NuMED
Summary of Safety and Clinical Performance
SSCP – Atrioseptostomy

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions for Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1. Device identification and general information	
Device trade name(s)	NuMED Atrioseptostomy Family Z-5 Z-6
Model Number	NuMED Atrioseptostomy Family – Model 1300 Z-5 – Model 210 Z-6 – Model 212
Manufacturer's name and address	NuMED, Inc. 2880 Main Street Hopkinton, NY 12965 USA
Manufacturer's single registration number (SRN)	US-MF-000010948
Basic UDI-DI	08877141300SK
Medical device nomenclature description / text	EMDN – C0199 - ARTERIO-VENOUS DEVICES - OTHER
Class of device	III
Year when first certificate (CE) was issued	1999 (Z-5) 2024 (Z-6)
Authorised Representative (AR)	EVOMED, S.L.U. Ctra. Torrejón-Ajalvir Km. 5,2 28864 Ajalvir (Madrid), Spain
AR SRN	ES-AR-000047116
Notified Body	SGS Belgium NV
Notified Body ID number	1639

2. Intended use of the device	
Indications for use	Intended Use – Balloon Atrioseptostomy. The Atrioseptostomy Catheters are balloon catheters designed for the neonate with congenital heart disease requiring septostomy. Indications for Use – Recommended for balloon atrioseptostomy, an accepted technique in most pediatric cardiology centers for the palliation of several congenital cardiac defects. Balloon atrioseptostomy is performed in conjunction with diagnostic cardiac catheterization and has been carried out after the diagnosis of several congenital cardiac defects: transposition of the great arteries,

	total anomalous pulmonary venous drainage without pulmonary obstruction, tricuspid atresia, mitral stenosis, mitral atresia, and pulmonary atresia with intact ventricular septum.
Contraindications and/or limitations	Balloon atrioseptostomy should not be performed for infants older than six weeks. These infants will have thick atrial septums. Reference AHA/ACC guidelines.

3. Device description

Description of the device

The Atrioseptostomy Catheters are balloon catheters designed for the neonate with congenital heart disease requiring septostomy. The balloon catheter is used to create an ASD between the left and right atria, which leads to an immediate and significant increase in atrial level mixing. This increase in systemic oxygen saturation means that surgical intervention can be postponed beyond the critical neonatal period.

They are dual lumen catheters, 50cm in length. The **SPT002**/**Z695** has a 9.5mm ± 0.5mm non-compliant balloon, at 1.0cc volume, on the distal end. The **SPT003**/**Z6135** has a 13.5mm ± 0.5mm non-compliant balloon, at 2.0cc volume, on the distal end. The catheters also feature an end hole that will accommodate a guidewire. The inflated geometry of the balloon is a sphere. There is an imaging band under the balloon for balloon positioning in the left atrium. The catheter tip is angled at 35° to facilitate passage through the interarterial opening in the left atrium. To inflate the balloon of the **9.5mm** catheter to its maximum diameter, 1cc of diluted contrast media is pushed into the balloon extension after purging. To inflate the balloon of the **13.5mm** catheter to its maximum diameter, 2cc of diluted contrast media is pushed into the balloon extension after purging. Catheters are supplied with a one way stopcock for balloon sealing.

The balloon is designed to inflate to the diameter listed on the label at a specific volume. Thus, it is recommended that the device be used in conjunction with a syringe to monitor the volume of solution being used. This device is also designed to be used with an appropriately sized introducer and guidewire.

The balloon size is ± 10 % at the Rated Volume and the Rated Volume is not to be exceeded.

The catheters are supplied sterile, by ethylene oxide gas, and are intended for single use only. The catheters are invasive and intended for transient use (continuous use of <60 minutes) on patients.

Reference to previous generation(s) or variants

Device Variants:

Model	Catalog Number	Main Features						
		Balloon Diameter (mm)	Balloon Length (cm)	Introducer (Fr)	Shaft Size (Fr)	Usable Length (cm)	Guide Wire (inches)	Maximum Volume (cc)
Z-5	SPT002	9.5	0.95	5	4	50	0.014	1
Z-5	SPT003	13.5	1.35	6	5	50	0.021	2
Z-6	Z695	9.5	0.95	6	5	50	0.021	1
Z-6	Z6135	13.5	1.35	6	5	50	0.021	2

Accessories which are intended to be used in combination with the device

The catheter is supplied with a stopcock, that is intended to be used with this device.

Description of any other devices and products which are intended to be used in combination with the device

This device is also designed to be used with a guidewire, introducer, syringe, and balloon inflation media.

4. Risks and Warning	
Residual risks and undesirable effects	All significant risks were considered, mitigated as far as possible (AFAP), and are acceptable in regard to the clinical benefit of the device. Identified clinical residual risks/undesirable side-effects for the Atrioseptostomy Catheters are: • Infection • Inflammation • Thromboembolic Events • Air embolism • Potential balloon separation with subsequent need of snare • Vascular perforation requiring surgical repair • Rhythm and conduction disturbances • Perforation of the left atrial appendage • Damage to the vascular intima • Bleeding • Hematoma Formation • Conduction system Injury • Death
Warning and Precautions	The following Warnings, Precautions and Potential Complications have been identified and are called out in the Instruction for Use: **WARNING** • CAUTION: Do not exceed the rated volume of 1cc for the **9.5mm** catheter. Over inflation may cause balloon rupture. • CAUTION: Do not exceed the rated volume of 2cc for the **13.5mm** catheter. Over inflation may cause balloon rupture. • Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon. • Use only a 3cc syringe/inflation device with pressure gauge for inflation. • Use a 3cc syringe/inflation device with pressure gague for deflation. (For faster deflation, up to a 10cc syringe/inflation device with pressure gauge may be used). • Do not advance the guidewire, septostomy catheter, or any other component if resistance is met, without first determining the cause and taking remedial action. • This catheter is not recommended for pressure measurement or fluid injection. • This device is intended for single use only. Do not resterilize and/or reuse it, as this can potentially result in compromised device performance and increased risk of cross-contamination. • The use of excessive force to pull the balloon across the atrial septum must be avoided. **PRECAUTIONS** • NuMED recommends the SPT002 - 9.5mm catheter be used with a 5F introducer to insure admittance. (Z-5 only) • NuMED recommends the SPT003 - 13.5mm catheter be used with a 6F introducer to insure admittance. (Z-5 only) • Devices are intended to be used by cardiologists trained in catheterization procedures. • NuMED recommends the catheters be used with a 6F introducer to insure admittance. (Z-6 only) • Dilatation procedures should be conducted under fluoroscopic/MRI guidance with appropriate x-ray equipment. • Guidewires are delicate instruments. Care should be exercised while handling to help prevent the possibility of breakage. • Careful attention must be paid to the maintenance of tight catheter connections and by aspiration before proceeding to avoid air introduction into the system. • Under no circumstances should any portion of the catheter system be advanced against resistance. The cause of the resistance should be identified with fluoroscopy/MRI and action taken to remedy

	the problem. • If resistance is felt upon removal, then the balloon, guidewire and the sheath should be removed together as a unit, particularly if balloon rupture or leakage is known or suspected. This may be accomplished by firmly grasping the balloon catheter and sheath as a unit and withdrawing both together, using a gentle twisting motion combined with traction. • Before removing the catheter from the sheath it is very important that the balloon is completely deflated. • Proper functioning of the catheter depends on its integrity. Care should be used when handling the catheter. Damage may result from kinking, stretching, or forceful wiping of the catheter.
Other relevant aspects of safety, including a summary of any field safety corrective actions (FSCA including FSN) if applicable	There have not been any Field Safety Corrective Actions or Field Safety Notices for the Atrioseptostomy Catheters.

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

Summary of clinical data related to equivalent device:

NuMED has elected not to use the clinical data from an equivalent (clinical, technical, and biological characteristics) device(s) manufactured by another company. Data from the Z-5 is being considered equivalent for the Z-6 device. In the event there are devices from another company considered equivalent, their data will be considered as similar devices.

Summary of clinical data from conducted investigations of the device:

NuMED performed a clinical investigation on the Z-5 Catheter in 1994 and the results were submitted in the Z-5 Catheter US 510(k) submission [K960070]. All US sites received institutional review board (IRB) approvals for the study. Intended use was balloon atrioseptostomy.

The clinical investigation in 1994 was conducted outside the EU; however, the results are considered transferable to the European population. The study was conducted following the US Investigational Device Exemption (IDE) and IRB approval for each site. Clinical data generated through the IDE study were generated when the subject device was used in accordance with its intended purposes as documented in the IFU and subsequently received FDA clearance of the device in 1996. The group of patients (n=15) enrolled in the IDE study included 11 males and 4 females, with a mean age of 16 (range: 1 to 593) days. Various CHDs including transposition of the great vessels, HLHS, tricuspid atresia and mitral stenosis with double outlet right ventricle have been included in the study using the Z-5 Catheter (SPT003). These patients enrolled in the IDE study are representative of the patient target groups in the EU. And, the use of subject device in the clinical investigation would be consistent with the use and practice of medicine in the EU and the device does not have a systemic mode of action because of the kind of device (septostomy catheter), with its principle of action is to create an ASD between the left and right atria, which leads to an immediate and significant increase in atrial level mixing (improves bi-directional mixing of the pulmonary and systemic venous blood).

The US IDE clinical study concluded that the Z-5 Catheter was effective and safe in creating an adequate size defect without any mortality or morbidity. Improvements were shown for mean aortic oxygen saturation (0.74 ± 0.17 to 0.88 ± 0.07, $P<0.001$), mean a-wave gradient across the septum (9.3 ± 9.2 to 1.1 ± 1.8mm Hg, $P<0.002$), mean v-wave gradient (9.1 ± 6.2 to 1 ± 1 mmHg, $P<0.0001$) mean m-wave gradient (7.1 ± 5.3 to 0.6 ± 1.1mm Hg, $P<0.0001$), and mean PFO diameter as measured by 2-D and color flow echocardiography (2.8 ± 1.7 to 8.2 ± 2.3mm, $P<0.001$). All patients tolerated the procedures without untoward events.

1	**Study name:** Z-5 Atrioseptostomy Catheter Clinical Study		
	Purpose: To evaluate the Z-5 Atrioseptostomy Catheter		
	Clinical Study Methodology: Case series, at five sites. ***Reference to the clinical study plan (and amendment) n°: G940143***		
	Investigation Site: USA **Investigator** / **Site**	**Ethics Committee Approvals:** Each site provided IRB approval	**Regulatory Authority Approvals:** US FDA

	Ziyad Hijazi	New England Medical Center	***Reference to Document n°:*** N/A	***Reference to Documents n°:*** G940143 (IDE approval)
	John Cheatham	Children's of Omaha		
	Larry Latson	Cleveland Clinic		
	Donald Hagler	Mayo Clinic		
	Michael Kuhn	Loma Linda		

Inclusion / Exclusion:

Inclusion:

- Neonates whose parents/guardians who have signed an informed consent
- Neonates who require palliation of certain congenital cardiac defects: transposition of the great arteries, total anomalous pulmonary venous drainage without pulmonary obstruction, tricuspid atresia, mitral atresia, mitral stenosis, and pulmonary atresia with intact ventricular septum
- Neonates with an LA to RA pressure gradient of >3mmHg and/or an oxygen saturation of <80%, except in the case of total anomalous pulmonary venous drainage without pulmonary obstruction where the LA to RA pressure gradient should be >3mmHg and/or the oxygen saturation is >80%.

Exclusion:

- Patients enrolled in any other study for investigational devices or drugs
- Patient who do not require palliation of the above congenital cardiac defects. They are not cyanotic, the LA to RA pressure gradient is equal, and the oxygen saturation is> then 80% (except in cases of total anomalous pulmonary venous drainage without pulmonary obstruction, where the oxygen saturation would be <80%)
- Patients who will undergo complete surgical repair within 24 hours of diagnosis

Patient Population: fifteen neonates with congenital heart disease (8 transposition of the great vessels / 5 hypoplastic left heart syndrome / 1 tricuspid atresia / 1 mitral stenosis with double outlet right ventricle).

- Sex: 11 male, 4 female
- Mean age: 16 days (range: 1 – 593 days).
- Mean weight: 3.3 kg (range: 2.5 – 8.4kg).

Clinical Study Results:

Purpose	Criteria	Results
Performance evaluation	Mean aortic oxygen saturation	Improved from 0.74±0.17 to 0.88±0.07 (P<0.001)
	Mean a-wave gradient across the septum	Improved from 9.3±9.2mm Hg to 1.1±1.8mm Hg (P<0.002)
	Mean v-wave gradient	Improved from 9.1±6.2mm Hg to 1±1 mm Hg (P<0.0001)
	Mean m-wave gradient	Improved from 7.1±5.3mm Hg to 0.6±1.1mm Hg (P<0.0001)
	Mean Patent Foramen Ovale (PFO) diameter as measured by 2D and color flow echocardiography	Increased from 2.8±1.7mm to 8.2±2.3mm (P<0.001)
Safety evaluation	No adverse events.	All patients tolerated the procedures without untoward events.

Reference to the Clinical Study Report n°: G940143 Final Report (used for K960070[1] submission)

Device Used: NuMED Z-5 Atrioseptostomy Catheter [all SPT003 – 13.5mm]

Conclusion: The catheter was effective and safe in creating an adequate size defect without any mortality or morbidity.

Clinical Publication: Hijazi, ZM. (1996) – unpublished data used in 510(k) submission.

There is no potential for clinically significant impact by extrinsic and/or intrinsic ethnic factors on safety and efficacy. Consequently, clinical data collected from IDE G940143 clinical investigation can be considered transferrable to the European population.

Summary of clinical data from other sources:

The following is a summary of clinical data found during the literature review of the device:

[1] https://www.accessdata.fda.gov/cdrh_docs/pdf/K960070.pdf

First Author (Year)	Appraisal/Results

1. Gopalakrishnan et al. (2016)

Contribution	
S&P	x
SOA	

Safety & Performance

Appraisal

Level of Evidence	Study Method/Design	Question Applied	Oxford LOE 2011				
	Prospective echocardiographic follow-up study (January 2014 to June 2015)	Treatment Benefit	1	2	**3**	4	5

Suitability	Relevant Data	Grading		
Device	- Z-5 Catheter (NuMED) or Rashkind (Medtronic) - Note: since the data of the two devices are not reported separately, "D3" (other device) is applied.	D1	D2	**D3**
Application	- BAS	**A1**	A2	A3
Patient	- Neonates with the transposition of the great arteries who underwent BAS (all consecutive children with simple transposition of the great arteries who underwent BAS for restrictive interatrial communication and oxygen saturation below 75%) - Sampling: 25 neonates (11 NuMED Z-5 Catheter and 14 Medtronic Rashkind Catheter) - Mean age: 4 days (range 1-95 days) - Sex: Not reported - Note: mean age is 4 days; however, the upper age range of "95 days" (i.e., > 6 weeks for the subject device), "P2" is applied.	P1	**P2**	P3
Report	- Prospective study contains sufficient information to undertake a rational and objective assessment; however, the data for Z-5 Catheter (subject device) and Medtronic Rashkind (similar device) are not reported separately, "R2" is applied.	R1	**R2**	R3
	Suitability Grade (Range 4-12)	8		

Data Contribution	Relevant Data	Grading	
Outcomes/Endpoints	- Increase in oxygen saturation - Decrease in left ventricle mass - BAS procedure success rate and infants for subsequent surgery	**Yes 1**	No 2
Follow-up	- Babies with transposition of the great arteries and undergoing BAS had their left ventricle volume assessed prior to BAS, and then on days 1, 3, 6, 9, 12 and 15 after BAS.	**Yes 1**	No 2
Statistical analysis	- All P-values were two-tailed. A cut-off of less than 0.05 was considered for statistical significance.	**Yes 1**	No 2
Clinical significance	- BAS is associated with accelerated regression of the left ventricle in infants with simple transposition of the great arteries in the first 2 weeks after BAS irrespective of the age of the child. Left ventricle regression is faster in children who undergo BAS beyond 3 weeks of life. Left ventricle regression occurring beyond the third week of life in these infants suggests that the creation of a wide interatrial communication acts as a factor independent of the expected age-related left ventricle regression in transposition of the great arteries with intact IVS in the absence of a large ASD. The study data suggest that these babies could benefit by avoiding undue delay in definitive ASO.	**Yes 1**	No 2
	Data Contribution Grade (Range 4-8)	**4**	

Overall S&P Appraisal, Disposition and Weighting

S&P Grade (Range 9-25)	LOE (3) + Suitability (8) + Data Contribution (4) = 15	Disposition and Weighting (select)	Accepted and Pivotal 9-12 **Accepted but not Pivotal, 13-21** Excluded, 22-25

Relevant S&P Results

Safety data	- Not reported
Performance data	- BAS was successful in all 25 babies (100%). - Left ventricle mass decreased by 1.5 g/m^2 every day during the first 2 weeks following BAS adjusted for the age of the child in days (P<0.001). - Mean baseline left ventricle mass was 47.9 g/m^2, which decreased to 38.5, 36.2, 32.1, 32.4, 25.7 and 25.2 g/m^2 on Days 1, 3, 6, 9, 12 and 15, respectively. - Children who underwent BAS beyond 3 weeks of life had faster left ventricle regression than those who underwent the procedure earlier (unstandardized regression coefficient β 0.892, P < 0.001).
Benefits/claims data	- Oxygen saturation by pulse oximetry (SpO2) prior to BAS versus immediately post-BAS: 56±14.4% versus 77±9.5%. - Twenty patients underwent arterial switch operation at a mean of 9 days from BAS.
Strengths	- N/A
Weaknesses/ Potential bias	- Study was limited by the absence of a true control arm. - Investigators were part of the treating team and were not blinded from the results of the study.

2. Matter et al. (2011)

Contribution	
S&P	x
SOA	x

Safety & Performance Appraisal

Level of Evidence	Study Method/Design	Question Applied	Oxford LOE 2011				
	Retrospective study (January 2001 to January 2010)	Treatment Benefit, Treatment Harms (Common)	1	2	**3**	4	5

Suitability	Relevant Data	Grading		

Device	- BAS catheters:
	  - Z-5 Catheter by Numed (n=48)
	  - Miller catheter by Edwards-Baxter (n=144)
	- Note: although subject device was evaluated and the authors reported that there are no significant difference in oxygen saturation or the size of inter-atrial communication between the two catheters, "D3" is applied since the data from the devices are not reported separately.
		D1	D2	**D3**

Application	- BAS	**A1**	A2	A3
Patient	- Patients with different CHDs, including transposition of the great arteries, mitral atresia, tricuspid atresia, HLHS - Sampling: 192 patients (78.5% transposition of the great arteries, 10% mitral atresia, 7.5% tricuspid atresia, and 4% HLHS) - Mean age: 3.5 days (range 1-54 days); weight: 3.08 ± 0.37 kg - Sex: 110 (57.5%) M; 82 (42.5%) F - Note: the mean age is 3.5 days; however, the upper age range of "54 days" (i.e., > 6 weeks for the subject device), "P2" is applied.	P1	**P2**	P3
Report	- Retrospective study contains sufficient information to be able to undertake a rational and objective assessment; however, the data for Z-5 Catheter (subject device) and Miller Catheter (other devices) are not reported separately, "R2" is applied.	R1	**R2**	R3
	Suitability Grade (Range 4-12)	**8**		

Data Contribution	Relevant Data	Grading	
Outcomes/Endpoints	- Increase in diameter of the atrial communication - Increase in oxygen saturations - Decrease in mean pressure gradient - Death and complication rates	**Yes 1**	No 2
Follow-up	- Not reported	Yes 1	**No 2**
Statistical analysis	- Statistical significance was achieved when P was <0.05.	**Yes 1**	No 2
Clinical significance	- BAS is safe and an effective palliative procedure for different CHD with	**Yes**	No

	good immediate results reported in author's institution. - BAS improves the hemodynamics in a variety of compromised circulations and is similarly effective in palliation until definitive surgery can be attempted.	**1**	2
	Data Contribution Grade (Range 4-8)	**5**	

Overall S&P Appraisal, Disposition and Weighting

S&P Grade (Range 9-25)	LOE (3) + Suitability (8) + Data Contribution (5) = 16	Disposition and Weighting (select)	Accepted and Pivotal 9-12 **Accepted but not Pivotal, 13-21** Excluded, 22-25

Relevant S&P Results

Safety data	- Death:
	  - No procedural deaths
	  - Five patients developed a sepsis-like picture after the procedure and died
	- Complications:
	  - 54% premature ectopic beats
	  - 8% supraventricular tachycardia
	  - 2% venous thrombosis
	  - One patient with cardiac perforation of left atrial appendage (LAA) and managed surgically.
	  - 7% balloon rupture (all Miller type only; no Z-5 Catheter);
	  - No embolization of balloon fragments

Performance data	- 122 procedures (63.5%) performed in neonatal intensive care at bedside and 70 procedures (36.5%) in catheterization laboratory. - 78% Femoral access and 22 umbilical access. - Number of septostomies required to achieve good results was 5.23 ± 1.20. - Mean pressure gradient for patients done in catheterization laboratory decreased from 4.1± 2.4 to 0.5± 1.1 mmHg (p<0.0001).
Benefits/claims data	- Diameter of the atrial communication: increased from 2.75 ± 0.97 mm to 7.07 ± 0.79 mm (p< 0.0001) - Oxygen saturations: increased significantly from 65.38 ± 9.59% to 88.62 ± 3.13% (p< 0.0001) - Z-5 Catheter: radiopaque imaging band in the middle of the balloon for accurate positioning in the left atrium and catheter tip is angled at 35" facilitate entry into the left atrium
Strengths	- Comparison between two balloons (Z-5 Catheter versus Miller): no significant difference in oxygen saturation or the size of inter-atrial communication (p= 0.6). - Of the 7% balloon rupture, all were the Miller type and no Z-5 Catheter rupture were reported.
Weaknesses/ Potential bias	- Study limited by the retrospective nature of the review. - Spectrum of disease and underlying pathophysiology varied widely with a complex interplay of factors effecting outcomes.

State of the Art
Appraisal

Medical condition		Alternatives		Risk/benefit		Side-effects		Equivalence		Surrogate endpoints	
Yes 1	No 2	Yes 1	**No 2**	**Yes 1**	No 2	**Yes 1**	No 2	**Yes 1**	No 2	**Yes 1**	No 2

Overall SOA Appraisal and Disposition

SOA Grade (Range 6-12)	7	Disposition (select)	**Accepted, < 12** Excluded, 12

Relevant SOA Results

SOA data	- BAS was first described by Rashkind and Miller in 1966 as palliation for patients with transposition of the great arteries to improve saturation and remains an important interventional procedure in the palliation of certain forms of CHD. - Creating an atrial septa defect in patients with transposition of the great arteries will enhance bidirectional mixing of the pulmonary and systemic venous blood, hence improving oxygen saturation. - Bedside BAS significantly reduces the cost to the patient without a change in efficacy and might be

	safer by obviating the need for transport of a sick infant to the cardiac catheterization laboratory - Use of echocardiography in diagnosing transposition of the great arteries is the standard of care and has been used for 15 years. - Atrial septum can be easily evaluated by subcostal imaging, making it an ideal method for monitoring BAS - BAS using fluoroscopy or 2D- echocardiography is an acknowledged technique in the palliative treatment of cyanotic CHD in hypoxemic neonates due to inadequate intracardiac mix.
Comments	- N/A

3. Holzer et al. (2008)

Contribution	
S&P	x
SOA	

Safety & Performance

Appraisal

Level of Evidence	Study Method/Design	Question Applied	Oxford LOE 2011				
	Retrospective review (July 2002 to September 2007)	Treatment Benefit, Treatment Harms (Common)	1	2	3	**4**	5

Suitability	Relevant Data	Grading		
Device	- Z-5 Catheter (NuMED)	**D1**	D2	D3
Application	- BAS	**A1**	A2	A3
Patient	- Neonates with HLHS[2] and having BAS - Sampling: 56 neonates [Group A: standard atrial septal anatomy (n = 33); Group B: complex atrial septal anatomy (n = 23). BAS was used in 77.6% of procedures, additional techniques in 35.8% of procedures.] - Mean age: 26 days (range 1-231 days) - Sex: Not reported - Note: mean age is 26 days; however, the upper age range is "231 days" (i.e., > 6 weeks for the subject device), "P2" is applied.	P1	**P2**	P3
Report	- Retrospective report contains sufficient information to undertake a rational and objective assessment.	**R1**	R2	R3
	Suitability Grade (Range 4-12)	**5**		

Data Contribution	Relevant Data	Grading	
Outcomes/Endpoints	- Reduced mean trans-septal gradient - Survival rate up to Comprehensive Stage II palliation - Complications rate	**Yes 1**	No 2
Follow-up	- Median follow-up is 2.8 years (211 days–5.7 years)	**Yes 1**	No 2
Statistical analysis	- Statistical analysis with all tests were performed at $\alpha = 5\%$	**Yes 1**	No 2
Clinical significance	- In the majority of patients, standard BAS can be performed safely, and is usually the only intervention required to achieve adequate relief of atrial septal restriction until Comprehensive stage II palliation. Survival up to and including Comprehensive stage II palliation was 73% group A, and 57% in group B.	**Yes 1**	No 2
	Data Contribution Grade (Range 4-8)	**4**	

Overall S&P Appraisal, Disposition and Weighting

S&P Grade (Range 9-25)	LOE (4) + Suitability (5) + Data Contribution (4) = 13	Disposition and Weighting (select)	Accepted and Pivotal 9-12 **Accepted but not Pivotal, 13-21** Excluded, 22-25

Relevant S&P Results

Safety data	- Side effects occurred in 8.9% (6 majors, including 3 periprocedural deaths) and 26.8% (18 minor and transient) of procedures. - Minor side effects included transient arrhythmias and/or conduction anomalies in 12/67

	(17.9%) procedures and temporary bradycardia/hypotension in 5/67 (7.5%) procedures, frequently requiring administration of a small dose of epinephrine. One patient required cardioversion for sustained atrial flutter. In at least three procedures, the adverse events were unrelated to BAS, but resulted from additional interventional procedures performed in the same setting. - Side effects are less common in Group A (standard atrial septal anatomy). - Complex atrial septal anatomy is technically challenging and has a higher incidence of procedural side effects. Standard BAS can be performed safely in majority of the patients.
Performance data	- Mean trans-septal gradient was reduced significantly from seven to one mmHg with the median time to discharge being 3.5 days. - Survival up to and including Comprehensive Stage II palliation was 73% in Group A, and 57% in Group B. - With utilization of appropriate techniques and equipment, atrial septal interventions in HLHS can be performed successfully in virtually all patients. Success of the Hybrid approach in palliating patients with HLHS is crucially dependent on relieving any significant interatrial restriction. Note: The Hybrid approach to palliation of HLHS has emerged as an important treatment alternative to classical Norwood-type palliation. Its success is crucially dependent on relieving any significant interatrial restriction. If the interatrial restriction is not successfully relieved then it would not only likely lead to lower inter-stage saturations but also more crucially leave the patient exposed to pulmonary venous hypertension with its associated negative impact on outcome after subsequent Comprehensive stage II palliation.
Benefits/claims data	- Oxygen saturation post procedure (%): Group A: 87%/Group B: 85% - In the majority of patients, standard BAS is usually the only intervention required to achieve adequate relief of atrial septal restriction until Comprehensive stage II palliation.
Strengths	- In this study, the preferred atrial septal intervention is BAS, using the NuMED Z-5 atrioseptostomy catheter (NuMED, Hopkinton, NY), which is available with balloon sizes of 1 ml (9 mm diameter) and 2 ml (13.5 mm diameter) and can be passed over a 0.014”/0.021” wire (5/6Fr sheaths). - Noncompliant nature of the Z-5 septostomy catheter and its relatively small size offer distinct advantages when performing BAS in patients with HLHS and a small left atrial size. - Of note is that a radiopaque marker is located in the mid-portion of the balloon.
Weaknesses/ Potential bias	- Limitations posted by the Z-5 Catheter: In patients with thick interatrial septum, even a partially inflated balloon may not tear the atrial septum, causing shearing force on the pulmonary veins, as seen in one of our patient who died as a result of pulmonary vein avulsion. If the catheter does not tear the atrial septum with reasonable pulling force, it is important to consider other treatment alternatives, such as cutting and/or standard balloon atrial septoplasty, rather than attempting to force the balloon to overcome an unusually high septal resistance.

Safety & Performance Appraisal

Level of Evidence	Study Method/Design	Question Applied	Oxford LOE 2011				
	Case report (safety, n=1)	Treatment Harms (Rare)	1	2	3	**4**	5

4. Akagi et al. (2001)

Contribution	
S&P	x
SOA	

Suitability	Relevant Data	Grading		
Device	- Z-5 Catheter (NuMED)	**D1**	D2	D3
Application	- BAS	**A1**	A2	A3
Patient	- Patients diagnosis with critical aortic stenosis with severe mitral insufficiency with unusually thick atrial septum. - Sampling: 1 patient - Age: 35th week of gestation - Sex: M = 0; F = 1	**P1**	P2	P3
Report	- Case report (safety) of only one patient; thus not sufficient information to undertake a rational and objective assessment.	R1	**R2**	R3
	Suitability Grade (Range 4-12)	**5**		

Data Contribution	Relevant Data	Grading

Outcomes/Endpoints	- Safety (patient death).	Yes 1	**No 2**
Follow-up	- Not reported	Yes 1	**No 2**
Statistical analysis	- N/A	Yes 1	**No 2**
Clinical significance	- This experience could be considered as noteworthy when using this catheter in patients with unusually thick atrial septum.	Yes 1	**No 2**
	Data Contribution Grade (Range 4-8)	**8**	

Overall S&P Appraisal, Disposition and Weighting

S&P Grade (Range 9-25)	LOE (4) + Suitability (5) + Data Contribution (8) = 17	Disposition and Weighting (select)	Accepted and Pivotal 9-12 **Accepted but not Pivotal, 13-21** Excluded, 22-25

Relevant S&P Results

Safety data	- When Z-5 Catheter was pulled back, the tip of the balloon was torn off. The tip was seen, but could not be seized. - Patient died due to severe hypoxia and massive intracranial hemorrhage after 48 hours of the procedure.
Performance data	- N/A
Benefits/claims data	- N/A
Strengths	- N/A
Weaknesses/ Potential bias	- Case report of one patient.

5. Patel et al. (1998)

Contribution	
S&P	x
SOA	

Safety & Performance Appraisal

Level of Evidence	Study Method/Design	Question Applied	Oxford LOE 2011				
	Report of authors' experience	Treatment Benefit, Treatment Harms (Common)	1	2	3	**4**	5

Suitability	Relevant Data	Grading		
Device	- Z-5 Catheter (NuMED)	**D1**	D2	D3
Application	- BAS	**A1**	A2	A3
Patient	- Patients with CHD - Sampling: 16 patients (14 transposition of the great arteries, 1 HLHS, one double outlet right ventricle and mitral atresia) - Age: range <1 to 72 days (12 patients <24 hours old, three <1 week old and one 72 days old) - Mean weight: 3.4±0.6 kg - Sex: Not reported - Note: all patients were younger than 6 weeks with the exception of one patient >42 days old, "P2" is applied.	P1	**P2**	P3
Report	- Report contain sufficient information to be able to undertake a rational and objective assessment	**R1**	R2	R3
	Suitability Grade (Range 4-12)	**5**		

Data Contribution	Relevant Data	Grading	
Outcomes/Endpoints	- Increase in aortic saturation - Decrease in mean a-wave gradient between the left and right atrium - Decrease in mean v-wave gradient - Decrease in mean gradient - Increase diameter of the atrial communication - Report complications	**Yes 1**	No 2
Follow-up	- Fourteen infants underwent definitive surgical procedures (the arterial switch operation), one patient underwent stage one Norwood procedure,	**Yes 1**	No 2

	and one patient underwent a palliative pulmonary artery band).		
Statistical analysis	- Statistical significance was achieved when P was < 0.05.	**Yes 1**	No 2
Clinical significance	- All patients demonstrated a significant increase in the aortic saturation and reduction of gradient across the atrial septum following BAS using Z-5 Catheter. The mean size of the atrial septal communication increased from 2.0-6.5mm. - The authors concluded that BAS is a safe and effective palliative procedure. The new NuMED septostomy catheter has many features that should help facilitate the BAS and decrease the risk of complications. BAS using this new catheter (Z-5 Catheter) is safe and effective.	**Yes 1**	No 2
	Data Contribution Grade (Range 4-8)	**4**	

Overall S&P Appraisal, Disposition and Weighting

S&P Grade (Range 9-25)	LOE (4) + Suitability (5) + Data Contribution (4) = 13	Disposition and Weighting (select)	Accepted and Pivotal 9-12 **Accepted but not Pivotal, 13-21** Excluded, 22-25

Relevant S&P Results

Safety data	- Only complication encountered was an episode of atrial flutter in one patient, which responded to cardioversion. - All patients tolerated the procedure well. - No major complications or mortality encountered. - No mortality reported.
Performance data	- Mean a-wave gradient between the left and right atrium decreased from 5.4 ± 3.7 to 1.6 ± 2.6 mmHg (P < 0.001) - Mean v-wave gradient decreased from 5.9 ± 3.3 to 1.6 ± 2.6 mmHg (P < 0.001). - Mean gradient decreased from 3.9 ± 2.4 to 0.5 ± 1.1 mmHg (P < 0.001). - Diameter of the atrial communication increased from 2 ± 1.1 to 6.5 ± 1.1 mm (P < 0.001).
Benefits/claims data	- Aortic saturation increased from 75 ±19% to 90% ± 5% (P = 0.002). - Fourteen infants underwent definitive surgical procedures (the arterial switch operation), one patient underwent stage one Norwood procedure, and one patient underwent a palliative pulmonary artery band).
Strengths	- NuMED Z-5 Catheter is a balloon catheter designed for the neonate with CHD requiring septostomy. It is a 50-cm long dual lumen catheter with a 13.5 ± 0.5-mm diameter noncompliant balloon made of polymeric nylon material with a maximal capacity of 2 cc at the distal end. It has an end-hole that will accommodate a 0.021" guidewire. The inflated geometry of the balloon is a sphere. There is a radiopaque imaging band in the middle of the balloon for accurate positioning in the left atrium. The catheter tip is angled at 35" to facilitate entry into the left atrium. A small version of the balloon is available for premature neonates with 1 cc maximal capacity producing a 9.5-mm balloon diameter. - NuMED Z-5 Catheter requires a 5Fr-6Fr sheath, which is advantageous in the neonate. The catheter is curved to facilitate entry into the left atrium. It is a double lumen catheter, which allows the ability to confirm position by pressure measurement or hand injection of contrast. There is a radiopaque marker, which shows the position of the center of the balloon. It is a low profile and noncompliant balloon. The feature that allows for a guidewire lumen should make multiple septostomies faster by sliding the catheter over the wire positioned in the left atrium. All these features should decrease the rate of complications.
Weaknesses/ Potential bias	- When using this new septostomy catheter (Z-5 Catheter), the physician must avoid pulling beyond the inferior vena cava right atrial junction, since rupture of the inferior vena cava could result. Similar precautions are necessary using the conventional balloon. - Since the balloon of the NuMED Z-5 Catheter is noncompliant, care must also be exercised in how much force is used to pull the balloon through the atrial septum. In patients with an unusually thick atrial septum, it may be advisable to perform the initial septostomy with the balloon slightly less than fully inflated so that some deformation of the balloon can occur if there is excessive resistance.

An overall summary of the clinical performance and safety:

Treatment	Benefits	Risks

Subject devices (Atrioseptostomy Catheters)	- BAS using Z-5 Catheter is a safe and effective palliative procedure. Patients subsequent underwent surgical procedures (ASO, Norwood procedure, or palliative pulmonary artery band) reported.[5]
	- Z-5 Catheter is reported to have features that should decrease the rate of complications:
	  - Catheter tip angled at 35" to facilitate entry into the left atrium. [2,5]
	  - Requires 5Fr-6Fr sheath, which is advantageous in neonate.[5]
	  - A small version of balloon is available for premature neonates with 1 cc maximal capacity producing a 9.5mm balloon diameter.[5]
	  - Allows for a guidewire lumen should make multiple septostomies faster by sliding the catheter over the wire positioned in the left atrium.[5]
	  - Dual lumen catheter design allows the ability to confirm position by pressure measurement or hand injection of contrast.[5]
	  - Radiopaque imaging band in the middle of the balloon allows for accurate positioning in the left atrium. [2,3,5]
	  - Noncompliant nature catheter and its relatively small size offer distinct advantages when performing BAS in patients with HLHS and a small left atrial size.[3]
	- Can be performed in neonatal intensive care at bedside or in catheterization laboratory.[2]
	- Can be performed with femoral access or umbilical access.[2]
	- Performance includes:
	  - Increase in oxygen/aortic saturation [2,3,5, IDE G940143]
	  - Increase in diameter of atrial communication/PFO diameter [2,5, IDE G940143]
	  - Decrease in mean pressure gradients [2]
	  - Decrease in mean trans-septal/a-wave/v-wave/m-wave gradient [3,5, IDE G940143]
	- In the majority of patients, standard BAS is usually the only intervention required to
		- Patients with thick interatrial septum:
		  - Z-5 Catheter is limited in patients with thick interatrial septum, even a partially inflated balloon may not tear the atrial septum, causing shearing force on the pulmonary veins. If the catheter does not tear the atrial septum with reasonable pulling force, it is important to consider other treatment alternatives, such as cutting and/or standard balloon atrial septoplasty, rather than attempting to force the balloon to overcome an unusually high septal resistance.[3]
		  - Since Z-5 Catheter is noncompliant, care must be exercised in how much force is used to pull the balloon through the atrial septum. In patients with an unusually thick atrial septum, it may be advisable to perform the initial septostomy with the balloon slightly less than fully inflated so that some deformation of the balloon can occur if there is excessive resistance.[5]
		  - When using Z-5 Catheter, physician must avoid pulling beyond the inferior vena cava right atrial junction, since rupture of the inferior vena cava could result; however, similar precautions are necessary using the conventional balloon.[5]
		  - Balloon torn off and patient died; noteworthy when using Z-5 Catheter in patients with unusually thick atrial septum.[4]
		- Developed sepsis-like picture and died after procedure.[2]
		- Periprocedural death.[3]
		- Side-effects reported:
		  - Premature ectopic beat[2]
		  - Supraventricular tachycardia[2]
		  - Venous thrombosis[2]
		  - Cardiac perforation of left atrial appendage[2]
		- Minor and transient side-effects:
		  - Transient arrhythmias and/or conduction anomalies[3]
		  - Temporary bradycardia/hypotension[3]
		  - Atrial flutter requiring cardioversion [3]

	achieve adequate relief of atrial septal restriction until Comprehensive stage II palliation. Survival up to and including Comprehensive stage II palliation was 73% in standard atrial septal anatomy, and 57% in complex atrial septal anatomy.[3] - Left ventricle regression is faster in children who undergo BAS.[1] - Comparison between two balloon catheters (Z-5 Catheter versus Miller - other BAS catheter) in patients with different CHDs (transposition of the great arteries, mitral atresia, tricuspid atresia and HLHS) found no significant difference in oxygen saturation or the size of inter-atrial communication (p= 0.6).[2]	

Clinical Benefit	**Clinical Outcome Parameters**	**Supporting Clinical Data**
In BAS, the balloon catheter is used to create an ASD between the left and right atria, which leads to an immediate and significant increase in atrial level mixing (improves bi-directional mixing of the pulmonary and systemic venous blood). This increase in systemic oxygen saturation means that surgical intervention (e.g. arterial switch surgery, cardiopulmonary bypass) can be postponed beyond the critical neonatal period.	Increase of diameter of the atrial communication in mm	- US IDE (G940143) study: statistically significant increase in mean PFO diameter (2.8±1.7mm to 8.2±2.3mm, P<0.001) as measured by 2D and color flow echocardiography. - Matter et al. [2]: the diameter of the atrial communication has increased from 2.75 ± 0.97 mm to 7.07 ± 0.79 mm (p< 0.0001). As comparison between two balloons (Z-5 Catheter versus Miller), there has been no significant difference in the size of inter-atrial communication (p= 0.6). - Patel et al. [5]: the diameter of the atrial communication increased from 2 ± 1.1 to 6.5 ± 1.1 mm (P < 0.001).
	Increase in oxygen saturation in %	- US IDE (G940143) study: statistically significant improvement of mean aortic oxygen saturation (0.74±0.17 to 0.88±0.07, P<0.001). - - Gopalakrishnan et al. [1]: the oxygen saturation by pulse oximetry (SpO2) prior to BAS versus immediately post-BAS was 56±14.4% versus 77±9.5%. - Matter et al. [2]: oxygen saturations have increased significantly from 65.38 ± 9.59% to 88.62 ± 3.13% (p< 0.0001). As comparison between two balloons (Z-5 Catheter versus Miller), there has been no significant difference in oxygen saturation (p= 0.6). - Holzer et al. [3]: oxygen saturation post-procedure was 87% for Group A (standard atrial septal anatomy) and 85% for Group B (complex atrial septal anatomy). - Patel et al. [5]: aortic saturation was increased from 75 ± 19% to 90% ± 5% (P = 0.002). All

		patients demonstrated a significant increase in the aortic saturation following BAS using Z-5 Catheter.
	Postponement of the surgical intervention for total correction or surgical repair in days or months	- Gopalakrishnan et al. [1]: twenty patients underwent arterial switch operation at a mean of 9 days from BAS. - Holzer et al. [3]: survival up to and including Comprehensive Stage II palliation was 73% in Group A (standard atrial septal anatomy), and 57% in Group B (complex). - Patel et al. [5]: fourteen infants underwent definitive surgical procedures (the arterial switch operation), one patient underwent stage one Norwood procedure, and one patient underwent a palliative pulmonary artery band.
Radiopaque catheter body and balloon image marker: facilitate reliable positioning of the catheter. A Platinum image marker band is placed under the balloon for clear identification under fluoroscopy.	Procedural success (%)	- Gopalakrishnan et al. [1]: BAS was successful in all 25 babies (100%). - Holzer et al. [3]: survival up to and including Comprehensive Stage II palliation was 73% in Group A, and 57% in Group B. - As additional data: o Matter et al. [2]: the authors have identified that the Z-5 Catheter has a radiopaque imaging band in the middle of the balloon for accurate positioning in the left atrium and catheter tip is angled at 35° to facilitate entry into the left atrium. o Holzer et al. [3]: has also opined that the noncompliant nature of the Z-5 Catheter and its relatively small size offer distinct advantages when performing BAS in patients with HLHS and a small left atrial size. [3] o Patel et al. [5]: has also stated that the NuMED Z-5 Catheter has many features that should help facilitate the BAS and decrease the risk of complications. For instance, the NuMED Z-5 Catheter requires a 5Fr-6Fr sheath, which is advantageous in the neonate. The catheter is curved to facilitate entry into the left atrium. It is a double lumen catheter, which allows the ability to confirm position by pressure measurement or hand injection of contrast. There is a radiopaque marker, which shows the position of the center of the balloon. It is a low profile and noncompliant balloon. The feature that allows for a guidewire lumen should make multiple septostomies faster by sliding the catheter over the wire positioned in the left atrium. o 2011 AHA/ACC guideline [9]: compared to the Rashkind, Fogarty and Miller catheter,

		the AHA/ACC guideline describes that the NuMED septostomy catheter (Z-5) is the only one with an end hole that enables the operator to advance over a guidewire and to confirm position by injecting contrast in the left atrium.

A comprehensive, systematic, and critical evaluation of the pertinent clinical data and pre-clinical study data in relation to the Atrioseptostomy Catheters has been carried out. Based on the results of this evaluation, it is considered that:

a) Conformity with relevant general safety and performance requirements set out in MDR Annex I under the normal conditions of the intended use of the device has been confirmed.
b) Undesirable side-effects and acceptability of the benefit-risk ratio have been evaluated and are acceptable according to the current knowledge/the state of the art in the medical fields concerned and according to available medical alternatives.
c) The information materials supplied by NuMED, and the risk reduction measures are adequate taking into account the intended purpose of the device.
d) Usability aspects have been adequately considered and the Atrioseptostomy Catheters, including the IFUs, are suitable for the intended users.
e) The claims foreseen in the information materials provided with the CER are adequate taking into account the intended purpose of the device.
f) The information materials supplied and the RM documentation for the device under evaluation are consistent with the clinical data and pre-clinical study data presented in the CER and with the current knowledge/state of the art.

Overall, it is concluded that the risks associated with the use of the Atrioseptostomy Catheters are acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art; that the intended clinical performances are achieved by the device; and that known and foreseeable risks and undesirable side-effects are considered acceptable when weighed against the benefits from performance achieved by the device.

Ongoing planned post-market clinical follow-up:

Number of Activity	Method	Description	Aim of Activity	Rationale and known limitations of activity	Timeline
1.	☒ General ☐ Specific	Z-5 and Z-6 Devices: Clinical Evaluation of post-market surveillance activities - Literature and media searches - Post Market Surveillance of complaints, vigilance reports, recalls, and FSCAs.	- Monitoring of device safety and performance. - Identification of misuse or off-label use. - Detect new or emerging risks and side effects. - Review of data to continually update the benefit-risk determination.	Rationale: This method provides a regular review of data that provides data on product performance and patient safety. One literature review and media search is specific to NuMED devices only and one includes similar competitor products. PMS review is performed for both NuMED products as well as similar competitor products. Limitations: PMS of NuMED device complaint, vigilance, recalls, and FSCAs is reactive data.	Literature and media searches are conducted annually and are documented in the Annual Quality Management Meeting / Minutes. Complaint, vigilance, recalls, and FSCA data on NuMED products is reviewed both monthly as well as annually and is documented in the monthly and annual Quality Management meeting minutes. Data from both a scientific literature review as well as sales / complaint, vigilance, recalls, and FSCA data on both NuMED products as well as similar competitor products is documented in the CER when updated.

					Data from complaint, vigilance, recalls, and FSCAs are also updated annually in the PSUR document for NuMED products and similar competitor products.
2.	☒ General ☐ Specific	Z-5 Device: PMS forms are sent with every device shipped from NuMED that have a CE mark on the label / IFU.	- Proactive approach to generate more user data/feedback for all CE marked devices that NuMED markets. - Monitoring of device safety and performance. - Identification of misuse or off-label use. - Detect new or emerging risks and side effects. - Review of data to continually update the benefit-risk determination.	Rationale: This method is a proactive approach to generate user feedback on devices, whether positive or negative. Data will help determine if any new risks are introduced, which are currently not included in the risk analysis. Limitations: Dependent on users to fill out and return the forms.	Data from PMS forms is reviewed upon receipt, as well as, in monthly Quality Management meetings.
3.	☐ General ☒ Specific	Z-6 Device: PMCF clinical questionnaire form included in the device packaging for all products shipped with a Multi-language label and IFU.	- Pro-active collection of specific data on the Z-6 Atrioseptostomy devices which will include procedural information, complications, and general feedback. Information from the clinical questionnaires form will be entered in a database and an evaluation and write-up will be done by a clinician after review of the data. - Monitoring of Z-6 device safety and performance based on the data included on the questionnaire as well as any other type of PMS data. - Identification of misuse or off-label use of the Z-6 device. - Detect new or emerging risks and side effects for the Z-6 device. - Review of data to continually update the benefit-risk determination of the Z-6 device.	Rationale: This method differs from the PMS form in that it is has specific questions for the physicians regarding this device, clinical information, contraindications, risks and complications. Data will help determine if any new risks are introduced specific to the Z-6 device, which are currently not included in the risk analysis, and ongoing safety and performance of the device. Since the Z-6 is considered a WET device, based on the rationale outlined in the CER, a clinical questionnaire specific to the Z-6 device itself will be able to detect new or emerging risks associated with the slight differences when compared to the Z-5, and also the ongoing safety and performance of the device. Limitations: Dependent on users to fill out and return the forms, however, NuMED has worldwide distributors to help collect the information and send it to NuMED.	90 clinical questionnaire forms will be required, based on confidence intervals, in order to guarantee a 99% confidence level, 95% of the time. Questionnaires will be collected for a minimum of one year as well. If the 90 clinical questionnaire forms are received prior to the one year minimum, we will continue to collect them until the one year is complete. If they are not collected in one year, it will continue until a total of 90 are received. The clinician review will be performed once the data from the 90 clinical questionnaire forms are entered into the database. All PMCF clinical questionnaire form data is reviewed monthly and is documented in the monthly Quality Management meeting minutes. Any device related problems / complications will be entered into NuMED's complaint system for investigation according to our ISO 13485 compliant procedures. Adverse Event reporting will be performed as per the procedures and regulations.

PMCF Activity #1

Literature and media searches are conducted annually in January. This is to review all published data on the devices for information related to safety and performance. This includes a review to determine if the devices continue to be safe and perform as intended in the IFU by reviewing any complaints or emerging clinical risks. The search strategy is based on the device names.

An additional literature search of peer-reviewed scientific publications is performed as part of the update to the CER. This search is a broader search to identify all publications that report on the clinical use of the device or similar devices on the market. It includes searches of device names (both NuMED and similar competitor product names), indications, and product codes. This search is used to demonstrate the safety and performance of the devices in question within the state of the art, and to determine whether the devices continue to be safe and perform as intended in the IFU by reviewing any complaints or emerging clinical risks.

Post market surveillance includes review of data for both NuMED devices as well as similar competitor products. This includes both a reactive review of NuMED data, as well as, a proactive search to collect data from literature, recall, and vigilance databases. The reactive review is documented in NuMED's monthly and annual Quality Management reviews, and the proactive search is documented in both the annual update of the PSUR document, and the CER when it is updated. All PMS data is reviewed to determine if the risk management file or IFU needs to be updated based on the findings. All device related adverse events are evaluated for determination on vigilance reporting.

PMCF Activity #2

The PMS form is a proactive way for NuMED to gather additional information on their products. It is quick way for the physician to communicate both negative and positive things about the individual devices. PMS forms are reviewed upon receipt to determine if a complaint, corrective action, recalls, FSCA or any other vigilance reporting needs to be initiated. They are also reviewed to determine if any information is provided that would require updates to both the risk management file or IFU. It is also a way to determine if the devices are being used for off-label procedures.

PMCF Activity #3

The Post Market Clinical Follow-up (PMCF) clinical questionnaire form is to proactively gather real world evidence on the Z-6 catheter in clinical practice. This clinical questionnaire form will focus on clinical safety and performance of the device. 90 clinical questionnaire forms will be required, based on confidence intervals, in order to guarantee a 99% confidence level, 95% of the time. The clinical questionnaire forms will be collected for a minimum of one year as well. If the 90 clinical questionnaire forms are received prior to the one year minimum, we will continue to collect them until the one year is complete. If they are not collected in one year, it will continue until a total of 90 are received. The clinician review will be performed once the data from the 90 clinical questionnaire forms are entered into the database.

The objective of the PMCF study is to determine if there is an increase in complications and / or complaints with the Z-6 Catheters, vs. the currently approved Z-5, through actual clinical use, or if any new risks are introduced. All returned PMCF clinical questionnaire forms, sales & complaint data, as well as any applicable literature will be reviewed. These reviews will take place each month during the quality meeting. PMCF clinical questionnaire forms are reviewed upon receipt to determine if a complaint, corrective action, recalls, FSCA or any other vigilance reporting needs to be initiated specifically for the Z-6 device. They are also reviewed to determine if any information is provided that would require updates to both the risk management file or IFU. It is also a way to determine if the devices are being used for off-label procedures.

The study population will include all patients for which a Z-6 Catheter with a Multi-language Label/IFU is supplied. Physicians will be asked to complete a form after each procedure they perform. NuMED has distributors worldwide that will be able to help with the collection of the clinical questionnaire forms. Exclusions include off label use.

Selection of sites / investigators will include any / all orders for which a Z-6 Catheter with a Multi-language Label/IFU is supplied. This clinical questionnaire form will be shipped with each device in the Instructions for Use. It is printed on a high visibility color paper (bright pink) to draw attention to it within the IFU. All returned PMCF forms, sales & complaint data, as well as any applicable literature will be reviewed. These reviews will take place each month during the quality meeting.

Upon completion of PMCF Activity #3, the Z-6 devices will be added to the PMCF Activity #2 – General – with the Z-5 device so that information on the device is still proactively collected through the PMS form.

Rationale for PMCF

The Z-5 device has been on the market for over 30 years, which greatly exceeds its expected device lifetime. NuMED conducted a clinical study under the US IDE (G940143) in 1994, with data from that study reported in the CER. The clinical study included five sites and 15 patients. The catheter was found to be effective and safe in creating an adequate size defect without any mortality or morbidity.

According to MDCG 2020-6 the Z-5 Atrioseptostomy Catheter is considered a WET device. The Z-6 is then considered an equivalent device according to EU MDR Article 61(4) and Annex XIV Part A, Section 3. The Atrioseptostomy Catheters family meets all four criteria of a WET

device as demonstrated in the CER.

Since the Z-6 is considered a WET device, based on the rationale outlined in the CER, a clinical questionnaire form specific to the Z-6 device itself will be able to monitor the safety and effectiveness of the Z-6 device and detect new or emerging risks associated with the slight differences when compared to the Z-5.

The procedure being performed using NuMED's Atrioseptostomy devices is palliative in nature, with most adverse events and complications being reported within the first 24 hours.[3] The procedure itself is not novel and has been performed for over half a century.[4] Additionally, clinical literature reviewed has shown that complications related to balloon atrial septostomy are considered to be very rare.[1,5]

Recalls and removals of similar competitor products from the market have been based on balloon deflation problems. A complete review of PMS data shows that NuMED has not had any complaints for either the Z-5 or Z-6 device for this issue. The balloon on both of these devices is the exact same, so the safey and performance of the balloon is very well established. The Z-6 device has been on the market outside of the EU for over 3 years and has held specific EU country derogations for over a year. There have been over 3,000 devices sold, with no adverse events reported.

6. Possible diagnostic or therapeutic alternatives

Alternatives include the blade atrial septostomy, stenting of the atrial septum, and PGE1 infusion.

The blade atrial septostomy (Park Procedure) technique coupled a blade to catheter tip, in order to create an opening in intact or thick interatrial septum, common in infants older than 30 days of age or in certain CHD where the septum is abnormally thick, such as in mitral atresia (also in HLHS), in spite of the higher risk of mortality.[6] In addition, lacerations can appear and therefore this technique is very rarely used.[7]

Stenting of the atrial septum is a preferred method to obtain an interatrial communication for long-lasting result; however, it needs a good medical judgment because it is associated with many complications, including thrombus formation and possible embolic phenomena, especially in patients with Fontan physiology, stent erosion (especially in long stents), stent migration, and stent stenosis (approximately at three months distance). Long-term antiplatelet and or anticoagulation regimen should be carefully followed in this group of patients.[7]

Most hypoxemic neonates with transposition of the great arteries will benefit solely from early institution of PGE1. PGE1 can cause apnea, hypotension and fever (especially in low birth weight neonates). There may also be a false sense of security in the preoperative neonate on PGE1 who appears to have "adequate" oxygen saturations. While awaiting ASO, neonates remain at risk for mechanical ventilation, infection, medical errors, paradoxical emboli, increased cost and a longer hospital stay. A reassuring peripheral oxygen saturation may be associated with paradoxically low cerebral oxygen delivery. Cerebral venous oxygen saturation is significantly lower than predicted from the arterial or mixed venous oxygen saturation in neonates with a run-off lesion. Mean cerebral oxygen saturations in children with a PDA and normal systemic oxygen saturations range in the low 50s and are likely lower in transposition of the great arteries. Central nervous system injury, specifically to the white matter, has been associated with even a few days delay in ASO, particularly if accompanied by significant hypoxemia. Earlier elimination of hypoxemia may contribute to improved motor outcomes and brain growth in certain subgroups.[8]

7. Suggested profile and training for users

The Atrioseptostomy Catheter is intended for use by qualified cardiologists trained in catheterization.

8. Reference to any harmonised standards and CS applied

There are no Common Specifications for this type of device.

The following harmonised standards are followed for this device:

- EN ISO 10993-10: 2023 – Biological Evaluation of Medical Devices – Part 10: Tests for Skin Sensitization
- EN ISO 10993-18: 2020 / A1:2022 – Biological Evaluation of Medical Devices – Part 18: Chemical Characterization of

[3] Inuzuka R, Tachimori H, Kim SH, Matsui H, Kobayashi T, Kato A, Fujii T, Ho M, Morikawa H, Takahashi S, Shirato H, Haishima Y, Okamoto Y, Sakoda H, Tomita H. Practice and Safety of Static Balloon Atrial Septostomy Based on a Nationwide Registry Data. Circ J. 2022 Nov 25;86(12):1990-1997. doi: 10.1253/circj.CJ-22-0185. Epub 2022 Sep 1. PMID: 36047087.

[4] Cinteza E, Carminati M. Balloon atrial septostomy - almost half a century after. Maedica (Bucur). 2013 Sep;8(3):280-4. PMID: 24371500; PMCID: PMC3869120.

[5] Cirstoveanu C, Georgescu C, Bizubac M, Heriseanu C, Vasile CM, Margarint I, Filip C. Impact of Bedside Balloon Atrial Septostomy in Neonates with Transposition of the Great Arteries in a Neonatal Intensive Care Unit in Romania. *Life*. 2023; 13(4):997. https://doi.org/10.3390/life13040997

Medical Device Materials within a Risk Management Process

- EN ISO 10993-23: 2021 – Biological Evaluation of Medical Devices – Part 23: Tests for Irritation
- EN ISO 11135: 2014 / A1:2019 – Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices.
- EN ISO 11607-1: 2020 / A1:2023 – Packaging for Terminally Sterilized Medical Devices – Part 1: Requirements for materials, sterile barriers systems and packaging systems
- EN ISO 11607-2: 2020 / A1:2023 – Packaging for Terminally Sterilized Medical Devices – Part 2: Validation requirements for forming, sealing and assembly processes
- EN ISO 11737-1: 2018 / A1:2021 – Sterilization of medical devices – Microbiological methods – Part 1: Determination of a population of microorganisms on products
- EN ISO 13485: 2016 / A11:2021 – Medical devices – Quality management systems – Requirements for regulatory purposes
- EN ISO 14971: 2019 / A11:2021 – Medical Devices – Application of Risk Management to Medical Devices

EN ISO 15223-1: 2021 – Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements

9. References

1. Gopalakrishnan A, Sasidharan B, Krishnamoorthy KM, Sivasubramonian S, Dharan BS, Mathew T, Titus T, Valaparambil A, Tharakan J. Left ventricular regression after balloon atrial septostomy in d-transposition of the great arteries. Eur J Cardiothorac Surg. 2016 Dec;50(6):1096-1101.
2. Matter M, Almarsafawy H, Hafez M, Attia G, Abou MM. Balloon atrial septostomy: The oldest cardiac interventional procedure in Mansoura. The Egyptian Heart Journal. 2011 Jun;63(2):125-129.
3. Holzer RJ, Wood A, Chisolm JL, Hill SL, Phillips A, Galantowicz M, Cheatham JP. Atrial septal interventions in patients with hypoplastic left heart syndrome. Catheter Cardiovasc Interv. 2008 Nov 1;72(5):696-704.
4. Akagi T, Tananari Y, Maeno YV, Himeno W, Furui J, Ishii M, Kato H. Torn-off balloon tip of Z-5 atrial septostomy catheter. Catheter Cardiovasc Interv. 2001 Apr;52(4):500-503.
5. Patel HT, Cao QL, Hijazi ZM. Balloon atrial septostomy: the oldest pediatric interventional procedure. J Interven Cardiol. 1998;11:297-302.
6. Lopes LM, Kawano C, Cristóvão SA, Nagamatsu CT, Fonseca Ld, Furlanetto BH, Furlanetto G, Silva JP, Mangione JA. Balloon atrial septostomy guided by echocardiography in a neonatal intensive care unit. Arq Bras Cardiol. 2010 Aug;95(2):153-158.
7. Cinteza E, Carminati M. Balloon atrial septostomy - almost half a century after. Maedica (Buchar). 2013 Sep;8(3):280-284.
8. Villafañe J, Lantin-Hermoso MR, Bhatt AB, Tweddell JS, Geva T, Nathan M, Elliott MJ, Vetter VL, Paridon SM, Kochilas L, Jenkins KJ, Beekman RH 3rd, Wernovsky G, Towbin JA; American College of Cardiology's Adult Congenital and Pediatric Cardiology Council. D-transposition of the great arteries: the current era of the arterial switch operation. J Am Coll Cardiol. 2014 Aug 5;64(5):498-511.
9. Feltes TF, Bacha E, Beekman RH 3rd, Cheatham JP, Feinstein JA, Gomes AS, Hijazi ZM, Ing FF, de Moor M, Morrow WR, Mullins CE, Taubert KA, Zahn EM; on behalf of the American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, and Council on Cardiovascular Radiology and Intervention. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2607–2652.

10. Revision History

SSCP revision number	Date Issued	Change Description	Revision validated by Notified Body
00	21 June 2022	Initial implementation	☐ Yes Validation Language: English ☒ No
01	18 October 2023	Revision for EU MDR TF review	☐ Yes Validation Language: English ☒ No
02	12 August 2024	Revision for update to PMCF study and harmonised standards listing. Added 2024 date for Z-6 in Section 1	☐ Yes Validation Language: English ☒ No
03	01 August 2025	Revised Section 1 for EU Authorized Rep information.	☒ Yes Validation Language: English ☐ No