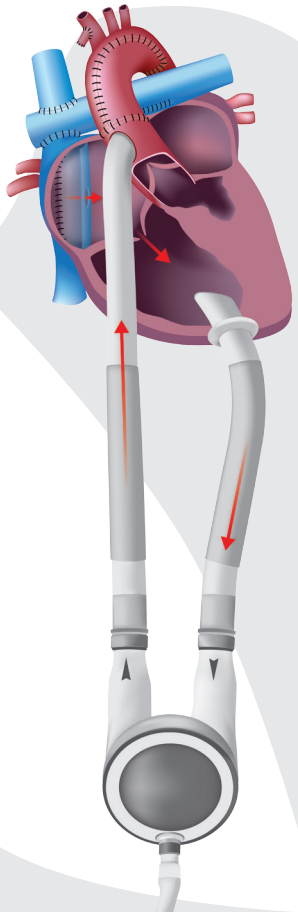
Berlin Heart®

EXCOR® Pediatric Experience in Single Ventricle Patients



Worldwide & US Experience

Introduction

While complex congenital heart disease is recognized as a significant risk factor affecting survival during VAD support, improved survival in pediatric patients with EXCOR® Pediatric has expanded its use to complex single ventricle physiologies including hypoplastic left heart syndrome (HLHS), double outlet right ventricle (DORV), unbalanced atrial ventricular (AV) canal or tricuspid atresia as well as other serious congenital heart defects.

Improvement in survival to transplantation has been achieved in recent years in this challenging group of single ventricle physiology patients. Major factors contributing to an improved survival are patient selection, surgical technique, and anti-coagulation management[1].

1 VanderPluym et al., The use of ventricular assist devices in pediatric patients with univentricular hearts, J Thorac Cardiovasc Surg. 2011 Feb;141(2):588-90

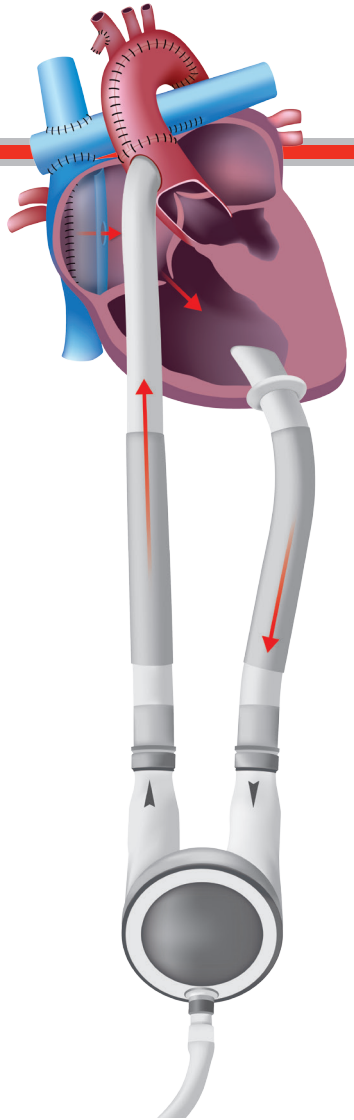


FIGURE 1 Patient with HLHS supported with EXCOR® Pediatric after previous lateral tunnel Fontan operation
HLHS is characterized by a diminutive left ventricle, which is unable to support systemic circulation. Lateral tunnel Fontan operation involves the attachment of the superior vena to right pulmonary artery, while the inferior vena cava is connected to the superior vena cava by a baffle (tunnel) inside the right atrium.
EXCOR® Pediatric implantation:
The apical inflow cannula is anastomosed to the anatomical right ventricle (functional left ventricle) and the arterial outflow cannula is anastomosed to the neo-aorta.

Worldwide Experience

- **Study type:**
  Retrospective, multicenter data analysis
- **Study objective:**
  To compare the 1-year survival of patients with single ventricle physiology (n=76) implanted with the EXCOR® Pediatric VAD to patients with a two-ventricle physiology (n=1,071) implanted with the EXCOR® Pediatric VAD during the same time period.
- **Patient population:**
  All patients implanted with the EXCOR® Pediatric VAD between April 2004 and March 2013*
- **Single ventricle physiology:**
  Includes a variety of cardiac defects in which there is only one functioning ventricle. Sometimes the ventricle is a single left ventricle, sometimes it is a single right ventricle, and sometimes it is difficult to tell. The lesions, which are grouped together because they are often treated the same, include hypoplastic left heart syndrome (HLHS), hypoplastic right heart syndrome (HRHS), double outlet left ventricle (DOLV), double outlet right ventricle (DORV), unbalanced AV-canal, tricuspid atresia, mitral atresia with ventricular septal defect (VSD), double inlet left ventricle (DILV), double inlet right ventricle (DIRV)

* Patients with unknown outcome have been excluded

Patient characteristics

Characteristics	Single ventricle physiology (n=76)	Two-ventricle physiology (n=1,071)
Age, Median (range)	28 months (12 days - 14 years)	43 months (2 days - 18 years)
Weight, Median (range)	11.9 kg (2.8 - 71.0 kg)	12.0 kg (2.6 - 112.0 kg)
Height, Median (range)	87 cm (48 - 160 cm)	90 cm (42 - 193 cm)
BSA, Median (range)	0.54 m^2 (0.20 - 1.78 m^2)	0.55 m^2 (0.19 - 2.4 m^2)

Primary and detailed diagnosis

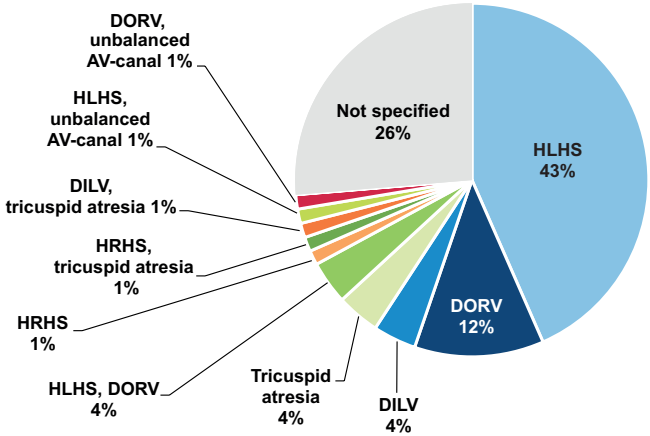


FIGURE 2 Detailed diagnosis in single ventricle physiology group (n=76)

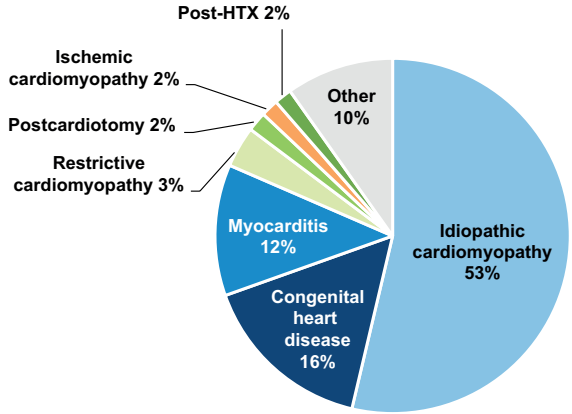


FIGURE 3 Primary diagnosis in two-ventricle physiology group (n=1,071)

Surgical procedure prior implantation

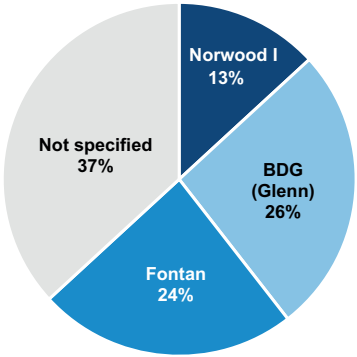


FIGURE 4 Surgical procedure prior to implantation in single ventricle physiology patients (n=76)

Type of VAD support

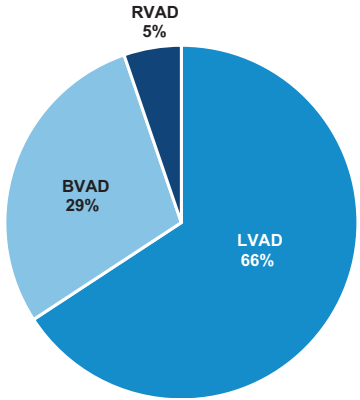


FIGURE 5 Type of VAD support in single ventricle physiology patients (n=76)

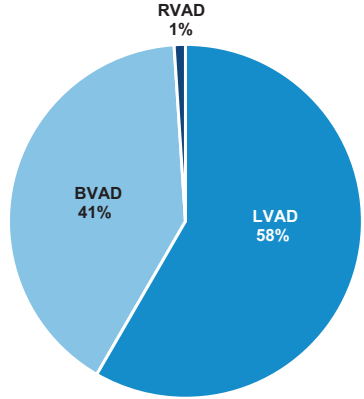


FIGURE 6 Type of VAD support in two-ventricle physiology patients (n=1,071)

Results

Competing outcome and overall survival

In single ventricle physiology patients, the median duration of VAD support was 28 days, as compared with 44 days for two-ventricle physiology patients. The longest duration of support in single ventricle physiology patients and two-ventricle physiology patients was 363 days and 1,191 days, respectively.

Many single ventricle patients in terminal heart failure are poor transplantation candidates due to multiple organ dysfunction.

Circulatory support with the EXCOR® Pediatric VAD may reverse end organ dysfunction, making these critically ill children better candidates for cardiac transplantation.

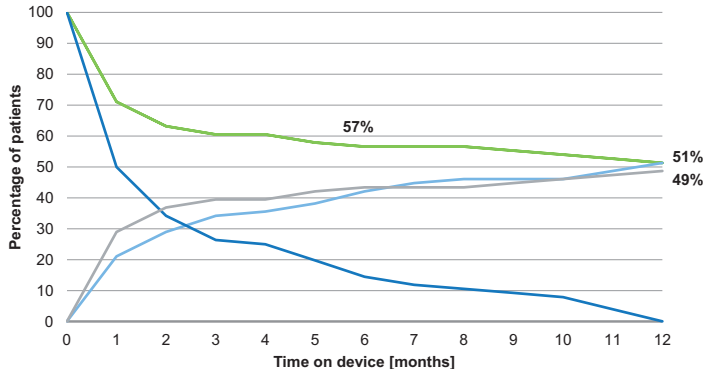


FIGURE 7 Competing outcome with 1-year survival of single ventricle physiology patients (n=76)
At 1 year, 51% of the patients had been transplanted and 49% had died during VAD support. 6-months and 1-year survival was 57% and 51%, respectively.

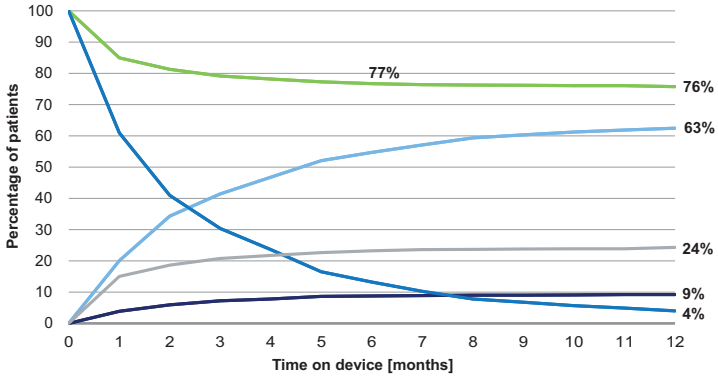


FIGURE 8 Competing outcome with 1-year survival of two-ventricle physiology patients (n=1,072)
In the two-ventricle physiology group, 63% of the patients had been transplanted, 9% had been weaned and 4% were still on support at 1 year. 24% of the patients had died during VAD support. 6-months and 1-year survival was 77% and 76%, respectively.

A 1-year survival of 51% has been observed in the high risk single ventricle patient population, whereas the 1-year survival for the two-ventricle physiology group was 76%.

US Experience

- **Study type:**
  Prospective, multicenter data analysis
- **Study objective:**
  To compare the survival of patients with single ventricle physiology (n=26) implanted with the EXCOR® Pediatric VAD to those patients with two-ventricle circulation (n=255) implanted during the same time period in the US.
- **Patient population:**
  All patients implanted with the EXCOR® Pediatric VAD between May 2007 and December 2011 in the US
- **Single ventricle physiology:**
  Includes a variety of cardiac defects in which there is only one functioning ventricle. Sometimes the ventricle is a single left ventricle, sometimes it is a single right ventricle, and sometimes it is difficult to tell. The lesions, which are grouped together because they are often treated the same, include hypoplastic left heart syndrome (HLHS), hypoplastic right heart syndrome (HRHS), double outlet left ventricle (DOLV), double outlet right ventricle (DORV), unbalanced AV-canal, tricuspid atresia, mitral atresia with ventricular septal defect (VSD), double inlet left ventricle (DILV), double inlet right ventricle (DIRV)

Patient characteristics

Characteristics	Single ventricle physiology (n=26)	Two-ventricle physiology (n=255)
Age, Median (range)	18.8 months (0.2 - 173.2 months)	20.6 months (0.4 - 239.3 months)
Weight, Median (range)	10.2 kg (2.8 - 71.0 kg)	10.8 kg (2.9 - 60.0 kg)
BSA, Median (range)	0.47 m^2 (0.19 - 1.75 m^2)	0.50 m^2 (0.19 - 1.67 m^2)
ECMO prior EXCOR®	46%	46%
Time on ECMO prior EXCOR®, Median (range)	6 days (2 - 12 days)	6 days (0 - 38 days)

Detailed diagnosis

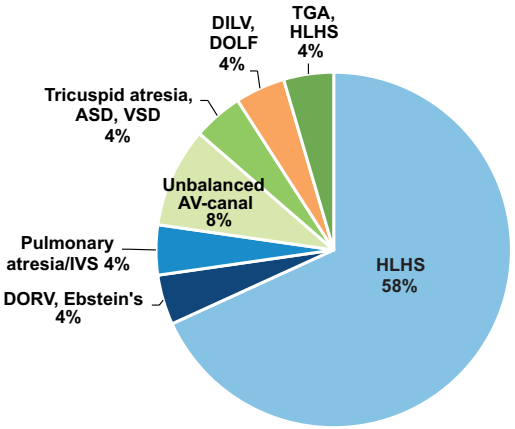


FIGURE 9 Detailed diagnosis in single ventricle physiology group (n=26)

Surgical procedure prior implantation

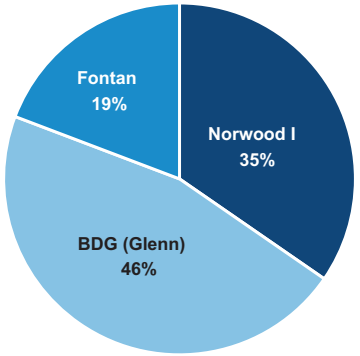


FIGURE 10 Surgical procedure prior to implantation in single ventricle physiology patients (n=26)

Type of EXCOR® support

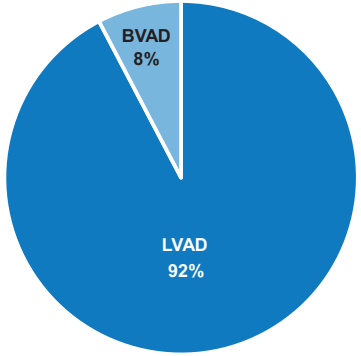


FIGURE 11 Type of EXCOR® support in single ventricle physiology patients (n=26)

Results

Competing outcome and overall survival

The longest duration of VAD support in single ventricle physiology patients and two-ventricle physiology patients was 363 days and 435 days, respectively.

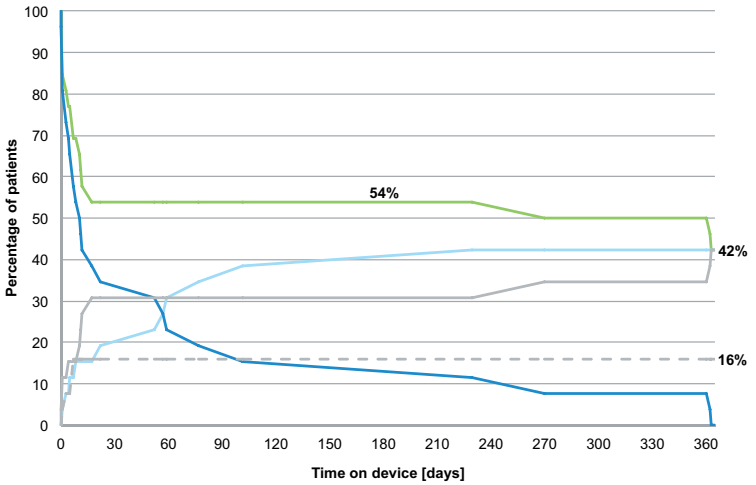


FIGURE 12 Competing outcome with 1-year survival of single ventricle physiology patients (n=26)
At 1 year, 42% of the patients were transplanted, 42% had died during support and 16% died within 30 days post-explantation or were considered a failed weaning. 6-months and 1-year survival was 54% and 42%, respectively.

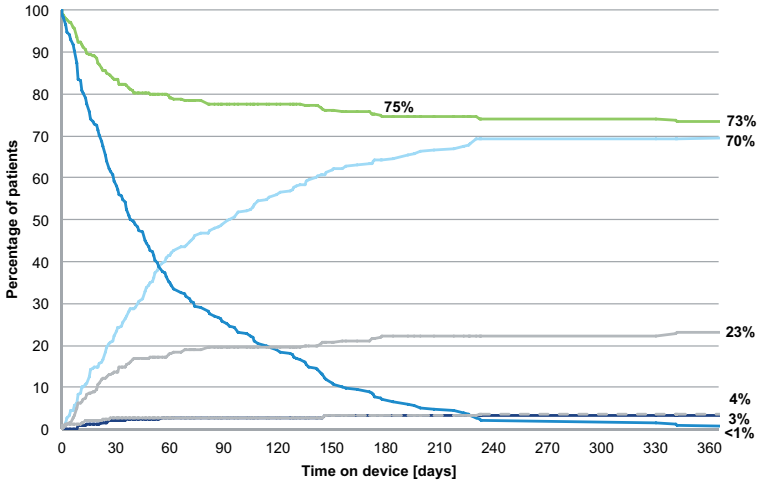


FIGURE 13 Competing outcome with 1-year survival of two ventricle physiology patients (n=225)
At 1 year, 70% of the patients were transplanted, 3% were successfully weaned and less than 1% were still on support. 23% of the two ventricle patients died during support and 4% died within 30 days post-explantation or were considered a failed weaning. 6-months and 1-year survival was 75% and 73%, respectively.

Patients with single ventricle physiology can be supported with the EXCOR® Pediatric VAD as a bridge to cardiac transplantation, though the results suggest that success will not be as high as in patients with a two-ventricle physiology (1-year survival 42% vs. 73%).

EXCOR® Pediatric VAD can allow for long term support up to one year in single ventricle patients.

Serious adverse events during VAD support

The frequency of serious adverse events was not significantly higher in patients with single ventricle physiology compared to two-ventricle physiology patients.

Serious adverse event*	Single ventricle physiology patients (n=26) % Patients with event (rate per 100 patient days)	Two-ventricle physiology patients (n=255) % Patients with event (rate per 100 patient days)
Major bleeding	39% (0.85)	44% (1.15)
Hypertension event	12% (0.24)	27% (0.43)
Major infection event	23% (1.28)	34% (1.42)
Neurological dysfunction	15% (0.24)	17.3% (0.29)
Arterial non-CNS thromboembolism	0% (0.00)	3% (0.04)
Venous thromboembolism	0% (0.00)	2% (0.03)
Acute renal dysfunction event	12% (0.18)	10% (0.17)
Chronic renal dysfunction event	0% (0.00)	1% (0.01)
Respiratory failure	42% (0.92)	27% (0.53)

* SAEs not completely adjudicated

Pump change due to thrombus formation occurred in 27% of the single ventricle physiology patients (1.28 events per 100 patient days) and 40% of the two-ventricle physiology patients (1.15 events per 100 patient days).

Survival in different palliative stages prior EXCOR® Pediatric implantation

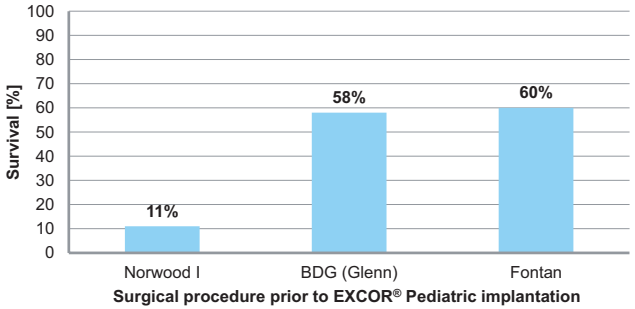


FIGURE 14 Survival in different palliative stages prior EXCOR® Pediatric implantation
Survival in Norwood I stage patients (n=9) was 11%, in BDG (Glenn) stage patients (n=12) was 58% and in Fontan stage patients (n=5) was 60%. Median time and range of time on support in Norwood I, BDG (Glenn) and Fontan stage patients was 4 days (1-57 days), 52 days (1-270 days) and 229 days (1-363 days), respectively.

Though the experience to this point is limited, success following BDG (Glenn) or Fontan procedures can be similar to the overall cohort of pediatric patients receiving an EXCOR® Pediatric VAD.

Case Studies – The Use of EXCOR® Pediatric in Patients with Single

Limited cases of single ventricle physiology supported with the EXCOR® Pediatric VAD have been reported.

Selected case studies at a glance

Publication	Age	Weight	Anatomy	Surgical procedure
Nathan et al., 2006[1]	4 years	12 kg	HLHS	Fontan
Chu et al., 2006[2]	4 years	14.6 kg	HLHS	Bidirectional cavopulmonary anastomoses (BCPA)
Calvaruso et al., 2007[3]	10 years	32 kg	Single RV, Mitral atresia, Pulmonary artery	Fontan (extracardiac total cavopulmonary)
Pearce et al., 2009[4]	1.3 years	n.s.	Double-outlet RV, Mitral atresia, transposition of the great arteries	Systemic-to-pulmonary shunt
Irving et al., 2009[5]	2.9 years	13 kg	Hypoplastic left heart syndrome	Bidirectional cavopulmonary anastomoses
Humpl et al., 2010[6]	10 years	n.s.	Post bidirectional Glenn shunt, no candidate for Fontan OP	n.s.
VanderPluym et al., 2011[7]	3 years	11.5 kg	Hypoplastic left heart syndrome, Mitral atresia	Fontan, bidirectional cavo-pulmonary anastomoses
Mackling et al., 2012[8]	4 years	n.s.	DORV, aortic artresia	Fontan, ECMO prior EXCOR®
	4 years	n.s.	HLHS	Glenn

Ventricle Physiology

	Duration of support	Complication	Outcome
	28 days	None	Transplanted
	13 days	Bowel necrosis, mesenteric, hepatic and renal insufficiency, thrombi	Died due to MOF
	7 days	None	Transplanted
	49 days	None	Transplanted
	7 days	None	Transplanted
	40 days	Required renal replacement therapy due to renal failure	Transplanted
	174 days	Re-thoracotomy due to bleeding, 3 pump exchanges due to fibrin clots	Transplanted
	363 days	Renal insufficiency, exit site infection, sepsis	Died due to MOF
	270 days	Renal insufficiency, pulmonary edema	Support withdrawn

1 Nathan et al., Successful implantation of a Berlin Heart biventricular assist device in a failing single ventricle, J Thorac Cardiovasc Surg, 2006;131:1407-8
2 Chu et al., Berlin Heart ventricular assist device in a child with hypoplastic left heart syndrome, Ann Thorac Surg, 2007;83:1179-81
3 Calvaruso et al., Implantation of a Berlin Heart as single ventricle by-pass on Fontan circulation in univentricular heart failure, ASAIO J. 2007 Nov-Dec;53(6):e1-2
4 Pearce et al., Successful cardiac transplant after Berlin Heart bridge in a single ventricle heart: use of aortopulmonary shunt as a supplementary source of pulmonary blood flow, J Thorac Cardiovasc Surg. 2009 Jan;137(1):e40-2
5 Irving et al., Successful bridge to transplant with the Berlin Heart after cavopulmonary stunt, Ann Thorac Surg. 2009 Mar;87(3):943-6
6 Humpl et al., The Berlin Heart EXCOR® Pediatrics - The SickKids Experience 2004-2008, Artif Organs. 2010 Dec;34(12):1082-6
7 VanderPluym et al., The use of ventricular assist devices in pediatric patients with univentricular hearts, J Thorac Cardiovasc Surg. 2011 Feb;141(2):588-90
8 Mackling et al., Management of single-ventricle patients with Berlin Heart EXCOR® Ventricular Assist Device: single-center experience, Artif Organs. 2012 Jun;36(6):555-9

Berlin Heart®

Patients with single ventricle physiology can be successfully supported with EXCOR® Pediatric as a bridge to transplantation or recovery, though the results suggest that success will not be as high as for patients with two ventricles.

To discuss the outcomes in this very complex group of patients in further detail, or to discuss a specific patient or the outcomes in a specific group of patients, please contact our Clinical Affairs Team seven days per week, 24 hours per day:

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We will be more than happy to assist you with your clinical and technical questions.

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The Berlin Heart EXCOR® Pediatric Ventricular Assist Device (EXCOR® Pediatric) is approved for use by the FDA under a Humanitarian Device Exemption.

Version MFE31.0
September 2013