Hospital Fujian Provincial Hospital Beijing Luhe Hospital, Capital Medical University Central Hospital of Xiangtan
Core medical imaging laboratory	Fuwai Hospital, CAMS & PUMC
Clinical Events Committee	Chairman: Professor Liu Huiliang Members: Professor Li Junxia, Professor Shen Zhujun
Data management and statistical analysis	GCP ClinPlus (Beijing) Medical Technology Development Co., Ltd.

XII. Ethical instructions

This trial was implemented in strict compliance with the Declaration of Helsinki (2000), Good Clinical Practice for Medical Device, and relevant national regulations.

Peking University First Hospital served as the leader unit. Its Ethics Committee reviewed and approved this trial protocol (protocol version number/date: V2.0/March 04, 2016) and informed consent form on March 16, 2016. Other cooperative hospitals conducted ethical approval or filing respectively before the start of the trial.

XIII. Results of clinical trial

A total of 239 subjects (121 in the Trial Group and 118 in the Control Group) were observed in this clinical

study in order to compare the safety and effectiveness of Vesselin Drug Coated Coronary Balloon Catheter produced by Lepu and the similar product - coronary artery balloon catheters for paclitaxel release (trade name: SeQuent Please) marketed by B.Braun.

(I) Included cases and follow-up

A total of 13 research centers participated in the trial, and 239 subjects (121 in the Trial Group and 118 in the Control Group) were included. 233 subjects were followed up at one year after surgery, including 117 in the Trial Group with a follow-up rate of 96.7% and 116 in the Control Group with a follow-up rate of 98.3%.

All subjects were included in FAS analysis, and there were 239 cases (121 in the Trial Group and 118 in the Control Group) in the FAS population. All subjects were included in SS analysis, and there were 239 cases (121 in the Trial Group and 118 in the Control Group) in the SS population. Among them, 6 subjects (4 in the Trial Group and 2 in the Control Group) were not included in the PPS population due to the loss of follow-up; 72 subjects (38 in the Trial Group and 34 in the Control Group) were not included in the PPS population due to the failure to obtain the main endpoint indicators; 5 subjects (2 in the Trial Group and 3 in the Control Group) were not included in the PPS population due to serious deviations from the protocol. There were 165 subjects (83 in the Trial Group and 82 in the Control Group) in the PPS population. See Table 1 for details.

Table 1 Identification of population under analysis

Indicator	Control Group	Trial Group	Total
Randomized inclusion	118 (100.0%)	121 (100.0%)	239 (100.0%)
Loss of follow-up	2 (1.7%)	4 (3.3%)	6 (2.5%)
Failure to obtain the main endpoint indicators	34 (28.8%)	38 (31.4%)	72 (30.1%)
Serious deviations from the protocol	3 (2.5%)	2 (1.7%)	5 (2.1%)
FAS population	118 (100.0%)	121 (100.0%)	239 (100.0%)
SS population	118 (100.0%)	121 (100.0%)	239 (100.0%)
PPS population	82 (69.5%)	83 (68.6%)	165 (69.0%)

Notes: PPS population =FAS population - population with the loss of follow-up - population with the failure to obtain the main endpoint indicators - population with serious deviations from the protocol. In this study, the subjects in the Trial Group with the failure to obtain the main endpoint indicators included 6 subjects with the loss of follow-up and serious deviations from the protocol, while the same in the Control Group included 2 subjects with the loss of follow-up and 1 subject with serious deviations from the protocol.

(II) Analysis on baseline conditions of selected cases

Comparison of general information: There was no statistical difference in age, vital signs (blood pressure and heart rate), medical history and clinical diagnosis between the Trial Group and the Control Group. There was a slight statistical difference in gender between the Trial Group and the Control Group, but both of them were dominated by male. In general, the general information of subjects in the two groups was basically the same, and they were comparable. See Tables 2-1 to 2-4.

Table 2-1 Comparison of demographic data between the two groups (FAS)

Indicator	Control Group	Trial Group	P
Age (years old)			0.346
N (Missing)	118 (0)	121 (0)	
Mean (SD)	65.0 (8.6)	63.8 (10.3)	
Gender			0.031
Male	79 (66.9%)	96 (79.3%)	
Female	39 (33.1%)	25 (20.7%)	
Total	118	121	

Table 2-2 Comparison of vital signs between the two groups (FAS)

Items	Control Group	Trial Group	P
Heart rate (beats/min)			0.867
N (Missing)	118 (0)	121 (0)	
Mean (SD)	73.3 (12.8)	73.5 (12.5)	
Systolic blood pressure (mmHg)			0.523
N (Missing)	118 (0)	121 (0)	
Mean (SD)	134.6 (17.2)	133.0 (19.4)	
Diastolic blood pressure (mmHg)			0.434
N (Missing)	118 (0)	121 (0)	
Mean (SD)	77.0 (9.8)	78.0 (10.0)	

Table 2-3 Comparison of medical history between the two groups (FAS)

Items	Control Group	Trial Group	P
Myocardial infarction			0.928
Yes	51 (43.2%)	53 (43.8%)	
No	67 (56.8%)	68 (56.2%)	
Previous CABG			1.000
Yes	1 (0.8%)	1 (0.8%)	
No	117(99.2%)	120 (99.2%)	
Diabetes			0.278
Yes	57 (48.3%)	50(41.3%)	
No	61 (51.7%)	71 (58.7%)	
JRJ BLOOD PRESSURE			0.530
Yes	90 (76.3%)	88 (72.7%)	
No	28 (23.7%)	33 (27.3%)	
Hyperlipidaemia			0.339
Yes	61 (51.7%)	70 (57.9%)	
No	57 (48.3%)	51 (42.1%)	
Smoking			0.266
Yes	34 (28.8%)	43 (35.5%)	
No	84 (71.2%)	78 (64.5%)	
Chronic nephrosis			1.000
Yes	3 (2.5%)	4(3.3%)	
No	115(97.5%)	117(96.7%)	
Renal function			0.725
Sufficient	112(94.9%)	116(95.9%)	
Insufficient	6(5.1%)	5(4.1%)	
Family history of coronary heart disease			0.902
Yes	12(10.2%)	13 (10.7%)	
No	105 (89.0%)	108 (89.3%)	

Missing	1 (0.8%)	0 (0.0%)

Table 2-4 Comparison of clinical diagnosis between the two groups (FAS)

Indicator	Control Group	Trial Group	P
Silent myocardial ischemia			1.000
Yes	2(1.7%)	3 (2.5%)	
No	116(98.3%)	118(97.5%)	
Stable angina			0.856
Yes	9 (7.6%)	10 (8.3%)	
No	109 (92.4%)	111 (91.7%)	
Unstable angina			0.533
Yes	101 (85.6%)	100 (82.6%)	
No	17(14.4%)	21 (17.4%)	
NSTEMI			1.000
Yes	4 (3.4%)	5(4.1%)	
No	114(96.6%)	116(95.9%)	
STEMI			1.000
Yes	3 (2.5%)	4 (3.3%)	
No	115(97.5%)	117(96.7%)	

(III) Surgery information and surgical procedure evaluation

Comparison of surgery information: There was no statistical difference in vital signs (blood pressure and heart rate), LVEF, intervention route, lesion site, restenosis type, pretreatment, drug balloon use and surgical complications between the Trial Group and the Control Group.

The success rate of surgery in the Trial Group was 99.2%, while that in the Control Group was 100% (p=1.000), showing no statistical difference between the two groups. One case in the Trial Group failed due to the tortuous lesion and failure of the drug balloon to pass the restenosis lesion in the stent, so PCI treatment was abandoned. Dissection or tear occurred in 1 case (0.7%) in the Trial Group and in 4 cases (3.0%) in the Control Group (P = 0.207), showing no statistical difference.

The comparison of surgery between the Trial Group and the Control Group is shown in Table 3.

Table 3 Comparison of surgery (FAS) between the two groups

Indicator	Control Group	Trial Group	P
Heart rate during surgery (beats/min)			0.312
N (Missing)	109(9)	107(14)	
Mean (SD)	71.8(12.0)	70.4 (8.4)	
Systolic blood pressure during surgery (mmHg)			0.080
N (Missing)	109(9)	107(14)	
Mean (SD)	133.2(17.9)	129.2(15.6)	
Diastolic blood pressure during surgery (mmHg)			0.477
N (Missing)	109(9)	107(14)	
Mean (SD)	76.1 (10.2)	75.1 (9.4)	
LVEF (%)			0.598

N (Missing)	107(11)	110(11)	
Mean (SD)	59.57 (7.87)	58.97 (8.97)	
Route			1.000
Ladder artery	113(95.8%)	114(94.2%)	
Femoral artery	5 (4.2%)	6 (5.0%)	
Others	0 (0.0%)	1 (0.8%)	
Lesion site			0.564
LAD	62 (46.3%)	72 (51.8%)	
LCX	19(14.2%)	20 (14.4%)	
LM	0 (0.0%)	1 (0.7%)	
RCA	53 (39.6%)	46 (33.1%)	
Restenosis lesion type			0.653
Type I	47 (35.1%)	49 (35.3%)	
Type II	74 (55.2%)	71 (51.1%)	
Type III	13 (9.7%)	18(12.9%)	
Missing	0 (0.0%)	1 (0.7%)	
Pretreatment			NA
Yes	134(100.0%)	139(100.0%)	
No	0 (0.0%)	0 (0.0%)	
Number of drug balloons used			0.700
N (Missing)	135(0)	141(0)	
Mean (SD)	1.1 (0.3)	1.1 (0.4)	
Maximum dilation pressure (ATM)			0.507
N (Missing)	135(0)	140(1)	
Mean (SD)	9.963 (2.714)	10,171 (2.484)	
Dilation time (s)			0.394
N (Missing)	135(0)	140(1)	
Mean (SD)	53.659(10.072)	52.571 (11.018)	
Whether the balloon is used successfully			1.000
No	1 (0.7%)	1 (0.7%)	
Yes	132(98.5%)	138 (99.3%)	
Missing	1 (0.7%)	0 (0.0%)	
Dissection or tear			0.207
Yes	4 (3.0%)	1 (0.7%)	
No	130 (97.0%)	138 (99.3%)	
Whether the surgery is successful			1.000
Yes	118(100.0%)	120 (99.2%)	
No	0 (0.0%)	1 (0.8%)	
Surgical complications			0.442
Yes	4 (3.4%)	2(1.7%)	

No	114(96.6%)	119(98.3%)

(IV) Quantitative coronary arteriography (QCA) analysis results

(1) Analysis results of QCA-related indicators before surgery

Comparison of QCA-related indicators before surgery: There was no statistical difference between the Trial Group and the Control Group in preoperative lesion length, stenosis degree, reference vessel diameter, minimum lumen diameter and reference diameters of the proximal end and the distal end.

The analysis results of QCA-related indicators of the subjects before surgery are shown in Table 4.

Table 4 QCA-related indicators (lesion level) of subjects in the two groups before surgery (FAS)

Indicator	Control Group	Trial Group	P
Preoperative lesion length (mm)			0.058
N (Missing)	127(0)	130(3)	
Mean (SD)	15,509 (7.600)	17.527 (9.346)	
Preoperative stenosis degree (%)			0.132
N (Missing)	127(0)	130(3)	
Mean (SD)	68.612(17.676)	65.452(15.834)	
Preoperative reference vessel diameter (mm)			0.536
N (Missing)	127(0)	130(3)	
Mean (SD)	2.587 (0.355)	2.616(0.395)	
Preoperative minimum lumen diameter (mm)			0.172
N (Missing)	127(0)	130(3)	
Mean (SD)	0.833 (0.522)	0.917(0.462)	
Preoperative reference diameter of the proximal end (mm)			0.996
N (Missing)	127(0)	130(3)	
Mean (SD)	2.788 (0.426)	2.788 (0.461)	
Preoperative reference diameter of the distal end (mm)			0.834
N (Missing)	127(0)	130(3)	
Mean (SD)	2.362 (0.421)	2.351 (0.411)	

Notes: Compared with the number of target lesions, 273, recorded in Table 3CRF, the number of target lesions under QCA analysis was 260 for the reason that QCA analysis was an analysis of the imaging information conducted by a third-party imaging laboratory in a blind state, during which two adjacent target lesions in CRF records were measured as one lesion, e.g. random numbers 032, 044, 098, 125, 153, 156, 161, 190, 194, 200, 236 and 219. Another case is that the target lesions retained in the imaging information of each center were unclear, leading to the failure to measure the lesions when they were sent to the core laboratory, e.g. random number 070.

(2) Analysis results of QCA-related indicators immediately after surgery

Comparison of QCA-related indicators immediately after surgery: There was no statistical difference between the Trial Group and the Control Group in postoperative stenosis degree, reference vessel diameter, minimum lumen diameter and reference diameters of the proximal end and the distal end. There was no statistical difference in the stent length in the damaged section, diameter stenosis degree, minimum and reference diameters of the proximal edge, diameter stenosis degree of the proximal edge, minimum and reference diameters of the distal edge and diameter stenosis degree of the distal edge. The

analysis results of QCA-related indicators of the subjects immediately after surgery are shown in Table 5.

Table 5 QCA-related indicators (lesion level) of subjects in the two groups immediately after surgery (FAS)

Indicator	Control Group	Trial Group	P
Postoperative stenosis degree (%)			0.124
N (Missing)	118(9)	127(6)	
Mean (SD)	18.622 (9.513)	20,574(10.239)	
Preoperative reference vessel diameter (mm)			0.473
N (Missing)	118(9)	127(6)	
Mean (SD)	2.563 (0.381)	2.528 (0.395)	
Postoperative minimum lumen diameter (mm)			0.087
N (Missing)	118(9)	127(6)	
Mean (SD)	2.081 (0.373)	2.001 (0.358)	
Postoperative reference diameter of the proximal end (mm)			0.613
N (Missing)	118(9)	127(6)	
Mean (SD)	2.791 (0.454)	2.821 (0.472)	
Postoperative reference diameter of the distal end (mm)			0.431
N (Missing)	118(9)	127(6)	
Mean (SD)	2.393 (0.427)	2.351 (0.406)	
Postoperative minimum diameter of stent in the damaged section (mm)			0.423
N (Missing)	118(9)	127(6)	
Mean (SD)	2.183 (0.362)	2.148 (0.326)	
Postoperative reference diameter of the damaged section (mm)			0.900
N (Missing)	118(9)	127(6)	
Mean (SD)	2.611 (0.369)	2.605 (0.391)	
Postoperative stent length in the damaged section (mm)			0.104
N (Missing)	118(9)	127(6)	
Mean (SD)	20,433 (6.164)	22,001 (8.739)	
Postoperative diameter stenosis degree of the damaged section (%)			0.379
N (Missing)	118(9)	127(6)	
Mean (SD)	16,194 (9.054)	17,168 (8.259)	
Postoperative minimum diameter of the proximal edge in the damaged section (mm)			0.577
N (Missing)	118(9)	127(6)	
Mean (SD)	2.508 (0.400)	2.538 (0.433)	
Postoperative reference diameter			0.710

of the proximal edge in the damaged section (mm)			
N (Missing)	118(9)	127(6)	
Mean (SD)	2.746 (0.373)	2.765 (0.416)	
Postoperative diameter stenosis degree of the proximal edge in the damaged section (%)			0.725
N (Missing)	118(9)	127(6)	
Mean (SD)	8.519(8.651)	8.134(8.461)	
Postoperative minimum diameter of the distal edge in the damaged section (mm)	0.177		
N (Missing)	118(9)	127(6)	
Mean (SD)	2.217(0.415)	2.143 (0.433)	
Postoperative reference diameter of the distal edge in the damaged section (mm)			0.648
N (Missing)	118(9)	127(6)	
Mean (SD)	2.493 (0.380)	2.471 (0.384)	
Postoperative diameter stenosis degree of the distal edge in the damaged section (%)			0.118
N (Missing)	118(9)	127(6)	
Mean (SD)	11,104 (8.937)	13.193 (11.793)	

(3) Imaging follow-up of the target lesion 9 months after surgery

Comparison of QCA results of imaging follow-up after surgery: There was no statistical difference between the Trial Group and the Control Group in diameter stenosis degree, reference vessel diameter, minimum lumen diameter and reference diameters of the proximal end and the distal end. There was no statistical difference in the minimum diameter, reference and length of the stent in the damaged section, diameter stenosis degree, minimum and reference diameters of the proximal edge, diameter stenosis degree of the proximal edge, minimum and reference diameters of the distal edge and diameter stenosis degree of the distal edge.

Table 6 shows the analysis results of QCA-related indicators of subjects in imaging follow-up at 9 months after surgery.

Table 6 QCA-related indicators (lesion level) of subjects in the two groups in imaging follow-up at 9 months after surgery (FAS)

Indicator	Control Group	Trial Group	P
Diameter stenosis degree in follow-up (%)			0.285
N (Missing)	88(39)	92(41)	
Mean (SD)	33,656 (18.934)	36.944 (21.972)	
Reference vessel diameter in follow-up (mm)			0.968
N (Missing)	88(39)	92(41)	
Mean (SD)	2.576 (0.322)	2.573 (0.415)	
Minimum lumen diameter in follow-up (mm)			0.278
N (Missing)	88(39)	92(41)	

Mean (SD)	1.714(0.542)	1.620 (0.612)	
Reference diameter of the proximal end in follow-up (mm)			0.908
N (Missing)	88(39)	92(41)	
Mean (SD)	2.754 (0.463)	2.762 (0.473)	
Reference diameter of the distal end in follow-up (mm)			0.674
N (Missing)	88(39)	92(41)	
Mean (SD)	2.348(0.410)	2.321 (0.431)	
Minimum diameter of stent in the damaged section in follow-up (mm)			0.313
N (Missing)	88(39)	92(41)	
Mean (SD)	1.792 (0.551)	1.702 (0.629)	
Reference diameter of the damaged section in follow-up (mm)			0.936
N (Missing)	88(39)	92(41)	
Mean (SD)	2.592 (0.319)	2.597 (0.407)	
Stent length in the damaged section in follow-up (mm)			0.402
N (Missing)	88(39)	87(46)	
Mean (SD)	20.431 (5.786)	21,297 (7.722)	
Diameter stenosis degree of the damaged section in follow-up (%)			0.297
N (Missing)	88(39)	92(41)	
Mean (SD)	31.048 (19.461)	34,346 (22.600)	
Minimum diameter of the proximal edge of the stent in follow-up (mm)			0.722
N (Missing)	88(39)	89(44)	
Mean (SD)	2.362 (0.478)	2.388 (0.486)	
Reference diameter of the proximal edge of the stent in follow-up (mm)			0.947
N (Missing)	88(39)	89(44)	
Mean (SD)			
Diameter stenosis degree of the proximal edge of the stent in follow-up (%)	2.709 (0.334)	2.713 (0.428)	0.562
N (Missing)	88(39)	89(44)	
Mean (SD)	12,974(13.236)	11.850(12.484)	
Minimum diameter of the distal edge of the stent in follow-up (mm)			0.232
N (Missing)	88(39)	87(46)	
Mean (SD)	2.131 (0.454)	2.045 (0.499)	
Reference diameter of the distal edge of the stent in follow-up (mm)			0.804
N (Missing)	88(39)	87(46)	
Mean (SD)	2.477 (0.320)	2.463 (0.415)	

Diameter stenosis degree of the distal edge of the stent in follow-up (%)			0.164
N (Missing)	88(39)	87(46)	
Mean (SD)	14,246(12.872)	17.090(14.034)	

(V) Analysis on clinical trial results of main therapeutic effect indicators

Main curative effect indicator: Intrasegmental late lumen loss (patient level/lesion level)

Patient level: In this clinical trial, there were 239 subjects (121 in the Trial Group and 118 in the Control Group) in the FAS population and 165 subjects (83 in the Trial Group and 82 in the Control Group, P = 0.881) in the PPS population. In the FAS population, the intrasegmental late lumen loss within 9 months after surgery was 0.39 vs 0.34mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95%CI was (-0.09, 0.19), with the upper limit of 0.19 which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. The results are shown in Table 7-1. In the PPS population, the intrasegmental late lumen loss at 9 months after surgery was 0.40 mm vs 0.35 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.19), and the upper limit was 0.19, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. Results are shown in Table 7-1.

Table 7-1 Intrasegmental late lumen loss of subjects in the two groups at 9 months after surgery (patient level)

Indicator		Control Group	Trial Group	Mean difference between the two groups (95%CI)
Intrasegmental late lumen loss	PPS	0.35	0.40	0.05 (-0.09, 0.19)
	FAS	0.34	0.39	0.05 (-0.09, 0.19)

Notes: 1. For one subject with multiple target lesions, the principle of lesion selection is as follows: the lesion with greater LL in the Trial Group and the lesion with smaller LL in the Control Group were selected as the LL at the patient level respectively.

2. The main result of this study was the endpoint LL. A covariance model was adopted. In the model, the preoperative diameter stenosis degree was taken as the covariate, and the role of the center and groups was considered.

Lesion level: In this clinical trial, there were 260 lesions (133 in the Trial Group and 128 in the Control Group) in the FAS population and 178 lesions (92 in the Trial Group and 86 in the Control Group, p=0.731) in the PPS population. In the FAS population, the intrasegmental late lumen loss at 9 months after surgery was 0.38 mm vs 0.34 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.19), and the upper limit was 0.19, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. Results are shown in Table 7-2. In the PPS population, the intrasegmental late lumen loss at 9 months after surgery was 0.39 mm vs 0.35 mm respectively in the Trial Group and the Control Group, which differed by 0.05 mm. The 95% CI was (-0.09, 0.18), and the upper limit was 0.18, which was less than the non-inferiority cut-off level of 0.23, indicating that the Trial Group was not inferior to the Control Group. Results are shown in Table 7-2.

Table 7-2 Intrasegmental late lumen loss of subjects in the two groups at 9 months after surgery (lesion level)

Indicator		Control Group	Trial Group	Mean difference between the two groups (95%CI)
Intrasegmental late lumen loss	PPS	0.35	0.39	0.05 (-0.09, 0.18)
	FAS	0.34	0.38	0.05 (-0.09, 0.19)

Note: The main result of this study was the endpoint LL. A covariance model was adopted. In the model, the preoperative diameter stenosis degree was taken as the covariate, and the role of the center and

groups was considered.

(VI) Analysis on secondary therapeutic effect indicators

1. Success rate of surgery

The device success rate was 98.6% vs 96.3% (p=0.275) respectively in the Trial Group and the Control Group, which had no statistical difference. The success rate for lesions was 98.6% vs 97.8% (p=0.680) respectively, which had no statistical difference. The clinical success rate was 98.3% vs 96.6% (p=0.442), which had no statistical difference. See Table 8 for details.

Table 8 Surgical success in the two groups

Indicator	Control Group	Trial Group	P
Device success	129 (96.3%)	137(98.6%)	0.275
Lesion success	131 (97.8%)	137(98.6%)	0.680
Surgical success	114(96.6%)	119(98.3%)	0.442

2. Restenosis rate of the target lesion (9 months after surgery)

FAS population in this clinical trial: The restenosis rate of the target lesion was 12.8% vs 13.4% (p=0.886) respectively in the Trial Group and the Control Group, which had no statistical difference. PPS population: The restenosis rate of the target lesion was 18.5% vs 19.8% (p=0.827) respectively in the Trial Group and the Control Group, which had no statistical difference. See Table 9.

Table 9 Restenosis of target lesions in the two groups (lesion level)

Indicator	Control Group	Trial Group	P
PPS Restenosis rate of target lesions	17(19.8%)	17(18.5%)	0.827
FAS	17(13.4%)	17(12.8%)	0.886

3. Target lesion failure (TLF)

Target lesion failure (TLF) includes cardiac death, myocardial infarction related to target vessels and revascularization of target lesions caused by ischemia.

The results of this clinical trial showed that the failure rate of target lesions at 30 days after surgery was 0% vs 1.7% (P = 0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 2.5% vs 3.4% (p=0.720) respectively, which had no statistical difference. That at 9 months was 8.3% vs 11.1% (p=0.471) respectively, which had no statistical difference. That at 1 year after surgery was 12.4% vs 12.7% (p=0.941) respectively, which had no statistical difference. See Table 10.

Table 10 shows the detailed results of cardiac death, myocardial infarction related to target vessels and revascularization of target lesions caused by ischemia in each follow-up period.

Table 10 Failure of target lesions (FAS) in the two groups (FAS)

Follow-up period	Indicator	Control Group	Trial Group	P
30 days	TLF	2(1.7%)	0 (0.0%)	0.243
	Cardiac death	0	0	NA
	Myocardial infarction related to target vessels	2 (1.69%)	0	0.243
	Revascularization of target lesions caused by ischemia	0	0	NA
6 months	TLF	4 (3.4%)	3 (2.5%)	0.720
	Cardiac death	0	1 (0.83%)	1.000
	Myocardial infarction related to target	2 (1.69%)	2 (1.65%)	1.000

	vessels			
	Revascularization of target lesions caused by ischemia	2 (1.69%)	1 (0.83%)	0.619
9 months	TLF	13(11.0%)	10(8.3%)	0.471
	Cardiac death	0	1 (0.83%)	1.000
	Myocardial infarction related to target vessels	2 (1.69%)	2 (1.65%)	1.000
	Revascularization of target lesions caused by ischemia	11 (9.32%)	8 (6.61%)	0.439
1 year	TLF	15(12.7%)	15(12.4%)	0.941
	Cardiac death	0	1 (0.83%)	1.000
	Myocardial infarction related to target vessels	2 (1.69%)	3 (2.48%)	1.000
	Revascularization of target lesions caused by ischemia	14 (11.86%)	13 (10.74%)	0.784

4. Related cardiovascular clinical composite endpoints (POCE) of patients

Related cardiovascular clinical composite endpoints (POCE) of patients include all-cause mortality, all myocardial infarction and any revascularization.

The results of this clinical trial showed that the POCE at 30 days after surgery was 0% vs 1.7% (P = 0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 2.5% vs 3.4% (p=0.720) respectively, which had no statistical difference. That at 9 months was 14.9% vs 18.6 (p=0.435) respectively, which had no statistical difference. That at 1 year after surgery was 19.8% vs 20.3% (p=0.922) respectively, which had no statistical difference. See Table 11.

Table 11 shows the detailed results of all-cause mortality, all myocardial infarction and any revascularization in each follow-up period.

Table 11 Related cardiovascular clinical composite endpoints of patients in the two groups (FAS)

Follow-up period	Indicator	Control Group	Trial Group	P
30 days	POCE	2(1.7%)	0 (0.0%)	0.243
	All-cause mortality	0	0	NA
	Myocardial infarction	2 (1.69%)	0	0.243
	Revascularization	2 (1.69%)	0	0.243
6 months	POCE	4 (3.4%)	3 (2.5%)	0.720
	All-cause mortality	0	1 (0.83%)	1.000
	Myocardial infarction	2 (1.69%)	2 (1.65%)	1.000
	Revascularization	4 (3.39%)	1 (0.83%)	0.209
9 months	POCE	22(18.6%)	18(14.9%)	0.435
	All-cause mortality	1 (0.85%)	3 (2.48%)	0.624
	Myocardial infarction	3 (2.54%)	2 (1.65%)	0.681
	Revascularization	21 (17.80%)	14 (11.57%)	0.173
1 year	POCE	24 (20.3%)	24(19.8%)	0.922
	All-cause mortality	1 (0.85%)	3 (2.48%)	0.624
	Myocardial infarction	3 (2.54%)	3 (2.48%)	1.000
	Revascularization	23 (19.49%)	20 (16.53%)	0.551

5. Thrombotic events

The results of this study showed that no thrombotic event occurred in the Trial Group and the Control Group at 30 days, 6 months and 9 months after surgery. One thrombotic event occurred at one year after surgery in the Trial Group, while no thrombotic event occurred in the Control Group. The occurrence rate of thrombotic events was 0.8% vs 0% (P = 1.000) respectively in the Trial Group and the Control Group, which had no statistical difference. See Table 12.

One thrombotic event occurred at 1 year after surgery in the Trial Group, which was a definite and late-onset thrombus.

Table 12 Thrombosis of patients in the two groups

Indicator		Control Group	Trial Group	P
Thrombus	30 days	0 (0.0%)	0 (0.0%)	NA
	6 months	0 (0.0%)	0 (0.0%)	NA
	9 months	0 (0.0%)	0 (0.0%)	NA
	1 year	0 (0.0%)	1 (0.8%)	1.000

(VII) Performance of balloon catheters

There was no statistical difference between the balloons in the two groups in terms of the evaluation of the pushability, patency, visibility, adaptability of the balloon to the blood vessel shape and retraction ability (P>0.05). See Table 13 for details.

Table 13 Comparison of clinical manipulation performance evaluation of balloon catheters in the two groups

Items			Control Group	Trial Group	P
Pushability	FAS	Good	97 (72.4%)	98 (70.5%)	0.609
			37 (27.6%)	38(27.3%)	
		Fair	0 (0.0%)	2(1.4%)	
		Poor	0 (0.0%)	0 (0.0%)	
	PPS	Excellent	65 (72.2%)	70 (73.7%)	0.869
		Good	25 (27.8%)	25 (26.3%)	
		Fair	0 (0.0%)	0 (0.0%)	
		Poor	0 (0.0%)	0 (0.0%)	
Patency	FAS	Excellent	96 (71.6%)	99 (71.2%)	0.582
		Good	38 (28.4%)	37 (26.6%)	
		Fair	0 (0.0%)	2(1.4%)	
		Poor	0 (0.0%)	0 (0.0%)	
	PPS	Excellent	64 (71.1%)	71 (74.7%)	0.621
		Good	26 (28.9%)	24 (25.3%)	
		Fair	0 (0.0%)	0 (0.0%)	
		Poor	0 (0.0%)	0 (0.0%)	
Visibility	FAS	Excellent	99 (73.9%)	102 (73.4%)	1.000
		Good	35 (26.1%)	35 (25.2%)	
		Fair	0 (0.0%)	1 (0.7%)	
		Poor	0 (0.0%)	0 (0.0%)	
	PPS	Excellent	67 (74.4%)	73 (76.8%)	0.734
		Good	23 (25.6%)	22 (23.2%)	
		Fair	0 (0.0%)	0 (0.0%)	
		Poor	0 (0.0%)	0 (0.0%)	

Items			Control Group	Trial Group	P
Adaptability of the balloon to the vessel shape	FAS	Excellent	98 (73.1%)	101 (72.7%)	1.000
		Good	35 (26.1%)	35 (25.2%)	
		Fair	1 (0.7%)	2(1.4%)	
		Poor	0 (0.0%)	0 (0.0%)	
	PPS	Excellent	67 (74.4%)	72 (75.8%)	0.930
		Good	22 (24.4%)	23 (24.2%)	
		Fair	1 (1.1%)	0 (0.0%)	
		Poor	0 (0.0%)	0 (0.0%)	
Retraction ability	FAS	Excellent	98 (73.1%)	101 (72.7%)	1.000
		Good	36 (26.9%)	36 (25.9%)	
		Fair	0 (0.0%)	1 (0.7%)	
		Poor	0 (0.0%)	0 (0.0%)	
	PPS	Excellent	66 (73.3%)	72 (75.8%)	0.738
		Good	24 (26.7%)	23 (24.2%)	
		Fair	0 (0.0%)	0 (0.0%)	
		Poor	0 (0.0%)	0 (0.0%)	

(VIII) Safety index analysis (SS)

1. Occurrence of all-cause mortality and myocardial infarction

The results of this study showed that there was no death in the Trial Group and the Control Group at 30 days after surgery. The death rate at 6 months was 0.8% vs 0% (p=1.000) respectively, which had no statistical difference. The mortality at 9 months and 1 year after surgery was 2.5% vs 0.8% (p=0.622) respectively, which had no statistical difference. See Table 14.

The causes of death of 3 subjects in the Trial Group included recurrent acute coronary syndrome (1 case), cerebral hemorrhage (1 case, according to telephone follow-up), and bronchial silicone stent implantation due to tracheal stenosis (1 case). One subject in the Control Group died due to lung cancer according to telephone follow-up.

Table 14 All-cause mortality of patients in the two groups

Indicator		Control Group	Trial Group	P
All-cause mortality	30 days	0 (0.0%)	0 (0.0%)	NA
	6 months	0 (0.0%)	1 (0.8%)	1.000
	9 months	1 (0.8%)	3 (2.5%)	0.622
	1 year	1 (0.8%)	3 (2.5%)	0.622

The results of this study showed that the myocardial infarction rate at 30 days after surgery was 0% vs 1.7% (P = 0.243) respectively in the Trial Group and the Control Group, which had no statistical difference. That at 6 months was 1.7% vs 1.7% (p=1.000) respectively, which had no statistical difference. That at 9 months was 1.7% vs 2.5% (p=0.681) respectively, which had no statistical difference. That at 1 year after surgery was 2.5% vs 2.5% (p=1.000), which had no statistical difference. See Table 15.

Table 15 Myocardial infarction of patients in the two groups

Indicator		Control Group	Trial Group	P
Myocardial infarction	30 days	2(1.7%)	0 (0.0%)	0.243
	6 months	2(1.7%)	2(1.7%)	1.000
	9 months	3 (2.5%)	2(1.7%)	0.681

1 year	3 (2.5%)	3 (2.5%)	1.000

2. Occurrence of thrombotic events

The results of this study showed that no thrombotic event occurred in the Trial Group and the Control Group at 30 days, 6 months and 9 months after surgery. One thrombotic event occurred at one year after surgery in the Trial Group, while no thrombotic event occurred in the Control Group. The occurrence rate of thrombotic events was 0.8% vs 0% (P = 1.000) respectively in the Trial Group and the Control Group, which had no statistical difference. See Table 12 for details.

3. Adverse events

A total of 165 cases and 433 times of adverse events (83 cases and 194 times in the Trial Group and 82 cases and 239 times in the Control Group) were reported during this study, including 91 cases and 149 times of serious adverse events (45 cases and 66 times in the Trial Group and 46 cases and 83 times in the Control Group). There was no statistical difference in AE and SAE between the Trial Group and the Control Group. Table 16 below shows the relationship between adverse events and serious adverse events and the device and conditions leading to the termination of the trial.

Table 16 Occurrence of AE and SAE in the two groups (FAS)

Indicator	Control Group		Trial Group		-P value
	Number of cases (%)	Times	Number of cases (%)	Times	
AE	82 (69.5)	239	83 (68.6)	194	0.881
AE related to the test device	16(13.6)	17	12 (9.9)	12	0.381
SAE	46 (39.0)	83	45 (37.2)	66	0.775
SAE related to the test device	12(10.2)	13	10(8.3)	10	0.611
Adverse events leading to shedding	1 (0.8)	1	3 (2.5)	3	0.622
AE related to the test device and causing the termination of the study	0 (0.0)	0	0 (0.0)	0	NA

Notes: 1. Adverse events related to the test device: including the relationship with the studied product - "definitely related", "may well be related", "probably related" and "unable to judge".

2. Adverse events leading to shedding: Judged as "Yes" for adverse events leading to withdrawal from the trial. All shedding cases in this trial were death cases.

XIV. Adverse events found during clinical trial and their handling

(I) Definition of adverse events

Definition of adverse events: Any adverse medical events occurring from the signing of the informed consent form by subjects and their inclusion in the trial to the last follow-up should be judged as adverse events regardless of the causality with the test device.

(II) Judgment of the severity of adverse events

Adverse events are classified into general adverse events and serious adverse events (SAE) according to severity. General adverse events are further divided into mild, moderate and severe ones by intensity:

- Mild: No impact on the normal function of subjects.
- Moderate: Certain impact on the normal function of subjects.
- Severe: Significant impact on the normal function of subjects.

When judging the severity of general adverse events, we should pay attention to distinguishing the intensity and severity of adverse events. "Severe" is used to describe "intensity". A "severe" adverse event is not necessarily a "serious adverse event". For example, the adverse event "headache" during the

trial may be judged as "severe", but it cannot be included in "serious adverse events" unless it meets the standard of "serious adverse events".

(III) Countermeasures against adverse events

The Principal Investigator or investigators should give necessary and appropriate treatment immediately and make explanation to the subjects if an adverse event occurs during the trial whether it has a causal relationship with the test device or not. Meanwhile, the adverse event should be followed up until the subjects return to normal or are in stable conditions and the Principal Investigator and investigators judge that there is no need to follow up. In addition, the Principal Investigator or investigators must record all adverse events in the case report form.

(IV) Serious adverse events

1. Criteria of serious adverse events

Events meeting one or more of the following criteria should be judged as SAE:

Causing death;

Threatening life;

Requiring hospitalization or extending hospitalization time;

Causing persistent or serious disability or dysfunction;

Causing congenital malformation or birth defects.

2. SAE records and reports

Appropriate treatment actions must be taken immediately in case of serious adverse events in the study and regardless of whether they are related to the test product. They should be reported to the Principal Investigator, the Ethics Committee of the clinical study unit, the Safety Supervision Department of the CFDA (China Food and Drug Administration), local food and drug administrations, the implementer and clinical supervisors by telephone or fax within 24 hours after learning. The record form of serious adverse events should be submitted within 24h after learning.

(V) Occurrence of adverse events

A total of 165 cases and 433 times of adverse events were reported in this study (83 cases and 194 times in the Trial Group and 82 cases and 239 times in the Control Group), including 91 cases and 149 times of serious adverse events (45 cases and 66 times in the Trial Group and 46 cases and 83 times in the Control Group). See Table 16 for details.

XV. Indications, scope, contraindications and precautions

(I) Indications and scope

(I) Indications:

Balloon dilation of restenosis in coronary stents.

2. Scope of application:

The specifications and models of Vesselin Drug Coated Coronary Balloon Catheter used in this study are as follows:

Balloon diameter: 2.5, 2.75, 3.0, 3.5 and 4.0 mm

Balloon length: 14, 20, 28 and 35 mm

(II) Contraindications

1. Those who are intolerant or allergic to the drug coating of the catheter balloon (paclitaxel and medicinal urea);

2. Pregnant or lactating women;

3. Unprotected left main disease;

4. Patients with coronary artery spasm without significant stenosis;

5. Those who are severely allergic to contrast agents;

6. Patients with cardiogenic shock;

7. Lesions that cannot be treated with PTCA or other intervention techniques

(III) Precautions

1. This product is for one-time use only. Do not reuse it.

2. This product is sterile and pyrogen-free. Do not use in case of damaged package.

3. Use this product within the sterilization validity.

4. Before use, learn about the application method and functions of this product to ensure effective and safe use.

5. Do not touch, bend or squeeze the balloon and soak the balloon in saline.

6. Keep the pressure of the expanded balloon not greater than the maximum allowable pressure of the balloon;

7. Use a hand-operated pressure device instead of an automatic pressure device;

8. Only use the recommended diluted contrast agent instead of air or other gases and other liquids to pressurize the balloon;

9. Before use, completely remove the air and liquid in the system and carefully adjust the sealing device of the joint;

10. Do not expose the device to organic solvents;

11. Do not operate the balloon dilation catheter during the dilation process. Change the position of the balloon dilation catheter only by positioning the guiding wire;

12. If resistance occurs during the operation, confirm the cause of the resistance before withdrawing or advancing the balloon catheter through the X-ray, path diagram or digital subtraction angiography;

13. Do not move the guiding wire when the catheter is dilated;

14. Completely empty and retract the balloon after operation and before removal of the balloon catheter from the coronary artery;

15. Ensure that only the doctor who has been trained in cardiovascular interventional therapy is allowed to use this product.

XVI. Clinical trial conclusions

The results of follow-up at 1 year after surgery in this trial came from 239 patients with coronary heart diseases and in-stent restenoses in 13 centers. The results showed that for in-stent restenoses, the intrasegmental late lumen loss at 9 months after surgery of Vesselin Drug Coated Coronary Balloon Catheter produced by Lepu Medical Technology (Beijing) Co., Ltd. was not inferior to that of coronary artery balloon catheters for paclitaxel release (trade name: SeQuent Please) produced by Braun. The clinical follow-up results at 30 days, 6 months, 9 months and 1 year after surgery showed that there was no significant difference in the occurrence rate of clinical events between the Trial Group and the Control Group, indicating similar safety and effectiveness of Vesselin Drug Coated Coronary Balloon Catheter produced by Lepu and SeQuent Please drug balloon catheters.

XVII. Problems and suggestions for improvement

No

XVIII. List of trial personnel

Centers	PI name	Title	Department
Peking University First Hospital	Chen Ming	Chief Physician	Department of Cardiology
People's Hospital of Tianjin	Yao Zhuhua	Chief Physician	Department of Cardiology
The Central Hospital of Wuhan	Chen Manhua	Chief Physician	Department of

			Cardiology
The Second Hospital of Jilin University	Liu Bin	Chief Physician	Department of Cardiology
Emergency General Hospital	Wu Di	Chief Physician	Department of Cardiology
Beijing Friendship Hospital, Capital Medical University	Chen Hui	Chief Physician	Department of Cardiology
The Third Medical Center, Chinese PLA General Hospital	Ma Dongxing	Chief Physician	Department of Cardiology
Central Hospital of Zibo	Wang Jun	Chief Physician	Department of Cardiology
The First Affiliated Hospital of Bengbu Medical College	Zhang Heng	Chief Physician	Department of Cardiology
Wuhan No.5 Hospital	Hong Lifeng	Deputy Chief Physician	Department of Cardiology
Fujian Provincial Hospital	Guo Yansong	Chief Physician	Department of Cardiology
Beijing Luhe Hospital, Capital Medical University	Guo Jincheng	Chief Physician	Department of Cardiology
Central Hospital of Xiangtan	Huang He	Chief Physician	Department of Cardiology

XIX. Other matters to be explained

None

XX. Opinions of investigators and the clinical trial management department of the clinical trial institution

<table>
<tr><td colspan="2">Peking University First Hospital</td></tr>
<tr><td>Opinions of investigators in the center:
Approved

Signature: Chen Ming

Date: June 3, 2019</td><td rowspan="2">Opinions of the clinical trial management department of the clinical trial institution:

(盖章)
Peking University First Hospital
National Clinical Trial Institution for Drugs

Date: June 4, 2019</td></tr>
<tr><td>Opinions of the Principal Investigator of the trial:
Approved

Signature: Huo Yong

Date: June 3, 2019</td></tr>
</table>