Summary of Safety and Effectiveness Data

AngioJet® Rheolytic™ Thrombectomy System

Table of Contents

Summary of Safety and Effectiveness Data

AngioJet® Rheolytic™ Thrombectomy System

Possis Medical, Inc.

1. General Information

Device Generic Name:	Percutaneous coronary thrombectomy catheter system (Class III)
Device Trade Name:	AngioJet® Rheolytic™ Thrombectomy LF140 Catheter AngioJet® Drive Unit AngioJet® Pump Set
Applicant's Name and Address:	Possis Medical, Inc. 9055 Evergreen Blvd. N.W. Minneapolis, Minnesota 55433-8003
PMA Application Number:	P980037
Date of Panel Recommendation:	None
Date of Notice of Approval to the Applicant:	March 12, 1999

2. Indications and Usage

The AngioJet System is intended for removing thrombus in the treatment of patients with symptomatic coronary artery or saphenous vein graft lesions in vessels $\geq$ 2.0 mm in diameter prior to balloon angioplasty or stent placement.

3. Contraindications

Do not use the AngioJet LF140 Catheter in patients:

- Who are contraindicated for other intracoronary interventional procedures, as the device only removes thrombus in preparation for balloon angioplasty or stent placement.
- In whom the lesion cannot be accessed with the guide wire.

4. Warnings and Precautions

See WARNINGS AND PRECAUTIONS in the final draft labeling (Information for Use)

5. Device Description

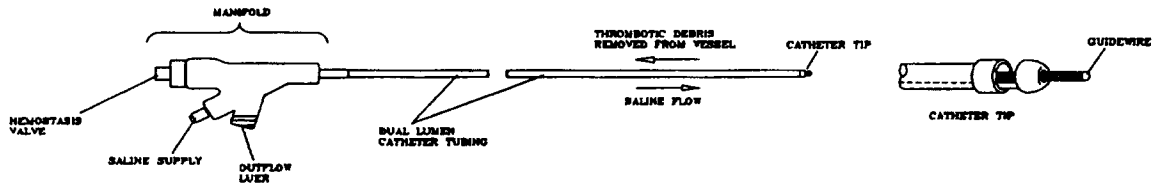


Figure 1. AngioJet LF140 Catheter

The AngioJet® LF140 Rheolytic™ Thrombectomy Catheter (AngioJet LF140 Catheter) is one component of the AngioJet® Rheolytic™ Thrombectomy System (AngioJet System). The other two components are the single-use AngioJet® Pump Set and the multi-use AngioJet® Drive Unit (both packaged and sold separately). The AngioJet LF140 Catheter may only be used in conjunction with the AngioJet Pump Set and AngioJet Drive Unit.
The AngioJet LF140 Catheter is a 140 cm, 5.0 French, dual lumen, sterile, single-use catheter designed for removing thrombus from coronary conduits. High velocity saline jets directed back into the catheter create a localized low pressure zone at the distal tip (Bernoulli effect) which results in the suction, break-up, and removal of thrombus through the exhaust lumen.

The AngioJet LF140 Catheter is introduced through a guide catheter. An 8 French high flow guide catheter (0.080 inch minimum internal diameter) is sufficient to allow passage of the AngioJet LF140 Catheter with adequate clearance for injection of standard contrast media, if desired. The AngioJet LF140 Catheter tracks and operates over a standard 0.018 inch (or smaller) guide wire.

6. Alternative Practices or Procedures

Alternative treatments include intravenous or intra-arterial infusion of thrombolytic drugs such as tissue plasminogen activator, streptokinase, or urokinase to lyse the thrombus. Other mechanical treatments include: intracoronary balloon angioplasty, intracoronary stenting, and a device, which uses rotating cutting blades at the catheter tip.

7. Marketing History

The AngioJet System (all components including the AngioJet LF140 Catheter) has been marketed in the U.S. for a different indication (treatment of thrombosed dialysis access grafts) since December 1996 under premarket notification K960970.

LF140 Catheter has been marketed for coronary artery treatment in Australia, Austria, Switzerland, Canada, France, Germany, Greece, India, Italy, Netherlands, Norway, Portugal, Russia, and Saudi Arabia

There have been no countries from which the device has been withdrawn from marketing for any reason related to safety or effectiveness of the device.

8. Adverse Events

5.1 Observed Adverse Events

A total of 731 patients were enrolled in two multi-center clinical trials of the AngioJet System, as summarized in Table 1.

Table 1. Clinical Trial Patient Enrollment

All patients in all Clinical Studies (n=731)

Study Group	Feasibility patients (AngioJet)	VeGAS 2 Randomized Study		
		AngioJet patients	Urokinase (control)	Total VeGAS 2 Patients
Vein Graft AngioJet Study (VeGAS 1 feasibility study)	90		-	
VeGAS 2 Randomized Trial:				
Qualification phase	80		-	
Randomization phase	-	180	169	349
VeGAS 2 AMI Treatment Arm	-	107	-	107
VeGAS 2 TE Treatment Arm	-	105	-	105
Patient Totals	**170**	**392**	**169**	**561**

Adverse events from the second Vein Graft AngioJet Study (VeGAS 2) Randomized Trial (AngioJet treatment arm), the Acute Myocardial Infarction (AMI) Treatment Arm, and the Thrombolysis Exclusion (TE) Treatment Arm are shown in Table 2 (n= 561 patients).

Table 2. Major Adverse Events (to 30 Days)

% (number) difference [95% confidence interval]

All patients in the VeGAS 2 Randomized Trial, AMI Treatment Arm, and TE Treatment Arm (n=561)

	Randomized Trial			AMI	TE
	AngioJet Arm (n=180)	Urokinase Arm (n=169)	Difference [95% CI]	Treatment Arm n=107	Treatment Arm n=105
Death	1.7% (3)	3.0% (5)	-1.3% [-4.5, 1.9][1]	7.5% (8)	1.9% (2)
MACE	13.9% (25)	21.9% (37)	-8.0% [-16.0, 0.0]	13.1% (14)	18.1% (19)
MACE (CK-MB)	15.6% (28)	32.5% (55)	-17.0% [-25.8, 8.2]	13.1% (14)	23.8% (25)
MI	11.1% (20)	19.5% (33)	-8.4% [-16.0, -0.9]	3.7% (4)	14.3% (15)
Q-MI	2.2% (4)	5.3% (9)	-3.1% [-7.1, 0.9]	0.0% (0)	1.0% (1)
Non-Q-MI	8.9% (16)	14.2% (24)	-5.3% [-12.0, 1.4]	3.7% (4)	14.3% (15)
MI (CK-MB)	14.4% (26)	30.8% (52)	-16.3% [-25.0, -7.7]	3.7% (4)	20.0% (21)
Q-MI	2.2% (4)	5.3% (9)	-3.1% [-7.1, 0.9]	0.0% (0)	1.0% (1)
Non-Q-MI	12.2% (22)	25.4% (43)	-13.2% [-21.3, -5.1]	3.7% (4)	20.0 (21)
TLR (TOTAL)	3.3% (6)	3.6% (6)	-0.2% [-4.0, 3.6]	2.8% (3)	5.7% (6)
CABG	0.6% (1)	3.0% (5)	-2.4% [-5.2, 0.4]	0.9% (1)	0.0% (0)
PTCA	2.8% (5)	0.6% (1)	2.2% [-0.5, 4.9]	1.9% (2)	5.7% (6)
Abrupt Closure	3.3% (6)	4.7% (8)	-1.4% [-5.5, 2.7]	4.7% (5)	5.7% (6)
Subacute Closure	2.8% (5)	4.1% (7)	-1.4% [-5.2, 2.5]	1.9% (2)	6.7% (7)
Bleeding Complication	5.0% (9)	11.8% (20)	-6.8% [-12.7, -1.0]	13.1% (14)	12.4% (13)
Vascular Complication	4.4% (8)	17.8% (30)	-13.3% [-19.8, -6.8]	12.1% (13)	9.5% (10)
CVA	1.7% (3)	1.2% (2)	0.5% [-2.0, 3.0]	1.9% (2)	1.0% (1)

MACE = Death, Q wave and non-Q wave MI (CPK > 2X upper limit normal), emergent CABG, repeat target lesion revascularization, or CVA within 30 days of index procedure, as determined by the Clinical Events Committee.

MACE (CK-MB) = Death, Q wave and CK-MB non-Q wave MI (CK-MB > 3X upper limit normal), emergent CABG, repeat target lesion revascularization, or CVA within 30 days of index procedure, as determined by the Clinical Events Committee.

MI includes non-Q wave MI = CPK > 2X upper limit normal

MI (CK-MB) includes non-Q wave MI = CK-MB > 3X upper limit normal

TLR= Target lesion revascularization.

Abrupt Closure = lesion-related new severely reduced flow (TIMI 0 or1) within the target vessel that persisted, and required rescue by a non-assigned treatment strategy, or persisted and resulted in MI or death.

Subacute closure = new reduced (TIMI 0 or 1) flow at the target vessel as a result of a mechanical obstruction, such as dissection or luminal thrombus, occurring after completion of the index procedure but within 30 days of the index procedure.

Bleeding Complications = procedure related blood transfusions.

Vascular Complications = hematoma > 4cm, retroperitoneal bleed, false aneurysm, AV fistula, peripheral ischemia/nerve injury, hemolysis and hemolytic anemia.

[1] Difference = $S_{AngioJet} - S_{urokinase}$, $SE_{diff} = sqrt(SE_{AngioJet}^2 + SE_{urokinase}^2)$, CI= Diff$\pm$ 1.96*SE_{diff}

Total Deaths: There were a total of 44 deaths among the 731 patients in all clinical studies. All deaths were reviewed by a masked, independent clinical events committee (ICEC). None of the deaths were judged by the ICEC to be directly attributable to the device. During the **Feasibility Study** 12 patient deaths occurred, four within 30 days of the assigned treatment (two due to cardiac arrest, and one each due to cardiogenic shock and intracerebral hemorrhage and cardiac arrest). In the **Randomized Trial,** 16 patients died, six in the AngioJet arm (one patient never received the assigned treatment) and ten in the urokinase treatment arm. Of the five patients that were treated with the AngioJet, the two deaths within 30 days were due to respiratory distress / electromechanical dissociation (n=1), and cardiomyopathy / congestive heart failure (n=1). The other three deaths occurred between 98 and 317 days post AngioJet treatment due to respiratory failure (n=1), and sudden cardiac death (n=2). Ten **AMI Treatment Arm** patients died during the study. The eight deaths which occurred within 30 days were due to cardiac arrest (n=4), cardiac tamponade (n=1), cardiogenic shock (n=1), myocardial rupture (n=1), and pericardial effusion / heart block (n=1). Six **TE Treatment Arm** patients died during the study. The two deaths within 30 days were due to cardiac arrest (n=1) and cardiogenic shock (n=1).

5.2 Potential Adverse Events

Potential adverse events (in alphabetical order) which may be associated with use of the AngioJet LF140 Catheter including those listed in Table 2 and the following:

- abrupt closure of treated vessel
- acute myocardial infarction
- arrhyhthmias, including VF and VT
- death
- dissection
- emboli, distal
- emergent CABG
- hemolysis
- hemorrhage, requiring transfusion
- hypotension/hypertension
- infection at the access site
- myocardial ischemia
- pain
- perforation
- pseudoaneurysm

- reactions to contrast medium
- stroke/CVA
- thrombosis/occlusion
- total occlusion of treated vessel
- vascular spasm

9. Summary of Preclinical Studies

9.1 Laboratory Studies

In Vitro Studies

In vitro studies were conducted early in design development to assess AngioJet LF140 Catheter performance in simulated use models. Assessments focused on the following parameters: clot cutting rate-axial speed at which the Catheter could be advanced through clot with complete removal of the clot; particle analysis- evaluation of size and relative percentage of proximal and distal embolic particles resulting from Catheter operation; and hemolysis resulting from Catheter operation. These baseline studies proved the AngioJet LF140 Catheter to be acceptable for further design verification studies and subsequent evaluation in animal models.

Design Verification Studies

Evaluation of critical design parameters was performed with AngioJet System during the design verification phase of product development. Functional testing included evaluation of critical performance parameters, simulated use testing, and critical bond testing. The physical and functional tests performed on the AngioJet LF140 Catheter and AngioJet Pump Set are summarized in Tables 3 and 4. Test results met the acceptance criteria in all cases.

Table 3: Physical and Functional Testing for the AngioJet LF140 Catheter

Test Parameter	Acceptance Criteria	Samples	Results [Mean + SD (Range)]	Results
Flow Rate – saline volume per time delivered by Catheter	47-53 ml/min	5 Catheters	49.0 ± 0.7 ml/min (48-50 ml/min)	All passed
Stagnation Pressure - outflow lumen pressure	60 psi minimum	5 Catheters	68.4 ± 3.2 psi (65-73 psi)	All passed
Net Evacuation Rate - difference between evacuated and infused volume per time	-8 to 18 ml/min with guide wire	5 Catheters	-3.2 ± 1.2 ml/min [(-1.8)-(-4.4) ml/min]	All passed
Push/Track Force - force needed to insert and advance catheter	1.0 lbf. maximum	5 Catheters	0.24 ± 0.06 lbf. (0.20-0.34 lbf.)	All passed
Pressurized Bend Test - minimum curvature in distal segment of pressurized catheter	Minimum of 0.5 cm bend radius over 180° without failure	5 Catheters	No failures recorded	All passed
Pressurized Torque Test – over-rotation along Catheter length without failure	720° rotation from tip to manifold without failure	5 Catheters	No failures recorded	All passed
High Pressure Test - sustained Catheter operation at high pressure	17,000 psi for 60 seconds without failure	5 Catheters	No failures recorded	All passed
Operating Pressure - system pressure caused by Catheter	6,700-10,300 psi	5 Catheters	7,290 ± 213 psi (7,000-7,500 psi)	All passed
Dynamic Pressure - exhaust pressure at the roller pump	20-65 psi	5 Catheters	49 ± 4.2 psi (45-55 psi)	All passed

Table 4: Physical and Functional Testing for the AngioJet Pump Set

Test Parameter	Acceptance Criteria	Samples Tested	Results [Mean + SD (range)]	Results
Pump Prime Time – time for pump to self prime	Prime time is 45 sec maximum	30 Pump Sets	14 ± 4.16 seconds (8-30 seconds)	All passed
Pump Volume (Mode 2) – volume of saline per time delivered by the pump	47 ml/min minimum 53 ml/min maximum	15 Pump Sets	48.6 ± 0.71 ml/minute (48-50 ml/minute)	All passed
Pump Leakage - presence of saline at a connection point	Leak proof at 18,000 psi for 1 min minimum	15 Pump Sets	No leaks	All passed
Check Valve Seal Test – saline leak at connection points	Leak proof at 18,000 psi for 1 min minimum	15 Pump Sets	No leaks	All passed
Pump Life - total run time before pump failure	20 min minimum	16 Pump Sets	138 ± 46 minutes (43-199 minutes)	All passed
Supply Line Pressure - pressure test to verify leak-tight assembly	Leak proof at 18,000 psi for 5 sec minimum	110 Pump Sets	No leaks	All passed

Critical bond test results for the AngioJet LF140 Catheter and AngioJet Pump Set are summarized in Tables 6 and 7. Test results met the acceptance criteria in all cases.

Table 5: Critical Bond Testing for the AngioJet LF140 Catheter System

Test Parameter	Acceptance Criteria	Samples Tested	Results [Mean + SD (Range)]	Results
Distal Catheter Tip-to-Pebax	2.2 lbf. minimum	5 subassemblies	7.56 ± 0.17 lbf. (7.337-7.745 lbf.)	All passed
Manifold-to-Pebax	1.0 lbf. minimum	5 Catheters	5.241 ± 0.202 lbf. (4.969-5.479 lbf.)	All passed
Hypotube-to-Filter Housing	4.0 lbf. minimum	15 Catheters	12 ± 1.36 lbf. (9.39-13.95 lbf.)	All passed
Cap-to-Loop	3.37 lbf. minimum	37 Catheters	4.988 ± 0.926 lbf. (3.791-7.635 lbf.)	All passed
Inner Body-to-Hypotube	2.0 lbf. minimum	15 Catheters	3.59 ± 0.759 lbf. (2.685-5.329 lbf.)	All passed

Table 5: Critical Bond Testing for the AngioJet Pump Set

Test Parameter	Acceptance Criteria	Samples Tested	Results [Mean + SD (Range)]	Results
Spike Assembly-to-Inflow Line Tensile Test	4.0 lbf. minimum	30 Pump Sets	18.3 ± 1.05 lbf. (13.9-19.3 lbf.)	All passed
Bag Drop Impact Test	Survive 6 feet drop with 1800 ml in bag	15 Pump Sets	No leaks	All passed
Inflow Line-to-Pump Tensile Test	2.0 lbf. minimum	15 Pump Sets	16.6 ± 2.4 lbf. (8.8-18.0 lbf.)	All passed
Pump Piston -to-Boot and Prime Cup-to-Boot Tensile Test	1.0 lbf. minimum	30 Pump Sets	11.3 ± 2.8 lbf. (4.9-17.9 lbf.)	All passed
Pump-to-Supply Line Tensile Test	18.5 lbf. minimum	15 Pump Sets	54.9 ± 4.3 lbf. (48.3-65.8 lbf.)	All passed
Supply Line-to-Quick Connect Nut Tensile Test	18.5 lbf. minimum	15 Pump Sets	38.6 ± 9.1 lbf. (28.8-51.2 lbf.)	All passed
Outflow Line-to-Male Luer Pressure Test	Hold 90 psi for 30 sec minimum	10 Pump Sets	No failures	All passed
Outflow Line-to-Female Luer Pressure Test	Hold 90 psi for 30 sec minimum	10 Pump Sets	No failures	All passed
Bag Tubing-to-Luer Tensile Test	5.0 lbf. minimum	16 Pump Sets	44.1 ± 1.26 lbf. (41.5-45.7 lbf.)	All passed
Bag Tubing-to-Bag Tensile Test	5.0 lbf. minimum	13 Pump Sets	33.2 ± 3.42 lbf. (26.8-38.1 lbf.)	All passed
Bag Tubing-to-Luer Pressure Test	100 psi minimum for 20 min	15 Pump Sets	No leaks	All passed
Paratube Male Luer Tensile Test	5.0 lbf. minimum	20 Pump Sets	20.8 ± 0.91 lbf. (26.8-38.1 lbf.)	All passed
Paratube Female Luer Tensile Test	5.0 lbf. minimum	20 Pump Sets	25.9 ± 0.86 lbf. (23.1-27.1 lbf.)	All passed

9.2 Biocompatibility Testing

Tables 8 and 9 summarize results of the biocompatibility tests performed on the AngioJet LF140 Catheter and the AngioJet Pump Set, as recommended in ISO 10993: Biological Evaluation of

Medical Devices (performed on AngioJet Catheters and subassemblies). All samples passed all screening tests after exposure to the manufacturing process conditions.

Table 7: Biocompatibility Testing for the AngioJet LF140 Catheter

Test Protocol	Sample	Result
Cytotoxicity- cultured mouse L929 fibroblast cells exposed to MEM media. Catheter material extract*.	1device	passed
Hemolysis- fresh rabbit blood incubated with 10ml of Catheter material extract, using 0.9% saline media. Adapted from ASTM 756-82 and ASTM 619.	1device	passed
Systemic Toxicity- mice injected with Catheter material extract using 0.9% saline, USP alcohol, PEG, and cottonseed oil media, per USP XXII, p. 1497 and USP- NF, p. 2703.	1device	passed
Intracutaneous Toxicity- rabbits injected with Catheter material extract using 0.9% saline, USP alcohol, PEG, and cottonseed oil media, per USP XXII, p. 1497 and USP- NF, p. 2703.	4 devices	passed
Carcinogenicity / Genotoxicity- *Salmonella typhimurium* and mouse L5178Y/TK lymphoma cells exposed to Catheter material extract using 0.9% saline and DMSO media per Ames Salmonella Mutagenicity Assay, and "Health Effects Guideline 476 (Genetic Toxicology: in vitro mammalian cell gene mutation tests,) April 1984, published by OECD.	2 devices	passed
Dermal Sensitization- Guinea pigs intradermally injected with Catheter material extract using Freund's complete adjuvant, per Magnusson and Linkgman, Allergic Contact Dermatitis, " Identification of Contact Allergans," 1970, and USP XXII, p. 1497.	1device	passed
Subchronic Toxicity- mice dosed 5 days with daily hematology and homeostatic evaluations, and gross necropsy at 14 days, per Page and Sawhney, "Proceedings of the Workshop on Subchronic Toxicity Testing," 1980.	1device	passed
Pyrogenicity- material mediated pyrogen testing per USP biological test <151>.	3 devices	passed
Intramuscular Irritant Implant- 30 day intramuscular Catheter extract material implant in rabbits.	4 devices	passed
Skin Irritation Implant- Modified Draize Test, ASTM F719-81, Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation	1device	passed

** Extraction method per USP <87>, XXII, as recognized by TC 194 (ISO 10993-12).*

Table 8: Biocompatibility Testing for the AngioJet Pump Set

Test Description	Sample	Results
Cytotoxicity- Cultured mouse L929 fibroblast cells exposed to MEM media (Pump material extract")	1 device	Passed
Hemolysis- Fresh rabbit blood incubated with 10ml of Pump material extract, using 0.9% saline media (adapted from ASTM 756-82 and ASTM 619)	1 device	Passed
Systemic Toxicity- Mice injected with Pump material extract using 0.9% saline, USP alcohol, PEG, and cottonseed oil media, per USP XXII, p. 1497 and USP NF, p. 2703	Saline flow pathway materials	Passed
Irritation or Intracutaneous Toxicity- Guinea pigs were sensitized to 0.9% saline extracts of Pump material and subsequently exposed to pump materials. Procedures referenced: Magnusson & Kligman, 1970, and USP XXII, pages 1497-1499.	Saline flow pathway materials	Passed
Subchronic Toxicity- Mice dosed 5 days with daily hematology and homeostatic evaluations, and gross necropsy at 14 days, per Page and Sawhney, "Proceedings of the Workshop on Subchronic Toxicity Testing", 1980.	1 device	Passed
Pyrogenicity- Material mediated pyrogen testing per USP biological test <151>.	3 devices	Passed

The materials used in the blood/ tissue contact and sterile fluid path of the AngioJet LF140 Catheter and AngioJet Pump Set have a history of safety, strength, and biocompatibility in short-

term use devices currently being marketed in the USA and internationally. The blood/tissue contact and sterile fluid path component materials are listed in Table10 and 11, respectively.

Table 9: Materials for the AngioJet LF140 Catheter

Component	Material
High Pressure Saline Inflow Path	304L stainless steel hypotubing, tip, manifold fitting; titanium ferrule
Catheter Shaft	Medical grade Pebax (polyether block amide)
Catheter Manifold	Medical grade Polycarbonate, silicone
Assembly Adhesives	Medical grade cyanoacrylate

Table 10: Materials for the AngioJet Pump Set

Component	Material
Outlet Adapter	303/304 stainless steel
Pump Sleeve	Polytetrafluoroethylene (PTFE)*
Silicone Ring	Medical grade silicone*
High pressure seal	Polyethylene*
Pump Housing	17-4 stainless steel*
Pump Filter	316 stainless steel*
Prime Sensor Cup	Polycarbonate*
Pump Boot	Medical grade silicone*
Check Valve Ball	304/316 stainless steel*
O-ring	Vinylidene Fluoride Hexafluoropropylene*
Pump Ferrule	Titanium*
Valve Block	17-4 stainless steel*
Retaining Collar	304 stainless steel
Supply Line Retainer	Titanium*
Nut	Polypropylene, 18-8 stainless steel
Supply Line	304L stainless steel*
Compression Spring	304 stainless steel*
Inlet Block	316 stainless steel*
Spike	Medical grade ABS plastic*
Drip Chamber	PVC plastic*
Tubing	Medical grade PVC plastic*
Tubing Clamp	Medical grade polypropylene
Spike Filter	Polypropylene/PTFE*
Paratubing	Medical grade PVC plastic
Heat Shrink Ring	(FEP)
Piston Head	6061 Aluminum
Piston	17.4 stainless steel*

* Fluid Pathway

Ex Vivo Studies

Testing was performed to evaluate possible injury to the vessel wall during AngioJet LF140 Catheter operation in an ex vivo porcine arterial model. Fifteen Catheters were tested. The results showed that treatment effects were limited to focal endothelial cell denudation and few mild focal disruptions of the internal elastic lamina. Similar findings were also observed with passage of guide catheters and guide wires in the ex vivo model.

The AngioJet LF140 Catheter was also evaluated in an ex vivo human coronary bypass graft model using excised thrombotic saphenous vein grafts obtained from patients at the time of repeat bypass surgery. Four grafts and AngioJet LF140 Catheters were tested. The results showed no

angiographic or histologic evidence of graft intimal dissection.

9.3 Animal Studies

Safety and effectiveness of the AngioJet System were evaluated in vivo in a canine model with treatment of simulated arterial thrombus. Twelve AngioJet LF140 Catheters were used to treat 10 coronary arteries, 10 peripheral arteries (femoral and renal) and five femoral veins in 12 dogs. Controls included sham Catheter treatment and vessel instrumentation with guide catheters and wires only. PTCA was also performed for comparison. In all cases, the AngioJet LF140 Catheter functioned properly and was successfully advanced to the target site using standard techniques. There were no perforations or observable hemorrhages caused by the Catheter, even when thrombolytic drugs were infused following Catheter treatment. Gross, histologic, and scanning electron microscopy (SEM) examination of explanted vessels revealed no serious injury to the vessel wall. There were no obvious differences between baseline, final procedure, and where applicable, four week and six month angiograms, ECGs, or ventriculograms.

A mild to moderate increase in serum free hemoglobin was observed following AngioJet System operation (baseline = 40.4 +/- 17.9 mg/dL; post-treatment operation = 643.3 +/- 270.9 mg/dL, mean Catheter operation time = 4.7 minutes); however, serum free hemoglobin returned to normal levels 1-4 days following operation. Blood urea nitrogen (BUN) and creatinine levels were within normal limits at all times and there were no significant effects of AngioJet System-related hemolysis noted.

In studies to simulate AngioJet LF140 Catheter treatment of a coronary thrombus, the total CK rose very little, while there was a slight increase in CK-MB (total CK, baseline = 168 IU/L; total CK, post- Catheter treatment = 571.5 IU/L-- largely attributed to surgical cutdown to establish vascular access; CK-MB, baseline = 1.25 ng/dL; peak CK-MB post- treatment = 5.65ng/dL). Thus, a slight amount of myocardial damage could not be excluded.

These studies demonstrated safety of the AngioJet System in an animal model, and provided the basis for clinical evaluation.

9.3.1 Clinical Relevance

Clinical use of the AngioJet System has shown that in some cases, arrhythmias and temporary heart block, requiring treatment with a temporary pacemaker, may occur during Catheter operation. The occurrence of arrhythmia has been noted especially during Catheter operation in the distal circulation supplying the AV node. Similar electrophysiologic aberrations have also been noted during coronary rotational atherectomy procedures. Animal testing was conducted using a porcine model to evaluate the mechanism for the generation of arrhythmias and heart block, which had not been previously observed in the canine studies. The results of these screening studies led to the hypothesis that heart block may be caused by localized transient increases in adenosine-- a cellular component of blood cells released during AngioJet LF140 Catheter-associated hemolysis-- and mediated by adenosine receptors on the SA and AV nodes. This hypothesis was supported by testing that showed a reduction in the incidence of heart block from 94% to 17% when subjects (N=8 pigs) were treated prior to device activation with aminophylline, a competitive antagonist for the adenosine receptor.

9.4 Additional Studies

Independent testing laboratories tested the AngioJet® Drive Unit according to the UL Standard for Safety of Medical and Dental Equipment (UL 544) and the IEC 60601-1 General Safety Standard and found it to be free from safety hazards and in compliance with the requirements of these standards.

An independent testing laboratory tested the AngioJet® Drive Unit according to FCC Class B and IEC 60601-1-2 Conducted and Radiated Mode and found it to be free from electromagnetic radiation hazards and in compliance with the requirements of these standards.

An independent testing laboratory tested the AngioJet® Drive Unit according to Clause 17h of EN 60601-1:1990 (defibrillation-proof safety) and found it to be in compliance with the requirements of that standard.

10. Summary of Clinical Studies

10.1 Overview

As summarized in Table 1, a total of 731 patients were enrolled in two multi-center trials of the AngioJet System with the LF140 Catheter under an approved IDE.

10.2 Objectives

The purpose of the Vein Graft AngioJet study was to establish the safety and effectiveness of thrombus removal by the AngioJet LF140 Catheter in saphenous vein bypass grafts or native coronary arteries $\geq$ 2.0 mm in diameter. The Randomized Trial was configured as a multicenter, 2-arm prospective trial comparing immediate AngioJet thrombectomy to urokinase thrombolysis (infusion for 6 to 30 hours), followed by definitive percutaneous treatment of the lesion.

10.3 Study design

The primary endpoint for the Randomized Trial and the AMI and TE treatment arms was defined as occurrence of death, Q wave MI, emergent CABG, target lesion revascularization, CVA, or stent rethrombosis by 30 days; or failure to achieve a post-procedure diameter stenosis <50%, or failure to achieve post-procedure TIMI 3 flow, or to achieve a $\geq$ 20% change in diameter stenosis.

Baseline clinical and angiographic data were collected to establish angiographic evidence of thrombus. Clinical follow-up was required at 30 days, six months, and one year. Quantitative coronary angiography was performed pre-procedure, following thrombectomy, and after final treatment. Endpoints for all clinical studies were immediately analyzed on an intent-to-treat basis. An independent Clinical Events Committee adjudicated all major adverse events.

10.4 Description of Patients and Gender Bias

The Randomized Trial was designed to evaluate 520 patients, but was stopped after 349 patients were enrolled because of a growing imbalance in some safety outcomes and increased difficulty in maintaining enrollment rates. The study population included patients with angiographically evident thrombus in either a saphenous vein bypass graft or a native coronary artery $\geq$ 2.0 mm in diameter who had not experienced an AMI within 24 hours. Patients who warranted percutaneous revascularization of one or two discrete thrombotic lesions within the same target vessel were eligible for enrollment. Patients experiencing an AMI (within 24 hr of symptom onset) were eligible for enrollment in an AMI Treatment Arm. Diagnosis of AMI was based on clinical symptoms, ECG evidence of ischemic ST changes, and elevated cardiac enzymes. Patients ineligible for enrollment in the randomized trial due to contraindications for urokinase thrombolysis were eligible for enrollment in the TE Treatment Arm.

The Randomized Trial and AMI and TE Treatment Arms enrolled patients of both genders. Of the 561 patients enrolled, 444 (79%) were male. This proportion of males (444/117 = 3.79) reflects the general referral pattern for patients undergoing percutaneous coronary intervention for symptomatic coronary artery disease. Analyses of efficacy and safety outcomes show that differences between the genders in pre-treatment reference vessel diameter in patients who received randomized AngioJet treatment resulted in outcome differences in post-procedure device success and minimum lumenal diameter. In addition, the rate of bleeding complications was higher in women in the TE Treatment Arm. No other variables examined showed a difference by gender.

10.5 Results:

The clinical trials enrolled patients with any duration of symptoms. Of the 440 patients reporting a duration of symptoms before AngioJet treatment, 135 (31%) reported symptoms less than 24 hours, 269 (61%) had symptom duration of 24 hours to two weeks, and 36 (8%) had symptoms lasting more than two weeks. Procedure success was 81%, 83%, and 75% for these three symptom duration categories, compared to 62%, 75%, and 63% for the same duration categories treated with the urokinase control. Examination of these results by lesion site (SVG vs. native) and post procedure minimum lesion diameter (MLD) did not show any interaction.

Table 11 shows the principal effectiveness and safety outcomes for the randomized cohort and the AMI and TE Treatment Arms. The primary endpoint for the trial combined efficacy measures at the end of treatment with freedom from major complications at 30 days. Results for this endpoint did not differ between randomized treatments (70.9% for AngioJet compared to 70.4% for urokinase).

Table 11. Principal Effectiveness and Safety Results

All Randomized, AMI, and TE Treatment Arm Patients Treated (561 Patients, 565 Lesions)

Cohort	AngioJet RCT (N=180)	Urokinase RCT (N=169)	% Difference (95% C.I.)	AMI Arm (N=107)	TE Arm (N=105)
Efficacy Measures					
Lesion Success	87.6% (156/178)	79.6% (129/162)	8.0 [0.1, 15.9]	83.0% (88/106)	77.9% (81/104)
Procedure Success	86.3% (151/175)	72.2% (117/162)	14.1 [5.5, 22.6]	77.1% (81/105)	76.0% (79/104)
Device Success	87.4% (153/175)	75.3% (122/162)	12.1 [3.9, 20.4]	82.9% (87/105)	76.9% (80/104)
Post-Procedure MLD (mm) Range (min, max)	2.59±0.82 (178) (0.00, 5.42)	2.45±1.08 (162) (0.00, 4.70)	0.14 [-0.1, 0.3]	2.41±0.81 (106) (0.00, 4.12)	2.61±1.03 (104) (0.00, 4.80)
Post-Procedure % DS Range (min, max)	22%±21% (178) (-30%, 100%)	28%±29% (162) (-31%, 100%)	-6.0 [-11.3, -0.7]	24%±24% (106) (-37%, 100%)	24%±27% (104) (-32%, 100%)
TLR-Free at 30 Days	96.7%	96.4%	0.2 [-3.6, 4.1]	97.1%	94.2%
TVR-Free at 30 Days	95.0%	95.8%	-0.8 [-5.2, 3.6]	96.2%	93.2%
TVF-Free at 30 Days	85.0%	77.5%	7.5, -0.7, 15.6]	86.0%	81.8%
MACE (CK-MB) Free at 30 Days	84.4%	67.5%	17.0 [8.1, 25.8]	86.9%	76.1%
Primary Endpoint-Free at 30 Days	70.9% (124/175)	70.4% (114/162)	0.5 [-9.2, 10.2]	75.2% (79/105)	68.9% (71/103)
Safety Measures					
In-Hospital MACE (CK-MB)	14.4% (26/180)	32.5% (55/169)	0.44 [0.30, 0.66]	13.1% (14/107)	20.0% (21/105)
Out-of-Hospital MACE (CK-MB) to 30 Days	3.9% (7/180)	1.2% (2/169)	3.29 [0.76, 14.23]	0.0% (0/107)	6.7% (7/105)
Abrupt Closure	3.3% (6/180)	4.7% (8/169)	0.70 [0.25, 1.98]	4.7% (5/107)	5.7% (6/105)
Subacute Closure	2.8% (5/180)	4.1% (7/169)	0.67 [0.22, 2.06]	1.9% (2/107)	6.7% (7/105)
Bleeding Complications	5.0% (9/180)	11.8% (20/169)	0.42 [0.20, 0.88]	13.1% (14/107)	12.4% (13/105)
Vascular Complications	4.4% (8/180)	17.8% (30/169)	0.25 [0.13, 0.49]	12.1% (13/107)	9.5% (10/105)
CVA to 30 Days	1.7% (3/180)	1.2% (2/169)	1.41 [0.24, 8.27]	1.9% (2/107)	1.0% (1/105)

Numbers are % (counts/sample size) and Mean±Standard Deviation. CI = Confidence Interval.

Relative Risk =AJ/UK SE = $\text{sqrt}\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = $RR^{*}\exp(\pm 1.96^{*}SE_{RR})$

Difference =AJ–UK SE = $\text{sqrt}(p_1^{*}q_1/n_1+p_2^{*}q_2/n_2)$ CI = $\text{Diff}\pm 1.96^{*}SE_{Diff}$

Lesion Success = Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory), and TIMI 3 flow post-procedure using any percutaneous method.

Procedure Success = Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory), and TIMI 3 flow post-procedure in the absence of death, emergent bypass surgery, or Q wave MI prior to hospital discharge as determined by the independent Clinical Events Committee.

Device Success = Achievement of a final residual diameter stenosis of <50% (by QCA core laboratory), and TIMI 3 flow post-procedure, using the assigned device only (without crossover use of AngioJet in patients randomized to urokinase).

Minimal Lumen Diameter = Mean minimum lumen diameter using the "worst view" analysis method.

Diameter Stenosis (DS) = 100% X (1-[MLD/RVD]), based on the mean value from 2 orthogonal views (when available) using QCA.

TLR-free = No target lesion revascularization.

TVR-free = No target vessel revascularization.

TVF-free = No death, Q wave and WHO non-Q wave MI, or target vessel revascularization.

In-Hospital MACE (CK-MB) = Death, Q wave and non-Q wave (CK-MB > 3X upper limit normal) MI, emergent CABG, repeat target lesion revascularization, or CVA prior to hospital discharge as determined by the independent Clinical Events Committee.

Out-of-Hospital MACE (CK-MB) = Death, Q wave and non-Q wave (CK-MB > 3X upper limit normal) MI, emergent CABG, repeat target lesion revascularization, or CVA after hospital discharge as determined by the independent Clinical Events Committee.

Primary Endpoint Free at 30 Days = No death, Q wave MI, emergent CABG, target lesion revascularization, CVA, or stent thrombosis to 30 days as determined by the independent Clinical Events Committee, with TIMI 3 flow and DS <50% post-procedure, and a ≥0.20 change in diameter stenosis.

Bleeding Complications = Procedure related blood transfusions.

Vascular Complications = Hematoma >4 cm, retroperitoneal bleed, false aneurysm, AV fistula, peripheral ischemia/nerve injury, hemolysis and hemolytic anemia.

*Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula:

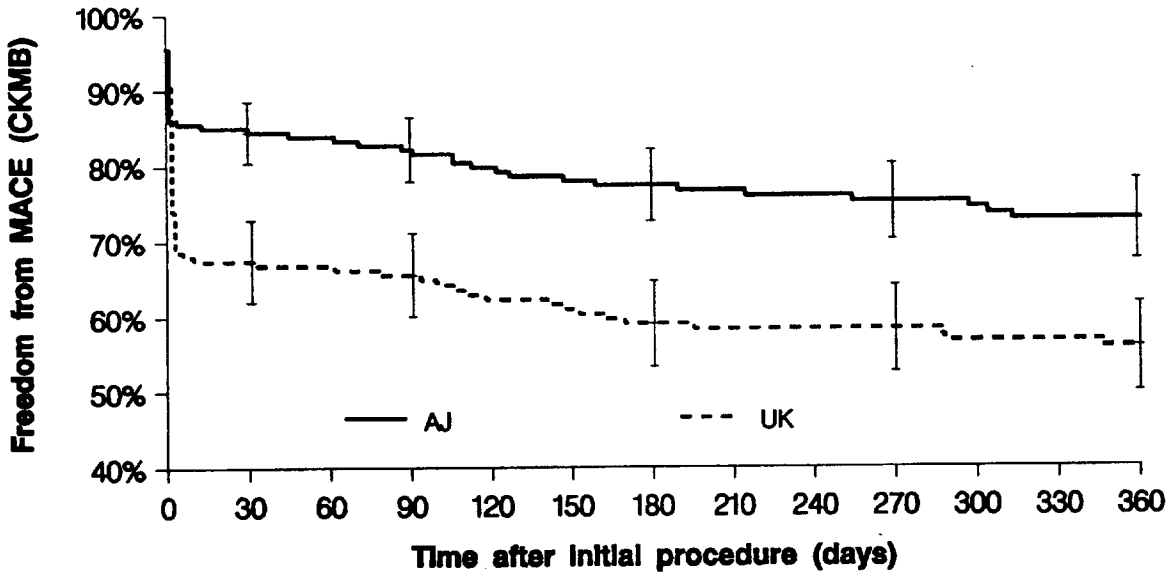
Difference = $S_{AJ}-S_{UK}$ $SE_{Diff} = \text{sqrt}\{SE_{AJ}^2+SE_{UK}^2\}$ CI = $\text{Diff}\pm 1.96^{*}SE_{Diff}$

Non-Q wave MI is an indicator of distal embolization and myocardial necrosis. MACE (CK-MB) is a composite of Death, Q wave and non-Q wave (CK-MB > 3X upper limit normal) MI, emergent CABG, repeat target lesion revascularization, or CVA. Figure 2 displays Kaplan-Meier actuarial curves of MACE (CK-MB)-free survival out to one year for the two treatments.

Figure 2. MACE (CK-MB)-Free Survival

Kaplan-Meier estimates and ± 1.5 standard errors of the mean

All Randomized Patients Treated (349 Patients)



Numbers of Patients at	30 days	90 days	180 days	270 days	360 days
AngioJet	152	142	130	120	95
Urokinase	114	105	94	87	73

10.6 Device Failures

Table 12 summarizes the device failures reported during the clinical trials. AngioJet Drive Units and Pump Set failures are also noted. In no case did a device failure jeopardize patient health or treatment.

Table 12. Device Failures

Failure Mode	Randomized Trial	AMI Treatment Arm	TE Treatment Arm	Qualifying Patient Arm	TOTAL
Mechanical drive unit failure	1	1	1	0	3
Pump set failure	0	2	2	0	4
Unable to deliver Catheter	4	6	2	2	14

11. Conclusions Drawn from the Studies

The preclinical laboratory evaluation of the AngioJet verified that it performed to design specification and provided adequate evidence of biocompatibility, sterility and shelf life. The *in vivo* preclinical studies demonstrated safety adequate to begin clinical evaluation.

In the randomized clinical trial, AngioJet treatment demonstrated lower rates than the control for major adverse cardiac events at both 30 days and 6 months follow-up. Safety outcomes for the two non-randomized registries did not differ significantly from the AngioJet randomized treatment arm.

AngioJet treatment was associated with higher acute clinical and angiographic success than with the control.

The foregoing results support the benefits of use of the AngioJet System for the target population outweigh the risk of illness or injury when used as indicated in accordance with the information for use.

12. Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13. FDA Decision

FDA issued an approval order to Possis Medical, Inc. advising that its PMA was approved. See Approval Order

FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

14. Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the Final Draft Labeling (Information for Use).

Post-approval Requirements and Restrictions: See Approval Order