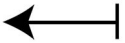
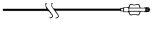
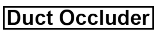
Amplatzer Piccolo™ Occluder

Symbol	Definition
	Caution, consult accompanying documents
	Not made with natural rubber latex
	MR Conditional
	Inner diameter
	Outer diameter
	Length
	Usable length
	Recommended delivery sheath dimensions
	Do not use if package is damaged
	Manufacturer
	Catalog number
	Lot number
	Duct Occluder

Symbol	Definition
	Use-by date
	Date of manufacture
	Do not re-use
	Sterilized using ethylene oxide
	Unique device identifier
	Quantity
	Consult instructions for use
	Follow instructions for use on this website
	Keep dry; keep away from rain.
	Do not resterilize
	Caution: Federal law restricts this device to sale by or on the order of a physician.

Amplatzer Piccolo™ Occluder

Device Description

The Amplatzer Piccolo™ Occluder is a self-expanding, nitinol mesh occlusion device for use in a patent ductus arteriosus (PDA). The device configuration is a central waist with two retention discs. The central waist is designed to be positioned within the ductus. The retention discs are deployed in the pulmonary and aortic ends of the ductus, or may be deployed completely within the duct when treating small infants. The device may be delivered via an anterograde (venous) or a retrograde (arterial) approach.

Radiopaque marker bands at each end of the occluder permit visibility during fluoroscopy.

Refer to Figure 1 and Figure 2 in this section for more information about the device. Refer to Table 2 and Table 3 in Appendix A: Supplemental Information for occluder dimensions and sizing.

Figure 1. Amplatzer Piccolo™ Occluder delivery components

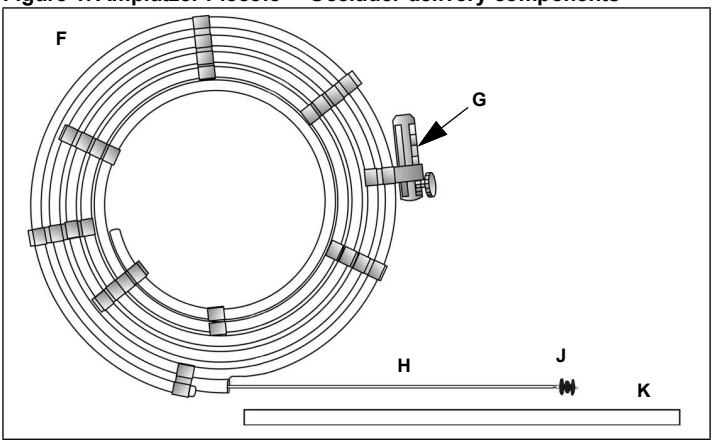


Figure 1 Components

F. Hoop dispenser
G. Vise
H. Delivery wire
J. Occluder
K. Occluder protector tube

Figure 2. Amplatzer Piccolo™ Occluder components

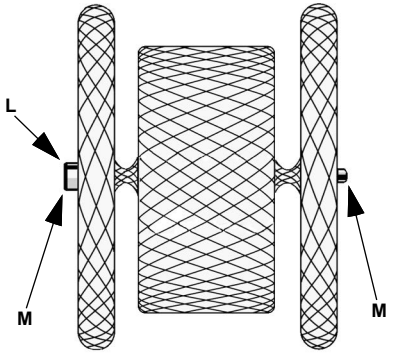


Figure 2 Components

L. Micro screw attachment

M. Radiopaque marker bands

Indications and Usage

The Amplatzer Piccolo™ Occluder is a percutaneous, transcatheter occlusion device intended for the nonsurgical closure of a patent ductus arteriosus (PDA).

Contraindications

- Weight <700 grams at time of the procedure
- Age <3 days at time of procedure
- Coarctation of the aorta
- Left pulmonary artery stenosis
- Cardiac output that is dependent on right to left shunt through the PDA due to pulmonary hypertension
- Intracardiac thrombus that may interfere with the implant procedure
- Active infection requiring treatment at the time of implant
- Patients with a PDA length smaller than 3 mm
- Patients with a PDA diameter that is greater than 4 mm at the narrowest portion

Warnings

- This device was sterilized with ethylene oxide and is for single use only. Do not reuse or re-sterilize this device. Attempts to resterilize this device can cause a malfunction, insufficient sterilization, or harm to the patient.
- Do not use the device if the sterile package is open or damaged.
- Use on or before the last day of the expiration month that is printed on the product packaging label.
- Patients who are allergic to nickel can have an allergic reaction to this device.
- Prepare for situations that require the removal of this device. Preparation includes access to a transcatheter snare kit and an on-site surgeon.
- Accurate measurements of the ductus are crucial for correct occluder size selection.
- Do not release the occluder from the delivery wire if either a retention disc protrudes into the pulmonary artery or aorta; or if the position of the occluder is not stable.

- Remove embolized devices. Do not remove an embolized occluder through intracardiac structures unless the occluder is fully recaptured inside a catheter.

Precautions

- This device should be used only by physicians who are trained in standard transcatheter techniques. Determine which patients are candidates for procedures that use this device.
- The physician should exercise clinical judgment in situations that involve the use of anticoagulants and antiplatelet drugs before, during, and/or after the use of this device.
- Patients should have an activated clotting time (ACT) of greater than 200 sec prior to device placement, unless the patient has a significant risk for bleeding and is unable to be anti-coagulated.
- The device may be delivered via an anterograde (venous) or a retrograde (arterial) approach. However, in small infants (≤2 kg), the device should be delivered using the anterograde (venous) approach since small infants are at an increased risk for arterial injury.
- In small infants (≤2 kg), the occluder size is chosen so that the entire device with both retention discs is placed within the duct (*intraductal placement*) to minimize the potential for protrusion into the aorta or left pulmonary artery.
- In larger infants (>2 kg), the occluder size is chosen so that the central waist spans the entire length of the duct with the retention discs placed just outside the duct or within the ampulla (extraductal disc placement) to achieve improved positional stability and minimize the potential for device embolization.
- Prior to releasing the device from the delivery wire, it is important to rely on imaging to ensure there is no obstruction of the aorta or left pulmonary artery.
- The Amplatzer Piccolo™ Occluder contains nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device for a minimum of 60 days following implant. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. Certain allergic reactions can be serious; patients should seek immediate medical attention if there is suspicion of an allergic reaction. Symptoms may include difficulty in breathing or swelling of the face or throat. While data are currently limited, it is possible that some patients may develop an allergy to nickel if this device is implanted.
- Use in specific populations
    - Pregnancy – Minimize radiation exposure to the fetus and the mother.
    - Nursing mothers – There has been no quantitative assessment for the presence of leachables in breast milk.
- Store in a dry place.
- Do not use contrast power injection with delivery catheter.

MR Conditional 

Non-clinical testing has demonstrated that the Amplatzer Piccolo™ Occluder is MR Conditional. A patient with the Amplatzer Piccolo™ Occluder can be safely scanned in an MR system under the following conditions:

- Static magnetic field of 1.5 Tesla (1.5T) or 3.0 Tesla (3.0T)
- Maximum spatial gradient field of 19T/m (1900 G/cm)
- Maximum MR system-reported, whole-body-averaged specific absorption rate (SAR) of 2.0W/kg (normal operating mode)

Under the scan conditions defined above, the device is expected to produce a maximum temperature rise of less than or equal to 3°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 9 mm from the Amplatzer Piccolo™ Occluder when imaged with a gradient echo pulse sequence and a 3.0T MRI System.

Potential Adverse Events

Potential adverse events that may occur during or after a procedure using this device may include, but are not limited to:

- Air embolus
- Allergic reaction
- Anemia
- Anesthesia reactions
- Apnea
- Arrhythmia
- Bleeding
- Cardiac perforation
- Cardiac tamponade
- Chest pain
- Device embolization
- Device erosion
- Death
- Endocarditis
- Fever
- Headache/migraine
- Hemolysis
- Hematoma
- Hypertension
- Hypotension
- Infection
- Myocardial infarction
- Palpitations
- Partial obstruction of aorta
- Partial obstruction of pulmonary artery
- Pericardial effusion
- Pericarditis
- Peripheral embolism
- Pleural effusion
- Pulmonary embolism
- Re-intervention for device removal
- Respiratory distress
- Stroke
- Thrombus
- Transient ischemic attack
- Valvular regurgitation
- Vascular access site injury
- Vascular occlusion
- Vessel perforation

Clinical Summary

Design

The Amplatzer Piccolo™ Occluder (studied under the name Amplatzer™ Duct Occluder II Additional Sizes—ADO II AS Study) was a single arm, open-label, multi-center, study designed to characterize the safety and effectiveness of the Amplatzer Piccolo™ Occluder device. A total of 50 subjects were enrolled in an initial Investigational Device Exemption (IDE) at eight centers in the United States from June 5, 2017 to January 25, 2018. At the time of implant, 18 subjects were ≤2 kg and 32 subjects >2 kg in weight.

Subject follow-up occurred post-procedure, at 30 days and six months. The primary effectiveness endpoint was the rate of effective closure of the ductus arteriosus (defined as a grade 0 or grade 1 shunt) at the six-month follow-up visit. The primary safety endpoint was the rate of major complications through 180 days after device implant. Major complications were defined as device or procedure related adverse events resulting in death, life-threatening adverse event, persistent or significant disability/incapacity, and/or a major open surgical intervention performed by a surgeon under general anesthesia.

Patients Studied

Key inclusion criteria included a PDA that was ≤4mm in diameter and ≥3mm in length. Patients were excluded if they weighed <700 grams or were younger than 3 days of age. Other key exclusion criteria included:

- Coarctation of the aorta
- Left pulmonary artery stenosis
- Cardiac output that is dependent on right to left shunt through the PDA due to pulmonary hypertension
- Intracardiac thrombus
- Active infection requiring treatment at the time of implant

Baseline characteristics are presented in and PDA type is presented in .

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Table 1. Baseline characteristics

	≤2 kg (N=18)	>2 kg (N=32)
Age, months		
Mean ± SD (n)	1.23 ± 0.55 (18)	24.88 ± 38.17 (32)
Range (Min, Max)	(0.49, 2.30)	(0.66, 168.54)
Sex, male	50.0% (9/18)	37.5% (12/32)
Weight (kg)		
Mean ± SD (n)	1.34 ± 0.38 (18)	10.29 ± 10.42 (32)
Range (Min, Max)	(0.76, 1.90)	(2.03, 47.80)
Minimal PDA Diameter (mm)		
Mean ± SD (n)	2.72 ± 0.65 (18)	2.64 ± 0.58 (32)
Range (Min, Max)	(1.4, 4.0)	(1.5, 4.0)
Maximal PDA Diameter (mm)		
Mean ± SD (n)	3.75 ± 0.44 (18)	4.37 ± 1.42 (32)
Range (Min, Max)	(3.0, 4.7)	(2.0, 8.7)
PDA Length (mm)		
Mean ± SD (n)	8.81 ± 2.55 (18)	7.98 ± 2.78 (32)
Range (Min, Max)	(4.6, 14.0)	(3.1, 16.0)

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Table 2. PDA type

	≤2 kg	>2 kg
Type A: Conical	16.7% (3/18)	53.1% (17/32)
Type B: Window	—	6.3% (2/32)
Type C: Tubular	38.9% (7/18)	6.3% (2/32)
Type D: Saccular	—	6.3% (2/32)
Type E: Elongated	5.6% (1/18)	15.6% (5/32)
Type F: Fetal	38.9% (7/18)	12.5% (4/32)

Results

A total of 46 subjects were successfully implanted with the Amplatzer Piccolo™ Occluder device, resulting in an implant success rate of 92% (18/18 ≤2 kg and 28/32 >2 kg). There were two subjects >2 kg who had an intra-procedural device embolization, where the embolized devices were successfully snared without complications. Both subjects were subsequently implanted with a different commercially available device. There were two additional subjects where the device was not released due to the inability to achieve a stable position. One subject received a different commercially available device and one underwent surgical ligation.

The primary effectiveness and safety endpoints are summarized in Table 3. Effective closure was assessed with echocardiography and defined as having no or a trivial residual shunt at six months. Echocardiography data were suitable for core lab assessment at 6 months for 44 subjects. Effective closure was achieved in all subjects (N=44) and no major complications were encountered in any subjects (N=50). Serious adverse events that did not meet the definition of the primary safety endpoint occurred in two subjects (4%) (1 desaturation and 1 coarctation of the aorta).

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Table 3. Primary endpoints

	≤2 kg	>2 kg
Rate of effective closure (%)	100.0% (17/17)	100.0% (27/27)
Rate of major complications (%)	0.0% (0/18)	0.0% (0/32)

Supplemental Clinical Information

Design

Following completion of enrollment in the IDE study, additional subjects were enrolled under a Continued Access Protocol (CAP). A total of 150 additional subjects were enrolled under the CAP from 26 March 2018 to 1 February 2019. At the time of implant, 82 subjects were ≤2 kg and 68 subjects were >2 kg in weight. The CAP allowed for enrollment of up to 150 subjects using a similar protocol to the IDE study with equivalent inclusion/exclusion criteria.

Patients Studied

Baseline characteristics are presented in Table 1, and PDA type is presented in Table 2.

Table 4. Baseline characteristics — CAP

	≤2 kg (N=82)	>2 kg (N=68)
Age, months Mean ± SD (*n*) Range (Min, Max)	1.26 ± 0.61 (82) (0.30, 3.15)	27.38 ± 47.18 (68) (0.49, 216.80)
Sex, male	62.2% (51/82)	44.1% (30/68)
Weight (kg) Mean ± SD (*n*) Range (Min, Max)	1.22 ± 0.34 (82) (0.70, 2.00)	11.68 ± 14.80 (68) (2.02, 68.50)
Minimal PDA Diameter (mm) Mean ± SD (*n*) Range (Min, Max)	2.64 ± 0.63 (74) (1.5, 4.0)	2.58 ± 0.70 (52) (1.0, 4.0)
Maximal PDA Diameter (mm) Mean ± SD (*n*) Range (Min, Max)	3.54 ± 0.80 (73) (2.0, 5.2)	4.44 ± 1.46 (52) (2.5, 10.0)
PDA Length (mm) Mean ± SD (*n*) Range (Min, Max)	9.41 ± 2.76 (73) (3.1, 18.0)	9.66 ± 3.28 (52) (4.0, 16.0)

Table 5. PDA type — CAP

	≤2 kg	>2 kg
Type A – Conical	3.7% (3/81)	40.0% (26/65)
Type B – Window	1.2% (1/81)	—
Type C – Tubular	11.1% (9/81)	15.4% (10/65)
Type D – Saccular	—	4.6% (3/65)
Type E – Elongated	4.9% (4/81)	12.3% (8/65)
Type F – Fetal	77.8% (63/81)	26.2% (17/65)

Results

A total of 145 subjects were successfully implanted with the Amplatzer Piccolo™ Occluder device, resulting in an implant success rate of 96.7% (81/82 ≤2 kg and 64/68 >2 kg). Unsuccessful implants occurred in one subject ≤2 kg and four subjects >2 kg. In all five subjects, the device was not released due to inability to achieve a stable position. Two subjects were implanted with a commercially available device, while two subjects were scheduled to undergo surgical ligation of the PDA. PDA closure for one additional subject was postponed to a later date. There were two subjects ≤2 kg and one subject >2 kg who had an intra-procedural device embolization, where the embolized devices were successfully snared without complications. All three subjects were subsequently implanted with a larger Amplatzer Piccolo™ Occluder without complications.

The primary effectiveness and safety endpoints are summarized in Table 6. Effective closure was assessed with echocardiography and defined as having no or a trivial residual shunt at six months. Eleven subjects discontinued prior to the 6-month visit and seven subjects did not complete the 6-month visit. Echocardiography data was suitable for core lab assessment at six months for 129 subjects. Effective closure was achieved in 99.2% of subjects (128/129).

The primary safety endpoint is the rate of major complications through 180 days after an attempted Amplatzer Piccolo™ Occluder implant, as adjudicated by the CEC. Six subjects with a successful implant withdrew before 180 days without an event and are excluded from the analysis. Major complications occurred in four CAP subjects (2.8%). Two subjects experienced procedural blood loss requiring transfusion ≤20 cc/kg. One subject with a history of congenital thrombocytopenia experienced hemolysis and required transfusions totaling ≤20 cc/kg until the event resolved without sequelae. One subject experienced device-related

obstruction of the aorta six days post-procedure that was treated by stent implantation. The subject died 14 days post-procedure secondary to severe respiratory failure, severe pulmonary hypertension leading to cardiorespiratory arrest.

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Table 6. Primary Endpoints — CAP

	≤2 kg	>2 kg
Rate of effective closure (%)	100.0% (72/72)	98.2% (56/57)
Rate of major complications (%)	5.1% (4/78)	0.0% (0/66)

Post-Approval Study

Summary of Post-Approval Study Methods

The post-approval study included continued follow-up of the subjects enrolled in the IDE and CAP cohorts described above. The study objective, design, population, and endpoints are the same. Subject data was collected by the clinical sites and entered onto either paper or electronic case report forms.

Study Visits and Length of Follow-Up

For IDE cohort subjects, in-person follow-up visits were scheduled at 1 month (+/- 7 days), 6 months (+/- 20 days), 12 months (+/- 30 days), 24 months (+/- 60 days), and 36 months (+/- 60 days).

CAP cohort subjects had in-person follow-up visits at 1 month (+/- 7 days) and 6 months (+/- 20 days), and telephone follow-up for AE assessment at 12 months (+/- 30 days), 24 months (+/- 60 days), and 36 months (+/- 60 days).

All follow-up visit window intervals were calculated based on the initial procedure date.

Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

IDE:

A total of 50 subjects were enrolled at 8 US clinical sites. The subject follow-up rates by visit are presented in Table 7.

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Table 7. IDE subject follow-up rates

Follow-up visit	Follow-up rate
1-month	98.0% (49/50)
6-month	100.0% (46/46)
12-month	91.3% (42/46)
24-month	78.3% (36/46)
36-month	91.3% (42/46)

CAP:

A total of 150 subjects were enrolled at 9 US clinical sites. The subject follow-up rates by visit are presented in Table 8.

Table 8. CAP subject follow-up rates

Follow-up visit	Follow-up rate
1-month	96.6% (143/148)
6-month	95.7% (134/140)
12-month	94.9% (131/138)
24-month	75.9% (104/137)
36-month	83.8% (114/136)

Summary of the Post-Approval Study Results

Final Safety Findings (Key Endpoints)

The primary safety endpoints for the IDE and CAP cohorts are presented in Table 3 and Table 6, respectively. Key safety endpoints throughout the 36-month follow-up are described below.

No deaths were reported in the IDE cohort. The rate of serious adverse events was 4.0% (2/50). One event was reported as procedure-related.

Nine deaths were reported in the CAP cohort. No death was adjudicated by the Clinical Events Committee (CEC) as procedure- or device-related. The rate of serious adverse events was 10.7% (16/150). As adjudicated by the CEC, three events were procedure- and device-related, three events were procedure-related only, and one event was device-related only. All other events were adjudicated as unrelated to the procedure and device.

Secondary Endpoint

The secondary endpoint was the rate of significant obstruction of the pulmonary artery or aorta through the 6-month follow-up visit, defined as:

- Significant obstruction of the left pulmonary artery was defined as less than 30% flow to the left lung by lung perfusion scan or a peak instantaneous gradient in left pulmonary artery ≥35 mmHg by echocardiogram if lung perfusion scan is not available.

  OR

- Significant obstruction of the aorta was defined as a gradient of ≥20 mmHg in the aortic isthmus by invasive aortic catheterization or a mean gradient ≥20 mmHg in the aortic isthmus by echocardiogram if invasive aortic catheterization is not available.

Results for the IDE and CAP cohorts are listed in Table 9 below:

Table 9. Rate of pulmonary artery or aortic obstruction for the IDE and CAP cohorts

	≤2 kg (N=100)	>2kg (N=100)	Total (N=200)
Rate of Significant Obstruction of the Pulmonary artery or Aorta (%) (IDE)	5.9% (1/17)	0.0% (0/24)	2.4% (1/41)
Rate of Significant Obstruction of the Pulmonary artery or Aorta (%) (CAP)	0.0% (0/73)	0.0% (0/57)	0.0% (0/130)

Descriptive Endpoints

LPA and aortic gradients for the IDE Cohort as assessed by the Echocardiography Core Laboratory are shown below in Table 10.

Table 10. LPA and aortic gradients over 36 months of follow-up for the IDE cohort

	Baseline	30 days	6 months	12 months	24 months	36 months
Proximal LPA Diameter (mm)						
Mean ± SD (n)	5.76 ± 2.66 (41)	6.28 ± 2.84 (31)	6.62 ± 1.55 (35)	7.35 ± 1.94 (40)	7.91 ± 1.89 (32)	7.89 ± 1.65 (33)
Range (min, max)	(2.70, 12.90)	(3.20, 13.80)	(3.80, 10.10)	(4.00, 12.56)	(4.42, 11.97)	(5.13, 11.39)
Peak LPA Gradient (mmHg)						
Mean ± SD (n)	9.37 ± 4.45 (16)	8.66 ± 4.56 (28)	5.83 ± 2.90 (38)	4.51 ± 2.32 (40)	4.34 ± 2.93 (32)	4.80 ± 3.07 (31)
Range (min, max)	(3.50, 17.60)	(3.10, 19.70)	(2.00, 13.20)	(1.66, 11.09)	(2.01, 12.38)	(1.20, 12.94)
Mean LPA Gradient (mmHg)						
Mean ± SD (n)	4.65 ± 2.56 (16)	4.37 ± 2.53 (28)	2.84 ± 1.46 (38)	2.51 ± 1.54 (35)	2.19 ± 1.51 (28)	2.57 ± 1.50 (25)
Range (min, max	(1.70, 10.80)	(1.30, 11.70)	(1.10, 6.80)	(1.04, 7.78)	(0.90, 6.41)	(0.72, 5.51)
Peak Desc. Aortic Gradient (mmHg)						
Mean ± SD (n)	13.95 ± 6.78 (40)	8.50 ± 4.88 (37)	8.31 ± 4.38 (40)	6.29 ± 9.41 (34)	5.04 ± 2.25 (26)	5.35 ± 1.76 (25)
Range (min, max)	(5.30, 28.50)	(3.40, 25.80)	(3.60, 29.20)	(1.81, 58.66)	(1.77, 11.30)	(1.61, 8.29
Mean Desc. Aortic Gradient (mmHg)						
Mean ± SD (n)	6.74 ± 3.37 (40)	3.98 ± 2.13 (36)	3.77 ± 1.71 (40)	2.80 ± 3.53 (34)	2.43 ± 1.04 (26)	2.52 ± 0.83 (25)
Range (min, max)	(2.50, 16.20)	(1.50, 11.10)	(1.70, 10.30)	(0.99, 22.25)	(0.86, 4.80)	(0.88, 4.36)

Left ventricular function and dimensions as measured by the Echocardiography Core Laboratory by visit for the IDE cohort are presented in Table 11.

Table 11. Left ventricular function and dimensions by visit for IDE cohort

Left ventricular function and dimensions	Baseline	30 days	6 months	12 months	24 months	36 months
LV end-diastolic area (mm^2)						
Mean ± SD (n)	6.08 ± 4.29 (43)	5.12 ± 3.91 (39)	6.06 ± 3.73 (41)	61.55 ± 34.19 (41)	73.11 ± 36.40 (33)	79.65 ± 29.66 (33)
Range (Min, Max	(1.1, 17.0)	(1.0, 16.6)	(2.7, 19.5)	(31.4, 190.7)	(37.6, 198.7)	(38.3, 189.3)
LV end-systolic area (mm^2)						
Mean ± SD (n)	2.77 ± 2.10 (43)	2.36 ± 1.89 (39)	2.71 ± 1.95 (41)	25.03 ± 16.28 (41)	30.12 ± 18.88 (33)	34.24 ± 16.58 (33)
Range (Min, Max)	(0.3, 8.0)	(0.4, 7.9)	(1.0, 9.6)	(9.0, 76.2)	(10.9, 98.0)	(12.9, 99.5)
LV apical length diastole (mm)						
Mean ± SD (n)	39.42 ± 14.84 (39)	36.12 ± 12.88 (38)	41.68 ± 11.40 (36)	46.38 ± 9.98 (40)	49.18 ± 10.29 (33)	51.36 ± 7.31 (33)
Range (Min, Max)	(18.1, 78.6)	(18.3, 77.3)	(27.3, 81.4)	(35.0, 79.0)	(40.0, 86.0)	(44.0, 81.0)
LV apical length systole (mm)						
Mean ± SD (n)	30.99 ± 11.38 (40)	29.18 ± 10.33 (38)	32.22 ± 9.22 (36)	36.83 ± 7.21 (40)	38.67 ± 7.33 (33)	40.61 ± 7.18 (33)
Range (Min, Max)	(14.1, 58.8)	(12.4, 62.3)	(22.1, 68.8)	(28.0, 60.0)	(31.0, 65.0)	(32.0, 70.0)
LV end-diastolic volume (mL)						
Mean ± SD (n)	10.58 ± 9.67 (35)	6.67 ± 8.42 (35)	8.18 ± 9.13 (32)	25.23 ± 22.20 (40)	32.36 ± 26.01 (33)	35.40 ± 19.94 (33)
Range (Min, Max)	(0.60, 38.10)	(0.50, 37.80)	(2.30, 44.40)	(10.29, 112.74)	(13.21, 131.35)	(15.32, 110.10)
LV end-systolic volume (mL)						
Mean ± SD (n)	2.83 ± 2.97 (36)	1.81 ± 2.46 (35)	2.23 ± 3.11 (32)	8.13 ± 7.78 (40)	10.68 ± 10.19 (33)	12.27 ± 9.21 (33)
Range (Min, Max)	(0.10, 11.60)	(0.10, 11.30)	(0.40, 15.40)	(2.66, 35.32)	(3.44, 52.93)	(4.22, 48.15)

Pulmonary and tricuspid regurgitation grades were assessed at each follow-up visit by the Echocardiography Core Laboratory. Results for the IDE Cohort are shown in Table 12.

Table 12. Pulmonary and tricuspid regurgitation grades by visit for IDE cohort

Grade	Baseline	30 days	6 months	12 months	24 months	36 months
Pulmonary Regurgitation						
None	14.0% (7/50)	7.0% (3/43)	15.2% (7/46)	29.3% (12/41)	21.2% (7/33)	15.2% (5/33
Trace	56.0% (28/50)	88.4% (38/43)	73.9% (34/46)	41.5% (17/41)	51.5% (17/33)	60.6% (20/33)
Mild	2.0% (1/50)	0.0% (0/43)	0.0% (0/46)	22.0% (9/41)	27.3% (9/33)	24.2% (8/33)
Moderate	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	2.4% (1/41)	0.0% (0/33)	0.0% (0/33)
Severe	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
N/A	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
Unknown	28.0% (14/50)	4.7% (2/43	10.9% (5/46)	4.9% (2/41)	0.0% (0/33)	0.0% (0/33)
Tricuspid Regurgitation						
None	6.0% (3/50)	11.6% (5/43)	17.4% (8/46)	26.8% (11/41)	39.4% (13/33)	15.2% (5/33)
Trace	72.0% (36/50)	74.4% (32/43)	71.7% (33/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
Mild	2.0% (1/50)	4.7% (2/43)	2.2% (1/46)	24.4% (10/41)	18.2% (6/33)	24.2% (8/33)
Moderate	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
Severe	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
N/A	0.0% (0/50)	0.0% (0/43)	0.0% (0/46)	0.0% (0/41)	0.0% (0/33)	0.0% (0/33)
Unknown	20.0% (10/50)	9.3% (4/43)	8.7% (4/46)	2.4% (1/41)	0.0% (0/33)	0.0% (0/33)

LPA and aortic gradient measurements as assessed by the Echocardiography Core Laboratory at baseline and the 6-month follow-up visit for the CAP Cohort are presented in Table 13.

Table 13. LPA and aortic gradients CAP cohort

	Baseline	6 month
Proximal LPA Diameter (mm) Mean ± SD (n) Range (min, max)	5.08 ± 2.44 (113) (2.0, 16.2)	6.60 ± 1.90 (107) (3.2, 14.9)
Peak LPA Gradient (mmHg) Mean ± SD (n) Range (min, max)	10.15 ± 7.73 (75) (2.0, 41.2)	6.54 ± 7.16 (94) (1.8, 58.4)
Mean LPA Gradient (mmHg) Mean ± SD (n) Range (min, max)	4.19 ± 3.08 (75) (1.0, 15.5)	3.19 ± 3.55 (94) (0.5, 28.2)
Peak Desc. Aortic Gradient (mmHg) Mean ± SD (n) Range (min, max)	12.14 ± 7.27 (119) (2.9, 51.0)	7.50 ± 4.35 (118) (2.0, 28.7)
Mean Desc. Aortic Gradient (mmHg) Mean ± SD (n) Range (min, max)	4.21 ± 2.39 (119) (0.6, 12.4)	3.42 ± 1.95 (118) (0.7,11.8)

Left ventricular function and dimensions as measured by the Echocardiography Core Laboratory at baseline and the 6-month follow-up visit for the CAP cohort are presented in Table 14.

Table 14. Left ventricular function and dimension by visit CAP cohort

Left Ventricular Function and Dimensions	Baseline	6 months
LV end-diastolic area (mm2)		
Mean ± SD (*n*)	4.55 ± 3.95 (135)	5.42 ± 3.36 (107)
Range (min, max)	(1.0, 20.4)	(2.3, 18.4)
LV end-systolic area (mm2)		
Mean ± SD (*n*)	2.06 ± 1.82 (135)	2.42 ± 1.66 (107)
Range (min, max)	(0.4, 9.1)	(0.9, 9.4)
LV apical length diastole (mm)		
Mean ± SD (*n*)	30.89 ± 12.14 (114)	39.58 ± 8.31 (96)
Range (min, max)	(17.6, 79.7)	(30.5, 75.3)
LV apical length systole (mm)		
Mean ± SD (*n*)	25.85 ± 10.13 (114)	32.58 ± 7.24 (96)
Range (min, max)	(15.0, 67.6)	(24.5, 66.2)
LV end-diastolic volume (mL)		
Mean ± SD (*n*)	5.78 ± 7.67 (110)	6.42 ± 6.90 (87)
Range (min, max)	(0.4, 49.5)	(1.2, 40.5)
LV end-systolic volume (mL)		
Mean ± SD (*n*)	1.40 ± 1.72 (110)	1.60 ± 1.93 (87)
Range (min, max)	(0.1, 9.2)	(0.2, 11.0)
Left ventricular ejection fraction (%)		
Mean ± SD (*n*)	75.47 ± 6.80 (110)	75.97 ± 5.20 (87)
Range (min, max)	(50.0, 87.5)	(62.1, 85.5)
IVSd (mm)		
Mean ± SD (*n*)	3.45 ± 1.25 (137)	3.98 ± 0.85 (112)
Range (min, max)	(1.6, 7.8)	(2.6, 7.2)

Pulmonary and tricuspid regurgitation grades were assessed at baseline and the 6-month follow-up visit by the Echocardiography Core Laboratory for the CAP Cohort. Results are shown in Table 15.

Table 15. Pulmonary and tricuspid regurgitation grades by visit CAP cohort

Grade		Baseline	6 months
Pulmonary Regurgitation			
	None	12.2% (18/148)	9.9% (13/131)
	Trace	12.2% (18/148)	81.7% (107/131)
	Mild	1.4% (2/148)	1.5% (2/131)
	Moderate	0.0% (0/148)	0.0% (0/131)
	Severe	0.0% (0/148)	0.0% (0/131)
	N/A	0.0% (0/148)	0.0% (0/131)
	Unknown	6.8% (10/148)	6.9% (9/131)
Tricuspid Regurgitation			
	None	12.2% (18/148)	8.4% (11/131)
	Trace	80.4% (119/148)	80.2% (105/131)
	Mild	3.4% (5/148)	5.3% (7/131)
	Moderate	1.4% (2/148)	1.5% (2/131)
	Severe	0.0% (0/148)	0.0% (0/131)
	N/A	0.0% (0/148)	0.0% (0/131)
	Unknown	2.7% (1/148)	4.6% (6/131)

Final Effectiveness Findings (Key Endpoints)

The primary effectiveness endpoints for the IDE and CAP cohorts are presented in Table 3 and Table 6, respectively.

PDA shunt grades over 36 months of follow-up for the IDE cohort are presented in Table 16.

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Table 16. PDA shunt grade over follow-up

	Baseline	30 Days	6 Months	12 Months	24 Months	36 Months
Grade 0/1	0.0% (0/45)	100.0% (41/41)	100.0% (44/44)	100.0% (39/39)	100.0% (32/32)	100.0% (33/33)
Grade 2	37.8% (17/45)	0.0% (0/41)	0.0% (0/44)	0.0% (0/39)	0.0% (0/32)	0.0% (0/33)
Grade 3/4	62.2% (28/45)	0.0% (0/41)	0.0% (0/44)	0.0% (0/39)	0.0% (0/32)	0.0% (0/33)

The CAP cohort was not required to undergo transthoracic echocardiography (TTE) after the 6-month follow-up visit.

Study Strength and Weaknesses

The Piccolo Clinical Study was a prospective, non-randomized, multicenter, observational study intended to characterize the safety and effectiveness of the Piccolo occluder to close a PDA in patients ≥700 grams and not designed to demonstrate the clinical benefits of PDA closure in premature infants. During follow-up, the IDE cohort was required to undergo TTE at each visit, while the CAP cohort did not receive TTE beyond the 6-month follow-up visit. However, no events of the PDA reopening were reported, and the IDE cohort had a 100% closure rate throughout follow-up, indicating the PDA remains closed after the Piccolo occluder is implanted. The 6-month safety and effectiveness results observed in this study led to FDA approval of the Piccolo occluder for use in patients ≥700 grams. Continued evaluation of the IDE and CAP cohorts over 36 months further support the performance and safety profile of the Piccolo occluder.

Directions for Use

Materials recommended for use with this device

- Amplatzer™ TorqVue™ LP Catheter (9-TVLPC4F90/080)
- 0.035-inch (0.89-mm) Guidewire

Procedure

1. Prepare the patient for a standard transcatheter procedure. Once vascular access is achieved administer anticoagulation to achieve an activated clotting time (ACT) of greater than 200 sec prior to device placement, unless the patient has a significant risk for bleeding and is unable to be anticoagulated. With small infants, it is recommended to deliver the device using an anterograde transvenous approach and to avoid arterial access whenever possible.

   CAUTION: Whenever possible, do not deliver the device in small infants (≤2 kg) using the retrograde approach since small infants are at an increased risk for arterial injury.
2. Do a right-heart catheterization or perform intra-operative echocardiography.
3. Take hemodynamic or echocardiographic measurements.
4. Use angiography or echocardiography to measure the PDA diameter at the narrowest portion (D) and the length (E) of the PDA. Refer to Figure 3 (in this section) for an example of measurement locations.

WARNING: Accurate measurements of the PDA is critical for correct occluder selection.

Figure 3. Measurement locations for the Amplatzer Piccolo™ Occluder

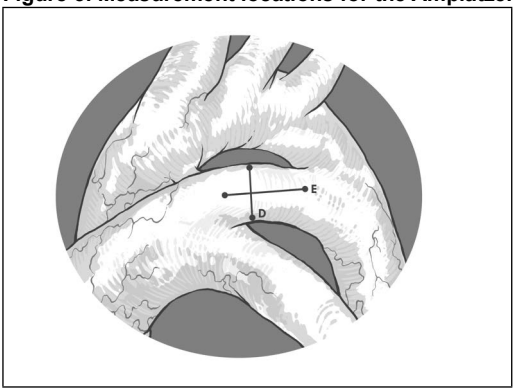


Figure 3 Measurements

D. Minimal ductus diameter

E. Ductus length

5. Use the PDA measurements to find the appropriate occluder size in Table 2 (in Appendix A: Supplemental Information) for patients >2 kg.

   NOTE: For small infants (≤2 kg), the length of the occluder may be shorter than the length of the PDA to minimize the potential for protrusion into the aorta or left pulmonary artery. For small infants, find the appropriate occluder size in Table 3 (in Appendix A: Supplemental Information). For small infants, the occluder is chosen so that the entire device including the retention discs is implanted within the duct (intraductal placement).

   NOTE: If there is inconsistency between angiography and echocardiography regarding the device size selection, then consider selecting the larger device size unless the use of a larger device size would result in protrusion into the aorta or left pulmonary artery. It is important to ensure that the most reliable imaging modality is utilized for guiding device size selection. Inconsistencies between imaging modalities may be due to multiple factors, such as variation in imaging angulation and windows, amount of contrast injected, and/or ductal vascular tone.

6. Prepare the device for use.
   - Inspect the sterile pouch.

   CAUTION: Do not use the device if the sterile pouch is open or damaged.
   - Open the sterile pouch. Inspect the device.

7. Prepare the catheter according to the manufacturer's instructions for use.
8. Prepare the occluder within the loader as follows:
   - Insert the proximal end of the delivery wire forward through the distal end of the loader and through the self-sealing hemostasis valve.
   - Make sure the occluder is threaded tightly onto the delivery wire. Turn the occluder counterclockwise 1/8 of a turn to make disconnection easier.

   CAUTION: Do not overtighten the connection.
   - Put the occluder and the loader assembly (loader + self-sealing hemostasis valve) in sterile saline. Retract the occluder into the loader.

- Flush the loader and the occluder with sterile saline through the self-sealing hemostasis valve.

9. Introduce the guidewire into the vasculature and advance through the PDA. Move the catheter forward over the guidewire and through the ductus.

   CAUTION: Do not advance the catheter over the guidewire without imaging guidance if resistance is encountered, or if there is significant mismatch between the catheter lumen and the guidewire diameter. Advancing the catheter under such circumstances has the potential to result in cardiovascular injury.

10. Utilize fluoroscopic and/or echocardiographic guidance to identify the catheter position. If using angiographic guidance for the procedure, do a test injection with contrast medium to see the position of the catheter. Placement of an esophageal temperature probe pre-procedure may serve as a useful landmark of the aortic isthmus in small infants (≤2 kg).
11. Remove the guidewire.
12. Permit blood backflow through the Tuohy-Borst hemostasis valve to remove air from the system and flush the delivery catheter with heparinized saline.
13. Move the loader forward through the Tuohy-Borst hemostasis valve and into the catheter until the loader stops.
14. Tighten the Tuohy-Borst hemostasis valve onto the loader. Remove any air that may have entered the delivery catheter system by aspirating and flushing with heparinized saline.
15. Hold the catheter, Tuohy-Borst hemostasis valve, and loader assembly as a single unit. Move the occluder forward from the loader into the catheter.

    NOTE: If it is difficult to transfer the occluder into the catheter, recapture the occluder in the loader and adjust the position of the loader.
16. Move the occluder forward to the distal tip of the catheter.

    CAUTION: Do not turn or twist the delivery wire.
17. Hold the delivery wire and retract the catheter to deploy the distal disc.

    WARNING: Do not push the delivery wire to deploy the occluder.

    CAUTION: Move the occluder carefully under imaging guidance to prevent damage to the vessels or cardiac tissue.
18. Retract the catheter and delivery wire as one unit until the distal retention disc of the occluder touches the vessel wall at the PDA.

    NOTE: For small infants (≤2 kg), it may be necessary to deploy the distal disc within the PDA to achieve an intraductal position.
19. Use angiography or echocardiography to make sure the distal retention disc of the occluder is placed correctly against the vessel wall.
20. Stabilize the delivery wire and slowly retract the catheter to deploy the waist of the occluder inside the PDA. The waist of the occluder must appose the ductus wall.
21. Stabilize the delivery wire and slowly retract the catheter to deploy the proximal retention disc.

    NOTE: For small infants (≤2 kg), it may be necessary to push the device forward while retracting the catheter to fully pack the device within the duct and achieve an intraductal position.
22. Do an aortic angiogram or evaluate device position with echocardiography.
    - Make sure the occluder is in the correct position and orientation without obstructing the aorta or left pulmonary artery.
    - Make sure the occluder is stable.
    - Make sure the occluder shape is correct.
    - Measure occlusion of the PDA and assess whether there is a residual shunt.

NOTE: The discs should not protrude or bulge into the surrounding vessels. Refer to Figure 4 (in this section) for an example of the correct shape for a deployed occluder when using an intraductal device placement in small infants (≤2 kg). Refer to Figure 5 (in this section) for an example of an incorrectly deployed occluder.

WARNING: Do not release the occluder from the delivery wire if a retention disc extends into a vessel or if the occluder is not stable or if there is a clinically relevant residual shunt. To recapture the occluder, move the catheter forward over the occluder. Redeploy the occluder or replace it with a new occluder.

CAUTION: Recapture and redeploy the occluder a maximum of two times. If the position of the occluder is still unsatisfactory after the second deployment, remove and replace the occluder and the catheter.

Figure 4. Correct placement of the Amplatzer Piccolo™ Occluder

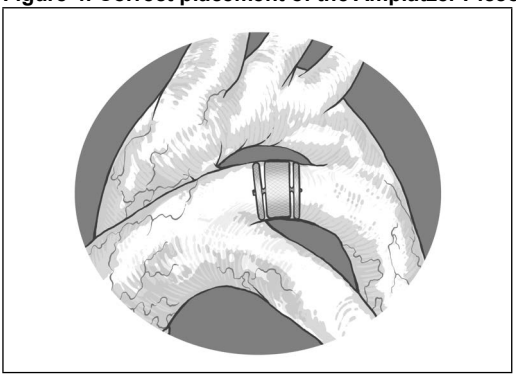
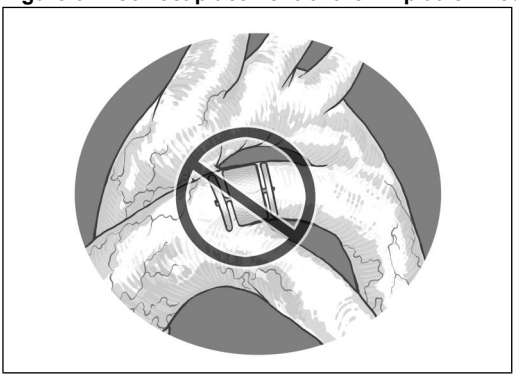


Figure 5. Incorrect placement of the Amplatzer Piccolo™ Occluder



23. Connect the vise to the delivery wire. Turn the vise counterclockwise to disconnect the occluder from the delivery wire.

    WARNING: Do not push the delivery wire or catheter forward after the occluder is released.

24. Remove the delivery wire and the catheter.

WARNING: Slowly remove the catheter from the patient to prevent the introduction of air.

Post-Procedure Care

- Monitor the patient post-procedure. Do a transthoracic echocardiogram or X-ray to make sure the occluder is in the correct position before the patient is released.
- Give endocarditis prophylaxis for six months. Prophylaxis beyond six months is at the physician's discretion.

Retrieval of Embolized Device

In the event a device embolizes, the following steps are recommended for transcatheter device retrieval:

1. Heparinize the patient to achieve an activated clotting time (ACT) of greater than 200 sec.
2. Advance a catheter over a guidewire into the vessel containing the embolized device.

   WARNING: To avoid injury to intracardiac structures during device retrieval, do not remove an embolized occluder through intracardiac structures unless the occluder is fully recaptured inside a catheter.
3. Using a goose-neck snare (5 mm or 10 mm in size), grab the occluder tightly, based on the instructions for use of the transcatheter snare kit, and recapture into the distal end of the catheter.
4. Once the device is fully recaptured into the catheter, pull the device through the catheter under fluoroscopic guidance and externalize.

   In the event the device cannot be retrieved using a transcatheter approach, consult with a surgeon for surgical retrieval of the device.

Post-Procedure Instructions

- Instruct the patient on when to seek medical attention.
- Temporary patient ID card: A temporary patient ID card is included in the product packaging. Complete this card and give it to the patient.
- Registration form: An implant registration form is located in each device box. Complete the patient information section and send the form to Abbott Medical.

Disposal

- The carton and instructions for use are recyclable. Discard all packaging materials appropriately.
- Devices can be returned to Abbott Medical for disposal. Contact an Abbott Medical representative or returns@amplatzer.com for instructions.
- Use solid biohazard waste procedures to discard devices.

Warranty

Abbott Medical warrants to buyer that, for a period equal to the validated shelf life of the product, this product shall meet the product specifications established by the manufacturer when used in accordance with the manufacturer's instructions for use and shall be free from defects in materials and workmanship. Abbott Medical's obligation under this warranty is limited to replacing or repairing at its option, at its factory, this product if returned within the warranty period to Abbott Medical and after confirmed to be defective by the manufacturer.

EXCEPT AS EXPRESSLY PROVIDED IN THIS WARRANTY, ABBOTT MEDICAL DISCLAIMS ANY REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY AS TO MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

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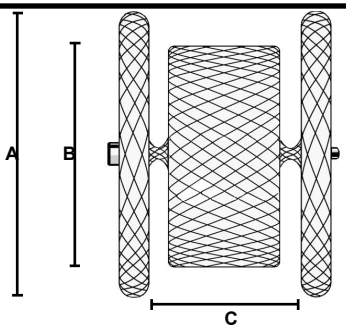
For U.S. --- California Only:

WARNING: This product can expose you to chemicals including ethylene oxide, which is known to the State of California to cause cancer and birth defects or other reproductive harm. For more information, go to www.P65Warnings.ca.gov.

Appendix A: Supplemental Information

Table 1. Occluder dimensions



REF	A ↔ mm (in)	B ↔ mm (in)	C ↔ mm (in)
9-PDAP-03-02-L	4.00 (0.157)	3.00 (0.118)	2.00 (0.079)
9-PDAP-03-04-L	4.00 (0.157)	3.00 (0.118)	4.00 (0.157)
9-PDAP-03-06-L	4.00 (0.157)	3.00 (0.118)	6.00 (0.236)
9-PDAP-04-02-L	5.25 (0.207)	4.00 (0.157)	2.00 (0.079)
9-PDAP-04-04-L	5.25 (0.207)	4.00 (0.157)	4.00 (0.157)
9-PDAP-04-06-L	5.25 (0.207)	4.00 (0.157)	6.00 (0.236)
9-PDAP-05-02-L	6.50 (0.256)	5.00 (0.197)	2.00 (0.079)
9-PDAP-05-04-L	6.50 (0.256)	5.00 (0.197)	4.00 (0.157)
9-PDAP-05-06-L	6.50 (0.256)	5.00 (0.197)	6.00 (0.236)

Dimensions

A. Retention disc diameter

B. Waist diameter

C. Length between retention discs

Table 2. Occluder sizing for patients >2 kg using extraductal disc placement

D mm (in)	E mm (in)		
	3–4 (0.118–0.157)	4.1–6 (0.161–0.236)	6.1–8 (0.240–0.315)
≤2 (≤0.079)	9-PDAP-03-02-L	9-PDAP-03-04-L	9-PDAP-03-06-L
2.1–3 (0.083–0.118)	9-PDAP-04-02-L	9-PDAP-04-04-L	9-PDAP-04-06-L
3.1–4 (0.122–0.157)	9-PDAP-05-02-L	9-PDAP-05-04-L	9-PDAP-05-06-L

Table 2 and Table 3 sizing

D. Minimal ductus diameter

E. Ductus length

Table 3. Occluder sizing for patients ≤2 kg using intraductal placement

 D mm (in)	 E mm (in)	
	3–12 (0.118–0.472)	≥12.1 (≥0.476)
≤1.7 (≤0.067)	9-PDAP-03-02-L	9-PDAP-03-04-L
1.8–3.2 (0.071–0.126)	9-PDAP-04-02-L	9-PDAP-04-04-L
3.3–4 (0.130–0.157)	9-PDAP-05-02-L	9-PDAP-05-04-L

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