PRODUCT PERFORMANCE REPORT

SUMMARY OF DATA FROM THE MEDTRONIC POST-MARKET REGISTRY

2022

v.1.0 20Mar2023

Medtronic
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Contents

3 Targeted Drug Delivery Systems

3.1 Study Participants

3.1.1 Centers

The targeted drug delivery tables and graphs were generated based on data collected between August 7, 2003 and the report cut-off date of October 31, 2022. Seventy-six centers spanning 13 countries/territories in North America, Europe and South America, enrolled patients and contributed patient data to the targeted drug delivery systems section of this report. Figure 3.1 shows a World Map, in which the countries that enrolled TDD patients are highlighted.

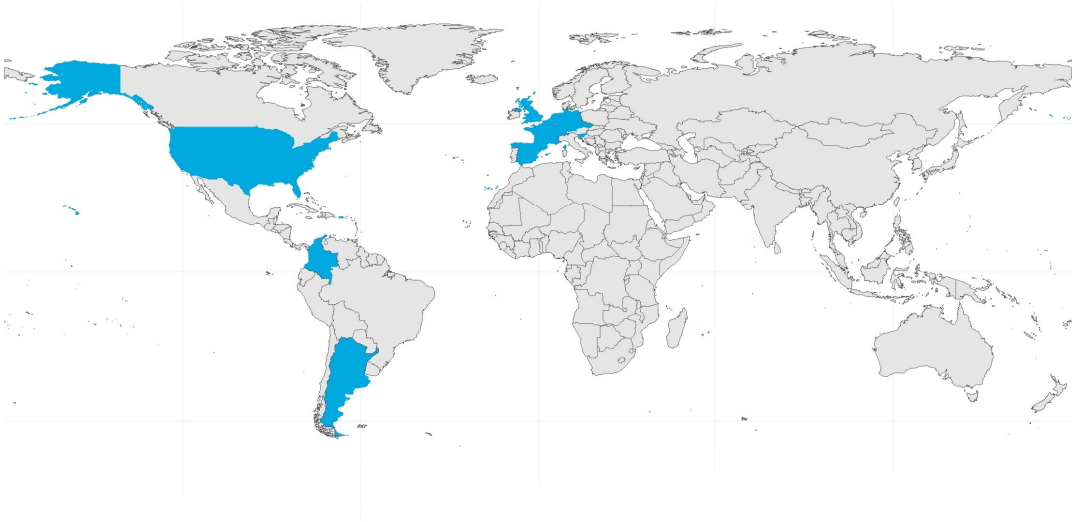


Figure 3.1: Countries with Targeted Drug Delivery Therapy Patients in Registry (Highlighted)

3.1.2 Patients

There were 10,053 total targeted drug delivery system patients enrolled through October 31, 2022. In Table 3.1 and Figure 3.2, 58.8% of patients were implanted with a targeted drug delivery system for treatment of non-malignant pain (pain not related to cancer and its treatment), followed by 21.7% for treatment of spasticity, and 17.3% for treatment of malignant pain (pain

related to cancer). Primary treatment indication is provided by the physician. The sites of pain for the malignant pain patients are presented in Table 3.2, while the sub-indications for the non-malignant pain and the spasticity patients are presented in Table 3.3 and Table 3.4, respectively.

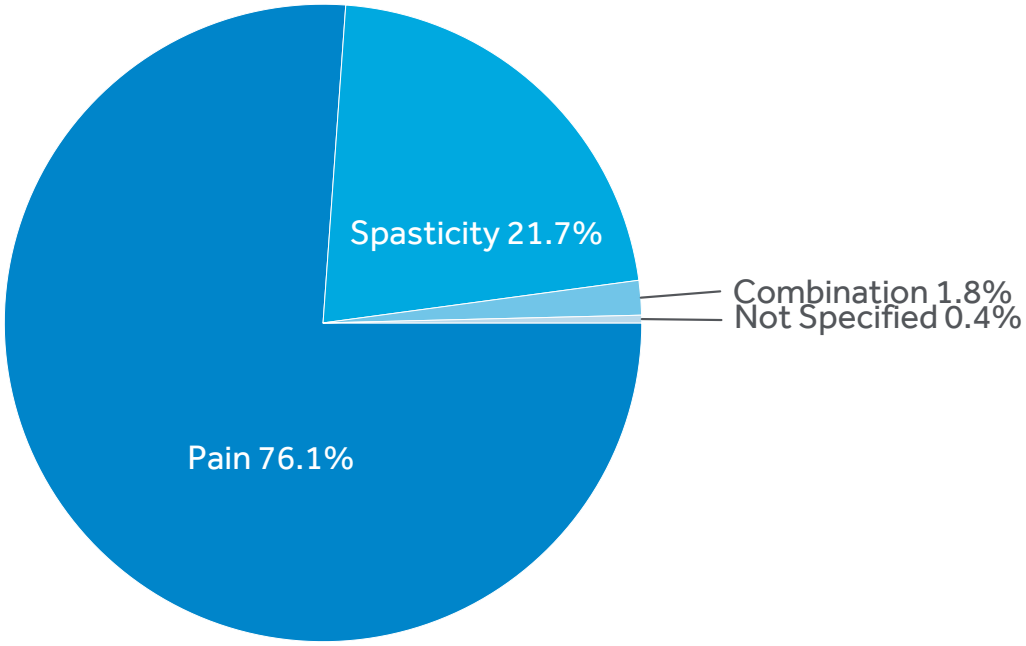


Figure 3.2: Targeted Drug Delivery Primary Treatment Indications

Table 3.1: Targeted Drug Delivery Primary Treatment Indications

Primary Treatment Indication[a]	Enrolled Patients (%)
Pain	**7,654 (76.14%)**
Non-malignant pain	5,911 (58.80%)
Malignant pain	1,742 (17.33%)
Pain, Not specified	1 (0.01%)
Spasticity	**2,184 (21.72%)**
Combination	**176 (1.75%)**
Non-malignant pain & Spasticity	173 (1.72%)
Malignant pain & Chemotherapy	1 (0.01%)
Malignant pain & Spasticity	1 (0.01%)
Non-malignant pain & Chemotherapy	1 (0.01%)
Not Specified[b]	**39 (0.39%)**
Total Patients	**10,053 (100%)**

[a] For approved indications refer to product labeling for your geography.

[b] Includes incomplete data forms at the time of the data snapshot and exited patients where indication was never provided.

Table 3.2: Targeted Drug Delivery Malignant Pain: Site of Pain

Malignant Pain: Site of Pain	N Site (%)
Spine/Back	692 (39.7%)
Abdominal/Visceral	417 (23.9%)
Extremity	312 (17.9%)
Pelvic	240 (13.8%)
Thoracic	193 (11.1%)
Head/Neck	117 (6.7%)
Other	186 (10.7%)
Not Specified	439 (25.2%)
Total Sites of Pain[a]	**2,596**

[a] In 1,744 patients with indications of malignant pain, malignant pain & chemotherapy, and malignant pain & spasticity. Total number of patients is not equal to number of reported sites of pain as patients may have multiple sites of pain.

Table 3.3: Targeted Drug Delivery Non-Malignant Pain: Sub-Indications

Non-Malignant Pain: Sub-Indications	Enrolled Patients (%)
Back Pain with Leg Pain	2,097 (34.5%)
Back Pain without Leg Pain	1,645 (27.0%)
General Neuropathic Condition	246 (4.0%)
CRPS I[a]	193 (3.2%)
Peripheral Neuropathy	83 (1.4%)
Joint Pain/Arthritis	74 (1.2%)
General Nociceptive Condition	57 (0.9%)
CRPS II[a]	37 (0.6%)
Osteoporosis	20 (0.3%)
Other	678 (11.1%)
Not Specified	955 (15.7%)
Total Patients[b]	**6,085**

[a] CRPS is complex regional pain syndrome.

[b] Includes patients with indications of non-malignant pain, non-malignant pain & spasticity, and non-malignant pain & chemotherapy.

Table 3.4: Targeted Drug Delivery Spasticity: Sub-Indications

Spasticity: Sub-Indications	Pediatrics (%) (<18 years)	Adults (%) (>= 18 years)	All Patients (%)
Cerebral Palsy	375 (77.0%)	267 (14.3%)	642 (27.2%)
Multiple Sclerosis	0 (0.0%)	566 (30.3%)	566 (24.0%)
Spinal Cord Injury	9 (1.8%)	370 (19.8%)	379 (16.1%)
Brain Injury	38 (7.8%)	128 (6.8%)	166 (7.0%)
Stroke	1 (0.2%)	97 (5.2%)	98 (4.2%)
Other	20 (4.1%)	213 (11.4%)	233 (9.9%)
Not Specified	44 (9.0%)	230 (12.3%)	274 (11.6%)
Total Patients[a]	**487**	**1,871**	**2,358**

[a] Includes patients with indications of spasticity, non-malignant pain & spasticity, and malignant pain & spasticity.

It is recognized that health care providers prescribe therapies to meet specific patient needs; however, Medtronic only directs the use of its products based on approved labeling. Product labeling varies by geography. Contact a local Medtronic representative for region-specific product labeling.

3.2 Event Summary

Events are reported via database by physicians trained in the PSR. Events are reviewed internally and coded as either a product performance event (e.g. catheter kink, motor stall) or a non-product performance event (e.g. adverse drug reaction, increased muscle tone, and incision site swelling).There were 2,506 product performance events reported between August 7, 2003 and October 31, 2022, in patients with targeted drug delivery systems. These events represent 16.4% of the total reported events (2,506/15,320), which occurred in 1,618 (16.1%) of the 10,053 total patients enrolled, and are presented graphically within this report (e.g. events per patient years as well as survival curves). As an ongoing registry, events not coded at the time of the data snapshot (waiting for further information) will be included in future reports (n=759).

All registry devices that are returned to Medtronic are analyzed via a Returned Product Analysis (RPA) process. If available, RPA findings assist in the classification of the events. Within this report, Table 3.5 and the event tables in the pump and catheter sections differentiate the events by those determined by the RPA process versus those determined by the physician. Please refer to the Methodology section for more information.

There were 2,676 deaths reported for patients with targeted drug delivery systems (see Table 3.12). None of these deaths were reported as a direct result of a product performance event. Early versions of the protocol required events to be reported only when the event required a surgical intervention, resulted in therapy abandonment, or resulted in death. The required event reporting definition was expanded in April 2010 to include all adverse events related to the device, implant procedure, and/or therapy. Table 3.5 includes combined data from these versions of the protocol.

3.2.1 Product Performance Events

Table 3.5: Targeted Drug Delivery System Product Performance Events

Product Performance Events[a]	Event Counts	Events Per 100 Patient Years	Patients with Events (%) N=10,053[b]
RPA Determination	**347**	**0.96**	**317 (3.15%)**
Pump Motor Stall[c]	195	0.54	188 (1.87%)
Laboratory Overinfusion Finding[d]	40	0.11	39 (0.39%)
Corrosion And/Or Gear Wear	28	0.08	28 (0.28%)
Battery High Resistance	11	0.03	11 (0.11%)
Confirmed Overinfusion[e]	11	0.03	5 (0.05%)
Reduced Battery Performance	10	0.03	10 (0.10%)
Reservoir Access Issues Due To Residue	9	0.02	8 (0.08%)
Deformed Pump Tube	8	0.02	7 (0.07%)
Motor Feedthrough Anomaly	8	0.02	8 (0.08%)
No Anomaly Found By RPA	5	0.01	5 (0.05%)
Alarm And/Or Resonator Anomaly	2	0.01	2 (0.02%)
Concave Pump Shield	2	0.01	2 (0.02%)

...continued

Product Performance Events[a]	Event Counts	Events Per 100 Patient Years	Patients with Events (%) N=10,053[b]
Hole In Pump Tube	2	0.01	1 (0.01%)
Other[f]	16	0.04	16 (0.16%)
Physician's Determination	**2,159**	**5.95**	**1,443 (14.35%)**
Catheter Occlusion	488	1.35	434 (4.32%)
Catheter Dislodgement	423	1.17	340 (3.38%)
Catheter Break/Cut	255	0.70	227 (2.26%)
Catheter Kink	244	0.67	216 (2.15%)
Device Malfunction[g]	127	0.35	109 (1.08%)
Pump Motor Stall[h]	101	0.28	83 (0.83%)
Catheter Leakage	84	0.23	77 (0.77%)
Catheter Disconnection At Pump	52	0.14	51 (0.51%)
Catheter Dysfunction	48	0.13	43 (0.43%)
Pump Reservoir Volume Discrepancy	46	0.13	35 (0.35%)
Pump Unable To Enter/Withdraw From Catheter Access Port	46	0.13	40 (0.40%)
Device Difficult To Use	27	0.07	26 (0.26%)
Pump Underinfusion	23	0.06	19 (0.19%)
Device Component Migration	22	0.06	22 (0.22%)
Catheter Related Complication	21	0.06	20 (0.20%)
Catheter Damage	19	0.05	18 (0.18%)
Pump Connector Break/Cut	19	0.05	18 (0.18%)
Device Issue[i]	15	0.04	15 (0.15%)
Catheter Disconnection Between Catheter Segments	11	0.03	10 (0.10%)
Device Connection Issue	8	0.02	8 (0.08%)
Device Damage	8	0.02	7 (0.07%)
Catheter Access Port Issue	6	0.02	6 (0.06%)
Device Breakage	6	0.02	6 (0.06%)
Device Charging Issue	4	0.01	4 (0.04%)
Device Displays Incorrect Message	4	0.01	4 (0.04%)
Medical Device Complication[j]	4	0.01	4 (0.04%)
Medical Device Site Infection	4	0.01	4 (0.04%)
Device Reset Issue	3	0.01	3 (0.03%)
Pump Not Infusing	3	0.01	3 (0.03%)
Catheter Disconnection Issue	2	0.01	2 (0.02%)
Device Infusion Issue	2	0.01	2 (0.02%)
Device Kink	2	0.01	2 (0.02%)
Device Material Corroded	2	0.01	1 (0.01%)
Physician Reported Overinfusion[k]	2	0.01	2 (0.02%)
Pump Inversion	2	0.01	2 (0.02%)

...continued

Product Performance Events[a]	Event Counts	Events Per 100 Patient Years	Patients with Events (%) N=10,053[b]
Other[f]	26	0.07	24 (0.24%)
Total	**2,506**	**6.91**	**1,618 (16.09%)**

[a] Medical Dictionary for Regulatory Activities (MedDRA) Lower-Level Term or Medtronic's coding system term for events that do not exist in the MedDRA dictionary.

[b] The total number of patients with events may not represent the sum of all rows, as a patient may have experienced more than one type of event.

[c] Of the 195 RPA-determined motor stalls, 194 had a pump etiology and 1 had other etiology. Motor stall count does not include temporary motor stalls that may be expected (e.g. due to MRI) and recovered within a 24-hour period. The SynchroMed II pump temporarily stops the rotor of the pump motor and suspend drug infusion for the duration of the MRI exposure for patient safety.

[d] Includes pumps that had a laboratory finding but the patient did not have clinical signs or symptoms consistent with pump overinfusion.

[e] Patient had clinical signs and symptoms consistent with pump overinfusion, pump returned and positive laboratory test.

[f] Composed of event codes with 1 event each.

[g] The majority of these events were attributed to the PTM.

[h] Of the 101 physician-determined motor stalls, 90 had a pump etiology and 11 had a MRI etiology. Of the 11 MRI etiology, 2 pumps were replaced, 3 were reprogrammed, and 6 had no action taken. Motor stall count does not include temporary motor stalls that may be expected (e.g. due to MRI) and recovered within a 24-hour period. The SynchroMed II pump is designed to temporarily stop the rotor of the pump motor and suspend drug infusion for the duration of the MRI exposure for patient safety.

[i] Of the 15 device issues, 12 have an etiology of catheter or other component. The 15 device issues include 8 unable to aspirate catheter, 4 PTM Error Codes, 2 pump alarms, and 1 pump in safe state.

[j] Includes 3 PTM Error Codes, 1 unable to activate PTM, and 1 de-coupled PTM.

[k] Patient had clinical signs and symptoms, but pump not returned and analyzed.

A total of 1,740 (69.4%) of the 2,506 product performance events were related to the catheter only. There were 533 (21.3%) events related to the pump only. There were 167 (6.7%) related to other component (e.g. PTM malfunction) and 66 (2.6%) related to other etiologies (e.g. bend in catheter anchor).Relatedness is reported by the physician.

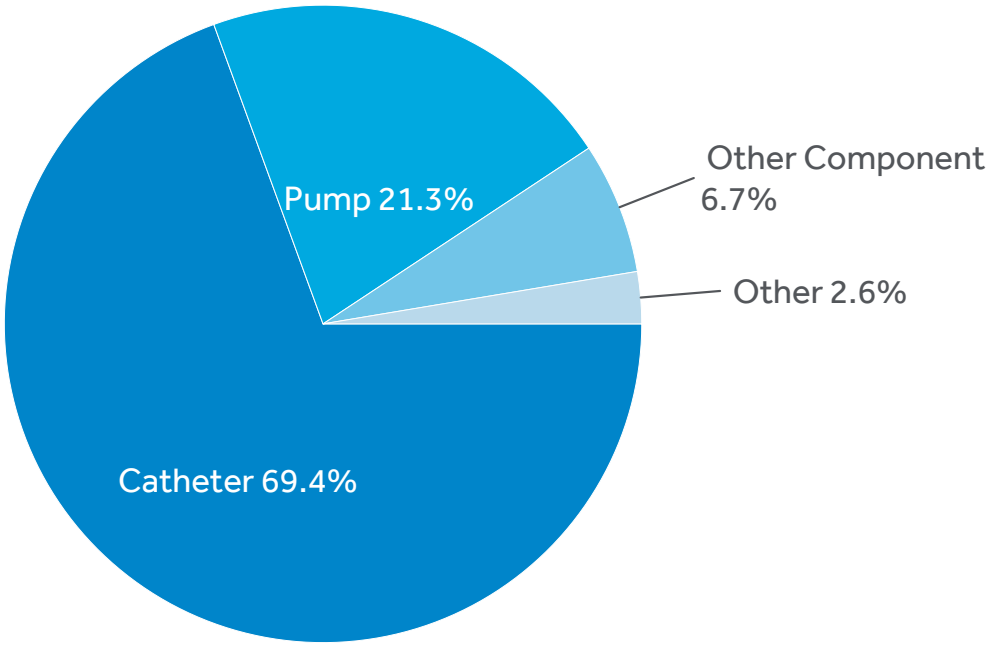


Figure 3.3: Targeted Drug Delivery System Product Performance Events by Relatedness

Table 3.6 describes the interventions completed for product performance events that required action from the health care provider and thereby, may have resulted in an incremental impact to the patient. Survival estimates presented in previous product performance reports included events where no action was taken. To present survival estimates that may better correlate with patient impact, events where no action was taken have been removed from the device survival estimates presented in this 2022 report. The far-left column lists the top five reported PPEs, and all other reported PPEs are listed under Other. The subsequent columns represent the actions taken by the reporting physician.

Table 3.6: TDD Product Performance Events by Intervention

Events by Intervention	Surgical Intervention	Reprogramming	Medical or Non-Surgical Intervention [a]	Therapy Suspension	No Action Taken	Total Events
Catheter Occlusion	445 (91.2%)	12 (2.5%)	16 (3.3%)	6 (1.2%)	9 (1.8%)	**488**
Catheter Dislodgement	372 (87.9%)	9 (2.1%)	8 (1.9%)	2 (0.5%)	32 (7.6%)	**423**
Catheter Break/Cut	242 (94.9%)	1 (0.4%)	5 (2.0%)	1 (0.4%)	6 (2.4%)	**255**
Pump Motor Stall	169 (69.0%)	15 (6.1%)	5 (2.0%)	9 (3.7%)	47 (19.2%)	**245**
Catheter Kink	226 (92.6%)	2 (0.8%)	11 (4.5%)	1 (0.4%)	4 (1.6%)	**244**
Other [b]	486 (63.3%)	32 (4.2%)	149 (19.4%)	5 (0.7%)	96 (12.5%)	**768**
Total	**1,940**	**71**	**194**	**24**	**194**	**2,423**

[a] Medical or Non-Surgical Therapy contains but is not limited to the following actions: medication adjustment based on disease symptoms, imaging (e.g. MRI or X-ray), other specialist referral.

[b] Other represents all reported PPEs that were not in the top five of occurrence.

3.2.2 Clinical Events Not Related To Product Performance

The clinical events not related to product performance are summarized if:

- The patient was enrolled in the PSR at the time in which the clinical event collection was initiated (n=3,477)
- Categorized as serious adverse events (SAEs, n=399)
- Occurred with a System Organ Class (SOC) threshold $\geq$1% of patients
- Other Considerations
  - Some events are described in high level group terms (HLGT) to provide more specificity, if needed
  - Some therapies will provide therapy relevant events (e.g., Inflammatory Mass, Cerebrospinal Fluid Leaks)

Table 3.7: Targeted Drug Delivery Clinical Events Not Related To Product Performance

Event Type	Number of SAE	Patients with SAE n (%) N=3,477	SAE Per 100 Patient Months	Patients with SAE Requiring Surgical Intervention n (%) N=3,477
General disorders and administration site conditions	**164**	**148 (4.26%)**	**0.17**	**34 (0.98%)**
Therapeutic and nontherapeutic effects (excl toxicity)	110	99 (2.85%)	0.11	8 (0.23%)
Complications associated with device	33	32 (0.92%)	0.03	19 (0.55%)
General system disorders NEC [a]	11	11 (0.32%)	0.01	1 (0.03%)
Administration site reactions	5	5 (0.14%)	0.01	4 (0.12%)
Other[b]	5	5 (0.14%)	0.01	4 (0.12%)
Infections and infestations	**92**	**86 (2.47%)**	**0.10**	**70 (2.01%)**
Infections - pathogen unspecified	76	72 (2.07%)	0.08	63 (1.81%)
Bacterial infectious disorders	15	15 (0.43%)	0.02	8 (0.23%)
Other[b]	1	1 (0.03%)	0.00	0 (0.00%)
Injury, poisoning and procedural complications	**60**	**56 (1.61%)**	**0.06**	**11 (0.32%)**
Procedural related injuries and complications NEC [a]	28	27 (0.78%)	0.03	9 (0.26%)
Overdoses and underdoses NEC [a]	25	23 (0.66%)	0.03	1 (0.03%)
Other[b]	7	7 (0.20%)	0.01	1 (0.03%)
Nervous system disorders	**46**	**44 (1.27%)**	**0.05**	**18 (0.52%)**
Neurological disorders NEC [a]	24	24 (0.69%)	0.02	10 (0.29%)
Neuromuscular disorders	9	9 (0.26%)	0.01	3 (0.09%)
Other[b]	13	13 (0.37%)	0.01	6 (0.17%)
Other SOC Terms (<1.0% Threshold)	**37**	**35 (1.01%)**	**0.04**	**9 (0.26%)**
Total	**399**	**331 (9.52%)**	**0.41**	**134 (3.85%)**

[a] Not Elsewhere Classified.
[b] Composed of high level group term event codes with fewer than 5 events each.

3.2.3 Therapy Relevant Events

3.2.3.1 Cerebrospinal Fluid Leaks

Potential cerebrospinal fluid leak (CSF) events are identified and assessed by Medtronic personnel and the site physician of the case to ascertain the case definition using Table 3.8.

Table 3.8: Cerebrospinal Fluid Leak Event Definition

Case Definition	Ascertainment
Definitive CSF Leak	▪ Observation of clear fluid leaking from the wound, or ▪ Contrast study demonstrates extravasation of dye outside dura, or ▪ Patient with persistent post-operative ***positional*** headache, plus one of the following: – Blood patch or suturing relieves headaches, or – Subcutaneous ***persistent*** fluid collection on the catheter tract, or – Meningeal enhancement on MRI with contrast.
Probable CSF Leak	**Reproducible** post-operative **positional** headache for >14 days with or without report of subcutaneous fluid collection. No contrast study performed or contrast study result inconclusive.
Possible CSF Leak	**Intermittent** post-operative **positional** headache for >14 days without report of subcutaneous fluid collection. No contrast study performed or contrast study result inconclusive.
Not CSF Leak	Acute post-operative non-positional headache lasting less than 14 days.

The potential CSF leak status (N=429) at the time of this analysis is presented in Table 3.9 with a definitive and probable CSF leak rate of 1.4% (142/10,053). The causality of the CSF leak event is dependent on the individual cases.

Table 3.9: Summary of Cerebrospinal Fluid Leak Adjudication

Cases Reviewed	Definitive CSF Leak	Probable CSF Leak	Possible CSF Leak	Not CSF Leak	Unspecified[a]
429	121	21	26	184	77

[a] Unadjudicated due to the timing of the data or due to the site no longer being active.

3.2.3.2 Inflammatory Masses

Inflammatory mass (IM), also sometimes reported as catheter-tip inflammatory mass or an intrathecal granuloma, is a potential complication of intrathecal opioid drug therapy. In order to better quantify the incidence of inflammatory mass, all events were evaluated for a report of inflammatory mass. For these identified cases, the medical records were reviewed by Medtronic personnel together with radiographic images when available. The radiographic images were reviewed to determine if there was evidence of an intradural extramedullary enhancing lesion. The adjudication team assessed each case based upon the case definition and ascertainment guideline presented in Table 3.10. A summary of cases evaluated for IM through the data cut-off is shown in Table 3.11.

Table 3.10: Case Definition and Ascertainment of Inflammatory Mass

Case Definition	Ascertainment
Definitive IM	Surgical and histological verification or clinical symptoms plus contrast enhanced MRI or CT myelogram and resolution of lesion following cessation of drug exposure
Probable IM	No surgical or histological verification, but clinical criteria and enhanced MRI or CT myelogram criteria are present
Possible IM	Medical records document IM, but there is no surgical or histological verification, there are no clinical criteria, and no radiographic data are available
Not IM	Surgical and histological verification that lesion is another disease process rather than IM, or radiographic data do not show an intrathecal lesion

There were a total of 135 suspected cases of inflammatory mass (Table 3.11) that were discerned from evaluation of patient records and reviewed by the adjudication team. Medtronic will continue to evaluate reports of inflammatory mass. Any previously classified case of IM will be re-evaluated if new evidence is received after this report. An analysis of the adjudicated definitive and probable inflammatory mass cases in the PSR from 2003 through October 2022 indicates an incidence of 0.24% (18/7,654) for pain patients and 0.00% (0/2,184) for spasticity patients.

Table 3.11: Summary of Inflammatory Mass Adjudication

Year of Event	Cases Reviewed	Definitive IM	Probable IM	Possible IM	Not IM
2004	4				4
2005	4	1		1	2
2006	7	1	1	2	3
2007	9	1	1	2	5
2008	4		1		3
2009	3	1			2
2010	11		1	1	9
2011	11	1	2	1	7
2012	13			1	12
2013	6			4	2
2014	10			2	8
2015	21	1		6	14
2016	10	1	1	2	6
2017	9			1	8
2018	4	1			3
2019	5	1			4
2020	3	1		1	1
2021	1		1		
2022	0				
Total	**135**	**10**	**8**	**24**	**93**

3.2.4 Patient Deaths

In earlier versions of the protocol, deaths were only assessed for the relatedness to the device product performance. After 2010, death assessments were expanded to also include the relationship to the implant procedure and/or therapy. As of the report cut-off, a total of 2,676 patients in the registry had expired. As with previous reports, no deaths were reported as a direct result of a product performance event. Although, three deaths were assigned by the physician as possibly related to the implant procedure and/or therapy.

Of the three deaths possibly related to the procedure and/or therapy, one death was due to a pulmonary embolism where the treating physician stated that the event could be possibly related to the withdrawal of the intrathecal medications. The patient had experienced a lack of therapy due to a missed refill visit leading to the withdrawal and not to the device malfunctioning. Medtronic Medical Safety assessed this death event as possibly related to the to the lack of therapy. A second death was reported by the treating physician as due to acute respiratory failure possibly related to the procedure and/or therapy. This patient had a history of persistent upper respiratory tract problems, difficulties swallowing and chronic aspiration as the

result of cancer related treatments. Medtronic Medical Safety assessed this death event as possibly related to the surgery/anesthesia during the implant procedure and therapy. The third death was reported by the physician as due to respiratory distress possibly related to the intrathecal medication. This patient had multiple comorbidities with multiple concomitant medications and a decreased level of physical activity. The death records state the cause of death as probable arteriosclerotic cardiovascular disease. Medtronic Medical Safety assessed this event as unassessable due to incomplete information.

Since 2003, a total of 1,405 (52.50%) deaths have been reported in this patient registry study based upon patients receiving therapy for malignant pain, 965 (36.06%) for non-malignant pain, 281 (10.50%) for spasticity, 22 (0.82%) for non-malignant pain & spasticity, 1 (0.04%) for malignant pain & chemotherapy , and 2 (0.07%) for not specified primary indication (see Table 3.12). The percentage is based upon the total patient death events and not based upon the rate of occurrence. **All tables depicted without a patient denominator should not be interpreted using other numbers within this report to calculate event rates**.

Table 3.12: Targeted Drug Delivery System Patient Deaths by Primary Indication

Number of Reports of Death by Primary Indication[a]	N (%) of Deaths
Malignant pain	1,405 (52.50%)
Non-malignant pain	965 (36.06%)
Spasticity	281 (10.50%)
Non-malignant pain & Spasticity	22 (0.82%)
Malignant pain & Chemotherapy	1 (0.04%)
Not Specified	2 (0.07%)
Total	**2,676 (100%)**

[a] For approved indications refer to product labeling for your geography.

3.3 Pumps

From August 7, 2003, to the report cut-off date of October 31, 2022, there were 12,741 pumps followed in the registry. The difference between the total number of patients (n=10,053) versus the total number of pumps is due to the fact that some patients were subsequently re-implanted with a pump multiple times. The aggregate prospective follow-up time for all pumps was 425,367 months (35,447 years). Table 3.13 provides the number and percentage of pumps by model.

3.3.1 SynchroMed II Design Change: Pump Enhancements

Design changes to the SynchroMed II 20 mL and 40 mL pump models were implemented to reduce the likelihood of non-recoverable motor stalls. These changes were released incrementally, allowing for the pumps to be considered in three groups: 1) Pre-Enhancements

(prior to 2016), 2) the Modified Gear Wheel Material and Encapsulated Feedthroughs (GW3/FT) enhancements (released January 2016) and 3) the Applied Diamond Like Coating (GW3/FT/DLC) enhancement (released July 2017). All enhancements were communicated in the August 2017 Medical Device Safety Notification: SynchroMed II Implantable Drug Infusion Pump Design Change Model Numbers 8637-20, 8637-40. For details, please visit https://www.medtronic.com/content/dam/medtronic-com/professional/documents/product-advisories/tdd/synchromed-pump-design-change-august-2017-hcp-letter.pdf. Table 3.13 provides the number and percentage of pumps by model and pump enhancement.

Table 3.13: Targeted Drug Delivery Pump Counts by Model and Pump Enhancement

Model Name	N (%)
SynchroMed II 40 mL	**7,179 (56.35%)**
Pre-Enhancements[a]	4,630 (36.34%)
GW3/FT/DLC Enhancements	2,012 (15.79%)
GW3/FT Enhancements[a]	537 (4.21%)
SynchroMed II 20 mL	**4,376 (34.35%)**
Pre-Enhancements[a]	2,963 (23.26%)
GW3/FT/DLC Enhancements	1,050 (8.24%)
GW3/FT Enhancements[a]	363 (2.85%)
SynchroMed EL 18 mL[a]	**1,146 (8.99%)**
SynchroMed EL 10 mL[a]	**34 (0.27%)**
SynchroMed Classic[a]	**5 (0.04%)**
Other/Unspecified	**1 (0.01%)**
Total	**12,741 (100%)**

[a] No longer manufactured.

The pump product performance-related events by model, pre-SynchroMed II enhancements and SynchroMed II enhancements are summarized in the pump models section. Please visit http://synchromed2enhancements.medtronic.com for specific pump details by serial number.

3.3.2 Pump Events

There were 538 product performance-related events with an underlying reported etiology related to pump function. This includes 533 events with a pump etiology and 5 events with both a pump and other etiology (including device and non-device etiologies). Of these, 459 were the initial product performance event that affected pump survival estimates. For pumps in the registry, the current return rate to Medtronic Returned Product Analysis (RPA) was 29.6% (1,929/6,522). The proportion was based upon the number of registry pumps received by RPA, divided by the sum of the total number of explanted devices and the total number of pumps in patients who have expired. In the 538 pump events, 36.6% (197/538) were assigned as device related by the physician, not returned to Medtronic RPA (see Figure 3.4).

For the purposes of survival analysis, a device's follow-up time is cut off for one of three reasons: 1) the occurrence of a product performance-related event; 2) the occurrence of a censoring event; or 3) the device is event-free and censored at the patient's last follow-up prior to the data cut-off. For pumps:

- 459 had follow up time cut-off due to product performance-related events.
- 9,786 were censored in the survival analysis for the following reasons: patient expired, pump explanted, site termination, patient discontinued, patient lost to follow-up, or therapy suspended.
- 2,496 were free from product performance-related events and censoring events, and were censored at the last follow-up visit prior to the report cut-off.

3.3.3 Pump Models

The following figures and tables represent the SynchroMed II pump characteristics, survival (including 95% confidence intervals), specifications and events by model. Since the survival estimate may become very imprecise with smaller sample sizes, the device survival curves below are truncated when the sample size is less than 20 active devices for each 3-month interval. The survival of SynchroMed EL model was not shown since it has no active devices in the PSR. For information on this model, please refer to the 2017 or earlier reports.

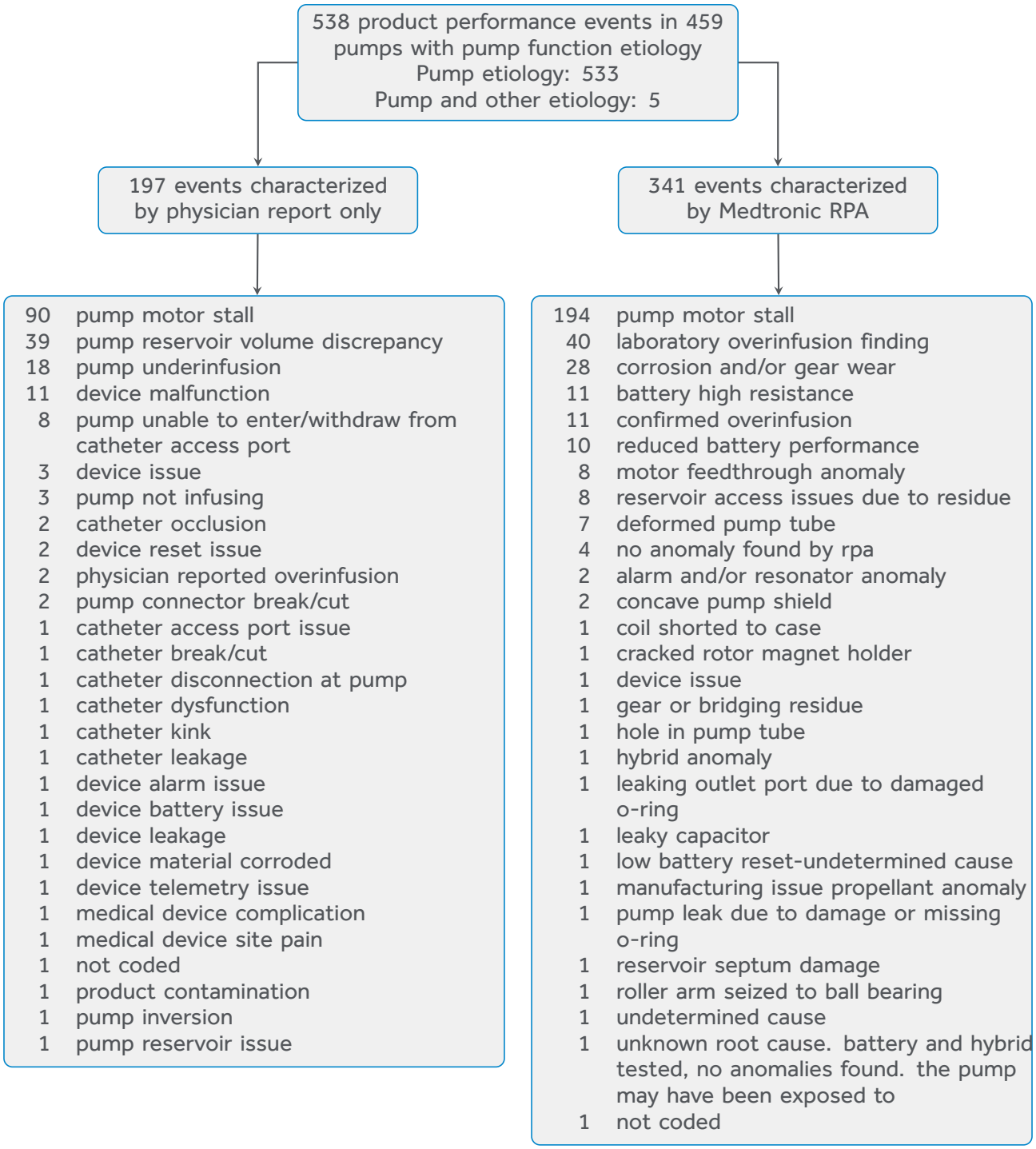
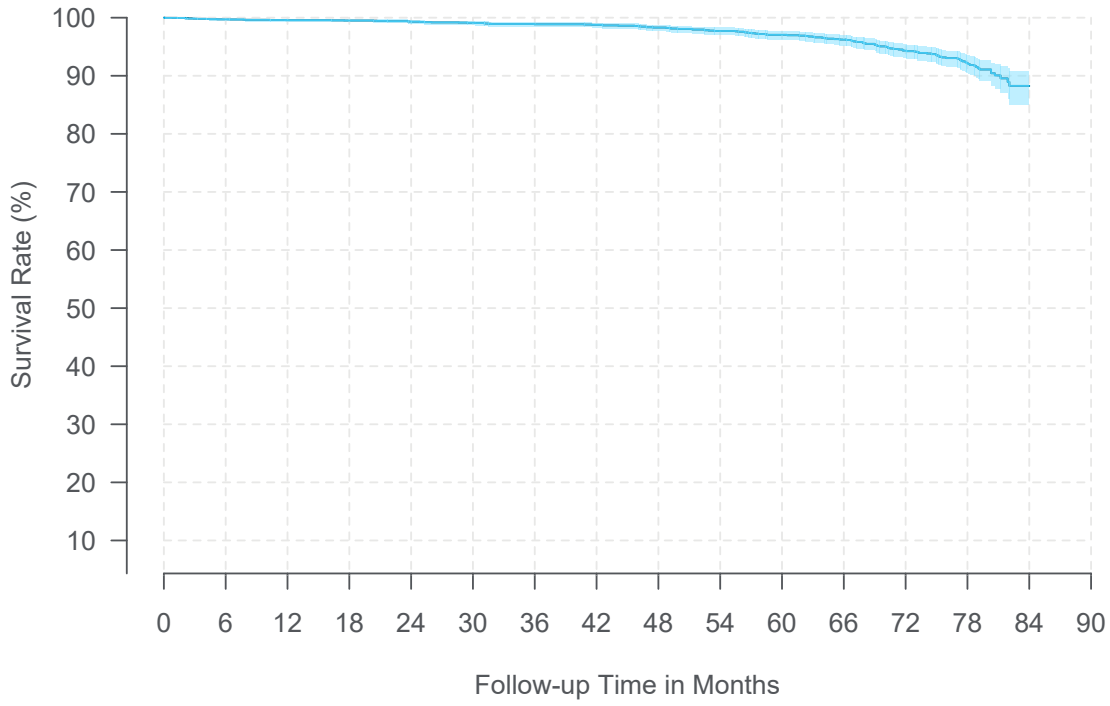


Figure 3.4: Distribution of Pump Function Etiology Product Performance Events

3.3.3.1 Model 8637-20

Model/Name	SynchroMed II 20 mL
FDA Approval Date	September 2003
Pumps Enrolled	4,376
Pumps Currently Active in Study	894
Initial Product Performance Events	128
Median Follow-up Time (Months)	36.6
Cumulative Follow-up Time (Months)	173,127



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	99.6% (99.3%, 99.7%)	99.3% (99.0%, 99.6%)	98.9% (98.4%, 99.2%)	98.3% (97.7%, 98.7%)	97.0% (96.2%, 97.7%)
Sample Size	3,287	2,771	2,258	1,780	1,387

Time Interval	6 Years	7 Years			
Survival (95% CI)	94.3% (93.0%, 95.4%)	88.3% (85.0%, 90.8%)	—	—	—
Sample Size	994	32			

Specification: 8637-20	
Expected battery life[a]	6-7 years
Thickness	0.77 in (19.5 mm)
Diameter	3.4 in (87.5 mm)
Capacity	20.0 mL
Minimal Programmable Flow Rate[b]	0.048 mL/day
Maximum Programmable Flow Rate[b]	24 mL/day
Minimum Rate Infusion Mode[c]	0.006 mL/day

[a] Dependent on flow rate. Designed to shut off at 84 months.

[b] Actual limits depend on pump calibration constant and selected infusion mode.

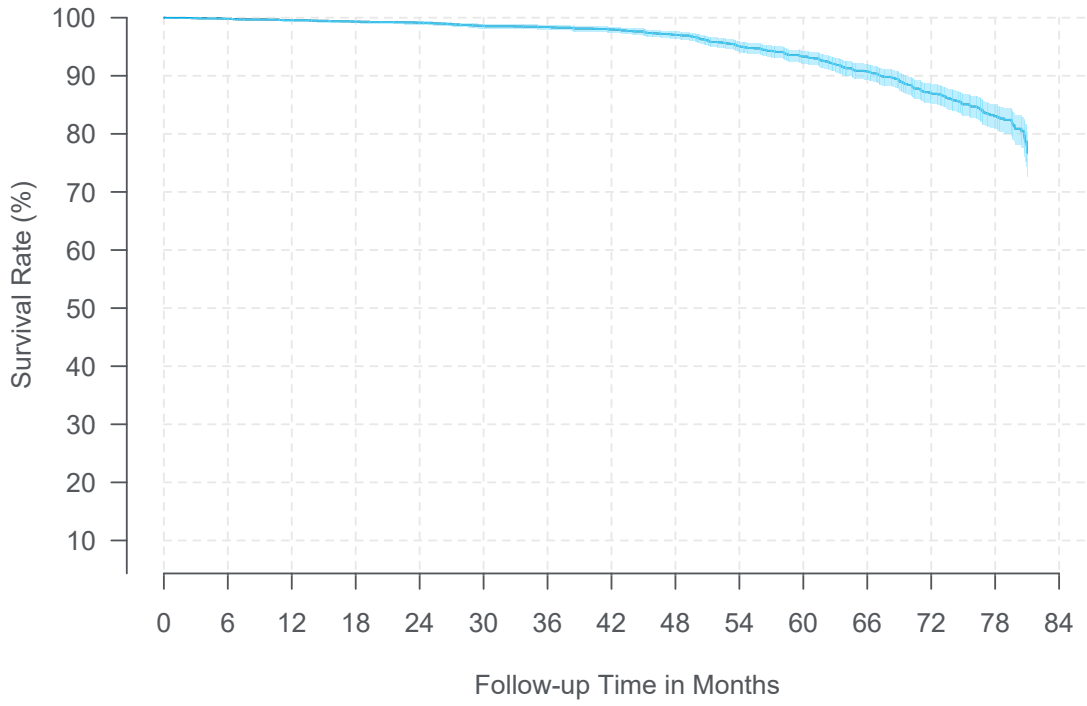
[c] Nontherapeutic (if therapy is to be temporarily discontinued).

Pump Event Summary: SynchroMed II 20 mL	N
RPA Determination	**75**
Pump Motor Stall	39
Laboratory Overinfusion Finding	8
Battery High Resistance	6
Corrosion And/Or Gear Wear	4
Motor Feedthrough Anomaly	3
Reduced Battery Performance	2
Reservoir Access Issues Due To Residue	2
Other[a]	11
Physician's Determination	**53**
Pump Motor Stall	21
Pump Reservoir Volume Discrepancy	10
Device Malfunction	6
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Device Issue	3
Other[a]	9
Total	**128**

[a] Composed of event codes with 1 event each.

3.3.3.2 Model 8637-40

Model/Name	SynchroMed II 40 mL
FDA Approval Date	September 2003
Pumps Enrolled	7,179
Pumps Currently Active in Study	1,604
Initial Product Performance Events	297
Median Follow-up Time (Months)	23.8
Cumulative Follow-up Time (Months)	219,981



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	99.6% (99.4%, 99.7%)	99.1% (98.8%, 99.4%)	98.4% (97.9%, 98.7%)	97.0% (96.3%, 97.6%)	93.3% (92.2%, 94.3%)
Sample Size	4,543	3,596	2,762	2,012	1,458

Time Interval	6 Years	At 81 Months			
Survival (95% CI)	87.0% (85.2%, 88.5%)	76.8% (72.7%, 80.3%)	—	—	—
Sample Size	929	116			

Specification: 8637-40	
Expected battery life[a]	6-7 years
Thickness	1.0 in (26 mm)
Diameter	3.4 in (87.5 mm)
Capacity	40.0 mL
Minimal Programmable Flow Rate[b]	0.048 mL/day
Maximum Programmable Flow Rate[b]	24 mL/day
Minimum Rate Infusion Mode[c]	0.006 mL/day

[a] Dependent on flow rate. Designed to shut off at 84 months.

[b] Actual limits depend on pump calibration constant and selected infusion mode.

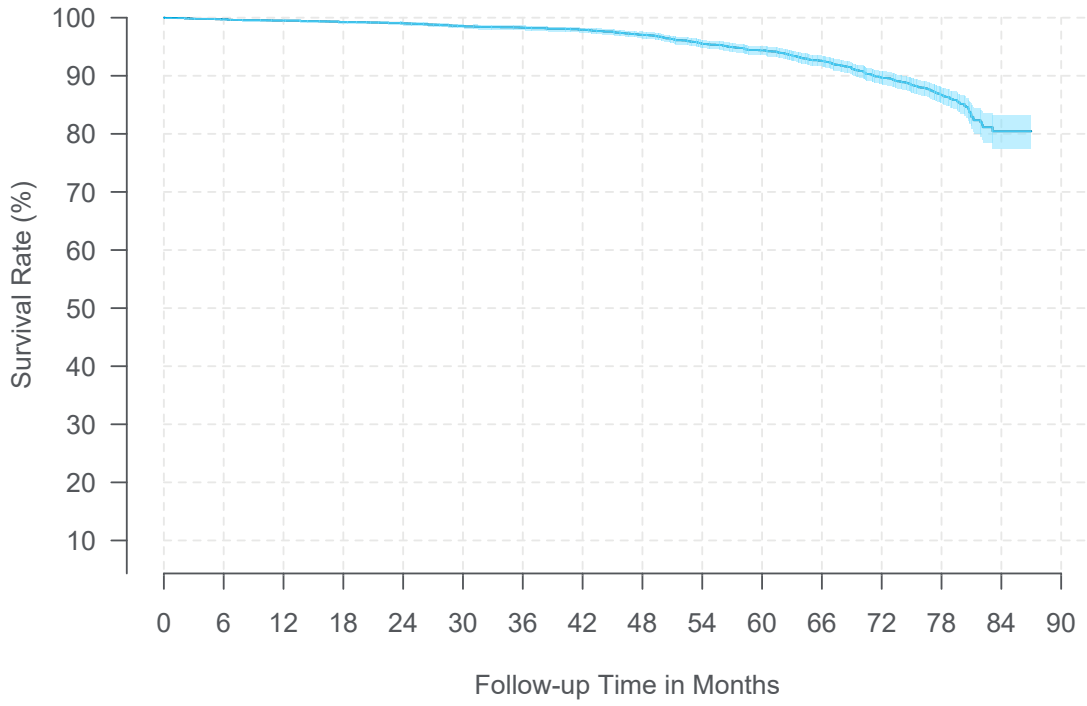
[c] Nontherapeutic (if therapy is to be temporarily discontinued).

Pump Event Summary: SynchroMed II 40 mL	N
RPA Determination	**204**
Pump Motor Stall	132
Laboratory Overinfusion Finding	29
Reduced Battery Performance	7
Corrosion And/Or Gear Wear	6
Deformed Pump Tube	5
Confirmed Overinfusion	4
Reservoir Access Issues Due To Residue	4
Battery High Resistance	3
Motor Feedthrough Anomaly	3
No Anomaly Found By RPA	3
Concave Pump Shield	2
Other[a]	6
Physician's Determination	**93**
Pump Motor Stall	39
Pump Reservoir Volume Discrepancy	21
Pump Underinfusion	10
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Device Malfunction	3
Pump Not Infusing	2
Other[a]	14
Total	**297**

[a] Composed of event codes with 1 event each.

3.3.3.3 SynchroMed II 20 mL and 40 mL: Pre-enhancements

Model/Name	Pre-Enhancements
FDA Approval Date	September 2003
Pumps Enrolled	7,593
Pumps Currently Active in Study	87
Initial Product Performance Events	398
Median Follow-up Time (Months)	34.7
Cumulative Follow-up Time (Months)	293,800



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	99.5% (99.3%, 99.7%)	99.0% (98.7%, 99.3%)	98.3% (97.9%, 98.6%)	97.0% (96.5%, 97.5%)	94.4% (93.5%, 95.1%)
Sample Size	5,294	4,575	3,818	3,158	2,563

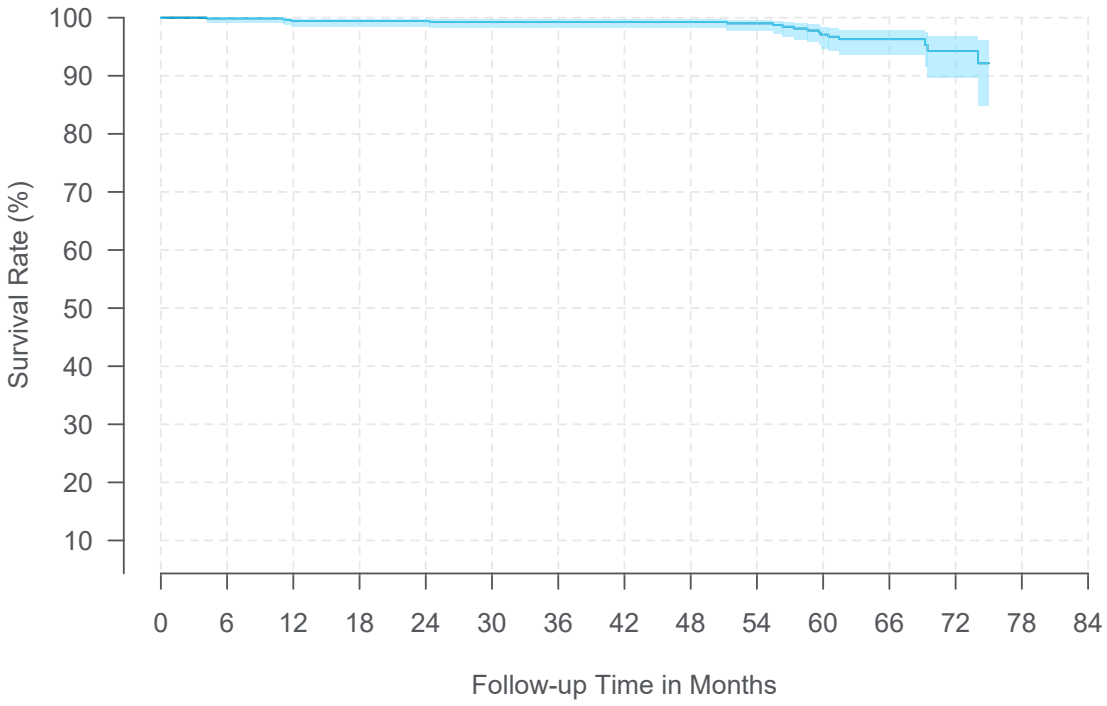
Time Interval	6 Years	7 Years	At 87 Months		
Survival (95% CI)	89.7% (88.5%, 90.8%)	80.4% (77.4%, 83.1%)	80.4% (77.4%, 83.1%)	—	—
Sample Size	1,861	48	24		

Pump Event Summary: SynchroMed II Pre-enhancements	Total
RPA Determination	**263**
Pump Motor Stall	164
Laboratory Overinfusion Finding	35
Corrosion And/Or Gear Wear	10
Battery High Resistance	9
Reduced Battery Performance	9
Deformed Pump Tube	6
Motor Feedthrough Anomaly	6
Confirmed Overinfusion	5
Reservoir Access Issues Due To Residue	4
Alarm And/Or Resonator Anomaly	2
Concave Pump Shield	2
No Anomaly Found By RPA	2
Other[a]	9
Physician's Determination	**135**
Pump Motor Stall	59
Pump Reservoir Volume Discrepancy	28
Pump Unable To Enter/Withdraw From Catheter Access Port	8
Pump Underinfusion	8
Device Malfunction	7
Device Issue	3
Pump Not Infusing	3
Catheter Occlusion	2
Physician Reported Overinfusion	2
Pump Connector Break/Cut	2
Other[a]	13
Total	**398**

[a] Composed of event codes with 1 event each.

3.3.3.4 SynchroMed II 20 mL and 40 mL: GW3/FT Enhancements

Model/Name	GW3/FT Enhancements
FDA Approval Date	September 2015 (GW3)/November 2015 (FT)
Pumps Enrolled	900
Pumps Currently Active in Study	345
Initial Product Performance Events	17
Median Follow-up Time (Months)	46.3
Cumulative Follow-up Time (Months)	35,357



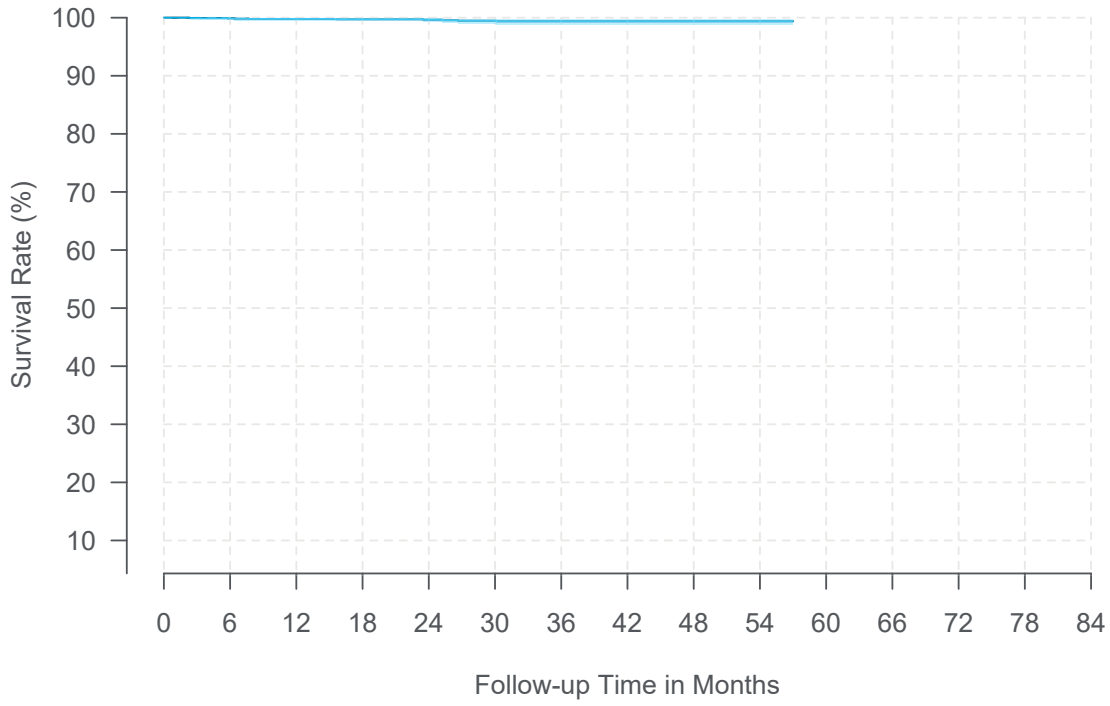
Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	99.4% (98.5%, 99.8%)	99.4% (98.5%, 99.8%)	99.3% (98.2%, 99.7%)	99.3% (98.2%, 99.7%)	97.1% (94.7%, 98.4%)
Sample Size	687	576	507	431	270

Time Interval	6 Years	At 75 Months			
Survival (95% CI)	94.3% (89.6%, 96.9%)	92.1% (84.8%, 96.0%)	—	—	—
Sample Size	62	34			

Pump Event Summary: SynchroMed II GW3/FT Enhancements	Total
RPA Determination	**11**
Pump Motor Stall	6
Reservoir Access Issues Due To Residue	2
Laboratory Overinfusion Finding	1
No Anomaly Found By RPA	1
Unknown Root Cause	1
Physician's Determination	**6**
Catheter Access Port Issue	1
Catheter Disconnection At Pump	1
Device Malfunction	1
Pump Motor Stall	1
Pump Reservoir Issue	1
Pump Reservoir Volume Discrepancy	1
Total	**17**

3.3.3.5 SynchroMed II 20 mL and 40 mL: GW3/FT/DLC Enhancements

Model/Name	GW3/FT/DLC Enhancements
FDA Approval Date	April 2017 (DLC)
Pumps Enrolled	3,062
Pumps Currently Active in Study	2,066
Initial Product Performance Events	10
Median Follow-up Time (Months)	17.8
Cumulative Follow-up Time (Months)	63,951



Time Interval	1 Year	2 Years	3 Years	4 Years	At 57 Months
Survival (95% CI)	99.8% (99.5%, 99.9%)	99.6% (99.2%, 99.8%)	99.4% (98.8%, 99.7%)	99.4% (98.8%, 99.7%)	99.4% (98.8%, 99.7%)
Sample Size	1,849	1,216	695	203	23

Pump Event Summary: SynchroMed II GW3/FT/DLC Enhancements	Total
RPA Determination	**5**
Laboratory Overinfusion Finding	1
No Anomaly Found By RPA	1
Pump Leak Due To Damage Or Missing O-Ring	1
Pump Motor Stall[a]	1
Reservoir Septum Damage	1
Physician's Determination	**5**
Pump Reservoir Volume Discrepancy	2
Pump Underinfusion	2
Device Malfunction	1
Total	**10**

[a] Motor stall that occurred within 7 months of implant due to unknown cause.

3.3.4 Pump Summary

Table 3.14: Targeted Drug Delivery Pump Characteristics

Model/Name	FDA Approval Date	Pumps Enrolled	Pumps Active	Initial Product Performance Events	Median Follow-up Time (Months)	Cumulative Follow-up Time (Months)
SynchroMed II 20 mL	September 2003	4,376	894	128	36.6	173,127
SynchroMed II 40 mL	September 2003	7,179	1,604	297	23.8	219,981
SynchroMed II Pre-enhancements[a]	September 2003	7,593	87	398	34.7	293,800
SynchroMed II GW3/FT enhancements[a]	September 2015 (GW3) November 2015 (FT)	900	345	17	46.3	35,357
SynchroMed II GW3/FT/DLC enhancements[a]	April 2017 (DLC)	3,062	2,066	10	17.8	63,951

[a] For explanation of enhancements see Section 3.3.1.

Table 3.15: Targeted Drug Delivery Pump Survival Probability (95% Confidence Intervals)

Model Name	1 Year	2 Years	3 Years	4 Years	5 Years
SynchroMed II 20 mL	99.6% (99.3%, 99.7%)	99.3% (99.0%, 99.6%)	98.9% (98.4%, 99.2%)	98.3% (97.7%, 98.7%)	97.0% (96.2%, 97.7%)
SynchroMed II 40 mL	99.6% (99.4%, 99.7%)	99.1% (98.8%, 99.4%)	98.4% (97.9%, 98.7%)	97.0% (96.3%, 97.6%)	93.3% (92.2%, 94.3%)
SynchroMed II Pre-Enhancements	99.5% (99.3%, 99.7%)	99.0% (98.7%, 99.3%)	98.3% (97.9%, 98.6%)	97.0% (96.5%, 97.5%)	94.4% (93.5%, 95.1%)
SynchroMed II GW3/FT Enhancements	99.4% (98.5%, 99.8%)	99.4% (98.5%, 99.8%)	99.3% (98.2%, 99.7%)	99.3% (98.2%, 99.7%)	97.1% (94.7%, 98.4%)
SynchroMed II GW3/FT/DLC Enhancements	99.8% (99.5%, 99.9%)	99.6% (99.2%, 99.8%)	99.4% (98.8%, 99.7%)	99.4% (98.8%, 99.7%)	__

Model Name	6 Years	7 Years			
SynchroMed II 20 mL	94.3% (93.0%, 95.4%)	88.3% (85.0%, 90.8%)	__	__	__
SynchroMed II 40 mL	87.0% (85.2%, 88.5%)	__	__	__	__
SynchroMed II Pre-Enhancements	89.7% (88.5%, 90.8%)	80.4% (77.4%, 83.1%)	__	__	__
SynchroMed II GW3/FT Enhancements	94.3% (89.6%, 96.9%)	__	__	__	__
SynchroMed II GW3/FT/DLC Enhancements	__	__	__	__	__

Table 3.16: Targeted Drug Delivery SynchroMed II Pump Events by Enhancements

Pump Event	Pre-Enhancements	GW3/FT Enhancements	GW3/FT/DLC Enhancements
RPA Determination	**263**	**11**	**5**
Pump Motor Stall	164	6	1
Laboratory Overinfusion Finding	35	1	1
Corrosion And/Or Gear Wear	10	0	0
Battery High Resistance	9	0	0
Reduced Battery Performance	9	0	0
Deformed Pump Tube	6	0	0
Motor Feedthrough Anomaly	6	0	0
Reservoir Access Issues Due To Residue	4	2	0
Confirmed Overinfusion	5	0	0
No Anomaly Found By RPA	2	1	1
Alarm And/Or Resonator Anomaly	2	0	0
Concave Pump Shield	2	0	0
Pump Leak Due To Damage Or Missing O-Ring	0	0	1
Reservoir Septum Damage	0	0	1
Unknown Root Cause	0	1	0
Other [a]	9	0	0
Physician's Determination	**135**	**6**	**5**
Pump Motor Stall	59	1	0
Pump Reservoir Volume Discrepancy	28	1	2
Pump Underinfusion	8	0	2
Device Malfunction	7	1	1
Pump Unable To Enter/Withdraw From Catheter Access Port	8	0	0
Device Issue	3	0	0
Pump Not Infusing	3	0	0
Catheter Occlusion	2	0	0
Physician Reported Overinfusion	2	0	0
Pump Connector Break/Cut	2	0	0
Catheter Access Port Issue	0	1	0
Catheter Disconnection At Pump	0	1	0
Pump Reservoir Issue	0	1	0
Other [a]	13	0	0
Total	**398**	**17**	**10**

[a] Composed of event codes with 1 event each for SynchroMed II Pre-Enhancements.

3.4 SynchroMed II Pumps Exposed to On-Label and Off-Label Medications

The purpose of this analysis is to provide additional information regarding the product performance of SynchroMed II pumps exposed to On-Label and Off-Label medications. This report contains information outside the FDA approved labeling for the Medtronic SynchroMed II Infusion System. The long-term drug stability/compatibility and safety and/or efficacy of drugs not listed in the SynchroMed II Infusion System product labeling have not been established in the United States. It is recognized that healthcare providers prescribe therapies to meet specific patient needs; however, Medtronic only directs the use of its products based on

approved regulatory labeling. For the purposes of this report, On-Label and Off-Label determinations have been made based on the United States FDA approved labeling. However, product labeling varies by geography, so please contact your local Medtronic representative (http://www.medtronic.com/us-en/about/locations.html) for region-specific product labeling.

In this registry, patient status updates were obtained at least annually, until discontinuation of therapy, or until the patient was lost to follow-up. Medications within the pump were recorded at least annually. The interim data collection provided a snapshot of medication use at these points in time.

3.4.1 Pump Groups On/Off-Label Categorization

Through October 31, 2022, 9,023 patients (55.8% female, mean/SD age 54.1/17.5 years) have enrolled in the registry and have been implanted with 11,555 SynchroMed II pumps. At least one drug record was available on each of 10,657 pumps; if no drug records were available (n=898 pumps), the pump was excluded from this analysis. 10,657 pumps were categorized as being On- or Off-Label using the following criteria:

- **On-Label:** If a pump has at least one drug record in the registry, and none of the records show Off-Label drug exposure, that pump is considered On-Label even if the complete drug history of that pump is unknown.
  - For pumps used for pain patients, if the drug record has only one drug and it was morphine or ziconotide (or their brand names), and it was not a compounded drug, these pumps were considered On-Label. Note: The classification was based on the name of the drug only, not the reported concentration of the drug.
  - For pumps used for spasticity patients, if the drug record has only one drug, and it is either Lioresal® (bacoflen injection) or Gablofen® (bacoflen injection), that drug record was considered On-Label. Note: The classification was based on the name of the drug only, not the reported concentration of the drug. For this analysis, if only the generic chemical classification, such as baclofen, was entered then the assumption was that the drug is On-Label.
  - Pumps with an On-Label drug history and currently containing preservative free water or preservative free saline, or if previously contained preservative free water/saline and currently containing On-Label drug were considered On-Label.
- **Off-Label:** Any drugs not within the approved indications specified above are considered Off-Label. Additionally, any drug record with more than one drug at a time in the pump (admixture) was considered Off-Label.
  - If a pump had any known exposure to Off-Label drugs (i.e., the Off-Label data have been collected in the registry), that pump was considered Off-Label, regardless of the amount of exposure time.
  - If a pump is filled with a medication that was reported as compounded, that pump was considered Off-Label.

The pumps were not stratified by design change sub-groups (GW3/FT and GW3/FT/DLC) due to the limited follow-up time.

3.4.2 Data Analysis

Survival estimates were calculated using the methods described in the Methodology section of this report. Statistical testing that compared survival curves was performed using a Cox proportional-hazards model. Since the survival estimate may become very imprecise with small sample sizes, Medtronic Neuromodulation's registry truncates device survival curves when the sample size is less than 20 active devices. At this threshold, one device failure yields a 5% decrease in cumulative survival. Additionally, the standard error for this survival estimate is approximately 5% (depending on previous conditional survival estimates), with 95% confidence intervals of approximately ± 10%. Overall, this large variability of 20% around the cumulative survival estimate would greatly reduce the precision for the point estimate.

Pump survival from product performance-related events was calculated and compared for the following groups:

- Total study population: On-Label vs. Off-Label Drugs (including all indications)
- Pain study population: On-Label vs. Off-Label Drugs (including all pain indications)
- Spasticity study population: On-Label vs. Off-Label Drugs (including all spasticity indications)

Additionally, the cumulative failure rate (i.e., the estimated probability that a pump will have a product performance-related event by a given time point) is presented in table and graph formats for each of the sub-groups listed above.

3.4.3 Results

A total of 3,264 (30.6%) SynchroMed II pumps were classified as On-Label where there was no evidence of Off-Label drug/admixture exposure. A total of 7,393 (69.4 %) pumps were classified as Off-Label where there was evidence of pump exposure to an Off-Label drug/admixture. There were a total of 425 reported SynchroMed II pump product performance events during the study observation period. Of the 425 pump product performance events, 422 of those were pump failures. In addition to the 422 pump failures, there were 15 SynchroMed II pumps explanted due to normal battery depletion by the physician, which were returned to Medtronic and had an RPA observation of high battery resistance. For this analysis, these pumps were not considered failures, because they represented normal implant duration (ranging from 5.6 to 6.8 years) with no associated physician or patient complaint.

Three of the 425 pump failure events occurred in pumps with no drug records available. Of the remaining 422 SynchroMed II pump failures, 231 were classified as pump failure due to motor stall (with or without documented motor corrosion). The remaining pump failures were due to events such as inconsistent pump reservoir volume, overinfusion, corrosion and/or gear wear, device malfunction, reduced battery performance, pump underinfusion, and other non-conforming reasons. Overall, the rate of pump failures in this cohort was 3.96% (422/10,657) with a median follow-up of 32.0 months.

For the 231 pump failures due to motor stall, 130 of the events were associated with the patient presenting clinical signs or symptoms of possible drug withdrawal or increasing pain or

spasticity. The other 101 events had no patient reported signs or symptoms associated with the event, but had a physician report of a motor stall occurrence.

Table 3.17: Targeted Drug Delivery Primary Indications by On/Off-Label Pump Groups

Primary Indication[a]	On-Label N=3,264	Off-Label N=7,393
Non-malignant Pain	956 (14.9%)	5,462 (85.1%)
Malignant Pain	46 (2.9%)	1,515 (97.1%)
Spasticity	2,262 (90.3%)	243 (9.7%)
Multiple/Unknown	0 (0.0%)	173 (100.0%)

[a] For approved indications refer to product labeling for your geography.

3.4.3.1 Total Study Population

A total of 3,264 SynchroMed II pumps were classified as On-Label for all therapies, where there was no evidence of Off-Label drug/admixture exposure. A total of 7,393 pumps were classified as Off-Label where there was evidence of pump exposure to an Off-Label drug/admixture. The cumulative survival and failure of the SynchroMed II pump for all indications, stratified by the On-Label or Off-Label pump group, are shown in Figure 3.5 and Figure 3.6 respectively.

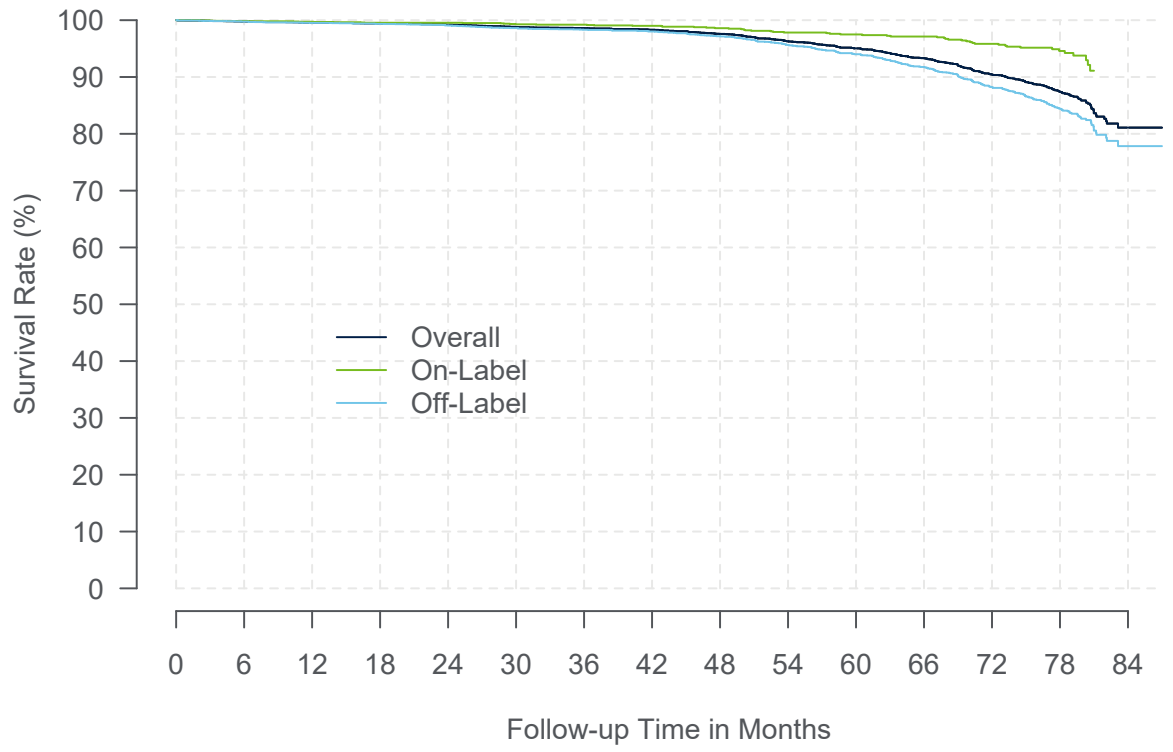


Figure 3.5: SynchroMed II Cumulative Survival (All Therapies)

Table 3.18: Survival Summary Table: All Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 81 Mos	7 Yrs	at 87 Mos
Overall	Survival	99.6%	99.2%	98.6%	97.6%	95.0%	90.4%	83.6%	81.1%	81.1%
	Sample Size	7,662	6,294	4,974	3,761	2,829	1,916	318	48	24
On-Label	Survival	99.7%	99.5%	99.2%	98.6%	97.5%	95.8%	91.1%	__	__
	Sample Size	2,369	1,939	1,523	1,102	832	604	76		
Off-Label	Survival	99.5%	99.1%	98.3%	97.1%	94.0%	88.2%	80.6%	77.8%	77.8%
	Sample Size	5,293	4,355	3,451	2,659	1,997	1,312	242	36	20

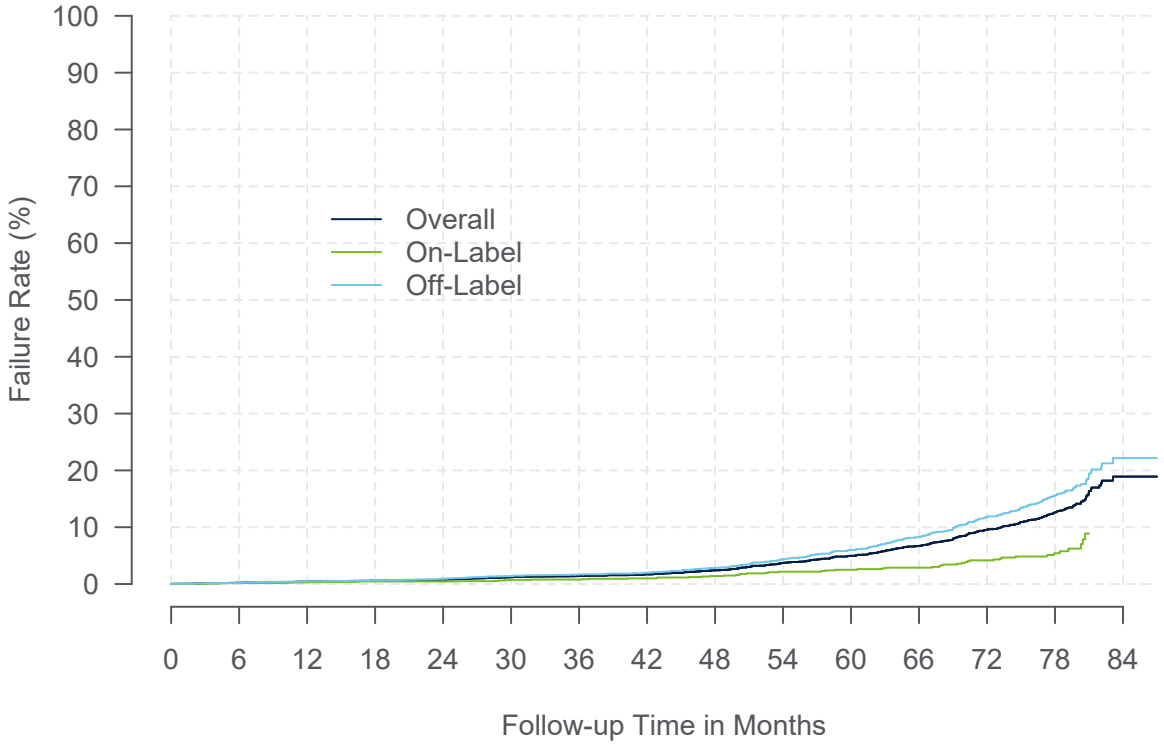


Figure 3.6: SynchroMed II Cumulative Failure (All Therapies)

Table 3.19: Failure Summary Table: All Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 81 Mos	7 Yrs	at 87 Mos
Overall	Failure	0.4%	0.8%	1.4%	2.4%	5.0%	9.6%	16.4%	18.9%	18.9%
	Sample Size	7,662	6,294	4,974	3,761	2,829	1,916	318	48	24
On-Label	Failure	0.3%	0.5%	0.8%	1.4%	2.5%	4.2%	8.9%	—	—
	Sample Size	2,369	1,939	1,523	1,102	832	604	76		
Off-Label	Failure	0.5%	0.9%	1.7%	2.9%	6.0%	11.8%	19.4%	22.2%	22.2%
	Sample Size	5,293	4,355	3,451	2,659	1,997	1,312	242	36	20

3.4.3.2 Pain Study Population

A total of 1,002 SynchroMed II pumps were classified as On-Label for pain therapies, where there was no evidence of Off-Label drug/admixture exposure. A total of 6,977 pumps were classified as Off-Label where there was evidence of pump exposure to an Off-Label drug/admixture. The cumulative survival and failure of the SynchroMed II pump for pain indications, stratified by the On-Label or Off-Label pump group, are shown in Figure 3.7 and Figure 3.8 respectively.

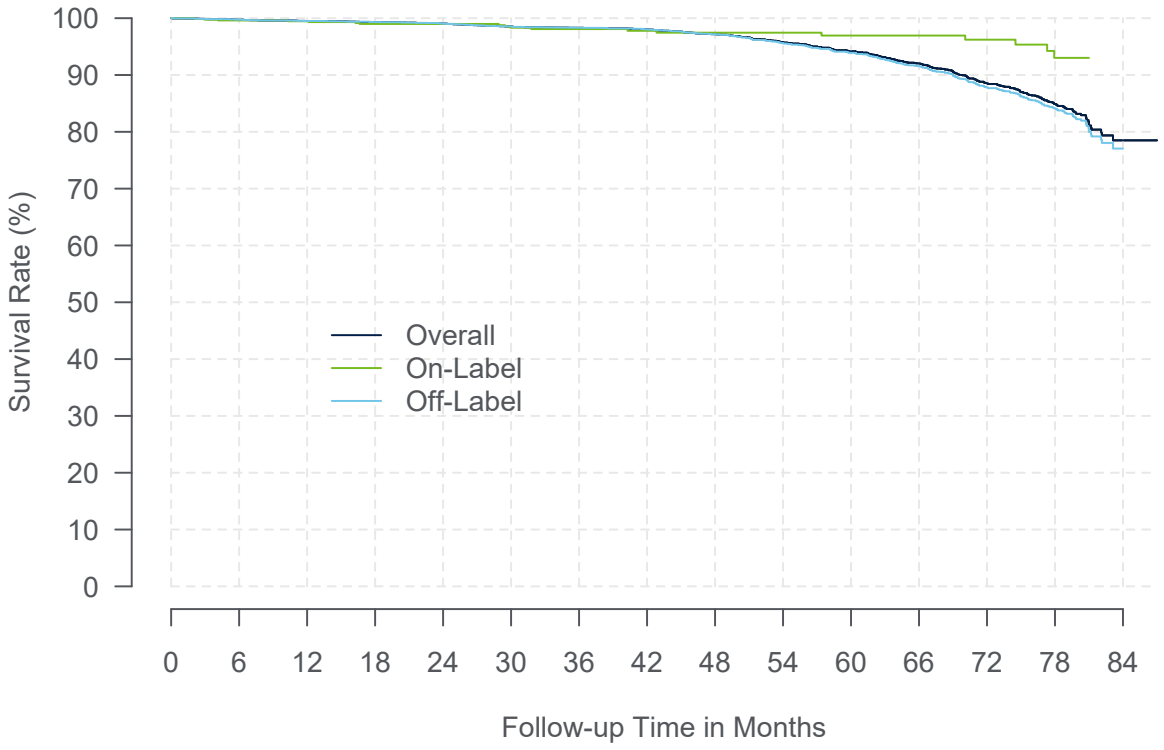


Figure 3.7: SynchroMed II Cumulative Survival (Pain Therapies)

Table 3.20: Survival Summary Table: Pain Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 81 Mos	7 Yrs	at 87 Mos
Overall	Survival	99.5%	99.0%	98.3%	97.2%	94.2%	88.5%	81.1%	78.5%	78.5%
	Sample Size	5,633	4,582	3,593	2,714	2,038	1,337	248	38	21
On-Label	Survival	99.5%	99.0%	98.1%	97.4%	96.9%	96.2%	93.0%	__	__
	Sample Size	675	509	373	246	184	126	25		
Off-Label	Survival	99.5%	99.1%	98.3%	97.1%	93.9%	87.8%	80.0%	77.1%	__
	Sample Size	4,958	4,073	3,220	2,468	1,854	1,211	223	34	

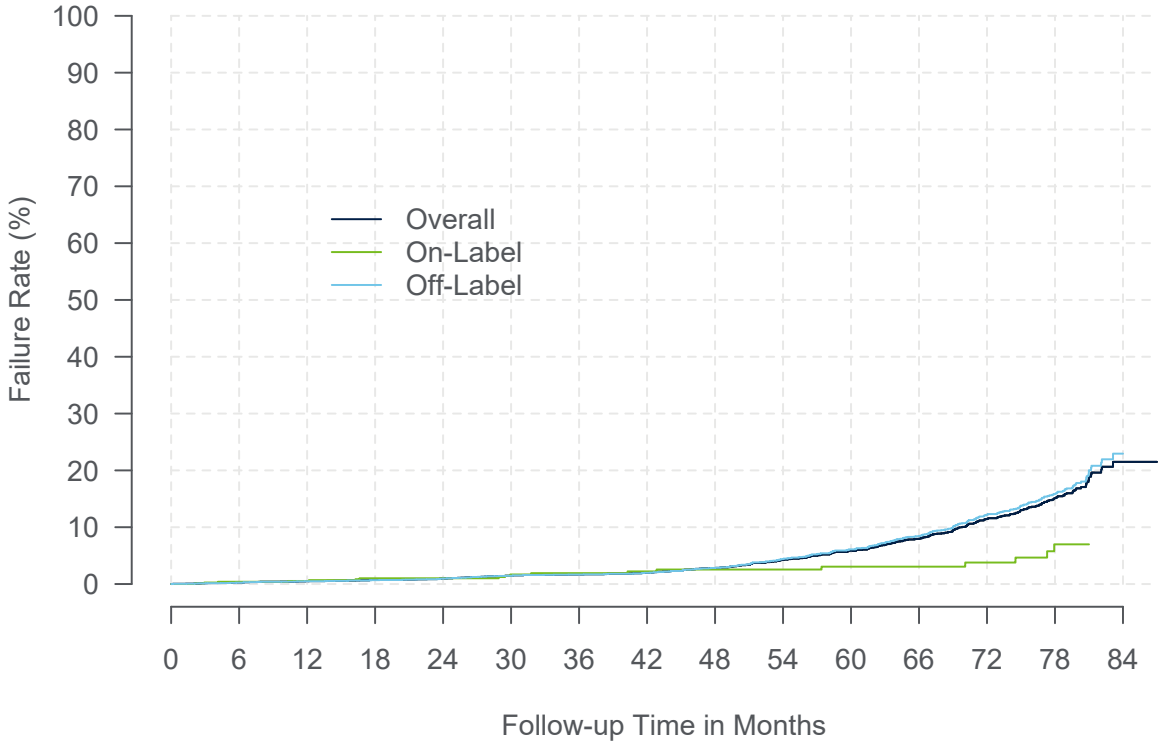


Figure 3.8: SynchroMed II Cumulative Failure (Pain Therapies)

Table 3.21: Failure Summary Table: Pain Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 81 Mos	7 Yrs	at 87 Mos
Overall	Failure	0.5%	1.0%	1.7%	2.8%	5.8%	11.5%	18.9%	21.5%	21.5%
	Sample Size	5,633	4,582	3,593	2,714	2,038	1,337	248	38	21
On-Label	Failure	0.5%	1.0%	1.9%	2.6%	3.1%	3.8%	7.0%	—	—
	Sample Size	675	509	373	246	184	126	25		
Off-Label	Failure	0.5%	0.9%	1.7%	2.9%	6.1%	12.2%	20.0%	22.9%	—
	Sample Size	4,958	4,073	3,220	2,468	1,854	1,211	223	34	

3.4.3.3 Spasticity Study Population

A total of 2,262 SynchroMed II pumps were classified as On-Label for spasticity therapies, where there was no evidence of Off-Label drug/admixture exposure. A total of 243 pumps were classified as Off-Label where there was evidence of pump exposure to an Off-Label drug/admixture. The cumulative survival and failure of the SynchroMed II pump for spasticity indications, stratified by the On-Label or Off-Label pump group, are shown in Figure 3.9 and Figure 3.10 respectively.

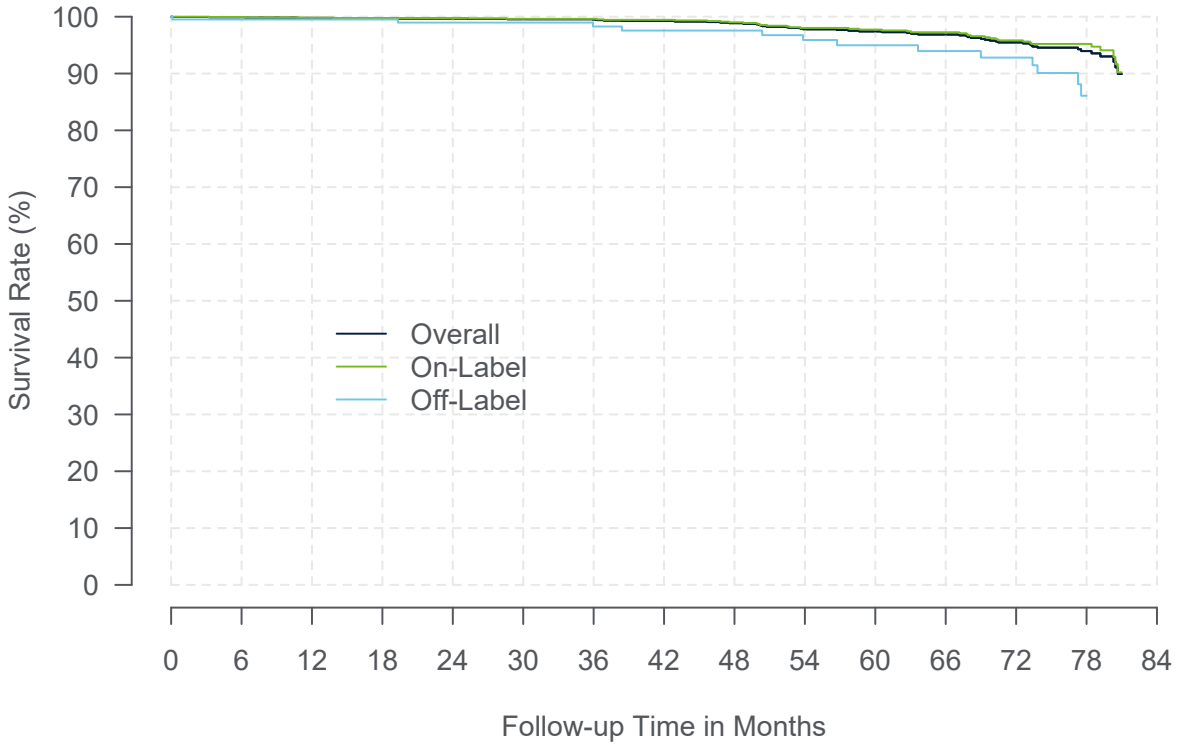


Figure 3.9: SynchroMed II Cumulative Survival (Spasticity Therapies)

Table 3.22: Survival Summary Table: Spasticity Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 78 Mos	at 81 Mos
Overall	Survival	99.8%	99.7%	99.5%	98.9%	97.4%	95.5%	94.0%	89.9%
	Sample Size	1,890	1,599	1,291	980	744	552	252	65
On-Label	Survival	99.8%	99.8%	99.6%	99.0%	97.7%	95.8%	95.2%	90.2%
	Sample Size	1,694	1,430	1,150	856	648	478	218	51
Off-Label	Survival	99.5%	99.0%	98.3%	97.6%	95.0%	92.8%	86.1%	__
	Sample Size	196	169	141	124	96	74	34	

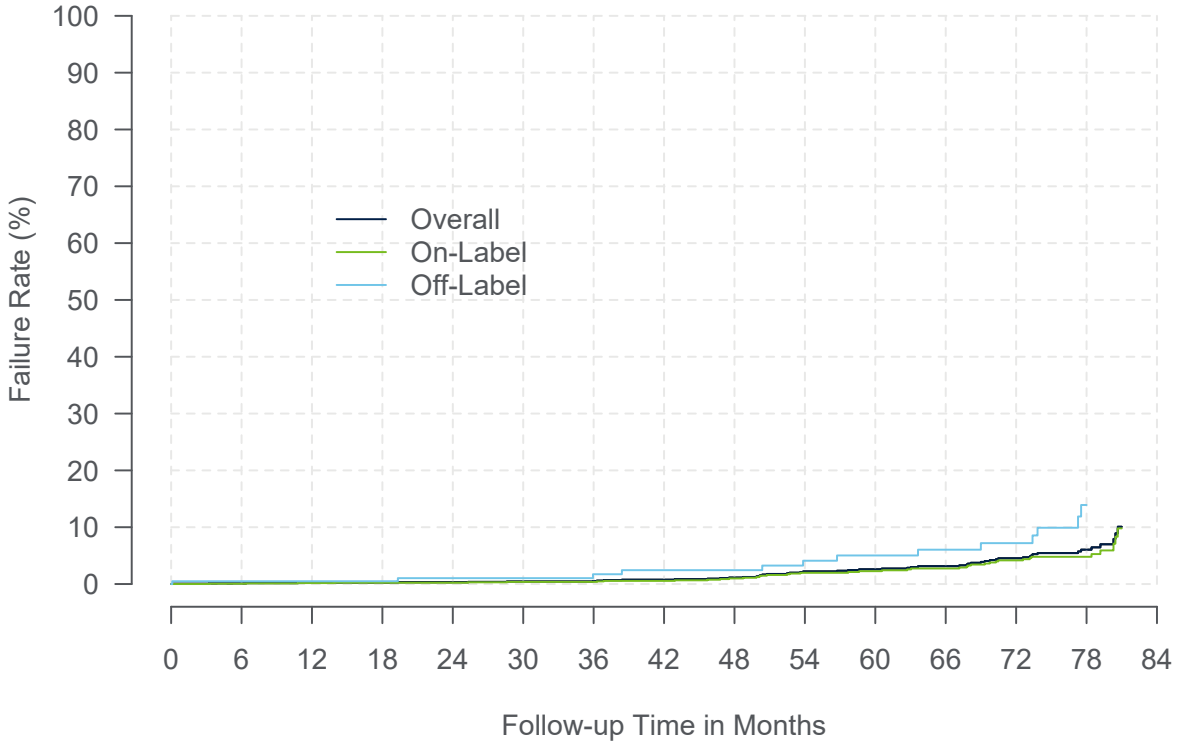


Figure 3.10: SynchroMed II Cumulative Failure (Spasticity Therapies)

Table 3.23: Failure Summary Table: Spasticity Therapies

Category	Time Interval	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs	at 78 Mos	at 81 Mos
Overall	Failure	0.2%	0.3%	0.5%	1.1%	2.6%	4.5%	6.0%	10.1%
	Sample Size	1,890	1,599	1,291	980	744	552	252	65
On-Label	Failure	0.2%	0.2%	0.4%	1.0%	2.3%	4.2%	4.8%	9.8%
	Sample Size	1,694	1,430	1,150	856	648	478	218	51
Off-Label	Failure	0.5%	1.0%	1.7%	2.4%	5.0%	7.2%	13.9%	__
	Sample Size	196	169	141	124	96	74	34	

3.4.4 Overall Summary and Limitations

- Pump failures have been observed in pumps with both On-Label and Off-Label medications used for all indications over the follow-up period.
- Off-Label medication exposure is associated with an overall 2.6 times greater risk of pump failure (95% confidence interval [1.966, 3.395]) compared to On-Label medication exposure for the entire pump population. The rate of pump failure accelerates in the Off-Label group after 48 months of follow-up. At 81 months of follow-up the survival from

pump failure for On-Label pumps was 91.1% compared to a survival of 80.6% for Off-Label pumps.

- The data represent the reported registry experience with a median follow-up time of 32.0 months. The longer-term data are based on a lower number of pumps and are subject to change as more follow-up data are obtained via the registry. Survival curve truncation or plateaus do not imply that the implanted devices will not be adversely impacted beyond the time points of the current data.
- The On-Label pump group was comprised of 69.3% of pumps with Spasticity as the indication (2,262 vs. 1,002: Spasticity versus Pain pumps respectively). While the Off-Label group consisted of 94.4% of pumps with pain indications (6,977 vs. 243: Pain versus Spasticity pumps respectively).
- Medication use was recorded as a snapshot at the time of follow-up. It is possible that some On-Label pumps received Off-Label medications in between follow-up periods. In addition, it is possible that some pumps designated as On-Label received compounded formulation of an On-Label equivalent but was not designated as such in the registry database. The time a pump was exposed to an Off-Label medication was not assessed. It is possible that some Off-Label pumps were exposed only for a brief period of time (e.g. < 6 months).
- The risk of pump failure by type of drug was not assessed. Many Off-Label pumps were exposed to multiple medications over the life span of the pump. This limits the ability to associate a specific drug, compounded drug, drug concentration, or drug combination with increased pump failure risk.

3.5 Catheters

From August 7, 2003, to the report cut-off date of October 31, 2022, there were 11,376 catheters followed in the registry. The total number of catheters was not equal to the total number of pumps (n=12,741) because patients may have undergone pump replacements but used the same catheters, or patients may have been implanted with Medtronic pumps and non-Medtronic catheters which were not registered with Medtronic Device And Registrant Tracking (DART) system. The aggregate prospective follow-up time for all catheters was 420,266 months (35,022 years). Table 3.24 provides the number and percentage of catheters by model.

Table 3.24: Targeted Drug Delivery Catheter Counts by Model

Model Name	N (%)
Currently Manufactured[a]	**3,036 (26.7%)**
8780 (US & OUS)	1,498 (13.2%)
8781 (US & OUS)	1,256 (11.0%)
8731SC (OUS)	282 (2.5%)
Revised Catheters	**2,524 (22.2%)**
Revised As Designed[b]	759 (6.7%)
Revised Not As Designed[c]	733 (6.4%)
Ascenda Revised As Designed[d]	528 (4.6%)
Grafted Not As Designed[e]	504 (4.4%)
No Longer Manufactured	**5,404 (47.5%)**
8709	2,918 (25.7%)
8709SC	1,104 (9.7%)
8711	661 (5.8%)
8731	534 (4.7%)
8703W	187 (1.6%)
Other/Unspecified	**412 (3.6%)**
Total	**11,376 (100%)**

[a] Manufactured for designated region; US=United States; OUS =Outside United States.
[b] 8731 catheters repaired with an 8596 proximal or 8598 distal revision kit.
[c] Medtronic non-Ascenda catheters repaired with a Medtronic revision kit, but not for the model it was intended.
[d] 8780 or 8781 Ascenda catheters repaired with the 8782 or 8784 revision kit.
[e] Catheters that involve the ad-hoc assembly of components other than a Medtronic repair kit or brand-new catheter.

3.5.1 Catheter Events

There were 1,751 product performance-related events with an underlying reported etiology related to catheter function. This includes 1,740 events with a catheter etiology and 11 events with both a catheter and other etiology (including device and non-device etiologies). The majority of the events were catheter occlusion (n=480), catheter dislodgement (n=416), catheter break/cut (n=253), or catheter kink (n=241). Of the 1,751 events, 1,500 were the initial product performance event that affected catheter survival estimates.

The catheter product performance-related events are summarized by model in the catheter models section.

For the purposes of survival analysis, a device's follow-up time is cut off for one of three reasons: 1) the occurrence of a product performance-related event; 2) the occurrence of a censoring event; or 3) the device is event-free and censored at the patient's last follow-up prior to the data cut-off. For catheters:

- 1,500 had follow-up time cut-off due to product performance-related events.
- 7,562 were censored in the survival analysis for the following reasons: patient expired, catheter explanted/capped, site termination, patient discontinued, patient lost to follow-up, or therapy suspended.
- 2,314 were free from product performance-related events and censoring events, and were censored at the last follow-up visit prior to the report cut-off.

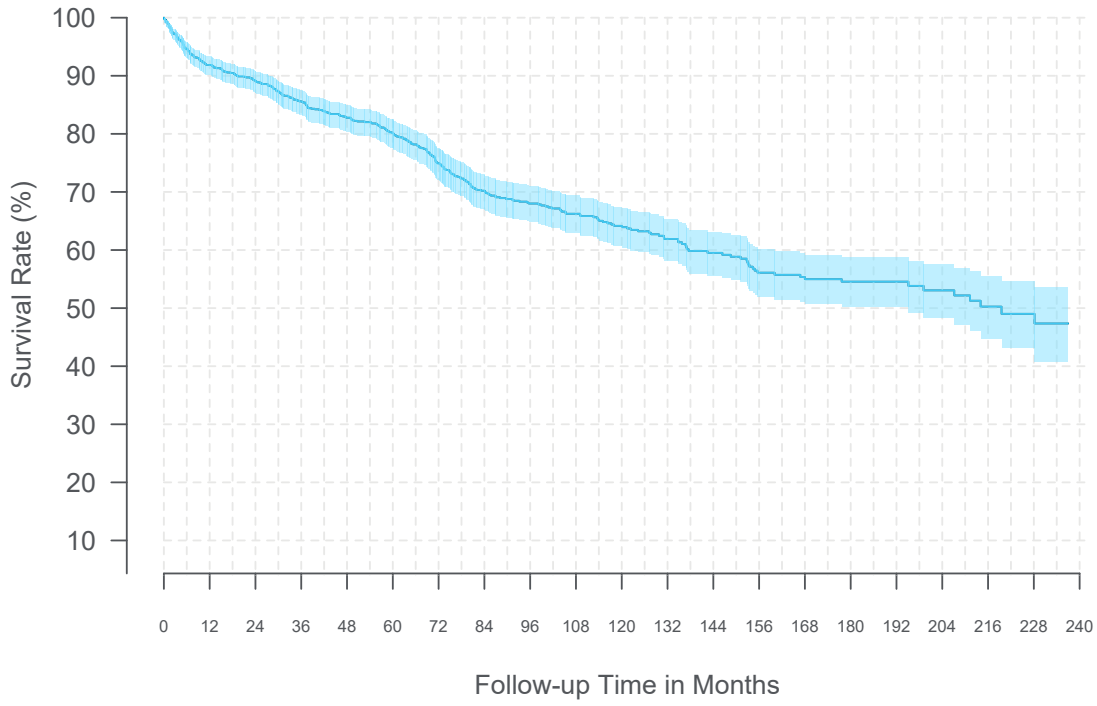
3.5.2 Catheter Models

The figures and tables below represent catheter survival and 95% confidence intervals where at least 20 catheters contributed to each 3-month interval. Survival curves are only shown if more than 20 devices had at least 12 months of follow-up at the time of the report cut-off for each model.

Medtronic catheter repair kits and 2-piece catheters include specially designed connector pins and strain relief sleeves to splice the catheter segments together. Catheters grafted not as designed, by definition, involve the ad-hoc assembly of components other than those from a Medtronic repair kit or brand-new catheter. Medtronic recommends that clinicians follow the labeling for the catheter revision kits.

3.5.2.1 Model 8709

Model/Name	8709/InDura
FDA Approval Date	May 1998
Catheters Enrolled	2,918
Catheters Currently Active in Study	128
Initial Product Performance Events	362
Median Follow-up Time (Months)	17.8
Cumulative Follow-up Time (Months)	100,121



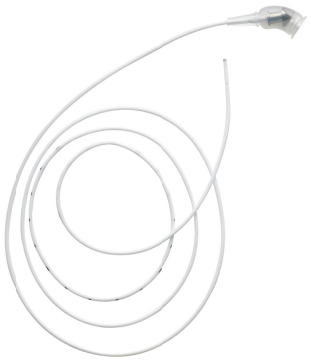
Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	91.9% (90.1%, 93.3%)	89.1% (87.2%, 90.8%)	85.6% (83.4%, 87.5%)	82.8% (80.4%, 84.9%)	80.1% (77.6%, 82.4%)
Sample Size	992	937	874	779	666

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	74.9% (72.1%, 77.6%)	70.2% (67.1%, 73.1%)	68.0% (64.8%, 71.0%)	66.2% (62.9%, 69.3%)	64.2% (60.7%, 67.4%)
Sample Size	572	505	422	338	285

Time Interval	11 Years	12 Years	13 Years	14 Years	15 Years
Survival (95% CI)	61.9% (58.3%, 65.3%)	59.5% (55.6%, 63.2%)	56.1% (51.9%, 60.1%)	55.0% (50.7%, 59.1%)	54.6% (50.2%, 58.7%)
Sample Size	227	180	158	145	117

Time Interval	16 Years	17 Years	18 Years	19 Years	At 237 Months
Survival (95% CI)	54.6% (50.2%, 58.7%)	53.1% (48.3%, 57.6%)	50.3% (44.8%, 55.5%)	49.0% (43.1%, 54.6%)	47.4% (40.8%, 53.6%)
Sample Size	84	62	41	29	21

Specification: 8709	
Total Length	89 cm
Outer Diameter (spinal segment)	1.4 mm (4.2 French)
Inner Diameter (spinal segment)	0.53 mm
Catheter Tip Description	Closed with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Pump end

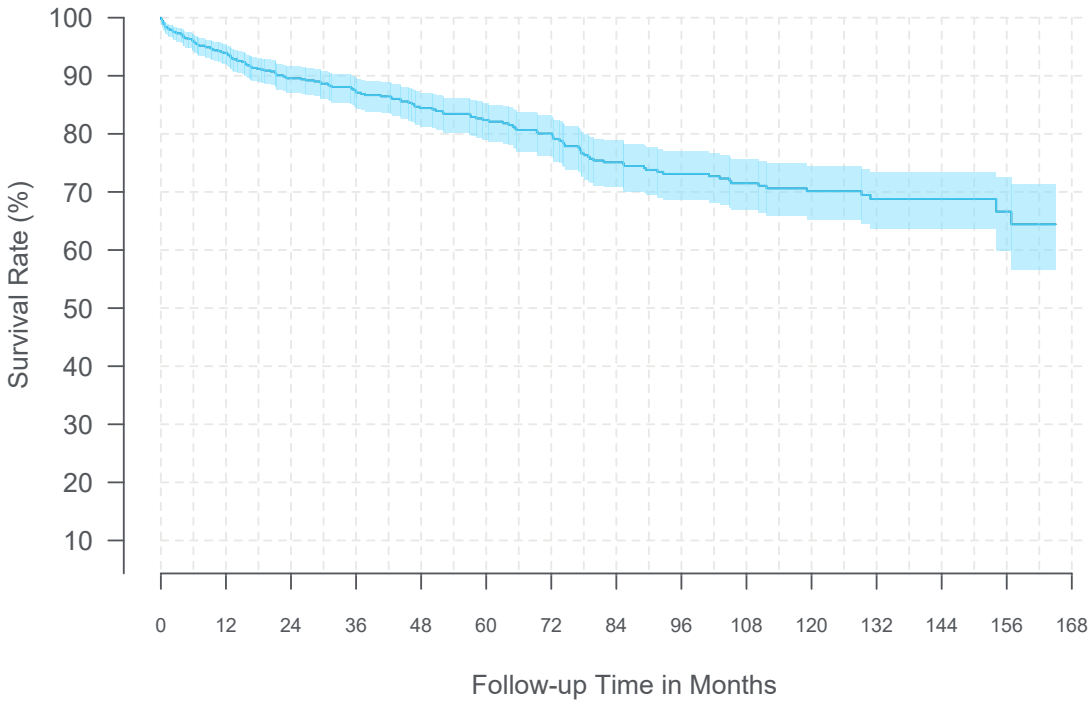


Catheter Event Summary: 8709	N
Catheter Dislodgement	95
Catheter Occlusion	86
Catheter Break/Cut	78
Catheter Kink	31
Catheter Disconnection At Pump	20
Catheter Leakage	16
Pump Connector Break/Cut	10
Catheter Dysfunction	6
Catheter Related Complication	3
Pump Unable To Enter/Withdraw From Catheter Access Port	3
Device Issue	2
Device Malfunction	2
Other[a]	10
Total	**362**

[a] Composed of event codes with 1 event each.

3.5.2.2 Model 8709SC

Model/Name	8709SC/InDura 1P
FDA Approval Date	March 2006
Catheters Enrolled	1,104
Catheters Currently Active in Study	141
Initial Product Performance Events	151
Median Follow-up Time (Months)	28.4
Cumulative Follow-up Time (Months)	48,161

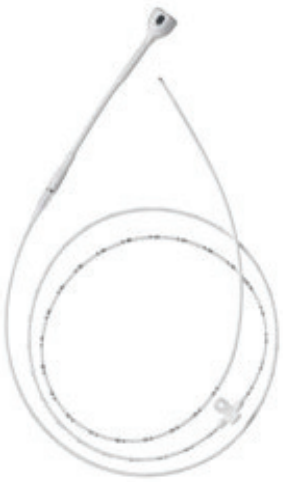


Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	94.0% (92.1%, 95.4%)	89.6% (87.1%, 91.6%)	87.3% (84.5%, 89.6%)	84.4% (81.3%, 87.1%)	82.4% (79.0%, 85.3%)
Sample Size	669	520	437	360	297

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	80.0% (76.3%, 83.2%)	75.1% (70.8%, 78.8%)	73.1% (68.6%, 77.0%)	71.5% (66.8%, 75.6%)	70.1% (65.3%, 74.4%)
Sample Size	259	241	195	167	137

Time Interval	11 Years	12 Years	13 Years	At 165 Months	
Survival (95% CI)	68.8% (63.7%, 73.4%)	68.8% (63.7%, 73.4%)	66.6% (59.9%, 72.5%)	64.4% (56.5%, 71.3%)	—
Sample Size	97	60	31	22	

Specification: 8709SC	
Total Length	89 cm
Outer Diameter (spinal segment)	1.4 mm (4.2 French)
Inner Diameter (spinal segment)	0.53 mm
Catheter Tip Description	Closed tip, radiopaque, titanium with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Pump end

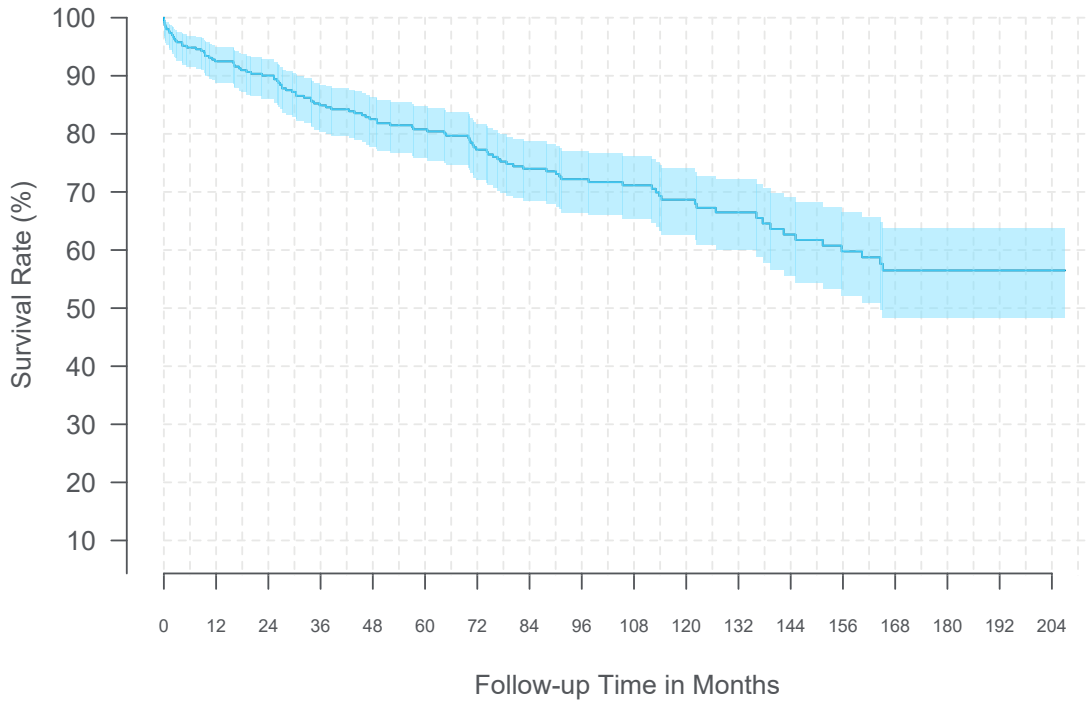


Catheter Event Summary: 8709SC	N
Catheter Occlusion	42
Catheter Break/Cut	34
Catheter Dislodgement	34
Catheter Leakage	8
Catheter Kink	6
Catheter Disconnection At Pump	5
Catheter Dysfunction	5
Catheter Related Complication	3
Pump Unable To Enter/Withdraw From Catheter Access Port	3
Catheter Damage	2
Device Damage	2
Device Malfunction	2
Other[a]	5
Total	**151**

[a] Composed of event codes with 1 event each.

3.5.2.3 Model 8711

Model/Name	8711/InDura
FDA Approval Date	October 1999
Catheters Enrolled	661
Catheters Currently Active in Study	60
Initial Product Performance Events	100
Median Follow-up Time (Months)	31.7
Cumulative Follow-up Time (Months)	32,077



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	92.5% (88.9%, 95.0%)	90.0% (86.1%, 92.9%)	84.9% (80.4%, 88.4%)	82.5% (77.8%, 86.3%)	80.8% (75.9%, 84.8%)
Sample Size	307	286	258	238	225

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	77.3% (72.0%, 81.6%)	74.0% (68.5%, 78.7%)	72.2% (66.5%, 77.1%)	71.1% (65.4%, 76.1%)	68.7% (62.6%, 74.0%)
Sample Size	189	179	148	124	100

Time Interval	11 Years	12 Years	13 Years	14 Years	15 Years
Survival (95% CI)	66.5% (60.0%, 72.1%)	62.7% (55.5%, 69.0%)	59.8% (52.2%, 66.5%)	56.5% (48.4%, 63.8%)	56.5% (48.4%, 63.8%)
Sample Size	76	65	60	44	30

Time Interval	16 Years	17 Years	At 207 Months		
Survival (95% CI)	56.5% (48.4%, 63.8%)	56.5% (48.4%, 63.8%)	56.5% (48.4%, 63.8%)	—	—
Sample Size	27	20	20		

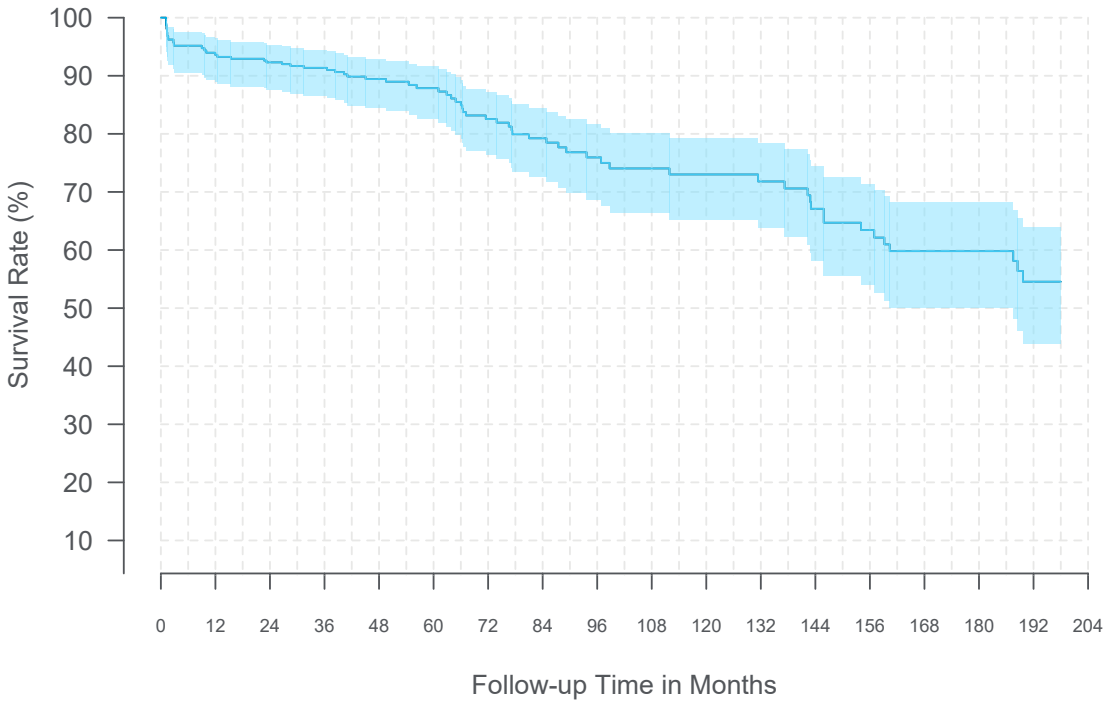
Specification: 8711	
Total Length	104.1 cm
Outer Diameter (spinal segment)	1.4 mm (4.2 French)
Inner Diameter (spinal segment)	0.53 mm
Catheter Tip Description	Closed with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Spinal and pump ends

Catheter Event Summary: 8711	N
Catheter Occlusion	32
Catheter Break/Cut	19
Catheter Dislodgement	13
Catheter Dysfunction	9
Catheter Kink	8
Catheter Leakage	4
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Catheter Disconnection At Pump	2
Catheter Related Complication	2
Device Issue	2
Other[a]	5
Total	**100**

[a] Composed of event codes with 1 event each.

3.5.2.4 Model 8731

Model/Name	8731
FDA Approval Date	October 2002
Catheters Enrolled	534
Catheters Currently Active in Study	41
Initial Product Performance Events	64
Median Follow-up Time (Months)	32.8
Cumulative Follow-up Time (Months)	24,448



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	93.6% (88.9%, 96.4%)	92.3% (87.6%, 95.3%)	91.4% (86.6%, 94.5%)	89.4% (84.5%, 92.9%)	87.9% (82.6%, 91.6%)
Sample Size	262	305	255	198	150

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	82.6% (76.4%, 87.2%)	79.2% (72.6%, 84.4%)	75.9% (68.8%, 81.7%)	74.0% (66.5%, 80.1%)	73.0% (65.3%, 79.3%)
Sample Size	134	107	82	71	65

Time Interval	11 Years	12 Years	13 Years	14 Years	15 Years
Survival (95% CI)	71.8% (63.8%, 78.4%)	67.1% (58.2%, 74.5%)	63.4% (54.1%, 71.4%)	59.8% (50.1%, 68.2%)	59.8% (50.1%, 68.2%)
Sample Size	60	55	49	47	40

Time Interval	16 Years	At 198 Months			
Survival (95% CI)	54.5% (44.0%, 64.0%)	54.5% (44.0%, 64.0%)	—	—	—
Sample Size	27	23			

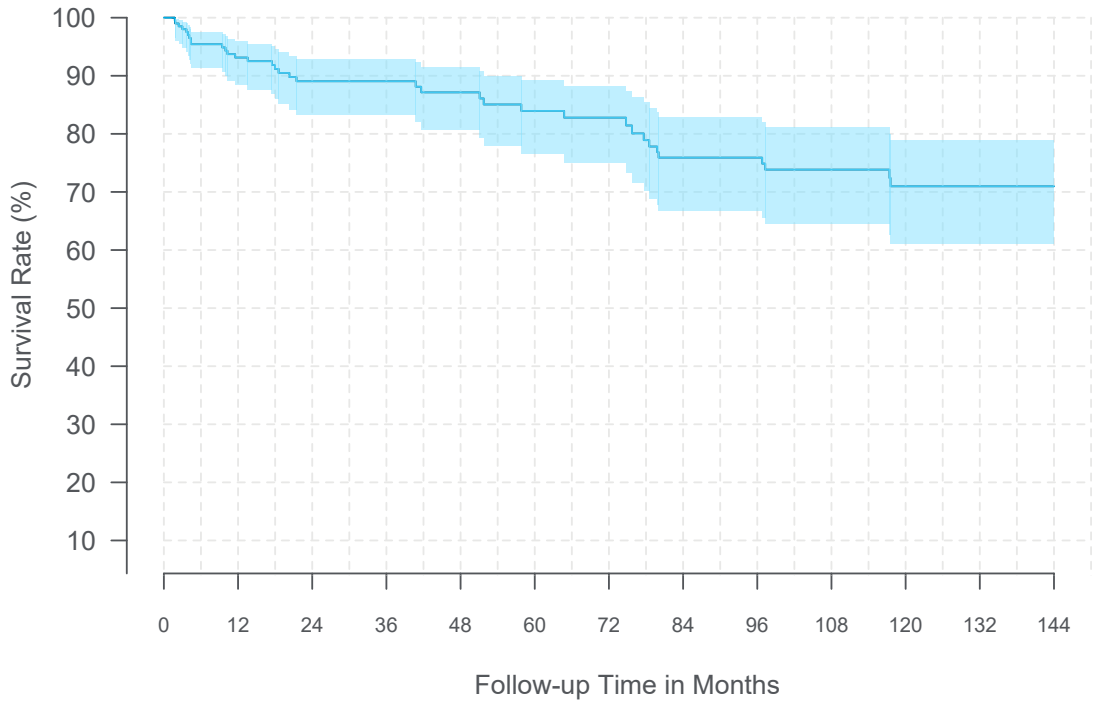
Specification: 8731	
Total Length	104.1 cm
Outer Diameter (spinal segment)	1.4 mm (4.2 French)
Inner Diameter (spinal segment)	0.53 mm
Catheter Tip Description	Closed tip, radiopaque, titanium with 6 side holes
Catheter Volume	2.22 mL/cm
Trimmable Segments	Spinal end

Catheter Event Summary: 8731	N
Catheter Occlusion	24
Catheter Dislodgement	19
Catheter Break/Cut	5
Catheter Kink	4
Catheter Disconnection At Pump	3
Catheter Related Complication	3
Catheter Dysfunction	2
Other[a]	4
Total	**64**

[a] Composed of event codes with 1 event each.

3.5.2.5 Model 8731SC

Model/Name	8731SC
FDA Approval Date	March 2006
Catheters Enrolled	282
Catheters Currently Active in Study	63
Initial Product Performance Events	38
Median Follow-up Time (Months)	37.9
Cumulative Follow-up Time (Months)	12,658



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	93.1% (88.5%, 96.0%)	89.1% (83.3%, 92.9%)	89.1% (83.3%, 92.9%)	87.1% (80.7%, 91.5%)	83.9% (76.5%, 89.2%)
Sample Size	155	117	99	87	75

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	82.8% (75.1%, 88.3%)	75.9% (66.8%, 82.9%)	75.9% (66.8%, 82.9%)	73.8% (64.5%, 81.1%)	71.0% (61.0%, 78.8%)
Sample Size	63	81	75	63	47

Time Interval	11 Years	12 Years			
Survival (95% CI)	71.0% (61.0%, 78.8%)	71.0% (61.0%, 78.8%)	—	—	—
Sample Size	27	20			

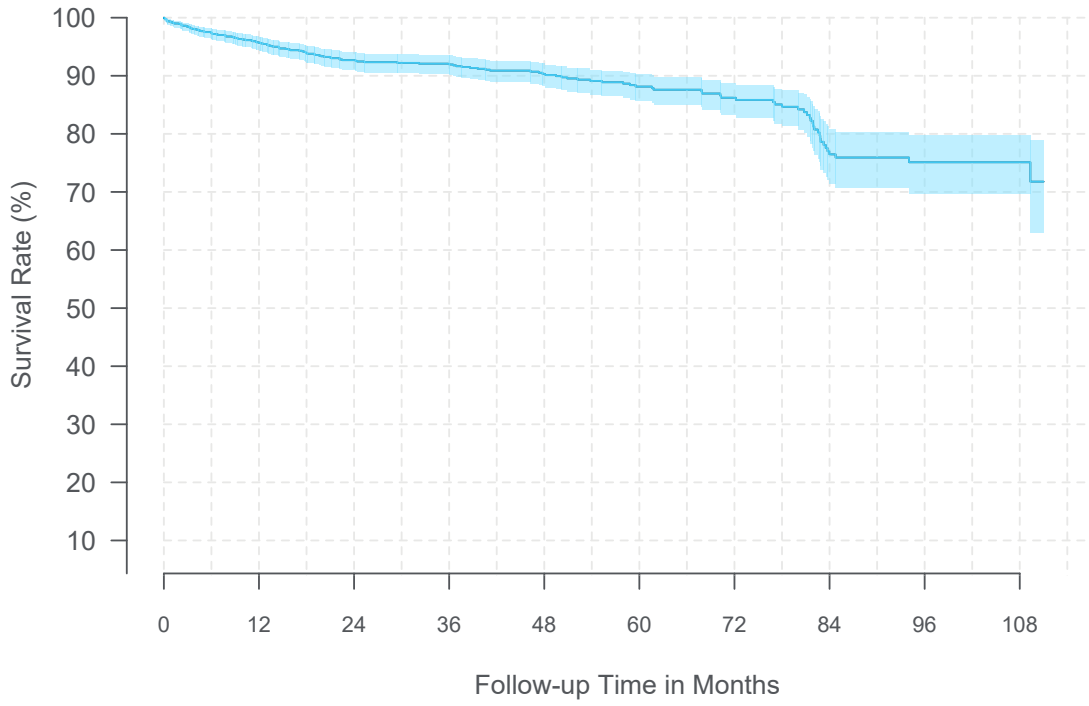
Specification: 8731SC	
Total Length	104.1 cm
Outer Diameter (spinal segment)	1.4 mm (4.2 French)
Inner Diameter (spinal segment)	0.53 mm
Catheter Tip Description	Closed with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Spinal and pump ends

Catheter Event Summary: 8731SC	N
Catheter Occlusion	14
Catheter Dislodgement	8
Catheter Kink	4
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Catheter Dysfunction	3
Catheter Leakage	2
Other[a]	3
Total	**38**

[a] Composed of event codes with 1 event each.

3.5.2.6 Model 8780

Model/Name	8780/Ascenda
FDA Approval Date	May 2012
Catheters Enrolled	1,498
Catheters Currently Active in Study	641
Initial Product Performance Events	139
Median Follow-up Time (Months)	30.6
Cumulative Follow-up Time (Months)	55,106



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	95.7% (94.4%, 96.7%)	92.7% (91.0%, 94.1%)	92.1% (90.3%, 93.5%)	90.3% (88.3%, 92.1%)	88.1% (85.6%, 90.2%)
Sample Size	1,019	801	640	472	336

Time Interval	6 Years	7 Years	8 Years	9 Years	At 111 Months
Survival (95% CI)	86.2% (83.3%, 88.7%)	76.5% (71.3%, 80.8%)	75.1% (69.7%, 79.7%)	75.1% (69.7%, 79.7%)	71.8% (62.9%, 78.9%)
Sample Size	230	139	82	25	21

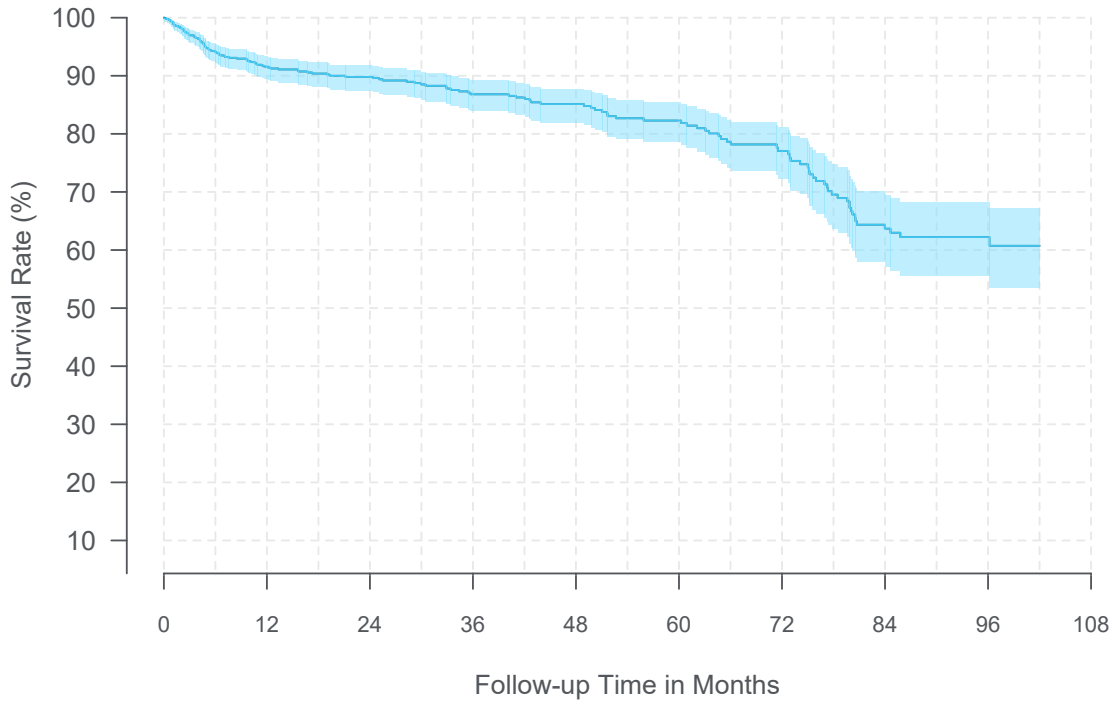
Specification: 8780	
Total Length	114 cm
Outer Diameter (spinal segment)	1.2 mm (4.0 French)
Inner Diameter (spinal segment)	0.5 mm
Catheter Tip Description	Closed with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Connector end of the spinal segment

Catheter Event Summary: 8780	N
Catheter Occlusion	55
Catheter Kink	27
Catheter Dislodgement	18
Catheter Break/Cut	15
Catheter Damage	7
Catheter Leakage	4
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Catheter Disconnection At Pump	2
Catheter Dysfunction	2
Other[a]	5
Total	**139**

[a] Composed of event codes with 1 event each.

3.5.2.7 Model 8781

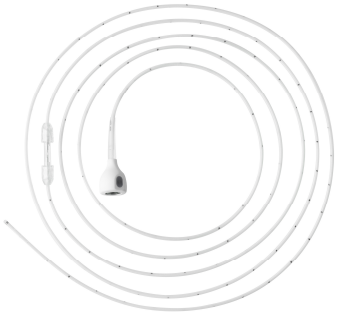
Model/Name	8781/Ascenda
FDA Approval Date	May 2012
Catheters Enrolled	1,256
Catheters Currently Active in Study	379
Initial Product Performance Events	149
Median Follow-up Time (Months)	12.7
Cumulative Follow-up Time (Months)	33,238



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	91.6% (89.5%, 93.3%)	89.8% (87.4%, 91.8%)	86.8% (83.9%, 89.2%)	85.1% (82.0%, 87.8%)	82.3% (78.6%, 85.4%)
Sample Size	568	440	347	265	191

Time Interval	6 Years	7 Years	8 Years	At 102 Months	
Survival (95% CI)	77.1% (72.3%, 81.1%)	63.7% (57.2%, 69.5%)	62.2% (55.5%, 68.2%)	60.7% (53.5%, 67.2%)	—
Sample Size	135	93	42	25	

Specification: 8781	
Total Length	140 cm
Outer Diameter (spinal segment)	1.2 mm (4.0 French)
Inner Diameter (spinal segment)	0.5 mm
Catheter Tip Description	Closed with 6 side holes
Catheter Volume	0.0022 mL/cm
Trimmable Segments	Catheter connector ends of the spinal and pump segments

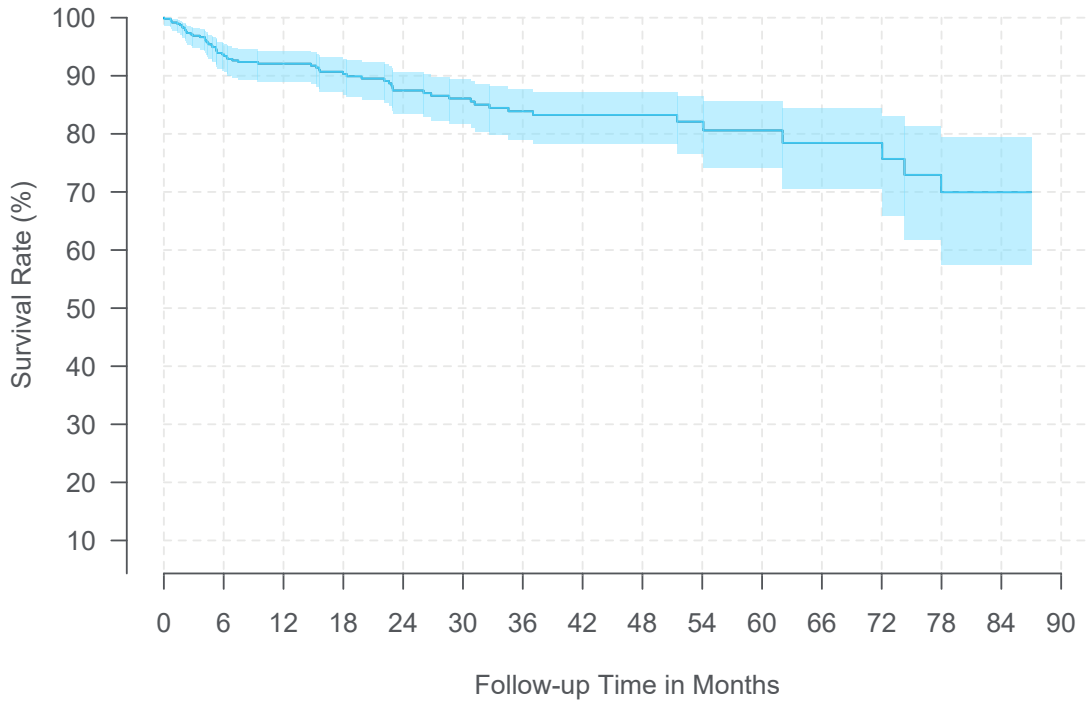


Catheter Event Summary: 8781	N
Catheter Kink	54
Catheter Occlusion	35
Catheter Dislodgement	34
Catheter Break/Cut	6
Catheter Dysfunction	4
Catheter Leakage	4
Catheter Disconnection At Pump	3
Device Malfunction	2
Pump Reservoir Volume Discrepancy	2
Other[a]	5
Total	**149**

[a] Composed of event codes with 1 event each.

3.5.2.8 Ascenda Revised As Designed

Model/Name	Ascenda Revised As Designed
FDA Approval Date	May 2012
Catheters Enrolled	528
Catheters Currently Active in Study	261
Initial Product Performance Events	59
Median Follow-up Time (Months)	16.9
Cumulative Follow-up Time (Months)	12,781



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	92.1% (89.0%, 94.3%)	87.5% (83.4%, 90.6%)	83.9% (79.1%, 87.7%)	83.3% (78.3%, 87.2%)	80.6% (74.2%, 85.6%)
Sample Size	292	204	138	79	41

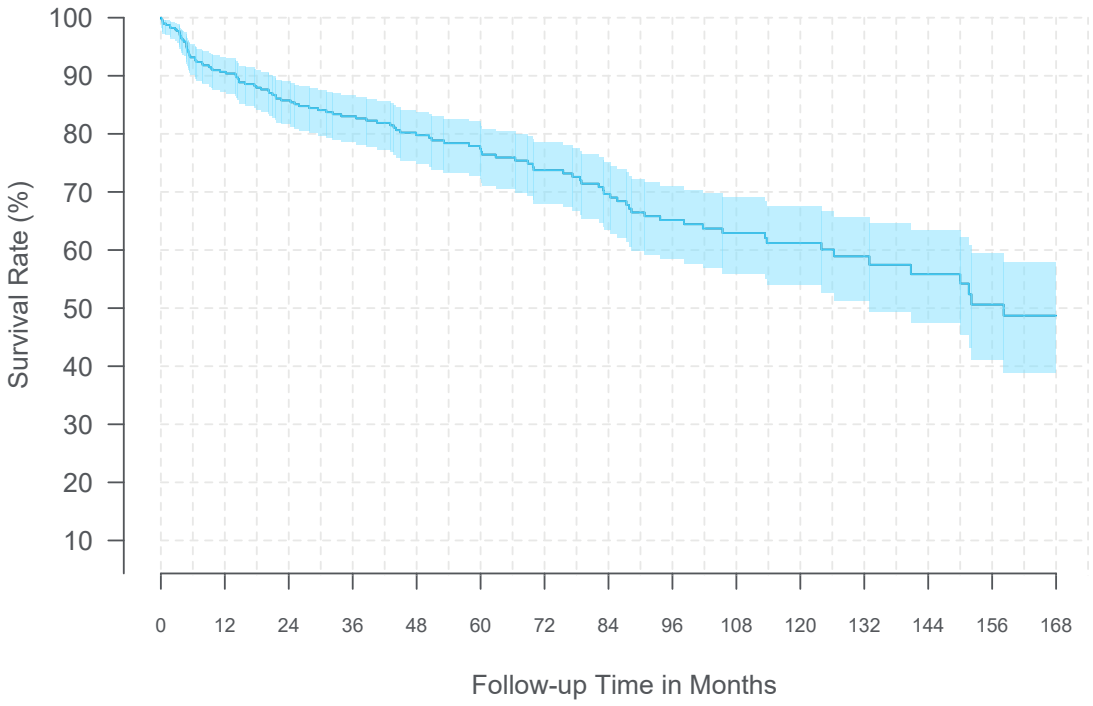
Time Interval	6 Years	7 Years	At 87 Months		
Survival (95% CI)	78.4% (70.6%, 84.4%)	70.0% (57.5%, 79.4%)	70.0% (57.5%, 79.4%)	—	—
Sample Size	28	24	23		

Catheter Event Summary: Ascenda RAD	N
Catheter Occlusion	18
Catheter Dislodgement	14
Catheter Kink	14
Catheter Break/Cut	3
Device Component Migration	3
Other[a]	7
Total	**59**

[a] Composed of event codes with 1 event each.

3.5.2.9 Grafted Not As Designed

Model/Name	Grafted Not As Designed
FDA Approval Date	NA
Catheters Enrolled	504
Catheters Currently Active in Study	99
Initial Product Performance Events	108
Median Follow-up Time (Months)	39.0
Cumulative Follow-up Time (Months)	24,939



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	90.7% (87.3%, 93.2%)	85.8% (81.7%, 89.0%)	83.0% (78.6%, 86.6%)	79.8% (74.9%, 83.8%)	77.4% (72.2%, 81.8%)
Sample Size	312	262	226	181	157

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	73.8% (68.1%, 78.6%)	69.6% (63.4%, 75.0%)	65.2% (58.5%, 71.0%)	62.9% (56.0%, 69.1%)	61.2% (54.0%, 67.6%)
Sample Size	131	114	92	80	58

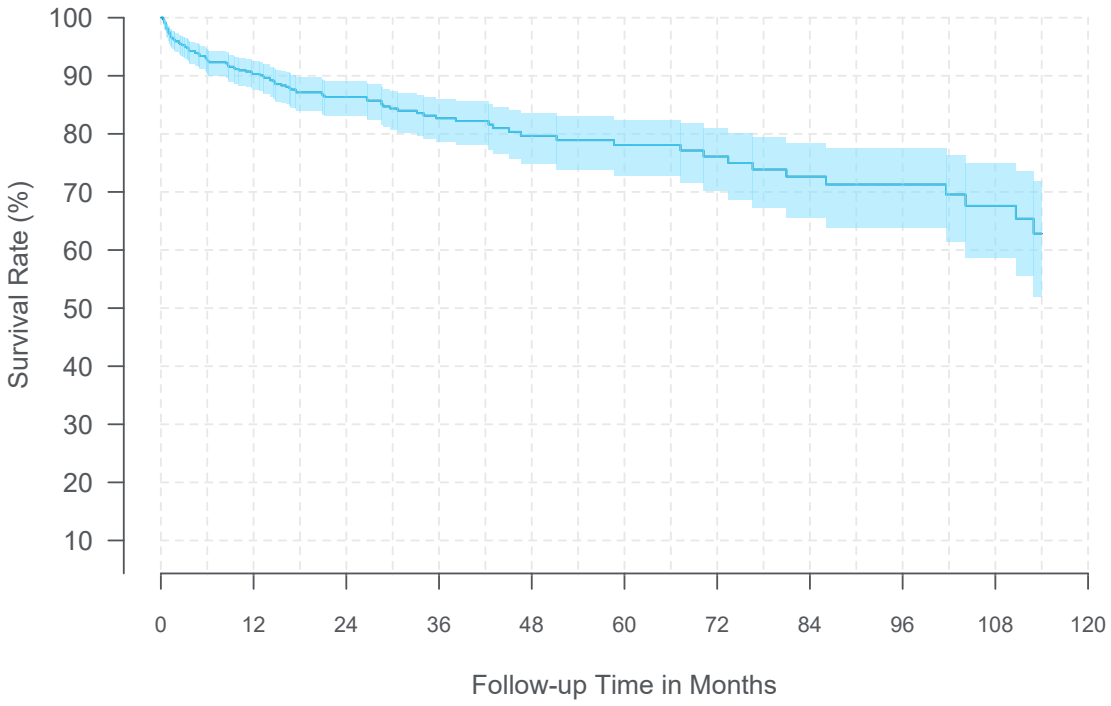
Time Interval	11 Years	12 Years	13 Years	14 Years	
Survival (95% CI)	58.9% (51.3%, 65.8%)	55.8% (47.4%, 63.4%)	50.6% (41.1%, 59.4%)	48.7% (38.8%, 57.9%)	—
Sample Size	41	33	26	20	

Catheter Event Summary: Grafted Not As Designed	N
Catheter Occlusion	31
Catheter Dislodgement	27
Catheter Break/Cut	14
Catheter Kink	8
Catheter Leakage	7
Pump Unable To Enter/Withdraw From Catheter Access Port	4
Catheter Dysfunction	3
Catheter Related Complication	3
Catheter Damage	2
Device Malfunction	2
Other[a]	7
Total	**108**

[a] Composed of event codes with 1 event each.

3.5.2.10 Revised As Designed

Model/Name	Revised As Designed
FDA Approval Date	October 2002
Catheters Enrolled	759
Catheters Currently Active in Study	379
Initial Product Performance Events	104
Median Follow-up Time (Months)	18.4
Cumulative Follow-up Time (Months)	20,675



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	90.3% (87.6%, 92.5%)	86.3% (83.1%, 89.0%)	82.7% (78.7%, 86.0%)	79.7% (74.9%, 83.6%)	78.1% (72.9%, 82.4%)
Sample Size	424	290	178	112	92

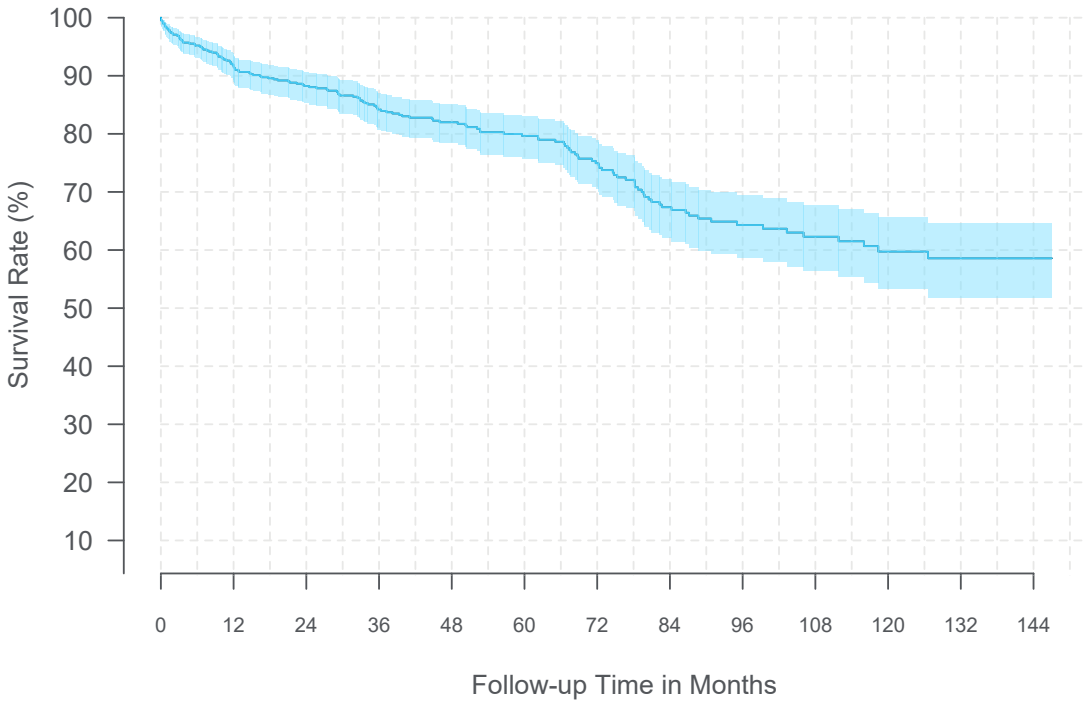
Time Interval	6 Years	7 Years	8 Years	9 Years	At 114 Months
Survival (95% CI)	76.1% (70.2%, 81.0%)	72.6% (65.6%, 78.5%)	71.3% (63.8%, 77.5%)	67.6% (58.7%, 75.0%)	62.8% (52.0%, 71.8%)
Sample Size	68	54	47	31	21

Catheter Event Summary: Revised As Designed	N
Catheter Dislodgement	54
Catheter Occlusion	24
Catheter Kink	7
Device Component Migration	7
Catheter Break/Cut	3
Catheter Leakage	3
Catheter Dysfunction	2
Pump Unable To Enter/Withdraw From Catheter Access Port	2
Other[a]	2
Total	**104**

[a] Composed of event codes with 1 event each.

3.5.2.11 Revised Not As Designed

Model/Name	Revised Not As Designed
FDA Approval Date	NA
Catheters Enrolled	733
Catheters Currently Active in Study	136
Initial Product Performance Events	151
Median Follow-up Time (Months)	41.1
Cumulative Follow-up Time (Months)	35,750



Time Interval	1 Year	2 Years	3 Years	4 Years	5 Years
Survival (95% CI)	91.5% (89.0%, 93.5%)	88.2% (85.3%, 90.6%)	84.2% (80.8%, 87.0%)	82.0% (78.4%, 85.1%)	79.6% (75.8%, 83.0%)
Sample Size	518	452	375	307	246

Time Interval	6 Years	7 Years	8 Years	9 Years	10 Years
Survival (95% CI)	74.9% (70.4%, 78.9%)	67.4% (62.1%, 72.1%)	64.3% (58.7%, 69.4%)	62.3% (56.3%, 67.7%)	59.7% (53.3%, 65.6%)
Sample Size	189	145	107	83	60

Time Interval	11 Years	12 Years	At 147 Months		
Survival (95% CI)	58.6% (51.9%, 64.7%)	58.6% (51.9%, 64.7%)	58.6% (51.9%, 64.7%)	—	—
Sample Size	43	24	21		

Catheter Event Summary: Revised Not As Designed	N
Catheter Occlusion	55
Catheter Dislodgement	24
Catheter Break/Cut	17
Catheter Kink	17
Catheter Leakage	10
Pump Unable To Enter/Withdraw From Catheter Access Port	5
Catheter Disconnection At Pump	4
Device Component Migration	4
Catheter Dysfunction	3
Catheter Related Complication	2
Other[a]	10
Total	**151**

[a] Composed of event codes with 1 event each.

3.5.3 Catheter Summary

Table 3.25: Targeted Drug Delivery Catheter Characteristics

Model/Name	FDA Approval Date	Catheters Enrolled	Catheters Active	Initial Product Performance Events	Median Follow-up Time (Months)	Cumulative Follow-up Time (Months)
8709	May 1998	2,918	128	362	17.8	100,121
8709SC	March 2006	1,104	141	151	28.4	48,161
8711	October 1999	661	60	100	31.7	32,077
8731	October 2002	534	41	64	32.8	24,448
8731SC	March 2006	282	63	38	37.9	12,658
8780	May 2012	1,498	641	139	30.6	55,106
8781	May 2012	1,256	379	149	12.7	33,238
Ascenda Revised As Designed	May 2012	528	261	59	16.9	12,781
Grafted Not As Designed	NA	504	99	108	39.0	24,939
Revised As Designed	October 2002	759	379	104	18.4	20,675
Revised Not As Designed	NA	733	136	151	41.1	35,750

Table 3.26: Targeted Drug Delivery Catheter Survival Probability (95% Confidence Intervals)

Model Name	1 Year	2 Years	3 Years	4 Years	5 Years
8709	91.9% (90.1%, 93.3%)	89.1% (87.2%, 90.8%)	85.6% (83.4%, 87.5%)	82.8% (80.4%, 84.9%)	80.1% (77.6%, 82.4%)
8709SC	94.0% (92.1%, 95.4%)	89.6% (87.1%, 91.6%)	87.3% (84.5%, 89.6%)	84.4% (81.3%, 87.1%)	82.4% (79.0%, 85.3%)
8711	92.5% (88.9%, 95.0%)	90.0% (86.1%, 92.9%)	84.9% (80.4%, 88.4%)	82.5% (77.8%, 86.3%)	80.8% (75.9%, 84.8%)
8731	93.6% (88.9%, 96.4%)	92.3% (87.6%, 95.3%)	91.4% (86.6%, 94.5%)	89.4% (84.5%, 92.9%)	87.9% (82.6%, 91.6%)
8731SC	93.1% (88.5%, 96.0%)	89.1% (83.3%, 92.9%)	89.1% (83.3%, 92.9%)	87.1% (80.7%, 91.5%)	83.9% (76.5%, 89.2%)
8780	95.7% (94.4%, 96.7%)	92.7% (91.0%, 94.1%)	92.1% (90.3%, 93.5%)	90.3% (88.3%, 92.1%)	88.1% (85.6%, 90.2%)
8781	91.6% (89.5%, 93.3%)	89.8% (87.4%, 91.8%)	86.8% (83.9%, 89.2%)	85.1% (82.0%, 87.8%)	82.3% (78.6%, 85.4%)
Ascenda Revised As Designed	92.1% (89.0%, 94.3%)	87.5% (83.4%, 90.6%)	83.9% (79.1%, 87.7%)	83.3% (78.3%, 87.2%)	80.6% (74.2%, 85.6%)
Grafted Not As Designed	90.7% (87.3%, 93.2%)	85.8% (81.7%, 89.0%)	83.0% (78.6%, 86.6%)	79.8% (74.9%, 83.8%)	77.4% (72.2%, 81.8%)
Revised As Designed	90.3% (87.6%, 92.5%)	86.3% (83.1%, 89.0%)	82.7% (78.7%, 86.0%)	79.7% (74.9%, 83.6%)	78.1% (72.9%, 82.4%)
Revised Not As Designed	91.5% (89.0%, 93.5%)	88.2% (85.3%, 90.6%)	84.2% (80.8%, 87.0%)	82.0% (78.4%, 85.1%)	79.6% (75.8%, 83.0%)

Model Name	6 Years	7 Years	8 Years	9 Years	10 Years
8709	74.9% (72.1%, 77.6%)	70.2% (67.1%, 73.1%)	68.0% (64.8%, 71.0%)	66.2% (62.9%, 69.3%)	64.2% (60.7%, 67.4%)
8709SC	80.0% (76.3%, 83.2%)	75.1% (70.8%, 78.8%)	73.1% (68.6%, 77.0%)	71.5% (66.8%, 75.6%)	70.1% (65.3%, 74.4%)
8711	77.3% (72.0%, 81.6%)	74.0% (68.5%, 78.7%)	72.2% (66.5%, 77.1%)	71.1% (65.4%, 76.1%)	68.7% (62.6%, 74.0%)
8731	82.6% (76.4%, 87.2%)	79.2% (72.6%, 84.4%)	75.9% (68.8%, 81.7%)	74.0% (66.5%, 80.1%)	73.0% (65.3%, 79.3%)
8731SC	82.8% (75.1%, 88.3%)	75.9% (66.8%, 82.9%)	75.9% (66.8%, 82.9%)	73.8% (64.5%, 81.1%)	71.0% (61.0%, 78.8%)
8780	86.2% (83.3%, 88.7%)	76.5% (71.3%, 80.8%)	75.1% (69.7%, 79.7%)	75.1% (69.7%, 79.7%)	—
8781	77.1% (72.3%, 81.1%)	63.7% (57.2%, 69.5%)	62.2% (55.5%, 68.2%)	—	—
Ascenda Revised As Designed	78.4% (70.6%, 84.4%)	70.0% (57.5%, 79.4%)	—	—	—
Grafted Not As Designed	73.8% (68.1%, 78.6%)	69.6% (63.4%, 75.0%)	65.2% (58.5%, 71.0%)	62.9% (56.0%, 69.1%)	61.2% (54.0%, 67.6%)
Revised As Designed	76.1% (70.2%, 81.0%)	72.6% (65.6%, 78.5%)	71.3% (63.8%, 77.5%)	67.6% (58.7%, 75.0%)	—
Revised Not As Designed	74.9% (70.4%, 78.9%)	67.4% (62.1%, 72.1%)	64.3% (58.7%, 69.4%)	62.3% (56.3%, 67.7%)	59.7% (53.3%, 65.6%)

Model Name	11 Years	12 Years	13 Years	14 Years	15 Years
8709	61.9% (58.3%, 65.3%)	59.5% (55.6%, 63.2%)	56.1% (51.9%, 60.1%)	55.0% (50.7%, 59.1%)	54.6% (50.2%, 58.7%)
8709SC	68.8% (63.7%, 73.4%)	68.8% (63.7%, 73.4%)	66.6% (59.9%, 72.5%)	—	—
8711	66.5% (60.0%, 72.1%)	62.7% (55.5%, 69.0%)	59.8% (52.2%, 66.5%)	56.5% (48.4%, 63.8%)	56.5% (48.4%, 63.8%)
8731	71.8% (63.8%, 78.4%)	67.1% (58.2%, 74.5%)	63.4% (54.1%, 71.4%)	59.8% (50.1%, 68.2%)	59.8% (50.1%, 68.2%)
8731SC	71.0% (61.0%, 78.8%)	71.0% (61.0%, 78.8%)	—	—	—
8780	—	—	—	—	—
8781	—	—	—	—	—
Ascenda Revised As Designed	—	—	—	—	—
Grafted Not As Designed	58.9% (51.3%, 65.8%)	55.8% (47.4%, 63.4%)	50.6% (41.1%, 59.4%)	48.7% (38.8%, 57.9%)	—
Revised As Designed	—	—	—	—	—
Revised Not As Designed	58.6% (51.9%, 64.7%)	58.6% (51.9%, 64.7%)	—	—	—

Model Name	16 Years	17 Years	18 Years	19 Years	
8709	54.6% (50.2%, 58.7%)	53.1% (48.3%, 57.6%)	50.3% (44.8%, 55.5%)	49.0% (43.1%, 54.6%)	__
8709SC	__	__	__	__	__
8711	56.5% (48.4%, 63.8%)	56.5% (48.4%, 63.8%)	__	__	__
8731	54.5% (44.0%, 64.0%)	__	__	__	__
8731SC	__	__	__	__	__
8780	__	__	__	__	__
8781	__	__	__	__	__
Ascenda Revised As Designed	__	__	__	__	__
Grafted Not As Designed	__	__	__	__	__
Revised As Designed	__	__	__	__	__
Revised Not As Designed	__	__	__	__	__