Dasiglucagon Delivery System

LITERATURE SEARCH REPORT

Including Vigilance Search Plan

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# Abbreviations

| **Term** | **Description** |
| --- | --- |
| AACE | American Association of Clinical Endocrinology |
| AE | Adverse Event |
| AID | Automated insulin delivery |
| AP | Artificial pancreas |
| BfArM | Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) |
| BP | Bionic Pancreas |
| CEP | Clinical Evaluation Plan |
| CER | Clinical Evaluation Report |
| CGM | Continuous Glucose Monitoring |
| CHI | Congenital Hyperinsulinism |
| CI | Confidence Interval |
| CL | Closed loop |
| CLC | Closed-loop control |
| CSII | Continuous subcutaneous insulin infusion |
| CV | Coefficient of variation |
| DIY | Do it yourself |
| DKA | Diabetic ketoacidosis |
| ESC | Endocrine Society Clinical |
| EU | European Union |
| FDA | Food and Drug Administration |
| GHTF | Global Harmonization Task Force |
| GIR | Glucose infusion rate |
| GSPR | General Safety and Performance Requirement |
| Hb1Ac | Hemoglobin A1c |
| HCL | Hybrid closed-loop |
| HPRA | Ireland’s Health Products Regulatory Authority |
| ICU | Intensive care unit |
| IFU | Instruction for Use |
| IIS | Insulin infusion set |
| IMDRF | International Medical Device Regulators Forum |
| IQR | Interquartile range |
| IUGR | Intrauterine growth restriction |
| IV | Intravenous |
| KATP | ATP-dependent potassium channel |
| LSP | Literature Search Plan |
| LSR | Literature Search Report |
| MARD | Mean absolute relative deviation |
| MAUDE | Manufacturer and User Facility Device Experience |
| MD | Mean difference |
| MDCG | Medical Device Coordination Group |
| MDI | Multiple daily injections |
| MDR | Medical Device Regulation as amended by April 2017 |
| MHRA | United Kingdom’s Medicines and Healthcare products Regulatory Agency |
| N/A | Not applicable |
| NAS | Non-Aqueous Soluble |
| NEC | Necrotizing enterocolitis |
| NICE | National Institute for Health and Care Excellence |
| NME | Necrolytic migratory erythema |
| NCBI | The National Center for Biotechnology Information |
| PAH | Pulmonary arterial hypertension |
| PES | Pediatric Endocrine Society |
| PET | Positron emission tomography |
| PHHI | Persistent hyperinsulinemic hypoglycemia of infancy |
| PICO | Population, intervention, control, outcome |
| PRO | Patient-reported outcomes |
| PSHI | Perinatal stress-induced hyperinsulinism |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| SAE | Serious Adverse Event |
| SAP | Sensor-augmented pump |
| SD | Standard Deviation |
| SoC | Standard of care |
| SOTA | State-of-the-Art |
| SSA | Somatostatin analogues |
| T1D | Type 1 Diabetes |
| T2D | Type 2 Diabetes |
| TAR | Time above range |
| TBR | Time below range |
| TiER | Time in expanded range |
| TiR | Time in range |
| TiTR | Time in tighter range |
| TPLC | Total Product Life Cycle |
| UADE | Unanticipated adverse device effect |
| US | United States |
| VAS | Visual Analog Scale |

# Scope and objective

This literature search report (LSR) is carried out according to EU Regulation 2017/745 (1), MEDDEV 2.7.1 (2), GHTF SG5/N2R8:2007 (3), IMDRF MDCE WG/N56FINAL:2019 (4), and MDCG 2024-10 (5)to identify, appraise and analyze literature in support of the general safety and performance requirements (GSPRs) and claims for the Dasiglucagon Delivery System. Furthermore, the scope of this LSR is to identify literature relevant to review the current knowledge regarding subcutaneous influsion pumps.

The objective of the literature search and review is to:

* identify the current knowledge (i.e., the state of the art; SOTA) within the medical field of subcutaneous influsion pumps,
* carry out literature and vigilance searches as part of the firstclinical evaluation report (CER) for the Dasiglucagon Delivery System per EU Medical Device Regulation 2017/745 (MDR). The objective of this literature search is to identify and appraise clinical data to support the clinical evaluation of the performance and safety of the Dasiglucagon Delivery System,
* report the literature findings based on the literature search plan (LSP) for the Dasiglucagon Delivery System [ref], and
* analyze how the identified relevant literature supports the performance and safety of the Dasiglucagon Delivery System.

# Device description

The product covered by this LSR is listed below in **Table 1**.

|  |  |
| --- | --- |
| Table 1:Products Covered | |
| Product name(s) | Dasiglucagon Delivery System |
| Manufacturer name and address | DEKA Research and Development Corporation  340 Commercial St  Manchester, NH 03101  United States |
| Classification, EU | The product listed above is classified as Class IIb, Rule 12 according to the MDR |
| Marketed | The Dasiglucagon Delivery System is not currently marketed in any geography |

The Dasiglucagon Delivery System is intended for continuous subcutaneous delivery of dasiglucagon for use in neonates, infants, children, and adolescents of up to 16 years of age. The pump is a durable product intended for single patient use and the cassette is a disposable product intended for single use. The system, when used as intended, is considered non-life supporting medical equipment and is not the sole treatment method for the acute symptoms of congenital hyperinsulinism (CHI).

The Dasiglucagon Delivery System is intended solely for use with dasiglucagon.

The Dasiglucagon Delivery System consists of the following components:

1. Pump: A durable pump that interfaces to an Dasiglucagon Delivery System cassette and the remote interface. It incorporates fluid delivery algorithms and is powered by a rechargeable lithium ion battery.
2. Cassette: A single-use pumping cassette that combines microfluidic valves, a pump chamber, drug reservoir, and Acoustic Volume Sensing (AVS) measurement chamber. The cassette interfaces to a Dasiglucagon Delivery System pump and off-the-shelf infusion set.
3. Remote Interface (Controller): A Bluetooth wireless controller that serves as the user interface to the Dasiglucagon system. This includes a display and buttons for ease of use. The remote interface is the same as was cleared in the predicate product.

In use, the single-user durable pump is connected to a single-use cassette, and these two components mated together are referred to as the pump assembly. The remote interface and pump assembly are separate to offer an improved user experience: the remote interface offers an easy to read screen and multiple buttons while the pump is small and unobtrusive to facilitate discrete dasiglucagon delivery.

The Dasiglucagon Delivery system interfaces / connects to an infusion set via a standard luer fitting. The infusion set is a sterile commercially available infusion set, which is connected from the pump assembly to the patient. The following infusion sets are labeled for use with the Dasiglucagon Delivery System: Convatec neria ™ guard 12 cm (704012-5226), 30 cm (704030-5226), 60 cm (704060-5226).

## Intended purpose and Indications for use

The Dasiglucagon Delivery System is intended for continuous subcutaneous delivery of dasiglucagon for the prevention and treatment of hypoglycemia in patients up to 16 years of age with congenital hyperinsulinism (CHI). The pump is able to reliably and securely communicate with compatible digitally connected devices. The pump is indicated for single-patient home use and requires a prescription. The pump is indicated for use with dasiglucagon.

**Source:** Instructions for use (IFU) (6)

## Target population

The Dasiglucagon Delivery System is intended for continuous subcutaneous delivery of dasiglucagon for use in neonates, infants, children, and adolescents of up to 16 years of age.

# Literature Search Plan

The literature search plan (LSP) is described in a separate document [ref].

## Deviations from the literature search plan

There were no deviations from the LSP.

# Literature Search Results

## Device-specific searches

The device-specific literature search results are presented in **Table 2**. Details of the retrieved publications from the device-specific searches are provided in **Appendix I** including reasons for exclusions of non-relevant publications.

**Table 2: Search strategy and results for device-specific searches. Search dates: 05-Sep-2024 to 16-Sep-2024**

| **Database**  **Search No.** | **Search String** | **Filters** | **Hits** | **Included** |
| --- | --- | --- | --- | --- |
| PubMed #1 | Deka AND Dasiglucagon Delivery System | None | 0 | 0 |
| PubMed #2 | ACCU-CHEK AND (Spirit OR Combo) AND Roche | None | 10 | 5 |
| PubMed #3 | “MiniMed 770G” AND Medtronic | None | 4 | 4 |
| PubMed #4 | “Minimed 630G” AND Medtronic | None | 0 | 0 |
| PubMed #7 | t:slim X2 AND Tandem Diabetes Care | None | 3 | 2 |
| PubMed #8 | iLet AND Beta Bionics | None | 10 | 10 |
| PubMed #9 | Remunity AND (Millyard OR DEKA OR United Therapeutics) | None | 0 | 0 |
| PubMed #10 | "CADD-MS3" AND (Smiths Medical OR United Therapeutics) | None | 0 | 0 |
| PubMed #12 | Cane AND (Crono SC OR Crono 50 SC) | None | 0 | 0 |
| PubMed #13 | (i-JET OR iJET) AND EverAid | None | 0 | 0 |
| Cochrane Library #1 | [All text]: Deka AND Dasiglucagon Delivery System | None | 0 | 0 |
| Cochrane Library #2 | [All text]: ACCU-CHEK AND (Spirit OR Combo) AND Roche | None | 6 | 0 |
| Cochrane Library #3 | [All text]: MiniMed 770G AND Medtronic | None | 1 | 0 |
| Cochrane Library #4 | [All text]: Minimed 630G AND Medtronic | None | 0 | 0 |
| Cochrane Library #7 | [All text]: t:slim X2 AND Tandem Diabetes Care | None | 9 | 2 |
| Cochrane Library #8 | [All text]: iLet AND Beta Bionics | None | 2 | 0 |
| Cochrane Library #9 | [All text]: Remunity AND (Millyard OR DEKA OR “United Therapeutics”) | None | 0 | 0 |
| Cochrane Library #10 | [All text]: "CADD-MS3" AND (Smiths Medical OR United Therapeutics) | None | 0 | 0 |
| Cochrane Library #12 | [All text]: Cane AND (Crono SC OR Crono 50 SC) | None | 0 | 0 |
| Cochrane Library #13 | [All text]: (i-JET OR iJET) AND EverAid | None | 0 | 0 |
| Google Scholar #1 | Deka AND “Dasiglucagon Delivery System” | No citations, no patents | 0 | 0 |
| Google Scholar #2 | “ACCU-CHEK Spirit Combo” AND Roche AND “Infusion pump” | No citations, no patents | 44 | 3 |
| Google Scholar #3 | “MiniMed 770G” AND Medtronic AND “Infusion pump” | No citations, no patents | 19 | 0 |
| Google Scholar #4 | “Minimed 630G” AND Medtronic AND “Infusion pump” | No citations, no patents | 12 | 1 |
| Google Scholar #7 | “t:slim X2” AND “Tandem Diabetes Care” AND “Infusion pump” | No citations, no patents | 45 | 4 |
| Google Scholar #8 | “iLet” AND “Beta Bionics” AND “Infusion pump” | No citations, no patents | 33 | 0 |
| Google Scholar #9 | Remunity AND (Millyard OR DEKA OR “United Therapeutics”) AND “Infusion pump” | No citations, no patents | 5 | 0 |
| Google Scholar #10 | CADD-MS3 AND “United Therapeutics” AND “Infusion pump” | No citations, no patents | 12 | 3 |
| Google Scholar #10b | “CADD-MS3” AND “Smiths Medical” | No citations, no patents | 9 | 0 |
| Google Scholar #12 | Cane AND (“Crono SC” OR “Crono 50 SC”) | No citations, no patents | 0 | 0 |
| Google Scholar #13 | iJET AND EverAid AND “Infusion pump” | No citations, no patents | 20 | 1 |
| ClinicalTrials.gov #1 | [Other terms]: Deka AND Dasiglucagon Delivery System | Studies with results | 0 | 0 |
| ClinicalTrials.gov #2 | [Other terms]: ACCU-CHEK AND (Spirit OR Combo) AND Roche | Studies with results | 1 | 0 |
| ClinicalTrials.gov #3 | [Other terms]: MiniMed 770G AND Medtronic | Studies with results | 0 | 0 |
| ClinicalTrials.gov #4 | [Other terms]: Minimed 630G AND Medtronic | Studies with results | 0 | 0 |
| ClinicalTrials.gov #7 | [Other terms]: t:slim X2 AND Tandem Diabetes Care | Studies with results | 14 | 10 |
| ClinicalTrials.gov #8 | [Other terms]: iLet AND Beta Bionics | Studies with results | 4 | 1 |
| ClinicalTrials.gov #9 | [Other terms]: Remunity AND (Millyard OR DEKA OR United Therapeutics) | Studies with results | 0 | 0 |
| ClinicalTrials.gov #10 | [Other terms]: "CADD-MS3" AND (Smiths Medical OR United Therapeutics) | Studies with results | 0 | 0 |
| ClinicalTrials.gov #12 | [Other terms]: Cane AND (Crono SC OR Crono 50 SC) | Studies with results | 0 | 0 |
| ClinicalTrials.gov #13 | [Other terms]: (i-JET OR iJET) AND EverAid | Studies with results | 0 | 0 |
| **Total**  **Total after deduplication** | | | **263**  **205** | **46**  **-** |
| Searches #5, 6 & 11 were removed as they were irrelevant due to a change in the selected similar devices | | | | |

## SOTA searches

### Systematic searches

The SOTA searches were carried out according to the PICO format. The SOTA literature search results are presented in **Table 3**. Details of the retrieved publications from the device-specific searches are provided in **Appendix I** including reasons for exclusions of non-relevant publications.

**Table 3: PICO search strategy and results for SOTA searches in PubMed. Hits from search strings in bold were screened for relevance.Search date: 11-Sep-2024**

| **Search No.** | **PICO criteria** | **Search String** | **Filters** | **Hits** | **Included** |
| --- | --- | --- | --- | --- | --- |
| SOTA #1\* | P | (Neonates OR Newborn OR Children OR Infants OR Adolescents) AND (”Congenital Hyperinsulinism” OR ”Neonatal hypoglycemia” OR ”Persistent hyperinsulinemic hypoglycemia of infancy” OR PHHI OR Hyperinsulinism) | Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years | 1,195 | N/A\* |
| **SOTA #1.1** | **P** | **(Neonates OR Newborn OR Children OR Infants OR Adolescents) AND ”Congenital Hyperinsulinism”** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **85** | **23** |
| **SOTA #2** | **I1** | **(Dasiglucagon OR Novel glucagon therapies OR Dasiglucagon infusion) AND (Infusion pump OR Open loop infusion pump OR Infusion therapy OR Continuous infusion OR Subcutaneous infusion OR Subcutaneous delivery)** | **10 years** | **74** | **3** |
| **SOTA #3** | **I2** | **Dasiglucagon** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **17** | **7** |
| SOTA #4\* | C1 | Diazoxide OR Somatostatin Analogues OR Octreotide OR Lanreotide OR Conventional Glucagon OR Pancreatectomy OR Gene therapy OR Glucagon-like Peptide-1 (GLP-1) Receptor Antagonists OR Pancreatic Islet Transplantation OR Artificial Pancreas Systems | Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, Humans, 10 years | 57,225 | N/A\* |
| **SOTA #4.1** | **C1** | **(Diazoxide OR Somatostatin Analogues OR Octreotide OR Lanreotide OR Conventional Glucagon OR Pancreatectomy OR Gene therapy OR Glucagon-like Peptide-1 (GLP-1) Receptor Antagonists OR Pancreatic Islet Transplantation OR Artificial Pancreas Systems) AND (”Congenital Hyperinsulinism” OR ”Neonatal hypoglycemia” OR ”Persistent hyperinsulinemic hypoglycemia of infancy” OR PHHI OR Hyperinsulinism)** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **20** | 1 |
| SOTA #5\* | C2 | Closed loop infusion pump OR Subcutaneous injection OR Pre-filled pen OR Auto-injector OR Intramuscular injection OR Intravenous administration OR Insulet OmniPod-5 OR Insulet Omnipod-Dash | Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years | 9,030 | N/A\* |
| **SOTA #5.1** | **C2** | **(Closed loop infusion pump OR Subcutaneous injection OR Pre-filled pen OR Auto-injector OR Intramuscular injection OR Intravenous administration** **OR Insulet OmniPod-5 OR Insulet Omnipod-Dash) AND Dasiglucagon** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **5** | **0** |
| **SOTA #5.2** | **C3** | **(Closed loop infusion pump OR Subcutaneous injection OR Pre-filled pen OR Auto-injector OR Intramuscular injection OR Intravenous administration) AND "Open loop infusion pump"** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **12** | **5** |
| SOTA #6\* | O | Infusion rate OR Dose accuracy OR Hypoglycemic episodes OR Plasma glucose OR Blood glucose OR Glucose level OR Glycemic control OR Time in range OR Time below range OR Time above range OR Continuous glucose monitoring OR Hypoglycemia management OR Emergency department visit OR Inpatient admission OR Hospital visit OR Treatment efficacy OR Safety profile OR Side effect OR Adverse Event OR Complication OR Occlusion detection OR Long term outcomes OR Device errors OR Treatment satisfaction OR Quality of life OR QoL OR Cybersecurity | Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years | 512,990 | N/A\* |
| **SOTA #6.1** | **O** | **(Infusion rate OR Dose accuracy OR Hypoglycemic episodes OR Plasma glucose OR Blood glucose OR Glucose level OR Glycemic control OR Time in range OR Time below range OR Time above range OR Continuous glucose monitoring OR Hypoglycemia management OR Emergency department visit OR Inpatient admission OR Hospital visit OR Treatment efficacy OR Safety profile OR Side effect OR Adverse Event OR Complication OR Occlusion detection OR Long term outcomes OR Device errors OR Treatment satisfaction OR Quality of life OR QoL OR Cybersecurity) AND "Infusion pump" AND subcutaneous** | **Review, Systematic review, meta-analysis, Guideline, Consensus Development Conference, 10 years** | **14** | **2** |
| **SOTA #7** | **PICO** | **(Neonates OR Newborn OR Children OR Infants OR Adolescents) AND (”Congenital Hyperinsulinism” OR ”Neonatal hypoglycemia” OR ”Persistent hyperinsulinemic hypoglycemia of infancy” OR PHHI OR Hyperinsulinism) AND (Dasiglucagon OR Novel glucagon therapies OR Dasiglucagon infusion OR Diazoxide OR Somatostatin Analogues OR Octreotide OR Lanreotide OR Conventional Glucagon OR Pancreatectomy OR Gene therapy OR Glucagon-like Peptide-1 (GLP-1) Receptor Antagonists OR Pancreatic Islet Transplantation OR Artificial Pancreas Systems) AND (Infusion pump OR Open loop infusion pump OR Infusion therapy OR Continuous infusion OR Subcutaneous infusion OR Subcutaneous delivery OR Closed loop infusion pump OR Subcutaneous injection OR Pre-filled pen OR Auto-injector OR Intramuscular injection OR Intravenous administration) AND (Infusion rate OR Dose accuracy OR Hypoglycemic episodes OR Plasma glucose OR Blood glucose OR Glucose level OR Glycemic control OR Time in range OR Time below range OR Time above range OR Continuous glucose monitoring OR Hypoglycemia management OR Emergency department visit OR Inpatient admission OR Hospital visit OR Treatment efficacy OR Safety profile OR Side effect OR Adverse Event OR Complication OR Occlusion detection OR Long term outcomes OR Device errors OR Treatment satisfaction OR Quality of life OR QoL OR Cybersecurity)** | ***None*** | **10** | **0** |
| **Total of included search strings**  **Total after deduplication** | | | | **237**  **224** | **38**  **-** |
| \* Due to the vast number of articles identified in the marked searches, it is not feasible to screen all of these. In order to make the searches more specific, the search terms have been combined in subsequent searches. All the planned search terms were included in the final PICO search (#7). | | | | | |

**Table 4: State of the Art search strings and results in the Orphanet database. *Search date: 11-Sep-2024***

| **Search No.** | **Search String** | **Filters** | **Hits** | **Included** |
| --- | --- | --- | --- | --- |
| Orphanet #1 | [Disease name]: Congenital Hyperinsulinism | Disease review articles, Guidelines | 11 | 3 |
| Orphanet #2 | [Disease name]: Neonatal hypoglycemia | Disease review articles, Guidelines | 0 | 0 |
| Orphanet #3 | [Disease name]: Persistent hyperinsulinemic hypoglycemia of infancy | Disease review articles, Guidelines | 9 | 0 |
| **Total**  **Total after deduplication** | | | **20**  **7** | **3**  **-** |

### Non-systematic searches

Additional literature for the ‘State of the Art’ discussion was obtained through hand searching as presented in the following tables.

|  |  |
| --- | --- |
| **Database, Search No.** | **PubMed hand search #1** |
| **Purpose of the search** | Finding incidence data for Congenital Hyperinsulinism |
| **Search string** | "Congenital Hyperinsulinism" AND incidence |
| **Filters** | Humans |
| **Date of Search** | **13. September 2024** |
| **Included articles** | * Mannisto JME, Jaaskelainen J, Otonkoski T, Huopio H. Long-term outcome and treatment in persistent and transient congenital hyperinsulinism: a Finnish population-based study. J Clin Endocrinol Metab. (2021) 106:e1542–51 * Yau D., Laver T.W., Dastamani A., Senniappan S., Houghton J.A.L., Shaikh G., Cheetham T., Mushtaq T., Kapoor R.R., Randell T., Ellard S., Shah P., Banerjee I. and Flanagan S.E. (2020). Using referral rates for genetic testing to determine the incidence of a rare disease: The minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. PLoS One 15, e0228417 * Rozenkova K, Malikova J, Nessa A, Dusatkova L, Bjorkhaug L, Obermannova B, et al. High incidence of heterozygous ABCC8 and HNF1A mutations in Czech patients with congenital hyperinsulinism. J Clin Endocrinol Metab. (2015) 100: E1540–9 * Nóvoa-Medina Y, Domínguez García A, Quinteiro González S, García Cruz LM, Santana Rodríguez A. Hiperinsulinismo congénito en Gran Canaria. An Pediatr (Barc). 2021;95:93–100. * Yamada Y, Kitayama K, Oyachi M, Higuchi S, Kawakita R, Kanamori Y, Yorifuji T. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017-2018): Congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). J Diabetes Investig. 2020 May;11(3):554-563. |

| **Database, Search No.** | **PubMed hand search #2** |
| --- | --- |
| **Purpose of the search** | Finding guidelines and consensus statements for subcutaneous infusion |
| **Search string** | Continuous subcutaneous infusion AND hypoglycemia AND (guideline OR Consensus) |
| **Filters** | Guideline; Consensus Development Conference; Consensus Development Conference, NIH |
| **Date of Search** | **15. October 2024** |
| **Included articles** | * Grunberger G, Sherr J, Allende M, Blevins T, Bode B, Handelsman Y, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocr Pract. 2021;27(6):505-37. * Choudhary P, Campbell F, Joule N, Kar P. A Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes. Diabet Med. 2019;36(5):531-8. * Peters AL, Ahmann AJ, Battelino T, Evert A, Hirsch IB, Murad MH, et al. Diabetes Technology-Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(11):3922-37. |

## References identified from retrieved studies

The publications in Table 5 were identified in the bibliography of other retrieved publications / clinical trials and were determined to be relevant for inclusion.

Table : Relevant publications identified in the bibliography of other references / clinical trials

| **Publication details** | **Source** |
| --- | --- |
| Kanapka LG, Wadwa RP, Breton MD, Ruedy KJ, Ekhlaspour L, Forlenza GP, et al. Extended Use of the Control-IQ Closed-Loop Control System in Children With Type 1 Diabetes. Diabetes Care. 2021;44(2):473-8. | A Study of t:Slim X2 With Control-IQ Technology (DCLP5): University of Virginia; 2023 [Available from: <https://clinicaltrials.gov/study/NCT03844789>]. |
| Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med. 2020;383(9):836-45. |
| Schoelwer MJ, Kanapka LG, Wadwa RP, Breton MD, Ruedy KJ, Ekhlaspour L, et al. Predictors of Time-in-Range (70-180 mg/dL) Achieved Using a Closed-Loop Control System. Diabetes Technol Ther. 2021;23(7):475-81. |
| Cobry EC, Kanapka LG, Cengiz E, Carria L, Ekhlaspour L, Buckingham BA, et al. Health-Related Quality of Life and Treatment Satisfaction in Parents and Children with Type 1 Diabetes Using Closed-Loop Control. Diabetes Technol Ther. 2021;23(6):401-9. |
| Cobry EC, Bisio A, Wadwa RP, Breton MD. Improvements in Parental Sleep, Fear of Hypoglycemia, and Diabetes Distress With Use of an Advanced Hybrid Closed-Loop System. Diabetes Care. 2022;45(5):1292-5. |
| Brown S, Raghinaru D, Emory E, Kovatchev B. First Look at Control-IQ: A New-Generation Automated Insulin Delivery System. Diabetes Care. 2018 Dec;41(12):2634-2636 | A Pilot Test of t:Slim X2 With Control-IQ Technology: University of Virginia; 2022 [Available from <https://clinicaltrials.gov/study/NCT03368937>]. |
| Graham R, Mueller L, Manning M, Habif S, Messer LH, Pinsker JE, Aronoff-Spencer E. Real-World Use of Control-IQ Technology Is Associated with a Lower Rate of Severe Hypoglycemia and Diabetic Ketoacidosis Than Historical Data: Results of the Control-IQ Observational (CLIO) Prospective Study. Diabetes Technol Ther. 2024 Jan;26(1):24-32. | Control-IQ Observational (CLIO) Post-Approval Study (CLIO): Tandem Diabetes Care, Inc.; 2023. [Available from <https://clinicaltrials.gov/study/NCT04503174>]. |
| Ekhlaspour L, Schoelwer MJ, Forlenza GP, DeBoer MD, Norlander L, Hsu L, Kingman R, Boranian E, Berget C, Emory E, Buckingham BA, Breton MD, Wadwa RP. Safety and Performance of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Toddlers and Preschoolers. Diabetes Technol Ther. 2021 May;23(5):384-391. | Safety of Artificial Pancreas Therapy in Preschoolers, Age 2-6: Marc Breton, University of Virginia; 2023. [Available from <https://clinicaltrials.gov/study/NCT04084171>]. |
| Levy CJ, Bailey R, Laffel LM, Forlenza G, DiMeglio LA, Hughes MS, Brown SA, Aleppo G, Bhargava A, Shah VN, Clements MA, Kipnes M, Bruggeman B, Daniels M, Rodriguez H, Calhoun P, Lum JW, Sasson-Katchalski R, Pinsker JE, Pollom R, Beck RW; TL1 Study Group. Multicenter Evaluation of Ultra-Rapid Lispro Insulin with Control-IQ Technology in Adults, Adolescents, and Children with Type 1 Diabetes. Diabetes Technol Ther. 2024 Sep;26(9):652-660. | Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev With the Tandem t:Slim X2 Insulin Pump With Control-IQ Technology in Adults, Adolescents and Children With Type 1 Diabetes: Tandem Diabetes Care, Inc.; 2024. [Available from <https://clinicaltrials.gov/study/NCT05403502>]. |
| Levy CJ, O'Malley G, Raghinaru D, Kudva YC, Laffel LM, Pinsker JE, Lum JW, Brown SA; iDCL Trial Research Group. Insulin Delivery and Glucose Variability Throughout the Menstrual Cycle on Closed Loop Control for Women with Type 1 Diabetes. Diabetes Technol Ther. 2022 May;24(5):357-361. | The International Diabetes Closed Loop (iDCL) Trial: Clinical Acceptance of the Artificial Pancreas (DCLP3 Extension): Sue Brown, University of Virginia; 2022. [Available from <https://clinicaltrials.gov/study/NCT03591354>]. |
| Wadwa RP, Reed ZW, Buckingham BA, DeBoer MD, Ekhlaspour L, Forlenza GP, Schoelwer M, Lum J, Kollman C, Beck RW, Breton MD; PEDAP Trial Study Group. Trial of Hybrid Closed-Loop Control in Young Children with Type 1 Diabetes. N Engl J Med. 2023 Mar 16;388(11):991-1001. | The Pediatric Artificial Pancreas (PEDAP) Trial of Control-IQ Technology in Young Children in Type 1 Diabetes: Marc Breton, University of Virginia; 2023. [Available from <https://clinicaltrials.gov/study/NCT04796779>]. |
| O'Malley G, Messer LH, Levy CJ, Pinsker JE, Forlenza GP, Isganaitis E, et al. Clinical Management and Pump Parameter Adjustment of the Control-IQ Closed-Loop Control System: Results from a 6-Month, Multicenter, Randomized Clinical Trial. Diabetes Technol Ther. 2021;23(4):245-52. | The International Diabetes Closed Loop (iDCL) Trial: Clinical Acceptance of the Artificial Pancreas (DCLP3) 2020 [Available from: <https://clinicaltrials.gov/study/NCT03563313>]. |
| Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med. 2019;381(18):1707-17. |
| Isganaitis E, Raghinaru D, Ambler-Osborn L, Pinsker JE, Buckingham BA, Wadwa RP, et al. Closed-Loop Insulin Therapy Improves Glycemic Control in Adolescents and Young Adults: Outcomes from the International Diabetes Closed-Loop Trial. Diabetes Technol Ther. 2021;23(5):342-9. |
| Ekhlaspour L, Town M, Raghinaru D, Lum JW, Brown SA, Buckingham BA. Glycemic Outcomes in Baseline Hemoglobin A1C Subgroups in the International Diabetes Closed-Loop Trial. Diabetes Technol Ther. 2022;24(8):588-91. |
| Ekhlaspour L, Nally LM, El-Khatib FH, et al. Feasibility Studies of an Insulin-Only Bionic Pancreas in a Home-Use Setting. Journal of Diabetes Science and Technology. 2019;13(6):1001-1007. |
| Kudva YC, Laffel LM, Brown SA, Raghinaru D, Pinsker JE, Ekhlaspour L, et al. Patient-Reported Outcomes in a Randomized Trial of Closed-Loop Control: The Pivotal International Diabetes Closed-Loop Trial. Diabetes Technol Ther. 2021;23(10):673-83. |
| Bionic Pancreas Research Group, Russell SJ, Beck RW, Damiano ER, El-Khatib FH, Ruedy KJ, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. N Engl J Med. 2022;387(13):1161-72. | The Insulin-Only Bionic Pancreas Pivotal Trial: Jaeb Center for Health Research; 2023 [Available from: <https://clinicaltrials.gov/study/NCT04200313>]. |
| Mauras N, Damiano ER, El-Khatib FH, Marak MC, Calhoun P, Ruedy KJ, et al. Utility and Safety of Backup Insulin Regimens Generated by the Bionic Pancreas: A Randomized Study. Diabetes Technol Ther. 2023;25(6):437-41. |

## Provided by Manufacturer

The publications in Table 6 were provided by DEKA Research and Development Corporation or Zealand Pharma and were determined to be relevant for the SOTA review.

Table : Relevant publications provided by the manufacturer

| **Publication details** |
| --- |
| Kerr D, Hoogma RP, Buhr A, Petersen B, Storms FE; study investigators. Multicenter user evaluation of ACCU-CHEK® Combo, an integrated system for continuous subcutaneous insulin infusion. J Diabetes Sci Technol. 2010 Nov 1;4(6):1400-7. |
| Pasquini TLS, Mesfin M, Schmitt J, Raskin J. Global Registries in Congenital Hyperinsulinism. Front Endocrinol (Lausanne). 2022 Jun 2;13:876903. |
| Salomon-Estebanez M, Yau D, Dunne MJ, Worth C, Birch S, Walewski JL, et al. Efficacy of Dose-Titrated Glucagon Infusions in the Management of Congenital Hyperinsulinism: A Case Series. Front Endocrinol (Lausanne). 2020;11:441. |
| Zealand Pharma. A Two-Period Open-label Trial Evaluating Efficacy and Safety of Dasiglucagon in Children With Congenital Hyperinsulinism; NCT03777176 2020 [Available from: <https://clinicaltrials.gov/study/NCT03777176>]. |

## Summary of search results

For this review, 263 publications were identified in the device-specific searches and 257 publications were identified in the systematic SOTA searches. In addition, 8 articles were found in non-systematic searches, 19 articles were found as references in clinicaltrials.gov studies, and 4 articles were provided by the manufacturer. Thus, a total of 551 articles were retrieved. Of these, 91 were excluded as duplicates and 339 were excluded for other reasons (see **Figure 1**). Of the remaining 121 studies, none investigated the safety and/or performance of the Dasiglucagon Delivery System, which was expected as the subject device is pre-CE mark. A total of 66 publications investigated the safety and/or performance of the similar devices and 55 articles were included for the SOTA evaluation.

Additional records identified through non-systematic searches, references identified in other publications, and articles provided by the manufacturer (n=31)

Records identified through systematic searches  
(n=520)

**Included**

**I**

**Screning/Appraisal**

**Identification**

Records retrieved

(n=551)

Records after deduplication

(n=460)

Records appraised

(n = 121)

Records excluded, with reasons (n = 339)

Exclusion criteria NRTA: 137

Exclusion criteria NRF: 12

Exclusion criteria DS: 30

Exclusion criteria NR: 12

Exclusion criteria CR: 42

Exclusion criteria MM: 6

Exclusion criteria GR: 27

Exclusion criteria P: 7

Exclusion criteria NF: 5

Exclusion criteria VLQ: 6

Exclusion criteria MA: 55

**Studies included in the CER**

Subject device evidence (n=0)

Similar device evidence (n=66)

State of the Art Discussion (n=55)

Excluded duplicates  
(n = 91)

**Figure 1: Process of literature selection**

# Literature Appraisal

## Appraisal results

An overall evidence level is assigned to the clinical data from the literature searches (Table 7) to evaluate its relative contribution to the safety and performance assessment.

Table . Appraisal results

| **Reference** | **Performance (P) or safety (S) data** | **Appraisal criteria for suitability** | | | | **Appraisal criteria for data contribution** | | | | | **Overall evidence level** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **D** | **A** | **P** | **R** | **T** | **O** | **F** | **S** | **C** |
| **Subject device/equivalent device** | | | | | | | | | | | |
| N/A |  |  |  |  |  |  |  |  |  |  |  |
| **Similar device: ACCU-CHEK Spirit Combo** | | | | | | | | | | | |
| Thornton (2024) (7) | P, S | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Boizel (2014) (8) | P, S | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | Level 3 |
| Breton (2017) (9) | P, S | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Howsmon (2018) (10) | P | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | Level 2 |
| Leelarathna (2014) (11) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Regittnig (2021) (12) | S | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | Level 3 |
| Ziegler (2013) (13) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Ziegler (2015) (14) | P, S | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Kerr (2010) (15) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| **Similar device: MiniMed 770G** | | | | | | | | | | | |
| Thrasher 2024 (16) | P | 2 | 2 | 2 | 1 | 1 | 1 | N/A | 1 | 1 | Level 2 |
| Akiyama (2024) (17) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Kubota (2024) (18) | P | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Pei (2023) (19) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| **Similar devices: MiniMed 630G & t:slim X2** | | | | | | | | | | | |
| Orbell (2024) (20) | S | 2 | 1 | 2 | 2 | 1 | 1 | N/A | N/A | 1 | Level 3 |
| **Similar device: t:slim X2** | | | | | | | | | | | |
| Reynolds (2024) (21) | P, S | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | Level 5 |
| Ekhlaspour (2019) (22) | P, S | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Usoh (2023) (23) | P | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Breton and Kovatchev (2021) (24) | P | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Forlenza (2018) (25) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Wang (2023) (26) | P, S | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | Level 4 |
| Carlson (2024) (27) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Shah (2024) (28) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Brown (2018) (29, 30) | P, S | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | Level 4 |
| Breton (2020) (31, 32) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Kanapka (2021) (33) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Schoelwer (2021) (34) | P | 2 | 1 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | Level 2 |
| Cobry (2021) (35) | P | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Cobry (2022) (36) | P | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Graham (2024) (37, 38) | P | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Levy (2024) (39, 40) | P, S | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | Level 3 |
| Ekhlaspour (2021) (41, 42) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Ekhlaspour (2019) (43) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Brown (2019) (44, 45) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| O’Malley (2021) (45, 46) | P | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Isganaitis (2021) (47) | P, S | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Ekhlaspour (2022) (48) | P | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Kudva (2021) (49) | P | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Brown (2020) (50) | P, S | 2 | 1 | 2 | 3 | 1 | 1 | 1 | 2 | 1 | Level 2 |
| Levy (2022) (51) | P | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | Level 3 |
| Wadwa (2023) (52, 53) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Brown (2021) (54) | P, S | 2 | 2 | 2 | 3 | 1 | 1 | 1 | 2 | 1 | Level 3 |
| Brown (2019) (55) | P, S | 2 | 1 | 2 | 3 | 1 | 1 | 1 | 2 | 1 | Level 3 |
| **Similar device: iLet Bionic Pancreas** | | | | | | | | | | | |
| Castellanos (2021) (56) | P, S | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Castellanos (2023) (57) | P | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Russell (2021) (58) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Sherwood (2024) (59) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Bionic Pancreas Research Group (2022) (60, 61) | P, S | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Kruger (2022) (62) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Messer (2022) (63) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Lynch (2022) (64) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| Mauras (2023) (65) | P, S | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Weissberg-Benchell (2023) (66) | P | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Beck (2022) (67) | P, S | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | Level 2 |
| Howard (2024) (68) | P | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | Level 3 |
| **Similar device: CADD-MS3** | | | | | | | | | | | |
| Sadushi-Koliçi (2012) (69) | P, S | 2 | 1 | 3 | 1 | 1 | 2 | 1 | 1 | 1 | Level 3 |
| Sadushi-Kolici (2019) (70) | P, S | 2 | 1 | 3 | 1 | 1 | 2 | 1 | 1 | 1 | Level 2 |
| Kingman (2010) (71) | P, S | 2 | 1 | 3 | 2 | 1 | 2 | 1 | 2 | 1 | Level 4 |
| **Similar device: Everaid iJET** | | | | | | | | | | | |
| Waligóra (2023) (72) | P, S | 2 | 1 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | Level 3 |
| N/A = Not applicable | | | | | | | | | | | |

## Appraisal conclusion

A total of 118 relevant clinical references were identified. No articles were included the subject device (principal data) as it is pre-CE mark. However, 66 studies included safety and/or performance data for a similar device. Furthermore, 52 references were included for the state-of-the-art evaluation.

An overview of the appraisal of the similar device articles is provided here. The following chart (Figure 2) represents the distribution of appraisal scores given to each article that included a similar device, considering its contribution to the clinical evaluation.

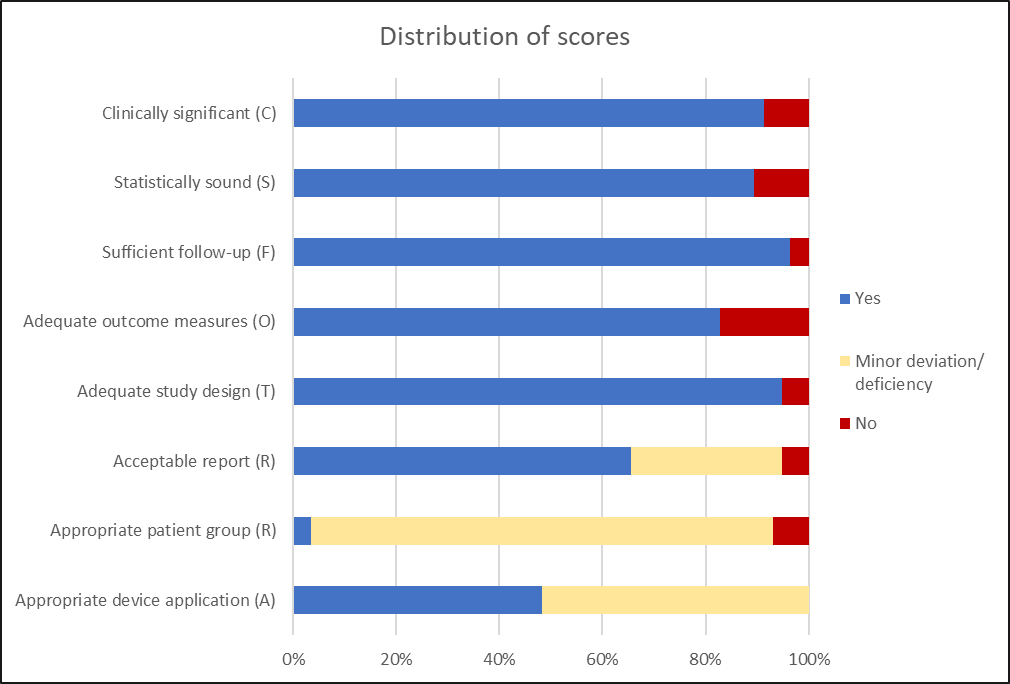
**

Figure . Distribution of appraisal scores for similar device articles

The chart shows that more than 50% of the articles were appraised as positively fulfilling the following criteria (Figure 2):

* Clinically significant (91.4%)
* Statistically sound (89.5%)
* Sufficient follow-up (96.4%)
* Adequate outcome measures (82.8%)
* Adequate study design (94.8%)
* Acceptable report (65.5% acceptable and 29.3% with minor deficiencies)

The criteria that did not receive a grade 1 score for at least 50% of the articles are:

* Appropriate patient group (3.4%)
* Appropriate device application (48.3%)

As shown, only 3.4% of articles included the intended patient group for the Dasiglucagon Delivery System (i.e., CHI patients). However, the majority of articles (89.7%) included another representative disease, namely type 1 diabetes. The reason for this is that the use of infusion pumps for treatment of CHI patients is seldomly described in the scientific literature as this is a rare disease. However, as with CHI, T1D is associated with frequent episodes of severe hypoglycemia and hence is considered a representative/ relevant proxy. Four articles (6.9%) included patients with another disease (pulmonary hypertension). Although this condition is not directly relevant for the Dasiglucagon Delivery System, the intended purpose and associated benefits of using an infusion pump are comparable.

All of the included articles used the infusion pumps for administration of a liquid medication, and therefore no articles (0%) were appraised with a grade 3 score regarding device application. However, 51.7% of the articles used the similar devices as closed-loop infusion pumps only, which we have graded as 2 (a minor deviation) as this type of device automatically adjusts the infusion rate based on data from a continuous glucose monitoring (CGM) device. The Dasiglucagon Delivery System does not include a CGM but is instead programmed to deliver a basal rate of dasiglucagon. The application of other open loop pumps and sensor-augmented pumps were considered to be the same (grade 1) as the Dasiglucagon Delivery System.

None of the included studies were appraised as level 1 evidence (systematic reviews). However, 48% were level 2 studies (randomized controlled trials; RCT) and 45% were level 3 studies (non-randomized cohort studies). As such, there were only four studies with a low evidence level (three level 4 studies [5%] and one level 5 study [2%]). The one level 5 case report was included despite the low quality, due to a high relevance as it involved a CHI patient, who was treated with dasiglucagon using a t:slim X2 infusion pump (21).

# Literature Analysis

## Subject device literature

This section is intended to summarize the literature articles that contain clinical data for Deka’s Dasiglucagon Delivery System. As expected, no such articles were retrieved since the subject device is pre-CE mark.

## Similar device literature

This section summarizes the articles that contain clinical data for the similar devices that were defined in the CEP. The literature searches found 66 clinical studies for the similar devices. As described in section 5, the available clinical data covered by this LSR were, overall, appraised to be suitable and of acceptable quality.

Details of the retrieved studies are provided in Table 8 for Roche ACCU-CHEK (n=9), Table 9 for MiniMed 770G (n=4), Table 11 for t:slim X2 (n=28), Table 12 for iLet Bionic Pancreas (n=12), Table 13 for CADD-MS3 (n=3), and Table 14 for Everaid iJET (n=1). Table 10 provides details of a study that included both MiniMed 630G and t:slim X2.

In brief, three studies used a similar device for infusion of dasiglucagon in pediatric CHI patients (n=2) (7, 21) or adult T1D patients (n=1) (56). In an RCT with 32 pediatric CHI patients, Thornton *et al.* (2024) found that patients randomized for dasiglucagon infusion with a Roche ACCU-CHEK pump achieved a 43% reduction in CGM-detected hypoglycemia (<3.9 mmol/L) compared to standard care (7). Moreover, the time below range (TBR) <3.9 mmol/L changed from 20.7% at baseline to 10.8% after 2-4 weeks of dasiglucagon treatment, and the TBR <3.0 mmol/L changed from 5.9% to 3.1%. Both were statistically significantly better than standard care (p = 0.0017 and p = 0.0061, respectively) (7). No adverse events (AEs) were attributed to the infusion pump, although two instances of needle occlusion occurred (7). In a case report with a 17-year old CHI patient, Reynolds *et al.* (2024) described that the initial use of an Omnipod® pump to deliver subcutaneous glucagon was associated with frequent pump site occlusions due to glucagon's limited stability and fibril formation (21). The patient was therefore transitioned to dasiglucagon treatment using a t:slim X2 pump for infusion, which allowed for better glucose control. The dasiglucagon therapy successfully minimized hypoglycemia episodes, and the patient was discharged from hospital and could return to school and resume physical activities (21). Over an 18-month period, only one AE was noted in this case report: a local reaction at the pump insertion site (21). In the third study with dasiglucagon infusion, Castellanos *et al.* (2021) used an iLet Bionic Pancreas for insulin and dasiglucagon delivery using a dual-hormone approach for treatment of ten T1D patients (56). This was compared to an insulin-only configuration using a random-order, crossover study design. The dual-hormone configuration was effective in minimizing hypoglycemia, with the median TBR<54 mg/dL at only 0.2%, compared to 0.6% in the insulin-only configuration. Similarly, TBR<70 mg/dL was reduced from 4% with the insulin-only approach to 2% in the bihormonal configuration (56). No pump-related AEs were reported in this study, although one patient reported vomiting, which is a well-known side-effect of dasiglucagon (56).

The majority of the retrieved studies reported on the use of the similar devices for insulin delivery in T1D patients (n=59). The studies generally found that the insulin infusion with an infusion pump improved glycemic metrics like increasing the time in range (TiR) while decreasing or maintaining TBR compared to standard diabetes care (e.g. multiple daily injections) (19, 23-25, 28, 52, 57). The studies that compared closed-loop pumps that use CGM data for automatic insulin delivery with other less advanced infusion pumps like open-loop and sensor-augmented pumps (SAPs) typically found that the closed-loop pumps improved the TiR compared to the other pumps. However, there was limited evidence of improved hypoglycemia management with the closed-loop pumps. As such, the majority of such studies (n=10) found that the percentage of TBR was comparable for the closed-loop pumps and the other pumps (17, 18, 22, 31, 41, 59, 60, 62, 63, 67), whereas only four studies found improved TBR with the closed-loop pumps (9, 44, 47, 64), and one study found that %TBR was higher with the closed-loop pumps (36). This suggests that although the closed-loop pump is advantageous for keeping the glucose levels within the recommended range in T1D patients, there is scarce evidence to support that the closed-loop pump improves hypoglycemia management compared to the less advanced pumps. Hypoglycemia management is the main concern for CHI patients. A limitation of the relevance of these study results is that the pumps were used for insulin infusion which, unlike dasiglucagon infusion, is not intended for hypoglycemia management. Another issue with closed-loop pumps is the risks that could occur when signals are lost before or during hypoglycemia events. Two publications reported that closed-loop operation was interrupted between 0.4% to 1.6% of the time (11, 30) and the CGM signal was unavailable for 5.6% of the time on average (30). Moreover, one study described that the frequency of required sensor calibrations increased when transitioning from one pump (MiniMed 640G) to another more advanced pump (MiniMed 770G), and that this “*might be related to worsened emotional distress and quality of life*” (17).

The remaining four studies used the similar devices (CADD-MS3 and Everaid i-JET) for treatment of pulmonary arterial hypertension (PAH). As this condition is not directly relevant for the Dasiglucagon Delivery System, these studies were mainly included to discuss technical issues with the pumps as well as device-related AEs and patient satisfaction.

Technical issues with the similar devices (both insulin infusion pumps and treprostinil infusion pumps) included: Bluetooth disconnections (13, 15), connectivity issues/interruptions (16, 44, 67), CGM malfunctions (not relevant for the subject device) (23, 59), pump failure (23, 69, 71), incorrect rate/dose programming (71), cartridge issues e.g. during changing (59, 67, 68), medication mix-up (71), leakage at the cartridge connector (56), flushing errors (71), infusion set malfunctions/occlusions (23, 59, 67, 69), tubing problems (59), unconfirmed alarms and alarm fatigue (13, 15, 68), battery problems (13, 67), software errors (44, 47), nonresponsive touchscreen (59), and disordered/dim screens (13, 68). One article described that the majority of technical issues (93%) were related to pump or blood glucose meter malfunctions (13). A multicenter RCT with 168 T1D patients reported that the users of the t:slim X2 device with the Control IQ feature experienced a median of 0.8 alarms per day (interquartile range [IQR]: 0.5-1.6) (e.g., due to occlusions) and 6.0 alerts per day (IQR: 4.7-7.3) (e.g., due to high or low blood glucose) (46).

There is a risk that the technical issues could lead to AEs for the patient. However, the majority of the reported device-related AEs were not caused by the pumps themselves but rather were related to the infusion sets. This included problems such as occlusions, kinks, loosened tape, dislodgements, cannula disconnection, hyperglycemia due to infusion set failures, and local reactions (discomfort, erythema, induration, edema, pruritus and rashes) at the insertion site (12, 15, 19, 21, 26, 31, 33, 39, 44, 47, 52, 58, 60, 62-65, 67). The only AE that was directly attributed to insulin infusion pumps was hyperglycemia, which was often reported and attributed to device problems such as pump failures, motor failure, battery failure, charging issues, cartridge issues, algorithm issues, screen issues, or user errors (15, 31, 59, 62, 63). Hyperglycemia is a relevant risk for diabetes patients, whereas hypoglycemia is the main concern for CHI patients, and could potentially be caused by the same device malfunctions for a dasiglucagon pump. Similarly, a study concerning the treprostinil infusion pump, CADD-MS3, reported that pump failure and infusion line obstruction triggered sudden-onset dyspnea in four patients (69), which is expected to be related to the PAH morbidities of the treated patients, and as such not relevant for the Dasiglucagon Delivery System.

Orbell et al. (2024) conducted a retrospective analysis of reports in the FDA MAUDE database regarding serious adverse events (SAEs) related to insulin pumps, specifically those resulting in intensive care unit (ICU) admissions or deaths (20). A total of 460 ICU admissions and 288 deaths were analyzed over a 21-month period. The ICU admissions were most frequently caused by issues with alarms (13.5%), infusion sets/sites (10.2%), pump tasks (9.3%), problems with the reservoir/cartridge (7%), battery or power problems (7%), user errors (3.5%), or issues with the integrated CGM (2.4%; not relevant for the subject device). The death events were most frequently associated with medical, physical or dietary issues of the patient (33.3%) or patient activities (9.0%), but were sometimes caused by problems with device components (10.4%) such as malfunctions of the reservoir/cartridge (7.3%) or battery/power (1.4%) (20). A detailed analysis of vigilance data from FDA MAUDE and other national regulatory databases is provided in **section 7.2**.

The majority of studies that investigated patient-reported outcomes found a high treatment satisfaction (15, 37, 38), and that most patients expressed that the infusion pumps made it easier to manage their disease (15, 26, 45, 49, 66, 68). In addition, there were findings of improved sleep quality for adults/parents, improved well-being, increased freedom, reduced hypoglycemia fear, and reduced treatment-related stress for diabetes patients that used a closed-loop pump compared to standard care (26, 32, 35, 36, 45, 49, 55, 66, 68). However, one study found a less positive mood in patients after transitioning from a SAP pump to a closed-loop pump (55). Moreover, there were concerns about a steep learning curve, alarm fatigue, control limitations, frequent insulin cartridge changes, and glucose fluctuations during exercise and at night (68). Despite these disadvantages, the perceived benefits of the pumps outweighed the burdens (66). Moreover, the usability of the Roche ACCU-CHEK, t:slim X2, and I-Jet pumps were generally perceived as good (8, 45, 49, 72).

Details of the 66 included studies are provided in the following subsections:

### Roche ACCU-CHEK Spirit Combo

Table . Summary of clinical studies for Roche ACCU-CHEK Spirit Combo

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Thornton et al. (2024) (7) | The **Accu-Chek Spirit Combo infusion pump** was used to administer dasiglucagon at rates of 10-70 μg/h for the treatment of congenital hyperinsulinism (CHI). | To evaluate the efficacy and safety of dasiglucagon delivered via a subcutaneous infusion pump in reducing hypoglycemia rates in infants and children with CHI when used alongside standard of care (SoC) therapies. | The study was a 2-part, open-label, randomized trial conducted over approximately 9 months (January 7, 2019, to October 5, 2020), with a follow-up period of 4 weeks after treatment discontinuation.  The study included 32 patients aged 3 months to 12 years diagnosed with CHI, experiencing at least three episodes of hypoglycemia per week.  The patients were randomized to receive either 1) dasiglucagon in addition to SoC or 2) SoC alone. Both groups consisted of 16 patients each during Part 1 of the trial. After the initial phase, all patients transitioned to receive dasiglucagon in Part 2. | Primary endpoint:   * Weekly rate of self-measured plasma glucose (SMPG) hypoglycemia episodes (<3.9 mmol/L).   Key secondary endpoints:   * Continuous glucose monitoring (CGM)-detected hypoglycemia rates (<3.9 mmol/L) * CGM-detected clinically significant hypoglycemia (<3.0 mmol/L) * CGM-detected Time in range (TiR; 3.9-10 mmol/L) * CGM-detected time below range (TBR; <3.9 mmol/L & <3.0 mmol/L) * CGM-detected time above range (TAR; > 10 mmol/L) * Adverse events (AEs) | The rate of SMPG-detected hypoglycemia episodes did not differ significantly between the dasiglucagon group and the SoC-only group.  However, there was a notable 43% reduction in CGM-detected hypoglycemia rates in the dasiglucagon group compared to SoC alone (p = 0.0029), with significant decreases observed across all measures of hypoglycemia assessed by CGM. Hypoglycemia rates also improved for the patients who switched from SoC alone to dasiglucagon  + SoC in Part 2.  No statistically significant difference was found between treatment groups with respect to CGM-detected TiR. However, the CGM-detected TBR<3.9 changed from 20.7% at baseline to 10.8% in the Dasiglucagon group compared to a change from 22.0% to 20.2% with SoC (p = 0.0017). Moreover, the TBR<3.0 changed from 5.9% at baseline to 3.1% in the Dasiglucagon group compared to a change from 7.4% to 6.3% with SoC (p = 0.0061).  Moreover, the TAR was higher for dasiglucagon compared to SoC alone (P = 0.0055).  Two instances of needle occlusion occurred; however, these did not result in AEs or hypoglycemic episodes. | Six serious adverse events (SAEs) were reported, including infections and episodes of hypoglycemia. None were attributed to dasiglucagon or the infusion pump.  One patient discontinued dasiglucagon treatment due to hyperglycemia and ketosis.  Most reported AEs were mild, particularly gastrointestinal issues, with vomiting being the most common side effect associated with glucagon treatments.  There were reports of skin-related AEs, including two cases of necrolytic migratory erythema, which were assessed as possibly or probably related to dasiglucagon but were manageable without treatment discontinuation.  No significant abnormalities were observed in biochemical, hematological, or electrocardiographic assessments during the study period, indicating that the infusion pump and dasiglucagon did not adversely affect patients’ overall health. | The Accu-Chek Spirit Combo infusion pump effectively delivered dasiglucagon while maintaining a good safety profile. The device facilitated improved monitoring of glucose levels, contributing to significant reductions in hypoglycemia episodes, demonstrating its utility in managing CHI in pediatric patients. |
| Boizel et al. (2014) (8) | The **Accu-Chek® Combo insulin pump system** was used for insulin delivery via remote control including blood glucose monitoring (BGM), bolus delivery, basal rate adjustment, and data management. | To evaluate the usefulness of the advanced features of the Accu-Chek® Combo insulin pump system in individuals with type 1 diabetes (T1D) during routine clinical practice. | Prospective, observational, multicenter study.  The study included 74 patients with T1D, recruited within 13 weeks of starting insulin pump therapy. Seventy-two patients completed the study. | * Frequency of advanced functions use * Patient usability perceptions (measured using a visual analog scale [VAS] ranging from 0 [useless] to 100 [indispensable]) * Device-related adverse events (AEs) | The majority of patients (94.4%) used the BGM function. A total of 86.1% of patients used the remote control for more than half of bolus administrations, and 27.8% used the bolus advisor for more than half of all boluses. The temporary basal rate function was used by 25.0% of patients. The ongoing basal rate function was used by 73.6%. The BGM reminder function was activated by 33.3%.  The advanced functions were widely perceived as easy to use, with median VAS usefulness ratings ranging from 72 to 85. | No device-related adverse events or safety issues were reported during the study period. | The study concludes that the Accu-Chek® Combo insulin pump system is practical, with its advanced features being extensively utilized and perceived as easy to use and beneficial by most patients. |
| Breton et al. (2017) (9) | Treatment subjects were fitted with a study-provided Tandem t:AP pump (used at the Virginia camp) or a **Roche Accu-CHEK Spirit Combo pump** (used at the Colorado camp).  These pumps were used to deliver insulin. The treatment subjects had their insulin delivery automatically controlled by the Diabetes  Assistant’s (DiAs) system. | To evaluate whether the University of Virginia (UVA) closed-loop control (CLC) system can enhance glycemic control during and after demanding physical activity, specifically skiing, in adolescents and young adults with T1D. | This was a multisite, randomized, controlled clinical trial involving 33 adolescent participants (age: 10-25 years) with type 1 diabetes.  Participants were randomly assigned to treatment with either the UVA CLC system or a remotely monitored sensor-augmented open loop pump (RM-SAP).  In the CLC group, the DiAs system was linked to the insulin pump and automatically controlled insulin delivery, adjusting it in real-time based on CGM data. In contrast, the RM-SAP participants had to manually adjust their basal rates and bolus insulin with guidance from the study team. | The study compared the performance and safety of the UVA CLC system versus RM-SAP (control group) in terms of glycemic control and response to physical activity in a challenging environment.  **Primary outcome:**   * %TiR (70–180 mg/dL).   **Secondary outcomes:**   * Percentage of time spent in tighter ranges (%TiTR: 70–140 mg/dL) * %TBR (<70 mg/dL) * %TAR (>250 mg/dL) * Average glucose levels * Insulin usage * Number of hypoglycemic events * Hypoglycemia treatments * Mean absolute relative deviation (MARD) of CGM | The UVA CLC system demonstrated a 7% improvement in TiR compared to the RM-SAP group (71.3% vs. 64.7%; p = 0.005).  The CLC system almost halved %TBR (1.8% vs. 3.2% with RM-SAP).  The CLC system reduced insulin usage overall and during skiing.  The system functioned 95% of the time, but the CGM performance was slightly reduced due to environmental factors such as cold and altitude. The accuracy of the CGM systems (Dexcom G4) was somewhat diminished due to cold temperatures, with a MARD of 18.9%.  The CLC system was particularly beneficial for beginner skiers, reducing hypoglycemia risk and improving TiR. | Three adverse events were reported: a tibia fracture (unrelated to the study), a wrist fracture, and a knee injury, both sustained during skiing. Additionally, one participant was excluded after experiencing repeated hypoglycemia.  The reported AEs were not related to the infusion pumps or diabetes control. | The UVA CLC system effectively improved glycemic control during and after physically demanding activities, reducing the risk of hypoglycemia and hyperglycemia.  Limiration: Mixed data were provided for **ACCU-CHEK** and Tandem t:AP. |
| Howsmon et al. (2018) (10) | The **Roche Accu-Chek Spirit Combo** pump was used to deliver insulin with zone model predictive control (MPC) and site failure (SF) detection.  In the control group, the patients’ personal sensor-augmented pump (SAP) was used to deliver insulin. | To evaluate the real-time detection of site failures (SF) in diabetes management using an artificial pancreas system equipped with a specialized SF detection algorithm. | The study was a 6-week, outpatient, randomized crossover clinical trial conducted at two centers.  The study included 20 adult participants with T1D, 19 of whom completed the trial.  Each participant underwent two evaluation periods separated by a one-week washout, with follow-up during each week of infusion set wear. | The study did not directly compare the performance or safety of the infusion pumps but instead focused on the performance of the SF detection algorithm between the two study arms.  Key endpoints:   * Sensitivity, false positives and false negatives of the SF detection algorithm * Infusion set survival * TAR (>250 mg/dL) | The most common cause of SFs was unexplained hyperglycemia that did not respond to correction doses.  In the ACCU-CHEK group, the SF detection algorithm showed a sensitivity of 88% with an average false-positive rate of 0.22 per day. In the control group, the sensitivity was 73.3% with a false-positive rate of 0.27 per day.  When the SF detection algorithm was applied retrospectively in the control group, the TAR in the four hours preceding an SF was reduced from a median of 92 minutes to 63 minutes. In the ACCU-CHEK group, real-time SF detection further reduced this duration from 63 minutes to 30 minutes, demonstrating a significant improvement in hyperglycemic control when real-time SF alerts were used. | The study did not report any AEs, complications, or side effects directly attributable to the infusion pumps. | The study focused on SF detection rather than pump performance or safety. |
| Leelarathna et al (2014) (11) | The **Accu-Chek Spirit Combo insulin pump** was used to deliver insulin. This pump was integrated with an automated closed-loop glucose control system, which was used to administer insulin according to the MPC algorithm's recommendations. | To assess the reliability of a CLC system. Secondary objectives included evaluating overnight glucose management and the accuracy of the Dexcom G4 CGM sensor. | This was a single-center, single-arm, open-label feasibility study.  The study included 8 adult patients diagnosed with T1D for at least one year, all of whom were already using insulin pump therapy.  The study involved an overnight follow-up period from 19:00 to 07:00 hours, with glucose control monitored for the entire duration. | Primary outcome:   * The percentage of time the CLC system functioned as intended.   Secondary outcomes:   * Failure rates of various system components, * TiR (3.9–8.0 mmol/L) * Time in expanded range (TiER; 3.9–10.0 mmol/L) * Mean glucose levels, * MARD of CGM. * Number of hypoglycemic events * Occurrence of ketosis * Nature/severity of any other AEs. | The CLC system performed as intended for 99.6% of the time during the study, with one brief interruption (20 minutes) caused by accidental detachment of the laptop power cable, which led to battery drainage.  Participants spent an average of 75.4% of the overnight period (22:00–07:00) within TiR. For the entire study period (19:00–07:00), participants spent 84.4% of the time within TiER.  The MARD of CGM was 8.3% (range 4.0–14.5%), which is consistent with accurate glucose monitoring and within clinically acceptable standards.  No failures were reported in the insulin pump or any other system components. | Two hypoglycemic events were reported. These events were related to insulin delivery following meal boluses rather than malfunctions of the infusion pump itself.  No other AEs were noted. | The study concluded that the closed-loop system, including the Accu-Chek Spirit Combo insulin pump, was highly reliable for automated insulin delivery, functioning as intended for nearly the entire study period without significant failures. |
| Regittnig et al. 2021 (12) | **Accu-Chek® Spirit Combo insulin pumps** were used for both insulin infusion and infusion of insulin-diluent medium (IDM) to compare the infusion pressures between insulin and the diluent. | To determine the tissue flow resistance (TFR) at the site of continuous subcutaneous insulin infusion (CSII) in individuals with T1D and compare it to that at an infusion site where insulin-free diluent was used, to clarify whether differences exist between insulin-exposed and unexposed tissue sites. | This was a 7-day crossover study.  The study included 30 adult T1D patients, who were being treated with CSII therapy.  Each participant wore two identical insulin pumps: one for insulin infusion and the other for insulin-free diluent. Infusion pressures and flow resistances were measured at both sites over the course of 7 days | * TFR * Maximum pressure (Pmax) during bolus delivery * Mean pressure (Pmean) * Flow resistance through the infusion set (RS) | There were no device related performance results. | No infusion pump-related AEs were reported during the study period. However, in 7 instances, the adhesive tape of the infusion set loosened, causing fluid leakage around the cannula, which was resolved by securing the adhesive with additional strips or tissue adhesive. There were also four cases of elevated infusion pressures (two for insulin and two for diluent), which were resolved by replacing the cannulas. | The study concludes that while the insulin pumps operated effectively and without malfunctions, tissue resistance increased significantly at insulin infusion sites compared to diluent sites over time. This suggests that while pumps reliably deliver insulin, tissue responses to insulin infusion may impact long-term infusion site viability. |
| Ziegler et al (2013) (13) | The **Accu-Chek Combo system** was used for insulin administration and glucose monitoring. | To evaluate the impact of switching from older insulin pumps to the Accu-Chek Combo system on the efficacy of diabetes management and safety in patients with T1D over a 6-month period. The study also examined the use and influence of the system's new features under routine clinical conditions. | This was an uncontrolled, prospective study conducted across five European countries (France, Germany, Italy, Spain, and Sweden).  The study included patients with T1D who had been using insulin pump therapy for over 6 months. A total of 299 patients above 12 years of age were enrolled.  Information was collected at baseline, 3 months, and 6 months after switching to the Accu-Chek Combo system. | * Hemoglobin A1c (HbA1c) levels * TiR (blood glucose 70–140 mg/dL) * Frequency of hypoglycemia (blood glucose < 70 mg/dL) * Frequency of hyperglycemia (blood glucose > 300 mg/dL) * Blood glucose levels * Insulin bolus frequency * Usage of new pump features (e.g., bolus advisor, remote control) * Technical incidents and adverse events | The Accu-Chek Combo system showed a non-significant improvement in glycemic control, with a decrease in HbA1c levels from 7.8% to 7.7%. Patients with poor glycemic control at baseline (HbA1c > 8%) showed a significant improvement in HbA1c, decreasing from 8.8% ± 0.8% to 8.4% ± 0.9% by the 6-month follow-up (P < 0.001).  Short-term pump users had a larger reduction in HbA1c compared to long-term users.  The TiR increased slightly, from 51.7% at baseline to 53.8% at the 6-month endpoint. The frequencies of hypoglycemic and hyperglycemic episodes decreased non-significantly.  A total of 28 technical incidents were reported by 12 patients. Common issues included Bluetooth disconnection (5 patients), unconfirmed alarms (4 patients), battery problems (4 patients), and disordered data views (3 patients). Most incidents (93%) were related to pump or blood glucose meter malfunctions. | Six AEs were reported, none of which were related to the therapy.  The most serious event was a death due to a heart attack, deemed unrelated to the device. | The Accu-Chek Combo system proved to be a useful tool in managing type 1 diabetes, with improvements in glycemic control and widespread adoption of its new features. The pump system showed a reliable safety profile with only a few minor technical incidents and no significant safety concerns related to its use. |
| Ziegler et al (2015) (14) | The study used the **Accu-Chek Aviva Combo insulin pump** **system**, which includes a remote-controlled insulin pump and a blood glucose meter with an integrated Bolus Advisor (BA). The BA feature was designed to assist in making insulin dose recommendations based on carbohydrate intake and blood glucose levels. | To evaluate the impact of frequent usage of the BA feature in the Accu-Chek Aviva Combo system on glycemic control in pediatric patients with T1D who were using insulin pumps. | This was a retrospective, non-interventional cohort study conducted at a single pediatric diabetology clinic.  The study included children and adolescents (<18 years) with T1D who were using the Accu-Chek Aviva Combo insulin pump as part of their routine care. A total of 158 patients were identified, 119 agreed to participate, and 104 patients were included in the full analysis set (FAS).  Data were collected for up to 24 months, with a primary focus on the first 6 months of insulin pump usage and BA feature adherence. | The focus was on comparing high-frequency (HF) versus low-frequency (LF) users of the Bolus Advisor feature in the same pump system.  The primary endpoint was the difference in HbA1c levels at 6 months between HF and LF users of the BA feature.  Secondary endpoints:   * %TBR (< 70 mg/dL) * Mean blood glucose levels | The %TBR increased from approx. 5.6% in both groups at baseline to 10.9% and 13.4% at 3 months for LF and HF users, respectively. The %TBR continued increasing to 12.5% at 24 months for the LF users, whereas it decreased steadily to 7.1% for the HF users.  At 6 months, significantly more HF users achieved the target HbA1c of ≤7.5% compared to LF users (66.2% vs. 27.3%, p = 0.0056). At 24 months, the difference between HF and LF users was no longer statistically significant due to a smaller sample size: HF users had an average HbA1c of 7.7% vs. 8.2% in LF users (p = 0.1487).  HF users also had lower blood glucose levels and less glycemic variability at 6 months as indicated by the standard deviation of blood glucose readings.  Furthermore, 66.2% of HF users reached the HbA1c target of ≤7.5% at 6 months, compared to only 27.3% of LF users. | The study reported on AEs such as hypoglycemia, diabetic ketoacidosis (DKA), and hospitalizations.  No AEs were related to infusion pump or BA feature usage. | The BA feature was found to be useful in achieving better diabetes management for pediatric patients with T1D.  However, the time in hypoglycemia was higher after initiating treatment compared to baseline for both groups. |
| Kerr et al. (2010) (15) | The study used the ACCU-CHEK Combo system, consisting of the ACCU-CHEK Spirit Combo insulin pump and either the ACCU-CHEK Aviva Combo or Performa Combo blood glucose meter.  The pump was remotely controlled by the meter to facilitate bolus dosing and manage blood glucose levels. | To evaluate the performance and usability of the ACCU-CHEK Combo system in individuals with T1D and type 2 diabetes (T2D) using CSII therapy. | Multicenter, prospective, single-group study.  The study included 90 adult patients with T1D or T2D on CSII for at least 6 months, targeting a population with HbA1c ≤ 10%.  Participants were followed over a 6-month period, with an initial 4-week observation period for device validation followed by a 22-week period assessing metabolic control and treatment satisfaction. | Primary Endpoint: Frequency of unexpected device errors, which are errors not described in product risk analysis.  Secondary endpoints:   * Treatment satisfaction (using the DTSQs and DTSQc questionnaires) * Frequency of system errors * Device usability * Hb1Ac levels * Number of hypoglycemic events * Number of hyperglycemic events | No unexpected device errors occurred.  Treatment satisfaction was high, and improved significantly by study end.  Most participants (81%) reported that the system made diabetes management easier.  Glycemic control showed minor but statistically significant improvements in HbA1c levels from 7.9% to 7.6%.  Minor Bluetooth communication issues were reported by 16 participants, and there were some occlusion alarms with an incidence of 15.3 per patient-year, 54% of which were triggered by a new detection algorithm. | There were 3 severe hypoglycemia events and 8 hyperglycemic events. The latter were attributed to device issues (three occlusions, three infusion set dislodgements, one meter failure with alarm, and one pump failure with alarm). The hypoglycemia events required third party assistance but were not attributed to device issues.  No cases of ketoacidosis occurred. | The ACCU-CHEK Combo system was found to be effective and well-received, aiding in diabetes management and offering high levels of user satisfaction. |
| **Abbreviations**: AE: Adverse Event; BA: Bolus Advisor; BGM: Blood Glucose Monitoring; CGM: Continuous Glucose Monitoring; CHI: congenital hyperinsulinism; CLC: closed-loop control; CSII: continuous subcutaneous insulin infusion; DiA: Diabetes Assistant; HbA1C: Hemoglobin A1c; IDM: insulin-diluent medium; MARD: mean absolute relative deviation; MPC: model predictive control; SoC = standard of care; SF: site failure; SMPG: self-measured plasma glucose; T1D: Type 1 Diabetes; T2D: type 2 diabetes; TAR: Time above range; TBR: Time below range; TFR: tissue flow resistance; TiER: Time in expanded range; TiR: Time in range; TiTR: time spent in tighter ranges; VAS: Visual Analog Scale | | | | | | | |

### MiniMed 770G

Table . Summary of clinical studies for MiniMed 770G

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Thrasher et al (2024) (16) | The MiniMed 780G (MM780G) infusion pump was used for automated insulin delivery, incorporating the Guardian 4 sensor (G4S) and Guardian Link 4 transmitter for continuous glucose monitoring (CGM). The system also utilized the Accu-Chek Guide Link blood glucose meter for manual blood glucose measurements.  A comparison was made between the MM780G and its predecessor, the MiniMed 770G (MM770G), focusing on glycemic metrics and system interactions. | To assess glycemic outcomes and the achievement of international consensus-recommended goals during the initial real-world use of the MiniMed 780G (MM780G) automated insulin delivery system among individuals with type 1 diabetes (T1D). | Retrospective real-world data analysis study.  Data was collected from the CareLink personal system since launched in the U.S. until August 22, 2023, with users averaging 28.0 ± 14.8 days of system usage.  The study included 7,499 individuals with type 1 diabetes who used the MM780G system and consented to data aggregation for analysis. Of these, 3851 individuals transitioned from MiniMed 770G to MiniMed 780G. | * Time in range (%TiR; 70–180 mg/dL) * Time in tight range (%TITR: 70–140 mg/dL) * Time above range (%TAR: >180 mg/dL and >250 mg/dL). * Time below range (%TBR: <70 mg/dL and <54 mg/dL) * Average sensor glucose (SG) level, * Glucose management indicator (GMI) * System use metrics incl. time spent in closed-loop (CL) mode, number of CL exits, and number of daily user-initiated boluses and blood glucose measurements. | For users transitioning from the MM770G to MM780G, significant improvements in glycemic control were observed. While using the MM770G, users achieved a %TIR of 73.2% on average. After transitioning to the MM780G, their %TIR increased by 5.1% to 78.3%, and %TITR improved from 45.8% to 52.6%. Additionally, %TAR>180mg/dL decreased by 4.8% with the MM780G, while %TAR>250mg/dL decreased by 1.7%.  During MM770G use, users experienced more frequent interruptions in CL mode, with an average of 4.3 CL exits per week. This number was significantly reduced when users transitioned to the MM780G, with only 0.8 exits per week. | No device-related adverse events or safety issues were reported during the study period. | The study’s results suggest that while the MM770G was beneficial in managing glucose levels, the newer MM780G provided notable advancements in glycemic control, system stability, and reduced user management. |
| Akiyama et al. (2024) (17) | The MM770G was used to improve glycemic control by automatically adjusting insulin delivery in T1D patients.  All participants switched from MiniMed 640G (MM640G) to MM770G, which used Auto Mode to maintain sensor glucose levels at around 120 mg/dL with the help of Guardian Sensor 3. | To evaluate the impact of MM770G on both glycemic management and psychological well-being in Japanese adults diagnosed with T1D. | Prospective, observational study.  The study included 22 adult T1D patients.  This 3-month study monitored participants who transitioned from the MM640G Predictive Low Glucose Suspend (PLGS) system to the MM770G hybrid closed-loop (HCL) system. | The study assessed the improvements in glycemic metrics and evaluated safety parameters before and after the switch.  Endpoints:   * TiR; 70–180 mg/dL * TAR: 181-250 mg/dL and >250 mg/dL. * TBR: 54-69 mg/dL and <54 mg/dL) * Mean glucose levels * GMI * Glycemic variability * HbA1c levels * Treatment satisfaction (DTSQ) * Emotional distress (PAID) * Quality of life (QoL) | After 3 months of using the MiniMed 770G, participants experienced significant improvements in glycemic control. The average TIR increased from 63.5% to 73.0% (P = 0.0010), while TAR (181–250 mg/dL) significantly decreased from 26.9% to 19.6% (P < 0.0005). There was no statistically significant overall change in TBR 54–69 mg/dL after using the MiniMed 770G.  The average glucose levels decreased from 164.5 mg/dL to 151.4 mg/dL (P = 0.0030), and the glucose management indicator dropped from 7.2% to 6.9% (P = 0.0072). Additionally, HbA1c levels improved from 7.7% to 7.2% (P = 0.0021).  The basal and bolus insulin doses remained unchanged, but the frequency of sensor calibrations increased.  There was an increase in the frequency of alarms, from 7.5 to 10.5 alarms per day (P < 0.0005).  The DTSQ, PAID and QoL scores were not signitificantly affected by the switch to MM770G. | There were  no episodes of diabetic ketoacidosis (DKA) and severe hypoglycemia  with the MM770G system. | There were no reported episodes of severe hypoglycemia during the 3-month follow-up with the MiniMed 770G, which suggests effective prevention of dangerous low blood glucose events. |
| Kubota et al. (2024) (18) | The MM640G was the initial pump used by participants for sensor-augmented pump (SAP) therapy.  The study transitioned participants to the MM770G pump to introduce HCL technology for improved insulin delivery and glycemic management. | To evaluate the impact of introducing HCL technology via the MM770G system on glycemic control, treatment satisfaction, burden, and QoL in Japanese adults with T1D. | Single-center, prospective, interventional study.  The study included 23 adults with T1D who were already using the MM640G system.  The follow-up time was 24 weeks. | Primary endpoint:   * TiR; 70–180 mg/dL   Secondary endpoints:   * TAR: * TBR * HbA1c changes * DTSQ score * PAID score * QoL score | The median TIR significantly improved from 64.1% to 70.9% over 24 weeks (p < 0.001). TAR decreased from 35.0% to 26.6% (p < 0.001), while TBR was unchanged (p = 0.059).  An analysis over the 24-week period after the transition showed that TIR increased significantly until the 12-week mark and remained stable thereafter. TAR decreased significantly initially and maintained the improvement over time. TBR increased significantly from 1.9% at baseline to 2.9% at 12 weeks (p = 0.001), but then decreased again to 2.6% at 24 weeks (p = 0.001). Overall, the TBR change over the 24 weeks was non-significant (p = 0.061).  HbA1c levels decreased significantly from 7.4% to 7.1% (p = 0.003). | No device-related adverse events or safety issues were reported during the study period | The MM770G system was effective in enhancing glycemic control, as indicated by a significant increase in TIR and a reduction in TAR, without significantly worsening TBR. |
| Pei (2023) (19) | The MM770G system, with Guardian Sensor 3 and Guardian Link 3 transmitter, was used to manage insulin delivery in Auto Mode.  The Accu-Chek Guide Link BG meter was used for checking blood glucose levels. | To assess the safety and performance outcomes of the MM770G system in Chinese adolescents and adults with T1D to meet the China Food and Drug Administration's (CFDA) requirements for device registration. | Prospective, single-arm, multicenter, nonrandomized trial.  The study included 60 T1D patients aged 14 to 75 years.  The study was conducted over a period from October 2020 to June 2021, with a follow-up duration of approximately 4 weeks after the initial 2-week baseline run-in period. | Primary endpoint:   * %TiR; 70–180 mg/dL   Secondary endpoints:   * TAR (>180, >250 and >350 mg/dL) * TBR (<54, <60 and <60 mg/dL) * Standard deviation (SD) of SG * Cefficient of variation (CV) of SG * Total daily dose (TDD) of insulin * Body weight | The mean TIR increased from 75.3% to 80.9%, with a statistically significant change of 5.6% (p < 0.001).  The time spent in hypoglycemia decreased substantially, with a mean TBR <70 mg/dL reduction of 2.5% (p < 0.001).  Other improvements included decreased glucose variability, with reductions in the SD of SG and CV of SG, and a reduced TDD of insulin without weight gain. | There were three episodes of severe hyperglycemia. Two of these were associated with device malfunctions. One incident was due to an infusion set cannula disconnection during the run-in phase, and another was potentially caused by an infusion set occlusion during the study period.  No incidents of DKA, severe hypoglycemia, serious adverse events (SAEs), or unanticipated adverse device effects (UADEs) were reported. | The MM770G system effectively minimized hypoglycemia risks, as evidenced by the significant decrease in the time spent below 70 mg/dL and no reported severe hypoglycemia events.  This suggests that the system is proficient in reducing the frequency of low glucose episodes, providing enhanced safety in hypoglycemia prevention. |
| **Abbreviations**: CFDA = China Food and Drug Administration; CL = Closed loop; CV = coefficient of variation; DKA = diabetic ketoacidosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; GMI = Glucose management indicator; HbA1c = Glycated hemoglobin; HCL = hybrid closed-loop; MM = MiniMed; PAID = Problem Area in Diabetes; PLGS = Predictive Low Glucose Suspend; QoL = Quality of life; SAE = serious adverse event; SAP = sensor-augmented pump; SD = standard deviation; SG = sensor glucose; T1D: Type 1 Diabetes; TAR = Time above range; TBR = Time below range; TDD = total daily dose; TiR = Time in range; TITR = Time in tight range; UADE = unanticipated adverse device effect | | | | | | | |

### MiniMed 630G & t:slim X2

Table . Summary of a clinical study that involved both MiniMed 630G and t:slim X2

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Orbell et al. (2024) (20) | The study analyzed data for five insulin pump models:   * MiniMed 670G (Medtronic) * **MiniMed 630G** (Medtronic**)** * Omnipod OP (Insulet Corp.) * Omnipod DASH (Insulet Corp.) * **T:slim X2** (Tandem Diabetes Care). | To investigate serious adverse events (SAEs) related to insulin pumps, specifically those resulting in intensive care unit (ICU) admissions or deaths. | This was a retrospective qualitative analysis using narrative data from adverse event reports in the FDA MAUDE database associated with insulin pumps. The study covered SAEs occurring between May 1, 2019, and January 31, 2021. Additional reports up to December 31, 2021, were included to account for delayed reporting of SAEs during the study period. | * SAE occurrence * Blood glucose levels at the time of the event * Device-related issues * Potential root causes | Device performance was not investigated. | A total of 745 events were included in the analysis. Of these, 460 were related to ICU admissions and 288 involved a death event.  Among the reported SAEs involving ICU admissions, the MiniMed 670G accounted for the highest proportion (33.7%), followed by the Omnipod OP (29.1%), MiniMed 630G (15.4%), t:slim X2 (12.4%), and Omnipod DASH (9.3%). The ICU admissions were most frequently caused by issues with infusion sets/sites (10.2%), problems with the pump or pod reservoir/cartridge (7%), and battery or power problems (7%).  In cases of death, the MiniMed 630G (37.5%) and 670G (37.2%) were associated with the most reported events, followed by the Omnipod OP (14.9%), t:slim X2 (5.6%), and Omnipod DASH (4.9%). The death events were most frequently associated with medical, physical or dietary issues of the patient, but were also frequently associated with problems with device components (10.4%) such as malfunctions of the pump or pod reservoir/cartridge (7.3%). | The study highlighted that while insulin pumps provide essential diabetes management, device malfunctions and user-related issues can lead to SAEs, emphasizing the need for better understanding and mitigation of pump-related risks. |
| **Abbreviations**: ICU: intensive care unit; SAE: serious adverse event | | | | | | | |

### t:slim X2

Table . Summary of clinical studies for t:slim X2

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Reynolds et al. (2024) (21) | Two infusion pumps were employed:  The Omnipod® pump (Insulet Corporation) was initially used to administer subcutaneous glucagon. However, issues with glucagon stability and pump site occlusions were encountered.  The **Tandem t:slim X2** pump was used for the continuous administration of dasiglucagon, to manage hypoglycemia. | To evaluate the effectiveness of dasiglucagon administered via a continuous subcutaneous infusion pump in managing severe hyperinsulinemic hypoglycemia unresponsive to conventional medical therapies. | Case report  The study involved a 17-year-old adolescent male presenting with persistent hyperinsulinemic hypoglycemia, refractory to standard medical management.  The data collection occurred during a six-month hospital stay, followed by continued monitoring for 12 months after discharge. | * Plasma glucose Levels * Frequency of hypoglycemia episodes * Stability of glucose control * Adverse effects (AEs) related to the treatment. | The use of the Omnipod® pump to deliver subcutaneous glucagon was associated with frequent pump site occlusions due to glucagon's limited stability and fibril formation.  Transitioning to the t:slim X2 pump for dasiglucagon administration allowed for better glucose control.  The continuous dasiglucagon infusion maintained plasma glucose levels above 3.6 mmol/L (65 mg/dL), enabling the discontinuation of intravenous dextrose support.  The dasiglucagon therapy successfully minimized hypoglycemia episodes, with plasma glucose levels dropping below 3.9 mmol/L (70 mg/dL) only 10% of the time and rarely falling below 3 mmol/L (54 mg/dL) (2% of the time). | The only reported AE with the dasiglucagon therapy was a local reaction at the pump insertion site. | The t:slim X2 pump was effective in delivering dasiglucagon continuously, achieving stable glycemic control and reducing the frequency of hypoglycemia episodes. This approach allowed the patient to discontinue intravenous dextrose.  The patient was pleased with the treatment and was able to return to school and resume physical activities. |
| Ekhlaspour et al. (2019) (22) | Experimental Group: Used the **Tandem t-slim X2** pump with Control-IQ\* Technology integrated with the Dexcom G6 CGM. This system operated in closed-loop mode to manage insulin delivery automatically.  Control Group: Used their personal SAPs, including Tandem t-slim, Insulet Omnipod, various Medtronic pumps (670G, 530G, Revel, Paradigm, 751), and Animas Ping. Automated insulin modes were deactivated, and continuous glucose monitor (CGM) data was collected using the Dexcom G5. | To evaluate the effectiveness and usability of the t-slim X2 insulin pump integrated with Control-IQ Technology, compared to standard Sensor-Augmented Pump (SAP) therapy, in improving glycemic control during a supervised winter sports camp for young patients with type 1 diabetes (T1D). | Multicenter, randomized controlled trial.  The study involved 24 children (6–12 years) and 24 adolescents (13–18 years) with T1D, who were experienced with insulin pump therapy.  The study compared the performance and safety of the Control-IQ system (experimental group) against SAP therapy (control group).  Participants were monitored for 48 hours during the ski camp at three skiing sites. For participants from two sites, the study extended to an additional 72 hours of home monitoring.  Participants were randomized at each site with a total of 24 participants in the experimental group and 24 in the control group. | Primary endpoint:   * Time in range (%TiR; 70–180 mg/dL)   Secondary endpoints:   * Time above range (%TAR: >180 and >250 mg/dL). * Time below range (%TBR: <70, <60, and <54 mg/dL) * Total number and amount of carbohydrate treatments for hypoglycemia | The Control-IQ system resulted in a significant 12% increase (approximately 3 hours) in %TIR compared to SAP therapy over the entire ski camp (66.4% vs. 53.9%, p = .010).  Overnight improvements were particularly notable, with a 28% increase in TIR for the Control-IQ group (78.6% vs. 50.9%, p = .001).  TAR>180 was reduced by 15% in the Control-IQ group (31.4% vs. 43%, p = .015), with an even more substantial reduction overnight (18.2% vs. 44.5%, p = .001).  The difference in the %TBR between groups was not statistically significant. The Control-IQ group reported an average of 2% TBR<70 compared to 0.8% for the SAP group.  Specific malfunctions included software errors, CGM connectivity issues, and repeated pump occlusions. One subject experienced a software error causing prolonged system downtime, and another had multiple occlusions, both without significant adverse glycemic events. | Glycemic adverse events were minimal, and no participant experienced serious side effects or complications related to the infusion pumps. | The t-slim X2 pump with Control-IQ Technology was effective in significantly improving glycemic control compared to SAP.  The use of the t-slim X2 pump with Control-IQ Technology was associated with a similar rate of hypoglycemia as the SAP system. |
| Usoh et al. (2023) (23) | The study utilized the t-slim X2 insulin pump in conjunction with the Dexcom G6 CGM. These were used to administer insulin with Control-IQ\* technology. | To evaluate the effectiveness and safety of t-slim X2 with Control-IQ technology in a diverse patient population at a general outpatient endocrine clinic, under real-world conditions. | Retrospective study.  The study included 66 patients diagnosed with diabetes mellitus (DM): 92% (n=61) had T1D and 8% (n=5) had type 2 diabetes (T2D). The average age of the participants was reported as 42 ± 18 years.  The study compared blood glucose control metrics before and after introducing the Control-IQ technology\*.  The data collection period spanned from January 2020 to June 2021. Participants were followed consistently over the data collection period. | * %TiR; (70–180 mg/dL) * %TAR: (>180 mg/dL). * %TBR: (<70 mg/dL) * Hb1Ac changes * Participant adherence * Total daily dose (TDD) of insulin * Body weight | The average TIR increased by 27.9% after transitioning to Control-IQ, from 49.5% to 63.3% (P < .0003).  There was a 25.4% reduction in TAR, from 46.8% to 34.9% (P < .0013).  The TBR decreased by 57%, from 4.0% to 1.7% (P = .017).  A significant decrease in HbA1c was observed, from 7.7% (61 mmol/mol) to 7.1% (54 mmol/mol) (P < .017).  Weight and TDD of insulin showed no significant changes (P = .4 and P = .98, respectively).  Four persons dropped out due to CGM malfunction (n=1), pump malfunction (n=1), insertion site malfunction (n=1) or changing to a DIY Loop (n=1). | No device-related AEs or safety issues were reported during the study period. | The t-slim X2 with Control-IQ technology showed a notable 57% decrease in time spent in hypoglycemia, indicating that the system is effective in minimizing low blood sugar events. |
| Breton and Kovatchev (2021) (24) | The t-slim X2 insulin pump was used in conjunction with the Dexcom G6 CGM and Control IQ technology. | To analyze the real-world performance, safety, and glycemic outcomes associated with 12 months of continuous use of t-slim X2 with Control-IQ\* technology. | Retrospective study.  The analysis included 9451 Control-IQ\* users, who uploaded their glycemic data to a database over a 12-month period.  83% of participants had T1D, while the rest had T2D or another form of diabetes. The study included children, adolescents and adults; mean age: 41.9 ± 20.8 years.  Data was collected from January 2020 until February 2021. | * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * Mean glucose levels * Percent time spent in closed-loop (CL) automation | The median TIR increased from 63.6% at baseline to 73.6% after 12 months of using Control-IQ (P < 0.001), with sustained improvements over the entire year.  %TBR<70 increased non-significantly from 0.8% at baseline to 0.9% after 12 months (p = 0.053). %TBR<54 saw a slight increase from 0.1% to 0.15% (p < 0.001).  Average glucose levels decreased from 167.5 mg/dL to 154.3 mg/dL.  Users maintained a median 94.2% time in CL automation throughout the 12 months. | No device-related AEs or safety issues were reported during the study period. | The t-slim X2 with Control-IQ technology effectively maintained low rates of hypoglycemia, with median time <70 mg/dL consistently around 1%.  The slight increase in severe hypoglycemia episodes (<54 mg/dL) is equivalent to less than 1 min/day. |
| Forlenza et al (2018) (25) | The Tandem Diabetes Care t-slim X2 insulin pump with Basal-IQ Predictive Low-Glucose Suspension (PLGS) technology and Dexcom G5 CGM was used to automatically suspend insulin delivery when low glucose levels were predicted and resume delivery when glucose levels stabilized. | To evaluate the effectiveness and safety of the t-slim X2 pump in reducing hypoglycemia compared to SAP therapy in individuals with T1D. | Multicenter, randomized, controlled, crossover outpatient pivotal trial.  The study included 103 T1D patients. Sixty of these (58%) were under 18 years old, with 16 participants aged 6 to under 12 years, and 44 participants aged 12 to under 18 years.  The study compared the performance and safety of the Basal-IQ PLGS system with the non-PLGS SAP therapy using the same pump and CGM setup.  The study involved two 3-week intervention periods following a run-in phase. | Primary endpoint:   * %TBR: (<70 mg/dL)   Secondary endpoints:   * %TBR: (<60, <54 & <50 mg/dL) * Frequency of hypoglycemic events * Area over the curve below 70 mg/dL * Low blood glucose index * Glucose coefficient of variation (CV) * %TiR; (70–180 mg/dL) * Hyperglycemia metrics * Daily insulin delivery details | The Basal-IQ PLGS system reduced median TBR<70 mg/dL from 3.6% at baseline to 2.6%, compared to 3.2% with SAP therapy. This represents a 31% reduction in hypoglycemia with the PLGS system (P<0.001).  Secondary outcomes also showed significant hypoglycemia reductions: TBR<60 mg/dL, TBR<54 mg/dL, and TBR<50 mg/dL all decreased.  The PLGS system resulted in better hypoglycemia control, with consistent performance during both daytime and nighttime. | There was one severe hypoglycemic event in the SAP therapy arm and none in the PLGS arm.  One serious adverse event (bowel obstruction) occurred during the SAP arm.  No safety issues were directly related to the t-slim X2 infusion pump. | The t-slim X2 insulin pump with Basal-IQ technology effectively reduces hypoglycemia without compromising overall glycemic control. |
| Wang et al (2023) (26) | The t-slim X2 insulin pump with Control-IQ\* technology was used to manage the participants’ glucose levels during pregnancy and the postpartum period through automated insulin delivery (AID), including features like Sleep and Exercise modes, bolus calculations, and insulin modulation. | To assess the glycemic control and qualitative experiences of pregnant women with T1D who were early adopters of Control-IQ\* technology. | Case series.  The study included 4 pregnant women diagnosed with T1D during pregnancy and postpartum.  Glycemic data were collected and assessed, alongside participant-reported experiences obtained through semi-structured interviews.  Participants were followed throughout their pregnancy and up to six weeks postpartum. | * %TiR; (3.5–7.8 mM) * %TBR: (<3.5 mM) * %TAR: (>7.8 mM) * Mean sensor glucose levels * Hb1Ac levels * Insulin delivery metrics * Neonatal hypoglycemia * Birth outcomes * Subjective experiences | All participants achieved over 70% TiR by the third trimester.  Participants maintained a minimal TBR (below 1.9% throughout pregnancy), and there were no severe hypoglycemic events.  Glycemic control improved significantly, with reductions in HbA1c and mean sensor glucose levels for most participants.  Participants experienced improved sleep quality, reduced stress, and greater confidence in diabetes management.  A CGM transmitter failure occurred in one case, and issues arose from exceeding the pump’s maximum bolus limit of 25 units, which required a workaround until resolved. | Case #1: An insulin infusion set kink and an incident where the participant fell asleep without the pump led to transient drops in TiR.  Neonatal hypoglycemia was reported for three cases, but only one neonate required minimal oral feeding intervention.  One neonate was born prematurely and required brief NICU support due to preeclampsia complications.  The safety issues were not attributed to the infusion pump. | The study concluded that ”*Participants with low pregnancy glucose time-in-range increased their time-in-range with Control-IQ technology use and participants with high pregnancy glucose time-in-range maintained and increased their time-in-range with less diabetes management burden*”. |
| Carlson et al (2024) (27) | The Tandem t-slim X2 pump equipped with Control-IQ\* v1.5 was used. It was paired with the Dexcom G6 continuous glucose monitor (CGM). The pump managed insulin delivery through an advanced algorithm, aiming to optimize glycemic control in individuals with high insulin requirements. | To assess the safety and performance of the updated version 1.5 of the Control-IQ\* algorithm, used with the t-slim X2 pump, in adults with T1D who require high basal insulin rates exceeding 3 units per hour. | Multicenter, single-arm, prospective study.  The study included 34 adult T1D patients, who required at least one programmed basal insulin rate of over 3 units per hour.  The participants used the study device over a period of 13 weeks, with data collection and monitoring conducted throughout this timeframe. | * Safety events * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 & >250 mg/dL) * Time in tight range (%TITR: 70–140 mg/dL) * CV * Mean glucose levels * Hb1Ac change * Total daily insulin usage | Over the study period, the mean HbA1c significantly decreased from 7.69% at baseline to 6.87% (P <0.001).  Participants achieved an average TiR of 64.8% ± 10.8%, with only 1.0% ± 1.0% in TBR<70. This stability in glycemic control was maintained throughout the study.  Mean total daily insulin increased by 17.0 units/day, from 138.6 ± 51.4 units/day to 155.5 ± 59.7 units/day, reflecting adjustments in insulin needs over the trial. | One severe adverse event (SAE) was reported: new onset atrial fibrillation, which was unrelated to the use of the study device. | The updated Control-IQ algorithm on the Tandem t-slim X2 pump proved to be effective and safe for individuals with T1D who have high insulin demands.  The infusion pump's Control-IQ technology effectively minimized hypoglycemia risk. |
| Shah et al (2024) (28) | The t-slim X2 pump with Control-IQ\* technology was used in the study. It was utilized as an AID system to manage and optimize insulin therapy, improve glycemic outcomes, and adjust basal rates (BR), insulin-to-carbohydrate ratio (ICR), and correction factor (CF). | To evaluate the safety, feasibility, and effectiveness of an automated decision support tool designed to provide initial and ongoing personalized insulin pump settings adjustments to improve glycemic control in adults with T1D transitioning from multiple daily injections (MDI) to the t-slim X2 insulin pump with Control-IQ\* technology. | Single-center, prospective, single-arm clinical trial.  The study included 29 adults with T1D who were using MDI therapy.  The participants used the t-slim X2 pump for a period of 13 weeks, with data collected throughout this duration. | * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 & >250 mg/dL) * Time in tight range (%TITR: 70–140 mg/dL) * Mean glucose levels * Hb1Ac change * Safety outcomes * Frequency of manual overrides * Patient satisfaction | Median TIR improved significantly, from 45.7% to 69.1%, with the majority of improvements seen early and sustained over the 13 weeks.  The %TBR<70 mg/dL decreased from 1.8% at baseline to 1.0% at Day90 (p = 0.03). This was not significant after adjusting for multiple comparisons.  Only 1.9% of settings changes were manually overridden by study physicians, indicating high reliability of the automated system.  Patient satisfaction was high, with reduced diabetes management burden and better quality of life (QoL) reported. | One participant experienced severe hypoglycemia twice, both following breakfast meals and associated with increased physical activity. This participant was hospitalized for pancreatitis and was subsequently withdrawn from the study.  No safety issues were attributed to the t-slim X2 pump. | The pump was successful in maintaining safe glucose levels and minimizing hypoglycemia, with high TiR outcomes and minimal adverse hypoglycemic events. |
| Brown et al (2018) (29, 30) | The Tandem t-slim X2 insulin pump with Control-IQ\* technology was employed. It was used to deliver insulin in an automated manner based on CGM data. | To evaluate the feasibility and effectiveness of a new artificial pancreas (AP) system, using a well-established control algorithm integrated into a novel platform. | Single-center, pilot trial.  The study involved 5 adult participants with T1D who had been on insulin therapy for at least one year and used insulin pumps for at least 6 months.  Data was collected over a single weekend. | * %TiR; (70–180 mg/dL) * %TBR: (<70, <60 and <54 mg/dL) * %TAR: (>180, >250 and >300 mg/dL) * Percent time spent in CL * System connectivity * Usability | The Control-IQ system maintained CL operation 98.4% of the time, with a CGM signal available 94.4% of the time.  Average TIR was 82% during the day and 94% overnight.  The time in hypoglycemia was low with 2.9% spent in TBR<70 mg/dL and 0.7% spent in TBR<54 mg/dL.  All participants achieved at least 75% TIR. | No safety issues or adverse events were reported. | The Control-IQ system demonstrated promising and reliable glycemic control, achieving high levels of TIR and minimal hypoglycemia. |
| Breton et al (2020) (31, 32) | The t-slim X2 pump with Control-IQ Technology was used in the CL group to automate insulin delivery based on CGM data.  The t-slim X2 pump with a PLGS feature was provided to the control group patients who previously used insulin injections.  The Dexcom G6 Continuous Glucose Monitor was used to monitor glucose levels and transmit data to the insulin pumps. | To evaluate the effectiveness and safety of a CL insulin delivery system, using a t-slim X2 insulin pump with Control-IQ\* Technology, in managing glucose levels among children with T1D. | Multicenter, randomized, open-label, parallel-group trial.  The trial included 101 children (ages: 6-13 years), who had T1D for at least one year, and had been treated with insulin for a minimum of 6 months prior to enrolment.  The patients were randomized 3:1 for treatment with either the CL system (n=78) or the control setup (n=23).  The study duration was 16 weeks. | * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * HbA1c levels * Safety outcomes | The CL group showed a significant increase in the %TiR, improving from 53% to 67%, while the control group had a minor increase from 51% to 55%. The adjusted difference between the groups was 11 percentage points, favoring the CL system (95% CI: 7-14, P<0.001).  The CL group had better glucose control during both daytime (TiR: 63% vs. 56%) and nighttime (TiR: 80% vs. 54%).  Although being statistically non-signitficant, the %TBR<70 increased slightly from 1.2% at baseline to 1.6% in the CL group and from 1.0% to 1.8% in the control group. | The study reported 16 AEs in 15 patients (19%) in the CL group and 3 AEs in 2 patients (9%) in the control group.  The AEs included 13 cases of hyperglycemia or hyperketosis, 2 cases of infection at the site of sensor insertion, 1 hospitalization for gastroenteritis leading to ketosis, 1 viral illness, 1 hypoglycemic event and 1 accidental overdelivery of insulin.  The hyperglycemia or hyperketosis AEs were all related to problems with the pump infusion set, except for one that was related to an issue involving the pump battery. | The closed-loop insulin delivery system improved TiR but did not improve TBR. |
| Kanapka (2021) (32, 33) | The t-slim X2 insulin pump with Control-IQ\* Technology was used in combination with the Dexcom G6 CGM for automated insulin delivery. | To evaluate the safety and efficacy of the Control-IQ\* CL insulin delivery system in children aged 6-13 years with T1D, through an extended 12-week follow-up phase following a previous 16-week randomized controlled trial (RCT). | RCT (follow-up of (31))  The study included the same 101 pediatric patients as in (31). Of these, 100 completed the study.  The study compared the performance and safety of the t-slim X2 Control-IQ\* system with a SAP. Randomization was as described in (31).  The study spanned 28 weeks: a 16-week RCT followed by a 12-week extension phase. | * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * HbA1c levels * Usability * Satisfaction * Safety outcomes | **SAP group**: The mean TIR increased significantly from 55% during the RCT to 65% in the extension phase. Daytime and nighttime TIR also improved.  TBR<70 decreased significantly from 1.8% to 1.34% (p < 0.001).  **CL group**: TIR remained stable from the RCT to the extension phase, maintaining a mean of approximately 66%.  TBR<70 decreased significantly from 1.57% to 1.50% (p = 0.006). | Ten AEs related to hyperglycemia occurred, which were due to pump infusion set issues (n=8), CGM connectivity loss (n=1), and illness (n=1). | Although the TBR decreased during the extension phase in both groups, neither reached the TBR at baseline. As such, the hypoglycemia risk has not improved overall with the use of CGM. |
| Schoelwer et al (2021) (32, 34) | The t-slim X2 insulin pump with Control-IQ\* Technology was used to deliver insulin. The pump was integrated with the Dexcom G6 CGM for hybrid CL control of blood glucose levels. | To investigate predictors of TiR while using the t-slim X2 insulin pump with Control-IQ\* Technology in children with T1D. The researchers sought to determine if higher baseline TiR, greater time spent in CL mode, and increased user engagement were associated with better glycemic outcomes. | RCT  The study included the same 101 pediatric patients as in (31) and (33).  Participants were divided into quartiles based on their TiR while using the Control-IQ system.  The study spanned 28 weeks: a 16-week RCT (31) followed by a 12-week extension phase (33). | Performance metrics such as TiR and insulin delivery patterns were analyzed.   * %TiR; (70–180 mg/dL) * %TBR: (<70 mg/dL) * %TAR: (>180 mg/dL) * Insulin delivery characteristics * User engagement metrics (e.g., frequency of boluses). | Although TBR<70 mg/dL was low across all groups, it was higher in the highest TiR quartile (median 1.66%) compared to the lowest (0.80%).  Participants with lower baseline TiR exhibited more significant improvements after starting on the CL system.  Participants in the lowest TiR quartile were less likely to use the CL mode consistently. In this group, 36% of participants used the closed-loop mode less than 90% of the time, compared to none of the participants in the highest TiR quartile (P < 0.001). | No device-related AEs or safety issues were reported. | The study concluded that, ”*user*  *engagement is important for optimal glycemic control*”. |
| Cobry et al (2021) (32, 35) | The t-slim X2 insulin pump with Control-IQ\* technology was used for automated insulin delivery in the CLC group, paired with a Dexcom G6 CGM.  Participants in the SAP group used a Dexcom G6 CGM and either their own insulin pump or a t-slim X2 with PLGS functionality. | To evaluate the experiences of children with T1D and their parents/caregivers using the Control-IQ system (closed-loop control, CLC) compared to a control group using a SAP. The study focused on diabetes device expectations, ease of use, impact on sleep, fear of hypoglycemia, and overall QoL. | Multicenter, unblinded, RCT.  The study included the same 101 pediatric patients as in (31, 33, 34).  The study compared the the t-slim X2 Control-IQ\* system with a SAP.  Randomization for CLC or SAP was as described in (31).  The study spanned 28 weeks: a 16-week RCT (31) followed by a 12-week extension phase (33). | Questionnaires:   * Pediatric Hypoglycemia Fear Survey (PHFS/CHFS) * Problem Areas in Diabetes (PAID) * Pediatric Quality of Life (PedsQL) * Pittsburgh Sleep Quality Index (PSQI) | **Parent-Reported Outcomes**: In the CLC group at the end of the 16-week RCT, the PHFS total score showed a reduction of 7.7 points, indicating decreased fear of hypoglycemia, and PAID scores dropped by 7.8 points, reflecting reduced emotional distress.  **Child-Reported Outcomes**: The CLC group exhibited improvements in CHFS scores.  Although not statistically significant, the CLC group showed a trend toward better psychological outcomes.  **Sleep Quality:** The PSQI scores in the CLC group improved, indicating a reduction in sleep disturbances, with baseline clinically significant scores (5.8) decreasing to below the clinical disturbance threshold (4.3). | No device-related AEs or safety issues were reported. | The t-slim X2 with Control-IQ technology appears to be beneficial in managing type 1 diabetes in children aged 6–13, as it is associated with improved QoL, reduced fear of hypoglycemia, and fewer sleep disturbances among both children and their parents. |
| Cobry et al (2022) (32, 36) | Tandem t-slim X2 insulin pump with Control-IQ\* technology was used by the intervention group for automated insulin delivery in combination with the Dexcom G6 CGM.  A SAP was used by the control group, consisting of the Dexcom G6 CGM and either the participant's existing pump or a study-provided t-slim X2 pump without Control-IQ. | To evaluate the effects of using the Control-IQ\* hybrid closed-loop (HCL) insulin pump system on parental sleep quality, particularly in parents with children who have type 1 diabetes and poor baseline sleep, and to explore associated glycemic and psychosocial outcomes. | Multicenter, unblinded, RCT.  The study enrolled the same 101 pediatric patients as in (31, 33-35). The PSQI survey was used at baseline to identify 49 parents who are “poor” sleepers (PSQI >5)  The study compared the t-slim X2 Control-IQ\* system with a SAP in managing nocturnal glycemic outcomes.  Randomization for CLC or SAP was as described in (31).  The study spanned 28 weeks: a 16-week RCT (31) followed by a 12-week extension phase (33). | Questionnaires:   * PSQI * Hypoglycemia Fear Survey (HFS-II) * PAID   Child nocturnal glycemic metrics:   * Mean sensor glucose * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 mg/dL) | Of the 49 included poor sleepers, 27 became good sleepers.  Children in the CLC group demonstrated significant improvements in mean sensor glucose levels, reduced glucose variability, and increased TIR during nighttime hours.  However, there was a slight increase in the %TBR<54 mg/dL from 0.0% to 0.1% (p = 0.040). | No device-related AEs or safety issues were reported. | The Control-IQ\* system generally maintained safe glucose levels at night. However, there was a slight but notable increase in very low glucose events (<54 mg/dL), suggesting a good but not perfect ability to prevent severe hypoglycemia. |
| Graham et al (2024) (37, 38) | The t-slim X2 insulin pump with Control-IQ\* technology was used for automated insulin delivery in conjunction with the Dexcom G6 CGM system. | To evaluate the safety, performance, and patient satisfaction of the t-slim X2 insulin pump with Control-IQ\* technology in real-world, decentralized settings during the COVID-19 pandemic, and to explore the feasibility of using decentralized study methods for post-market surveillance (PMS). | Decentralized, prospective, PMS study.  The study included 2,998 children (6–13 years), adolescents (14–17 years), and adults (18+ years) with T1D.  Participants agreed to use the device for 12 months, with monthly surveys and CGM data being collected at least every 3 months.  Data collection spanned a 19-month period from August 2020 to March 2022. | Primary endpoint:   * Incidence rate of severe hypoglycemia * Incidence rate of diabetic ketoacidosis (DKA) * Safety issues   Secondary endpoints:   * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * Patient satisfaction * Sleep quality * Diabetes impact | The rate of severe hypoglycemia was reduced compared to historical rates, with children experiencing 9.31 events per 100 patient years versus 19.31 events historically (P < 0.01) and adults showing 9.77 events per 100 patient years compared to 29.49 historically (P < 0.01). Similarly, DKA rates were significantly lower in both age groups.  The %TiR was 70.1% (61.0–78.8) for adults, 61.2% (52.4–70.5) for children, 60.9% (50.1–71.8) for adolescents, and 67.3% (57.4–76.9) overall.  The %TBR<70 was 1.1% (0.5–2.1) overall and the %TBR<54 was 0.2% (0.1–0.4) overall.  The patient-reported outcomes found a 25% increase in device satisfaction. | No device-related AEs or safety issues were reported. | The authors concluded that, ”*use of the Tandem t:slim X2 insulin pump with Control-IQ technology is safe and effective in individuals with T1D*”. |
| Levy et al (2024) (39, 40) | The study utilized the t-slim X2 insulin pump equipped with Control-IQ\* technology version 1.5. The pump was used to deliver insulin (lispro and URLi) and support automated closed-loop insulin delivery. | To evaluate the safety and investigate the efficacy of using the Control-IQ\* technology with ultrarapid insulin URLi in managing T1D. | Multicenter, single-arm trial.  The study included 179 children (6-13 years), adolescents (14-17 years) and adults (18+ years) with T1D. They had been using a Tandem insulin pump with Control-IQ technology for at least 3 months and had a minimum of 85% active CL system use in the 14 days prior to enrollment.  Participants were followed for a total of 13 weeks during the URLi usage period, after a 16-day lead-in period using lispro insulin. | * Incidence of severe hypoglycemia * Incidence of DKA * SAEs * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * %TITR: (70-140 mg/dL) * Mean glucose levels * HbA1c levels * Insulin Treatment Satisfaction Questionnaire (ITSQ) * Treatment-Related Impact Measure of Diabetes (TRIM-D) * Treatment-Related Impact Measure of Diabetes Device (TRIM-DD). | During the URLi period, participants had a mean TIR of 67%, which was a 2% improvement compared to the 65% observed during the lispro period.  There was no significant difference in %TBR<54 between URLi and lispro periods, whereas %TBR<70 was lower for the URLi period (1.2% vs 1.4%; p<0.001).  The number of infusion set changes per week were similar between both insulin types. | Three severe hypoglycemia events occurred during the URLi period, with one involving seizure or loss of consciousness. These events were attributed to user errors, such as manual bolusing without eating or bolusing before exercise.  Two SAEs were noted: one case of breast cancer and one case of hypovolemic shock, unrelated to the insulin pump or study insulin.  Infusion site reactions (n=445) were noted by 101 patients including: discomfort (77%), erythema (37%), induration (23%), edema (15%), and pruritus (11%). In addition, two patients developed a rash that may have been caused by insulin. | The t-slim X2 insulin pump with Control-IQ technology, in combination with ultrarapid insulin URLi, demonstrated a favorable safety profile and slight improvements in glycemic control compared to lispro. |
| Ekhlaspour et al (2021) (41, 42) | The Tandem t-slim X2 insulin pump with Control-IQ\* technology was used to manage insulin delivery. The purpose was to automate insulin dosing and improve glycemic control by utilizing real-time adjustments based on sensor glucose data from the Dexcom G6 CGM. | To assess the safety and effectiveness of a modified version of the Tandem t-slim X2 Control-IQ\* delivery system for young children aged 2 to 5 years with T1D, first under continuous supervision by a study team and subsequently in a home environment with parental monitoring | Multicenter, prospective two-phased interventional study.  The study included 12 young children (2-5 years) diagnosed with T1D. These children had been using an insulin pump and a Dexcom CGM for at least 3 months prior to enrollment.  The study compared the glycemic outcomes of using the modified Control-IQ\* system against baseline data collected in an open-loop (manual insulin delivery) setting.  The data collection period spanned from the initial training and baseline open-loop assessment (lasting 2–7 days) through the 48-hour supervised hotel phase and the subsequent 72-hour home use phase. | * Participants achieving less than 6% time <70 mg/dL and less than 40% time >180 mg/dL. * %TiR; (70–180 mg/dL) * %TBR: (<70 and <60 mg/dL) * %TAR: (>180 and >250 mg/dL) * Sensor glucose levels * Hypoglycemic events * Time in CL mode | The proportion of participants achieving the predefined targets of spending less than 6% of the time <70 mg/dL and less than 40% of the time >180 mg/dL rose from 33% at baseline to 83% with the use of Control-IQ.  TiR increased from 61.7% at baseline to 71.3% during Control-IQ usage (p = 0.016).  There was a decrease in hyperglycemia, with %TAR>180 dropping from 34.1% at baseline to 25.7% with the system (p = 0.042).  The TBR did not decrease significantly from baseline to Control-IQ.  The system performed especially well overnight, reducing the average sensor glucose values significantly and maintaining stability without increasing hypoglycemia. | No safety issues directly attributed to the use of the infusion pump were reported. | The time spent in hypoglycemia was statistically similar for the periods with open-loop and closed-loop pumps. |
| Ekhlaspour et al. (2019) (43) | The t-slim infusion pump (Tandem) was used as part of a Bionic Pancreas (BP) system to deliver insulin. It worked alongside a Dexcom G4 Platinum AP CGM and an iPhone-based BP app that managed insulin dosing, calculated intended glucagon doses (though glucagon was not administered), and managed device connectivity. | To evaluate the safety and performance of an insulin-only BP system in a real-world home-use setting, focusing on its ability to manage glucose levels with a conservative approach to minimize hypoglycemia risk. | Open-label, non-randomized, pilot safety and feasibility study.  The study included 13 adult T1D patients. Participants should have used an insulin pump for at least six months.  The study duration for each participant was 21 days, spread over three 7-day arms  There was a comparison of the BP system's performance and safety across different configurations (static and dynamic glucose targets) against participants' usual-care settings:   * Static Set-Point: A fixed glucose target (e.g., 130 mg/dL) used consistently, with adjustments only in response to pre-specified conditions.   Dynamic Set-Point: A flexible glucose target that automatically varied between 110 and 130 mg/dL, | * Mean CGM glucose levels * %TBR: (<70, <60 and <50 mg/dL) * %TiR; (70–180 mg/dL) * %TAR: (>180, >250 and >300 mg/dL) * Total daily insulin dose | The BP system, using a static glucose target, significantly reduced the percentage of time glucose levels fell below 70 mg/dL and 60 mg/dL compared to the usual-care arm. For the static set-point, TBR<60 decreased from 2.3% to 0.84%, and TBR<70 was reduced from 5.5% to 1.8%.  The %TBR also improved with the dynamic set-point configuration compared to usual care, although not statistically significantly.  No significant differences were observed in %TiR or %TAR.  There were 157 alerts related to connectivity issues or hypoglycemia. The study team intervened for 71% of these alerts. | No AEs were reported. | The insulin-only BP system, particularly with a static glucose target, showed promise in effectively managing glucose levels and reducing hypoglycemia risk in a home-use setting. |
| Brown et al. (2019) (44, 45) | The study used the t-slim X2 insulin pump with Control-IQ\* Technology in the CL group. This pump was used as part of the CL system to automate insulin delivery, including automated correction boluses and basal rate adjustments.  The control group used personal SAP insulin pumps or t-slim X2 without automation features for insulin delivery. | To evaluate the efficacy and safety of the Control-IQ\* CL insulin delivery system compared to a standard SAP for improving glycemic outcomes in patients with T1D. | Parallel-group, unblinded, RCT  The study included 168 T1D patients, who were at least 14 years old. Using a 2:1 randomization ratio, 112 patients were assigned to the CL system group and 56 to the control group.  The patients were monitored over a 26-week period. | * %TiR; (70–180 mg/dL) * %TAR: (>180 mg/dL) * %TBR: (<70 and <54 mg/dL) * Mean glucose level * HbA1c levels * AEs | The CL system significantly increased the %TiR from 61% at baseline to 71% over the 6 months, while the control group remained at 59%.  The %TBR<70 decreased from 3.6% at baseline to 1.6% in the CL group, which was significantly better than the change from 2.8% to 2.25% in the control group (p<0.001).  The benefits appeared within the first month and persisted over 26 weeks.  There were 137 device-related problems in the closed-loop group, most frequently related to connectivity issues. Additionally, a temporary suspension of the Control-IQ software was necessary due to a software error affecting insulin delivery, but this did not result in any serious adverse events. | 17 AEs were reported in the CL group (16 patients), including one case of DKA due to a pump infusion set failure as well as 3 SAEs: hospitalizations for concussion, otitis, and cardiac bypass surgery.  The AEs also included 13 cases of hyperglycemia or ketosis events in the CL group compared to 2 in the control group. These were predominantly caused by infusion set failures. | The closed-loop system effectively minimized the time spent with glucose levels below 70 mg/dL, demonstrating its ability to prevent hypoglycemia. |
| O’Malley et al. (2021) (45, 46) | As described for (44) the study used the t-slim X2 pump with the Control-IQ\* CLC algorithm for the CLC group. In the SAP group, participants used their own or study-provided insulin pumps but did not have access to the CLC system.  The CL system provides alarms for high priority events (e.g., occlusion or manual suspension) and alert for lower priorities (e.g., hyperglycemia). | To analyze how clinical adjustments and the usage patterns of a CLC system, specifically Control-IQ\*, influenced glycemic outcomes when compared to SAP therapy over a six-month period within the iDCL trial. | Multicenter RCT  The study included the same 168 T1D patients as in (44), using the same randomization process.  The patients were monitored and followed over a 6-month period. | * %TiR; (70–180 mg/dL) * %TBR: (<70 and <54 mg/dL) * %TAR: (>180 and >300 mg/dL) * Number of alarms and alerts * Parameter changes | The %TiR during exercise was 93.1% and the %TBR<70 was 3.4%  The %TiR during sleep was 85.8% and the %TBR<70 was 1.4%  Participants experienced a median of 0.8 alarms per day (IQR 0.5-1.6) and 6.0 alerts per day (IQR 4.7-7.3). The most frequent alerts were related to high glucose (50%) or low glucose (26%) risks.  A total of 607 parameter changes were carried out. This translates to 3.4 changes per participant in the CL group and 4.1 changes per participant in the SAP group. These changes did not affect the %TiR, %TBR or %TAR significantly overall. | No device-related AEs or safety issues were reported | Although the parameter changes overall did not affect the TiR, TAR or TBR, they may matter more during discrete periods of the day or during suboptimal control. |
| Isganaitis et al (2021) (45, 47) | As described for (44) the study used the t-slim X2 pump with the Control-IQ\* CL algorithm for the CL group.  In the SAP group, participants used their own or study-provided insulin pumps but did not have access to the CL system. | To evaluate the effectiveness and safety of the Control-IQ\* CL insulin delivery system in enhancing glycemic control and reducing adverse events in adolescents and young adults with T1D, specifically examining outcomes in the 14–24 age range over a 6-month period. | RCT  The study enrolled the same 168 T1D patients as in (44) and (46), using the same randomization process. Of these, 63 participants in the 14–24 age range were included for the present study.  The patients were monitored and followed over a 6-month period. | * %TiR; (70–180 mg/dL) * %TAR: (>180 mg/dL) * %TBR: (<70 and <54 mg/dL) * Mean glucose level * HbA1c levels * AEs | The CL system significantly increased %TIR by 13% (3.1 hours/day) compared to the SAP group. Improvements in TIR were particularly evident during nighttime hours (1 AM - 8 AM), with an increase of 19% in the CL group versus the SAP group.  The CL group demonstrated sustained TIR improvement from the first day of use throughout the 26-week period.  The %TBR<70 decreased from 3.2% to 1.6% in the CL group compared to a decrease from 2.9% to 2.1% in the SAP group, which was a significant difference (p = 0.002). The %TBR<54 also decreased in the CL group but not significantly more than the SAP group (p = 0.21).  During the study, a software error was identified that temporarily suspended Control-IQ system functionality for approximately four weeks. No adverse events were associated with this software error. | No severe hypoglycemia episodes were reported in either group.  However, there was one episode of DKA in the CL group, caused by an infusion set failure, and 6 additional episodes of hyperglycemia with ketosis were reported in the CL group compared to 1 in the SAP group. | The majority (63%) of participants in the CL group achieved a simultaneous increase in TIR and reduction in TBR<70 compared to only 22% in the SAP group, which highlights the Control-IQ’s capability in minimizing hypoglycemia. |
| Ekhlaspour et al (2022) (45, 48) | The t-slim X2 insulin pump was used as part of the Control-IQ\* system, which modulates basal rates and delivers periodic automated correction boluses. The infusion pump was critical for automating insulin delivery based on CGM readings and optimizing insulin dosing. | To assess whether improvements in TIR with the Control-IQ\* CL insulin delivery system are consistent across patients with T1D with varying baseline HbA1c levels. | RCT subgroup analysis  The study enrolled the same 168 T1D patients as in (44) and (46), using the same randomization process. Only the 112 patients in the CL group were included for the present study.  The patients were stratified into 5 subgroups based on HbA1c levels (<6.5%,  6.5%–7.0%, 7.0%–8.0%, 8.0%–8.5%, and ≥8.5%).  The patients were monitored and followed over a 6-month period with a 2- to 8-week run-in phase to collect baseline information. | * %TiR; (70–180 mg/dL) * %TAR: (>180 mg/dL) * %TBR: (<70 and <54 mg/dL) | All HbA1c subgroups showed improved TIR with the CL system.  The largest decrease in %TBR<70 was observed in participants with baseline HbA1c levels below 6.5%, with a 4.4% reduction, particularly overnight (6.8%).  Participants with the highest baseline HbA1c (≥8.5%) experienced the greatest decrease in hyperglycemia, with a 21.9% reduction overall and 30.4% reduction overnight. | No device-related AEs or safety issues were reported. | The Control-IQ system effectively reduced time spent in hypoglycemia (<70 mg/dL), especially in participants with lower baseline HbA1c values. |
| Kudva et al. (2021) (45, 49) | As described for (44) the study used the t-slim X2 pump with the Control-IQ\* CLC algorithm for the CLC group. In the SAP group, participants used their own or study-provided insulin pumps but did not have access to the CLC system. | To assess both glycemic and patient-reported outcomes (PROs) for users of a CLC insulin delivery system versus SAP therapy, examining whether CLC use affects diabetes management burden, QoL, and acceptance. | RCT  The study enrolled the same 168 T1D patients as in (44) and (46), using the same randomization process.  The PROs of the CLC-equipped t-slim X2 pump were compared to the SAP system.  The patients were monitored and followed over a 6-month period. | * Diabetes distress scale (DDS) * Hypoglycemia fear survey (HFS-II) * Clarke’s Hypoglycemia Awareness Survey * Hypoglycemia confidence scale (HCS) * Hyperglycemia avoidance scale (HAS) * Technology experience using INSPIRE survey * Technology Expectation Survey * Technology Acceptance Survey * System Usability Survey (SUS) | Adults in the SAP group reported significantly higher distress than in the CLC group at 3 months, with scores on the powerless subscale being higher (p = 0.04), but not at 6 months.  From HFS-II at 6 months, the CLC group had lower behavior subscale scores to avoid hypoglycemia (p = 0.02).  The awareness of hypoglycemia symptoms was similar for the groups.  The CLC group reported increased confidence in managing hypoglycemia from baseline to 6 months, with increases ranging from 2% to 23% in 8 out of 9 areas. The SAP group experienced increased confidence in only two areas and declines in six areas.  At 3 and 6 months, the CLC group’s perceived benefits with the CL system remained high, and perceived burdens remained low.  At both 3 and 6 months, the CLC group reported high usability. | No device-related AEs or safety issues were reported. | The CLC system, provided significant QoL benefits by reducing the burden of diabetes management and enhancing users' confidence in managing their condition. |
| Brown (2020) (50) | The t-slim X2 insulin pump with the Control-IQ\* CLC system was used to automate insulin delivery, including adjusting basal rates and delivering correction boluses.  The Basal-IQ PLGS system and SAP therapy were used for comparative purposes. | To assess the effectiveness and safety of the Control-IQ\* CLC system in individuals with T1D, who transitioned from PLGS or SAP to Control-IQ\* CLC. | RCT  The study included 164 patients with T1D, ranging in age from 14 to 71 years.  Participants were randomized into three groups: CLC treatment (n=54), PLGS treatment (n=55) or SAP treatment (n=55).  There was a comparison of performance and safety among the different insulin pumps. This involved evaluating the transition from SAP or PLGS systems to the CLC system.  Data were collected over an initial 6 month trial with a 3 month extension. | * %TiR; (70–180 mg/dL) * %TAR: (>180, >250 and >300 mg/dL) * %TBR: (<70, <60 and <54 mg/dL) * %TITR: (70-140 mg/dL) * Hypoglycemia events | The %TIR was 67.6% in the CLC group, 60.4% in the PLGS group and 69% in the SAP group.  The %TAR>180 was 31% in the CLC group, 38% in the PLGS group and 29% in the SAP group.  The %TBR<70 was 0.53% in the CLC group, 0.59% in the PLGS group and 1.76% in the SAP group.  The %TBR<54 was 0.2% in the CLC group, 0.22% in the PLGS group and 0.19% in the SAP group.  The %TITR was 42% in the CLC group, 37.1% in the PLGS group and 45% in the SAP group.  The number of hypoglycemia events per week was 3.0 in the CLC group, 3.1 in the PLGS group and 3.8 in the SAP group. | There were no device-related AEs or SAEs in either group.  In addition, there were no severe hypoglycemia events. | The time spent in hypoglycemia (<70 mg/dL) was higher in the SAP group compared to the other groups, whereas the time spent in severe hypoglycemia (<54 mg/dL) was similar for the groups. |
| Levy et al. (2022) (51) | The t-slim X2 insulin pump, equipped with the Control-IQ\* algorithm, was used. Its purpose was to automate insulin delivery, modulate basal rates, and administer correction boluses to optimize glucose control and prevent hypoglycemia. | To evaluate the glycemic outcomes of menstruating women using the Tandem Control-IQ\* AID system, focusing on variations across different menstrual cycle phases during a 12-month extension of the International Diabetes Closed Loop (iDCL) trial. | RCT subgroup analysis  The study included 16 menstruating women, aged 15 to 45 years, who had T1D and used the Control-IQ system.  The data was collected during the 12-month extension phase of the iDCL trial, though participants provided menstrual tracking information over an average period of 145 days (6 cycles). | * %TiR; (70–180 mg/dL) * Mean glucose levels | The mean 24-hour CGM glucose levels were 161 ± 26 mg/dL during menstruation, 165 ± 25 mg/dL during the luteal phase, and 159 ± 20 mg/dL during the rest of the cycle.  %TiR was 69% ± 14% during menstruation, 67% ± 13% during the luteal phase, and 69% ± 12% during the rest of the cycle.  No significant variations were noted in insulin delivery patterns or rates across different cycle phases. | No device-related AEs or safety issues were reported. | The study found that the t-slim X2 insulin pump with Control-IQ technology provided consistent and effective glucose control across different phases of the menstrual cycle for women with T1D. |
| Wadwa et al. (2023) (52, 53) | The HCL infusion pump used was the t-slim X2 insulin pump with Control-IQ\* Technology, which was combined with a Dexcom G6 CGM. The system was used for automated insulin delivery, aiming to maintain blood glucose levels within the target range.  Standard diabetes care involved either a personal insulin pump or MDI paired with a CGM. | To evaluate the safety and effectiveness of a HCL insulin delivery system in young children aged 2 to under 6 years with T1D, assessing whether the system can be remotely initiated and managed effectively. | Multicenter, unblinded, parallel-group, RCT  The study involved 102 young children (2-6 years) diagnosed with T1D, who had been receiving insulin treatment for at least 6 months.  The trial used a 2:1 randomization of participants between the CL insulin delivery system and standard diabetes care. The study included options for both virtual and in-person visits,  Data was collected during a 13-week period between April 28, 2021, and January 13, 2022. | * %TiR; (70–180 mg/dL) * %TAR: (>180 and >250 mg/dL) * %TBR: (<70 and <54 mg/dL) * Mean glucose levels * HbA1c levels * Incidence of severe hypoglycemia * Incidence of DKA * SAEs | The HCL system significantly improved %TiR from 56.7% at baseline to 69.3% over 13 weeks. The standard-care group saw only a minor increase from 54.9% to 55.9%. The HCL group showed a mean adjusted improvement of 12.4 percentage points over the standard-care group.  Improvements were apparent within the first week and remained consistent throughout the follow-up period.  The %TBR was similar for the HCL and standard care groups, and did not change much during the study. | Two cases of severe hypoglycemia were observed in the HCL group (2.94%) compared to one in the standard-care group (2.94%).  There were 51 hyperglycemia events in the HCL group, often related to infusion set failures, compared to 8 in the standard care group.  There was one case of DKA in the HCL group due to infusion-set failure. | The HCL system did not significantly reduce the time spent with glucose levels below 70 or 54 mg/dL compared to standard care. |
| Brown (2021) (54) | The t:slim X2 insulin pump with Control-IQ\* technology was used for automatic insulin delivery | To test the safety and feasibility of using two or three research modules (Behavioral Adaptation Module (BAM); Auto Titration Module (ATM); Web-based Simulation Tool (WST)) in conjunction with an AID. | Randomized, Controlled Pilot Study  The study included 30 adult T1D patients, who used or anticipated to use the t-slim X2 pump with Control IQ\* at study start.  After two weeks baseline use of personal AID systems, the patients were randomization 1:1 into two groups:   * Group 1: Personal AID system plus ATM and WST. * Group 2: Personal AID system plus ATM, WST and BAM.   The patients were followed for 6 weeks. | * SAEs * Adverse device effects (ADEs) * %TiR; (70–180 mg/dL) * %TBR: (<70 mg/dL) * Technology experience using INSPIRE survey | The %TiR changed from 77.0% to 73.8% for Group 1 (p = 0.064) and remained stable on 74.6% for Group 2 (p = 0.97).  The %TBR<70 decreased from 2.35% to 1.41% for Group 1 (p < 0.05) and from 1.58% to 1.48% for Group 2 (p = 0.93). | No SAEs or ADEs were reported for either group. | The glycemic metrics improved more for the group without BAM than the group with BAM, which is a behavioral adaptation module deployed in a mobile app to assist a person's adaptation to AID by information and risk assessment primarily regarding glycemic risks. |
| Brown (2019) (55) | During the SAP phase, participants use their personal insulin pumps without automated insulin delivery but with the Dexcom G6 CGM.  In the CLC phase, participants use the Tandem t-slim X2 pump with Control-IQ software integrated with the Dexcom G6 CGM, designed to adjust insulin delivery in response to real-time glucose readings. | To evaluate the effectiveness of an AP System, particularly the t-slim X2 with Control-IQ\*, in maintaining stable glucose control in two specific populations with T1D: children aged 6-10 and adults aged 65 and older. Additionally, the study seeks to determine whether improved glycemic stability is associated with improved cognitive function. | Pilot, interventional trial  The study includes T1D patients aged 6-10 years (n=13) or ≥65 years (n=15).  The study included two sequential phases:   * A 4-week period using a SAP without AID. * A subsequent 4-week period using a CLC system with the Tandem t-slim X2 with Control-IQ\* and Dexcom G6 CGM. | * %TiR; (70–180 mg/dL) * Positive mood scores (assessed via Ecological Momentary Assessments on a Likert scale from 0 to 4). * Sleep patterns, measured by the PSQI (0-21 scale). * AEs * SAs | The %TiR changed from 69.6% during SAP to 79.6% during CLC for the elderly group (p = 0.002) and from 50.9% to 69.2% for the children (p < 0.001).  The positive mood scores decreased for both groups, indicating a less positive mood after transitioning to CLC.  The sleep pattern analysis showed that the scores decreased from baseline to SAP in both groups, indicating a better sleep quality. The change from SAP to CLC also improved sleep for the elderlies but not for the children. | There were no AEs or SAEs for either group. | The TIR improved for both children and elderlies after transitioning from SAP therapy to CLC therapy. However, this was not associated with a more positive mood for the patients. |
| **Abbreviations**: AE = adverse event; AID = automated insulin delivery; AP = artificial pancreas; ATM = Auto Titration Module; BAM = Behavioral Adaptation Module; BP = Bionic Pancreas; BR = basal rates; CF = correction factor; CGM = continuous glucose monitor; CL = closed-loop; CLC = closed-loop control; CV = coefficient of variation; DIY = Do it yourself; DKA = diabetic ketoacidosis; HbA1c = Glycated hemoglobin; HCL = hybrid closed-loop; HFS = Hypoglycemia Fear Survey; ICR = insulin-to-carbohydrate ratio; iDCL = International Diabetes Closed Loop; IQR = Interquartile range; ITSQ = Insulin Treatment Satisfaction Questionnaire; MDI = multiple daily injections; PAID = Problem Areas in Diabetes; PedsQL = Pediatric Quality of Life; PHFS = Pediatric Hypoglycemia Fear Survey; PLGS = Predictive Low-Glucose Suspension, PMS = post-market surveillance; PRO = patient-reported outcomes; PSQI = Pittsburgh Sleep Quality Index; QoL = quality of life; RCT = randomized controlled trial; SAE = severe adverse event, SAP = Sensor-Augmented Pump; T1D = type 1 diabetes; T2D = type 2 diabetes; TAR = Time above range; TBR = Time below range; TDD = Total daily dose; TiR = Time in range; TITR = Time in tight range; TRIM-D = Treatment-Related Impact Measure of Diabetes; TRIM-DD = Treatment-Related Impact Measure of Diabetes Device; WST = Web-based Simulation Tool  \*Control-IQ is an automated insulin delivery (AID) system designed to optimize blood glucose levels by adjusting insulin doses and administer automatic correction boluses. | | | | | | | |

### iLet Bionic Pancreas

Table . Summary of clinical studies for iLET Bionic Pancreas

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Castellanos et al. (2021) (56) | The iLet bionic pancreas (BP) was used in both its insulin-only and bihormonal configurations. In the insulin-only configuration, it delivered insulin lispro or aspart, while in the bihormonal configuration, it delivered both insulin and dasiglucagon.  The iLet bionic pancreas receives glucose data for the continuous glucose monitor (CGM). | To evaluate the function and safety of the iLet BP in adults with type 1 diabetes (T1D), comparing an insulin-only configuration and a bihormonal configuration that delivers both insulin and dasiglucagon in a home setting. | Open-label, random-order, crossover, home-use trial.  The study involved 10 adults with T1D.  The study compared the performance and safety of the iLet BP in its insulin-only and bihormonal configurations.  Each participant used the insulin-only iLet for 7 days and the bihormonal iLet for 7 days in random order. | * iLet operational thresholds * Time below range (%TBR: <70 and <54 mg/dL) * Time in range (%TiR: 70–180 mg/dL) * Time above range (%TAR: >180 and >250 mg/dL) * Mean glucose levels * Mean total daily dose (TDD) of dasiglucagon * Carbohydrate intake to manage hypoglycemia * Adverse events (AEs) | The iLet BP achieved high CGM capture rates during both the insulin-only (90.7%) and bihormonal (88.7%) periods, with drug dosing availability exceeding 95%.  For insulin, the delivery ratio was within 95-105% of the target volume, demonstrating reliable performance.  TBR<54 mg/dL was reduced in the bihormonal configuration (0.2%) compared to the insulin-only configuration (0.6%). Similarly, TBR<70 was reduced from 4% in the insulin-only approach to 2% in the bihormonal configuration.  The bihormonal setup also achieved a lower mean CGM glucose (139 mg/dL) and higher TiR (79%) compared to the insulin-only setup (149 mg/dL, 72%).  There were five instances of insulin leakage at the insulin cartridge connector, occurring once in the bihormonal period and four times in the insulin-only period. The issue was traced to off-center needle piercing of the cartridge septum, which resulted in leakage through an enlarged hole. | One participant reported vomiting during the bihormonal period.  No severe hypoglycemia, diabetic ketoacidosis (DKA), serious adverse events (SAEs), or unexpected side effects were reported. | The bihormonal iLet BP with dasiglucagon and insulin was effective in minimizing hypoglycemia, with the median time below 54 mg/dL at only 0.2%, compared to 0.6% in the insulin-only configuration. |
| Castellanos et al. (2023) (57) | The study used the iLet bionic pancreas for insulin-only delivery, which autonomously adjusts insulin dosing based on CGM data.  The control group continued their usual method of insulin delivery, which varied among participants (e.g., multiple daily injections [MDI], traditional insulin pumps, hybrid closed-loop [HCL] systems). | To examine the impact of the iLet BP on glycemic control compared with standard care across diverse racial and ethnic groups with T1D, addressing potential differences in outcomes due to racial/ethnic and socioeconomic disparities. | Randomized controlled trial (RCT).  The study included 165 children and 161 adults with T1D.  The patients were randomized, while matching ethnicity, for either iLET BP treatment (157 whites and 60 minorities) or standard care (83 whites and 24 minorities).  The study compared glycemic outcomes between the iLet BP and standard care.  Participants were followed for a 13-week period after randomization. | * Time in range (%TiR: 70–180 mg/dL) * HbA1c levels | The %TIR also improved substantially with Whites showing an increase from 53% to 65% in the BP group and minorities from 47% to 63%, whereas the %TIR in the standard care group increased from 52% to 56% among Whites and from 45% to 47% among the minorities. The adjusted differences were statistically significantly higher for the BP group compared to standard care (p < 0.001 for both ethnicities).  In White participants, the iLet BP group saw an average HbA1c reduction from 7.7% to 7.2%, while minority participants experienced a reduction from 8.3% to 7.4%. | No device-related AEs or safety issues were reported. | The iLet bionic pancreas demonstrated effective glycemic control in both White and minority participants, highlighting its potential to help reduce racial disparities in diabetes outcomes. |
| Russell et al. (2021) (58) | The iLet BP in its insulin-only configuration was used to deliver faster aspart insulin in participants.  The iLet BP automatically adjusts insulin delivery based on CGM data. | To assess the safety of different, shortened insulin delivery intervals (tmax settings) using faster aspart insulin with the iLet insulin-only BP in adults with T1D. Additionally, the study aimed to evaluate glucose control under various non-default tmax settings in comparison to the device’s standard setting. | Single-center, randomized, single-blinded, sequential-cohort trial with a two-period crossover design.  The study included 24 adults with T1D who had been on continuous subcutaneous insulin infusion (CSII) therapy for at least a year.  Participants were randomized within each cohort to one of two treatment sequences (default or non-default tmax setting first) in a crossover manner. The performance and safety were compared between the default tmax setting (t65) and non-default settings (t50, t40, and t30).  Each participant completed a 7-day screening period, two 7-day treatment periods (one with each tmax setting) as well as a 7-day follow-up period. | * %TBR: (<54 mg/dL) * %TiR (70–180 mg/dL) * Time above range (%TAR: >180 mg/dL) * Mean glucose levels * TDD of insulin * Hypoglycemia episodes * AEs | The %TBR<54 was consistently below 1% across all tmax settings, but tended to be slightly higher with the non-default settings compared to t65.  Non-default settings improved %TiR slightly compared to t65, although not statistically significantly.  Mean glucose levels were significantly lower in the non-default settings for two of the three cohorts.  The TDD of insulin was comparable across settings, showing no notable differences. | Two participants experienced non-serious infusion-site reactions on the default setting.  No severe hypoglycemic episodes occurred.  No SAEs were reported. | The study suggests that the iLet bionic pancreas with faster aspart insulin and shorter tmax settings may provide safe and effective glucose control with minimal time spent in hypoglycemia. |
| Sherwood et al. (2024) (59) | The iLet BP was used in the intervention arm for automated insulin delivery, alongside the Dexcom G6 CGM and Inset I infusion set.  During the control (usual care) arm, participants continued their regular diabetes management, with additional devices such as the Medtronic InPen for some. | To evaluate the effectiveness and safety of the iLet BP in an insulin-only configuration in comparison to standard diabetes care in adults with cystic fibrosis–related diabetes (CFRD) over a two-week period. | Single-center, open-label, randomized, crossover trial.  The study included 20 adults with CFRD, who managed their glucose levels with insulin.  The study included two treatment periods of two weeks each. Participants were randomly assigned to either begin with the iLet BP or usual care. | * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Hypoglycemia episodes (self-reported) * TDD of insulin * AEs | The BP showed significantly better glucose control than usual care, with an average TiR of 75% (compared to 62% in usual care, p=0.001).  Mean glucose levels were lower in the BP group (150 mg/dL vs. 171 mg/dL in usual care, p=0.007).  Additionally, there was a significant reduction in %TAR with the BP, both >180 mg/dL and >250 mg/dL (p=0.014 for both).  %TBR was statistically similar for the two treatments (p = 1.0 for both TBR<54 and <70 mg/dL)  There were eight device issues reported in the BP arm, primarily related to the infusion set, tubing, insulin cartridge, and CGM sensor, as well as one instance of a temporarily nonresponsive touchscreen interface. | In total, 12 AEs were reported during the periods of treatment with 7 in the BP arm and 5 for the usual care.  In the BP arm, there were 6 events of hyperglycemia without ketosis, mostly related to device issues.  There were no incidents of severe hypoglycemia or DKA in either arm. | The iLet BP appears to improve glucose control in CFRD patients significantly when compared to usual care, offering greater time in target glucose range without increased hypoglycemia risk. |
| Bionic Pancreas Research Group (2022) (60, 61) | The study used the **iLet BP** with the Inset I infusion set for insulin infusion. This device, along with the Dexcom G6 CGM, administered insulin based on weight-adjusted algorithms.  The participants in the standard care group continued using their own pumps, which for some included the **t-slim X2** insulin pump with Control-IQ (19%; n=20) or the **MiniMed 770G/**670G systems (11%; n=12), whereas others used MDI, predictive low-glucose suspension (PLGS) or open-loop pumps. Additionally, a Dexcom G6 CGM was provided. | To assess the effectiveness and safety of an insulin-only BP in managing blood glucose levels compared to standard care in patients with T1D. | Multicenter, parallel-group, randomized, and unblinded clinical trial.  The trial included 326 T1D patients from 6-79 years of age, who had been using insulin for at least one year.  Participants were randomly assigned to either the BP group (n=219) or the standard care (SC) group (n=107) in a 2:1 ratio.  The patients were followed for 13 weeks. | * HbA1c levels * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * AEs | The iLet BP significantly reduced Hb1Ac levels by 0.5 percentage points (from 7.9% to 7.3%) compared to the standard care group, which showed no change (7.7% to 7.7%).  The iLet BP improved %TiR (51% to 65%) by 11 percentage points more than standard care (51% to 54%).  There was no significant difference in %TBR between the two groups.  The mean glucose level was 16 mg/dL lower in the iLet BP group. | The iLet BP group had 214 episodes of hyperglycemia, primarily attributed to infusion-set failures.  10 severe hypoglycemia episodes occurred in the iLet BP group compared to 3 in the standard care group.  There were 3 SAEs in the iLet BP group, which were related to two suicide attempts and one non-severe hypoglycemia event.  No DKA episodes were reported.  No AEs were attributed to the pumps. | The insulin-only BP effectively improved blood glucose management in T1D patients compared to standard care, although the time in hypoglycemia was not different. |
| Kruger et al. (2022) (62) | The study used the **iLet BP** with the Inset I infusion set for insulin infusion. This device, along with the Dexcom G6 CGM, administered insulin based on weight-adjusted algorithms.  The participants in the standard care group continued using their own pumps as described above (60). | To assess the effectiveness and safety of an insulin-only BP system using insulin aspart or insulin lispro in adults with T1D, compared to standard diabetes care. | Multicenter, parallel-group, randomized trial.  The study included 161 adult T1D patients, who had been using insulin for at least one year.  Participants were randomly assigned to either the BP group (n = 107) or the SC group (n = 54) in a 2:1 ratio.  The patients were followed for 13 weeks. | * HbA1c levels * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * AEs | The BP group showed a significant reduction in HbA1c, dropping from a baseline of 7.6% to 7.1% at 13 weeks, compared to the SC group’s slight decrease to 7.5%.  The BP group also demonstrated a significant increase in TIR by 11%, and a reduction in mean glucose levels by 16 mg/dL.  %TBR<70 increased from 1.7% to 1.9% in the BP group and from 1.3% to 1.5% in the SC group, which was a statistically similar change (p=0.51).  Similarly, %TBR<54 increased from 0.21% to 0.33% in the BP group and from 0.11% to 0.18% in the SC group (p = 0.33). | The BP group experienced seven severe hypoglycemia events, involving 6.5% of participants, compared to two events in one participant (1.9%) in the SC group. These were not attributed to issues with the infusion pumps.  There were no instances of DKAs.  The 34 relevant hyperglycemia events were mainly related to infusion set failures (n=30) but also cartridge issues (n=2), a CGM issue (n=1), and a motor issue (n=1). | The CGM-measured hypoglycemia increased from baseline to follow-up at 13 weeks for both the BP and SC group. |
| Messer et al. (2022) (63) | The study used the **iLet BP** with the Inset I infusion set for insulin infusion. This device, along with the Dexcom G6 CGM, administered insulin based on weight-adjusted algorithms.  The participants in the standard care group continued using their own pumps as described above (60). | To assess the effectiveness and safety of an insulin-only BP system using insulin aspart or insulin lispro in youths with T1D, compared to standard diabetes care. | Multicenter, parallel-group, randomized trial.  The study included 165 children and adolescents (6-17 years of age) with T1D.  Participants were randomly assigned to either the BP group (n = 112) or the SC group (n = 53) in a 2:1 ratio.  The patients were followed for 13 weeks. | * HbA1c levels * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * TDD of insulin * Weight changes * AEs | Participants using the BP showed a significant reduction in HbA1c, averaging a decrease of 0.5% over 13 weeks compared to no change in the SC group.  BP participants also had increased TiR (by approximately 10%, equivalent to 2.4 hours per day) and reduced mean glucose levels (by an average of 15 mg/dL).  %TBR<70 increased from 1.3% to 1.8% in the BP group and from 1.5% to 2.3% in the SC group, which was a statistically similar change (p=0.07).  Similarly, %TBR<54 increased from 0.20% to 0.33% in the BP group and from 0.22% to 0.37% in the SC group (p = 0.24). | Three participants in the BP group and one in the SC group experienced severe hypoglycemia events. These were not attributed to issues with the infusion pumps.  There were no instances of DKA in either group.    The 126 relevant hyperglycemia events were mainly related to infusion set failures (n=103) but also cartridge issues (n=7), user errors (n=6), battery charging issues (n=5), algorithm issues (n=2), a CGM issue (n=1), an iLet screen issue (n=1), and a motor issue (n=1). | The CGM-measured hypoglycemia increased from baseline to follow-up at 13 weeks for both the BP and SC group. |
| Lynch et al. (2022) (64) | During the initial RCT, the participants continued using their own pumps for infusion as described above (60). Additionally, a Dexcom G6 CGM was provided.  During the present extension study, the participants transitioned to the **iLet BP** with the Inset I infusion set. This device, along with the Dexcom G6 CGM, administered insulin based on weight-adjusted algorithms. | To evaluate the transition to BP treatment in adults and children, who were previously treated by standard diabetes care (60). | RCT extension study.  The study enrolled the 107 T1D patients, who were treated with standard care in a previous RCT (60). Of these, 90 consented to participate in the present extension study.  The study spanned 26 weeks in total: the initial 13-week RCT followed by the present 13-week extension.  The data from the initial RCT (60) were used as baseline for comparison. | * HbA1c levels * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * TDD of insulin * AEs | After the 13-week extension, participants using the BP device demonstrated an overall reduction in HbA1c from 7.7% to 7.1%, with 46% achieving HbA1c reductions of more than 0.5%.  %TIR improved from an average of 53% to 65%, and mean CGM glucose dropped from 182 to 164 mg/dL. Improvements were similar across both adult and pediatric groups.  %TBR<70 decreased statistically significantly from 2.53% at baseline to 2.08% after 13-weeks (p=0.02).  %TBR<54 decreased non-significantly from 0.56% to 0.49% (p = 0.24). | Two severe hypoglycemia events were reported for an adult participant, both unrelated to device malfunctions.  Some hyperglycemia events and one DKA were noted as being associated with infusion set failures. | The study concluded that, “*Glycemic control improved after adult and pediatric participants in the SC arm in the Insulin-only BP Pivotal Trial transitioned to use of the BP. Improvement* *using the BP was of similar magnitude to that observed during the RCT*.” |
| Mauras et al. (2023) (65) | Participants had used the iLet BP for insulin delivery in the initial RCT (60).  During the present extension study, the participants transitioned back to their usual care with or without therapeutic guidance from the iLet BP. For the BP Guidance group, the iLet BP provided a recommended basal insulin profile with four specified periods for pump users, along with meal and correction doses based on glucose monitoring.  The insulin infusion in the other group (pre-study IR group) was based on their pre-study insulin regimen. | To assess the safety and efficacy of the backup insulin regimen generated by the iLet BP system, referred to as "BP Guidance," compared to a control group following their pre-study insulin regimen (IR). | RCT extension study.  The study involved 295 participants with T1D who had completed a 13-week RCT (60) using the BP system.  Participants were randomized in a 1:1 ratio to either the BP Guidance group (n=148) or the Pre-study IR group (n=147).  Data were collected over a 2- to 4-day transition phase immediately following the 13-week RCT. | * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180, >250 and >300 mg/dL) * AEs | During the transition phase, glycemic outcomes were comparable between the BP Guidance and Pre-study IR groups, and generally consistent with pre-RCT values across all insulin delivery types.  %TBR<70 for pump users changed from 1.7% pre-RCT to 2.4% during RCT and to 2.9% during transition for the BP guidance group. For the pump users in the pre-study IR group, these numbers were 2.1%, 1.9% and 1.7%.  %TBR<54 for pump users changed from 0.20% pre-RCT to 0.37% during RCT and to 0.41% during transition for the BP guidance group. For the pump users in the pre-study IR group, these numbers were 0.35%, 0.32% and 0.14%. Corresponding numbers can be found for MDI and AID users in the article (65). | Seven adverse hyperglycemic events were reported during the transition phase, 4 in the BP Guidance group and 3 in the Pre-study IR group. These were attributed to infusion set failures, illness, ineffective insulin, and unknown changes.  No episodes of severe hypoglycemia, DKA, or other SAEs were reported. | The authors concluded that, “*a backup insulin regimen automatically generated by the BP can be safely implemented if need arises to discontinue use of the BP*”. |
| Weissberg-Benchell et al. (2023) (66) | The iLet BP system used in the study included an insulin pump and a CGM. The infusion pumps were used to administer insulin, aiming to automate insulin delivery and improve glycemic control.  The standard care (SC) group continued using their own personal insulin and insulin delivery method. | To evaluate the psychosocial impact, user experiences, and satisfaction with the BP system compared to SC, as well as to examine psychosocial factors that may influence the BP's effects on HbA1c levels in individuals with T1D. | Multicenter RCT.  A total of 440 participants (275 adults, 71 adolescents, and 94 children) were included.  Patients were randomized into three groups: (1) BP with fast-acting insulin aspart (BP-F), (2) BP with insulin aspart or insulin lispro (BP-A/L), and (3) standard care (SC) group.  Participants were followed for a period of 13 weeks. | * Diabetes distress scale (T1-DDS) * Hypoglycemia fear survey (HFS) * WHO-5 Wellbeing index * Diabetes treatment satisfaction questionnaire (DTSQ) * Hypoglycemia confidence scale (HCS) * Problem Areas in Diabetes (PAID) * EQ5D-5L * EQ5D-5Y * INSPIRE (Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations) * Bionic Pancreas User Opinion Survey (BPUOS) * Diabetes-specific attitudes about Technology (DSAT) | The T1-DDS score improved from 1.9 at baseline to 1.6 at week 13 in the BP group (P<0.001).  The adult BP group had a 6-point lower HFS score at week 13 compared to the SC group, indicating a significant reduction in fear of hypoglycemia (P=0.005). No significant treatment effect on the HFS was observed in youths.  The adult BP group showed significant improvement in WHO-5, with a 5-point higher total score compared to the SC group at week 13 (P=0.02).  A significant improvement in DTSQ treatment satisfaction was observed in caregivers of children in the BP group (P<0.001). A smaller, non-significant improvement was observed in caregivers of teenagers.  No significant change was observed in the PAID scores for teenagers or children throughout the study.  Significant improvements in perceived EQ5D health status were observed in the BP group (P<0.001).  Baseline and endpoint INSPIRE scores for the BP system were high, ranging from 79 to 82 at baseline and 69 to 77 at endpoint. This indicates that participants had positive expectations about the BP system both before and after using it.  Participants in all groups reported significantly greater benefits from the BP system compared to burdens based on BPUOS. The benefits included feelings of increased freedom, reduced worry, and a desire to continue using the BP system after the trial. | No device-related AEs or safety issues were reported. | The BP system demonstrated a positive impact on the quality of life and emotional well-being compared to standard care. |
| Beck et al. (2022) (61, 67) | The study used the iLet BP device with Dexcom G6 CGM for insulin infusion in the BP groups.  The iLet pumps delivered either fast-acting insulin aspart (BP-F group) or a choice of insulin aspart or lispro (BP-A/L group) to regulate blood glucose autonomously.  The standard care (SC) group continued using their own personal insulin and insulin delivery method. | To evaluate the efficacy and safety of a fully automated, insulin-only BP using fast-acting insulin aspart in adults with T1D, comparing it to standard subcutaneous insulin delivery methods and a BP variant using either insulin aspart or lispro. | Multicenter, parallel-group RCT.  The study included 275 adults with T1D who had been using insulin for at least one year, through MDI or pump therapy.  Patients were randomized into three groups: (1) BP with fast-acting insulin aspart (BP-F), (2) BP with insulin aspart or insulin lispro (BP-A/L), and (3) standard care (SC) group.  Performance and safety comparisons were conducted between the BP groups and the SC group.  Participants were followed for a period of 13 weeks. | * HbA1c levels * %TiR (70–180 mg/dL) * %TBR (<70 and <54 mg/dL) * %TAR: (>180 and >250 mg/dL) * Mean glucose levels * AEs | The BP-F group showed a greater reduction in HbA1c (from 7.8% to 7.1%) compared to the SC group (from 7.6% to 7.5%), with an adjusted difference of -0.5% (p < 0.001).  %TIR increased from 54% to 71% in the BP-F group, which was significantly more than for SC (53% to 58%; p < 0.001) and BP-A/L (56% to 69%; p = 0.005).  Notably, performance benefits were more prominent during nighttime, with consistent glucose control across participants regardless of baseline glucose levels.  %TBR<70 increased from 1.3% to 1.7% in the BP-F group, which was similar for SC (1.3% to 1.5%) and BP-A/L (1.7% to 1.9%). %TBR<54 also increased to a similar degree for all groups.  Some participants experienced interruptions in insulin dosing due to technical issues, such as empty insulin cartridges, battery depletion, infusion set occlusions, and insulin delivery pauses (e.g., for exercise). | AEs included severe hypoglycemia events, with 3 occurrences in the BP-F group, 2 in the SC group, and 7 in the BP-A/L group.  In addition, there were 52 hyperglycemia events in the BP-F group and 34 in the BP-A/L group. These events were attributed to infusion set failures.  There were 2 cases of DKA in the BP-F group and none in the other groups. | The study concluded that, “*In adults with T1D, HbA1c was improved with the BP using fast-acting insulin aspart compared*  *with standard care without increasing CGM-measured hypoglycemia. However, the effect was no better than*  *the reduction observed with the BP using aspart or lispro*.” |
| Howard et al. (2024) (68) | The iLet BP was used for automatic insulin delivery. | To explore the experiences and perceptions of youths and their caregivers participating in the BP pivotal trial, focusing on usability, quality of life (QoL), and device efficacy in managing T1D. | Multicenter pivotal trial  The study involved 25 youths (8-17 years) with T1D, and 27 caregivers.  The participants’ experiences with the BP system were qualitatively compared to their previous diabetes management routines, highlighting perceived improvements and challenges.  After an initial 13-week RCT (60), the current focus groups were completed within 2-10 weeks. | There were no measurable endpoints. Qualitative endpoints included:   * Time burden * Cognitive and emotional burden * Glucose control * Independence * Flexibility in daily routine * Participant satisfaction | Youths and caregivers reported significant improvements in managing diabetes with the BP, noting reduced time and cognitive load dedicated to diabetes management as well as better overnight glucose stability and increased freedom in daily life.  However, some reported challenges with high and low glucose levels, especially during exercise and at night.  Additionally, there were mixed feelings about the BP algorithm's ability to adapt, with some reporting a steep learning curve and frustration with control limitations.  Users expressed concerns about issues such as alarm fatigue, the frequency of insulin cartridge changes, and the dimness of the BP screen. | There were no AEs reported.  Safety concerns included instances of hypoglycemia, especially during exercise or when reattaching the pump after being disconnected.  Some parents noted high glucose levels overnight that the BP system struggled to bring back into range. | The BP system was generally well-regarded for reducing the daily burden of diabetes management and improving glucose control for many youths and caregivers.  However, some concerns regarding blood glucose stability limited the BP’s perceived efficacy for a subset of users. |
| **Abbreviations**: AE = Adverse event; BP = bionic pancreas; BPUOS = Bionic Pancreas User Opinion Survey; CFRD = cystic fibrosis–related diabetes; CGM = continuous glucose monitor; CSII = continuous subcutaneous insulin infusion; DDS = Diabetes distress scale; DKA = diabetic ketoacidosis; DSAT = Diabetes-specific attitudes about Technology; DTSQ = Diabetes treatment satisfaction questionnaire; HbA1c = Glycated hemoglobin; HCL = hybrid closed-loop; HCS = Hypoglycemia confidence scale; HFS = Hypoglycemia fear survey; INSPIRE = Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations; IR = insulin regimen; MDI = multiple daily injections; PAID = Problem Areas in Diabetes; PLGS = predictive low-glucose suspension; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SC = Standard care; T1D = type 1 diabetes; TAR = Time above range; TBR = Time below range; TDD = Total daily dose; TiR = Time in range; TITR = Time in tight range | | | | | | | |

### CADD-MS3

Table . Summary of clinical studies for CADD-MS3

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sadushi-Koliçi et al. (2012) (69) | Initially, treprostinil was administered via the MiniMed 407C insulin infusion pump (Medtronic).  Starting in 2004, the CADD-MS3 infusion pump (Smith Medical MD Inc) was used.  The pumps were utilized for subcutaneous (SC) delivery of treprostinil to achieve therapeutic goals based on functional and clinical response. | To evaluate the long-term effects, including functional capacity, exercise tolerance, hemodynamic measures, survival rates, and tolerability, of first-line SC treprostinil therapy in patients with severe pre-capillary pulmonary arterial hypertension (PAH). | Prospective registry study.  The study included 111 adult patients diagnosed with severe pre-capillary PAH, specifically World Health Organization (WHO) functional class (FC) III or IV.  Data collection spanned from June 1, 1999, to November 30, 2010. The median observation period per patient was 56 months, with an interquartile range (IQR) of 31–91 months. | * WHO FC * 6-minute walking distance (6MWD) * Mean pulmonary arterial pressure (mPAP) * Mean right atrial pressure (mRAP) * Cardiac Index (CI) * Time to clinical worsening * Survival rates * Tolerability/ Adverse events (AEs). | The study's results focus primarily on the efficacy of treprostinil rather than on infusion pump performance.  Issues with primary pump failure and infusion line obstruction were reported in 4 patients (3.6%). | The study noted frequent infusion site reactions and pain, with 80% of patients experiencing pain at the infusion site.  The issues with primary pump failure and infusion line obstruction (n=4) triggered sudden-onset dyspnea.  Some patients stopped treatment due to drug side effects (n=13). In addition, 49 patients died from any cause; not attributed to the pump.  Other AEs included right heart decompensation that led to an average of 2.2 hospitalizations per affected patient, requiring interventions such as intravenous diuretics or vasopressors. | SC treprostinil, delivered via infusion pumps provided substantial long-term benefits in functional capacity, exercise tolerance, and hemodynamics for patients with severe pre-capillary PAH. However, practical support for pump management is essential to mitigate common infusion-related issues and ensure effective treatment. |
| Sadushi-Kolici et al. (2019) (70) | The CADD-MS3 infusion pump was used to administer subcutaneous treprostinil.  Patients were trained to independently use these pumps, adjusting infusion rates and refilling cartridges as needed. | To determine the impact of high-dose versus low-dose subcutaneous treprostinil on the 6MWD after 24 weeks in patients with severe non-operable chronic thromboembolic pulmonary hypertension (CTEPH) or recurrent PAH following pulmonary endarterectomy. | Double-blind, randomized, controlled phase 3 trial.  The study included 105 adult patients diagnosed with severe, non-operable CTEPH or persistent/recurrent PAH post-pulmonary endarterectomy.  Patients were randomized 1:1 for high-dose or low-dose treprostinil treatment.  Period of Data Collection: March 9, 2009, to November 24, 2016.  The patients were followed for 24 weeks. | * 6MWD * WHO FC * Borg Dyspnea Score * Heart rate * Oxygen saturation * Quality of life (QoL) scores * mPAP * Cardiac output * Clinical worsening * Levels of N-terminal pro-brain natriuretic peptide. | The study's results focus primarily on the efficacy of treprostinil rather than on infusion pump performance.  Both dosage groups effectively received the medication via the infusion pumps, with no significant issues related to infusion delivery itself affecting study results. | 74% of patients on high-dose and 81% on low-dose treprostinil reported infusion site pain. Additional local infusion site reactions occurred in approximately half of both groups, with some patients discontinuing due to pain.  Serious adverse events (SAEs) included cases requiring hospitalization, and three deaths (two in the high-dose group due to heart failure, one in the low-dose group from appendicitis with sepsis).  Other AEs included diarrhea, headache, and pain in extremities, which were more common in the high-dose group.  The SAEs and AEs were related to the effects of subcutaneous treprostinil administration rather than specific to the infusion pumps. | The study supports the use of continuous SC treprostinil delivered via ambulatory infusion pumps, as it enabled safe and effective administration, particularly for high-dose therapy, without major issues related to pump performance. |
| Kingman et al. (2010) (71) | Various infusion pumps were utilized:   * 12% of centers used **CADD-MS3 Pumps**. * 59% of centers used the patients’ own ambulatory infusion pumps. * 28% of centers transitioned patients to regular hospital infusion pumps.   The pumps administered continuous intravenous epoprostenol or treprostinil, essential treatments for advanced PAH. | To assess the types and frequencies of administration errors in intravenous prostacyclin infusions for PAH patients in hospital settings and to explore related hospital policies. | Survey  The study targeted professionals involved in the care of patients with pulmonary arterial hypertension (PAH) receiving intravenous prostacyclin therapy. Approximately 1,200 individuals were invited to the electronic survey, with 97 responding.  The study compared error rates and types of errors between centers using home infusion pumps and those transitioning patients to hospital pumps | * Frequency and Types of Errors in prostacyclin administration. * Severity of Errors (including whether errors resulted in symptoms or SAEs). | Errors occurred at similar rates regardless of whether home or hospital pumps were used. Serious errors occurred in both settings.  Errors stemmed from issues such as:   * Incorrect rate programming. * Failure to restart the pump. * Accidental stops of the pump. * Mix-up of medication cassettes. * Errors with flushing the dedicated prostacyclin line * Wrong dosing   Some institutions reported that transitioning to hospital pumps did not mitigate these errors. | 68% noted serious or potentially serious errors. However, this was noted by 94% of PAH nurses in a separate interview.  SAEs (n=28) included hypotension, cardiopulmonary arrest, syncope, and 9 deaths.  Most severe incidents involved dosage and administration errors, such as incorrect rate settings, administering the wrong medication or wrong dose due to calculation or concentration errors. | While infusion pumps are critical, the risk of severe, sometimes fatal, administration errors during PAH therapy underscores the need for standardized procedures and careful monitoring to improve their safety in hospital settings. |
| **Abbreviations**: AE = Adverse event; CI = Cardiac Index; CTEPH = chronic thromboembolic pulmonary hypertension; FC = functional class; IQR = interquartile range; MPAP = Mean pulmonary arterial pressure; MRAP = Mean right atrial pressure; PAH = pulmonary arterial hypertension; QoL = Quality of life; SAE = Serious adverse event; SC = subcutaneous; WHO = World Health Organization; 6MWD = 6-minute walking distance | | | | | | | |

### Everaid iJET

Table . Summary of clinical studies for Everaid iJET

| **Reference** | **Infusion pump usage** | **Study objective** | **Study design and Population** | **Measurable endpoints** | **Performance results** | **Safety issues** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Waligóra et al. (2023) (72) | The I-Jet infusion pump was used for the continuous subcutaneous infusion of treprostinil. | To evaluate satisfaction, usability, reliability, and the overall experience of first-time pulmonary arterial hypertension (PAH) patients using the I-Jet infusion pump for treprostinil administration. | Prospective, observational, single-center, non-interventional study.  The study included 13 adult patients diagnosed with PAH who were stable on subcutaneous treprostinil therapy.  Patients were recruited and followed from August to October 2021. Follow-up Duration: 2 months. | * Patient satisfaction * Technical performance * Usability * Medical device incidents * Adverse drug reactions (ADR) | Most participants (92.3%) expressed satisfaction with key features such as the water resistance of the pump, precise flow rate settings, and the ease of changing the battery.  Patients also found the settings menu accessible (69.2%) and were generally satisfied with the handling of the syringe and the design of the software interface.  Only one occlusion alarm was reported, and no patients required hospital visits or experienced technical malfunctions necessitating pump replacement during the observation period. | No medical device incidents or ADRs were found during the study. | The I-Jet infusion pump was found to be a reliable and user-friendly device for PAH self-management, enhancing patient confidence and satisfaction with daily use. |
| **Abbreviations**: ADR = Adverse drug reactions; PAH = pulmonary arterial hypertension | | | | | | | |

# Clinical Background / State of the Art

A presentation of the clinical conditions and general analysis of the treatment options (highlighting risks, benefits and limitations) is used to establish the current state of the art and current knowledge in the corresponding medical field associated with the subject devices.

## Clinical problem

### Definition

Congenital hyperinsulinism (CHI) is a rare disorder that results from dysregulated insulin secretion, leading to recurrent and often severe episodes of hypoglycemia (7). This condition, predominantly affecting neonates, infants, and young children, is recognized as the most common cause of persistent hypoglycemia in these age groups (8). It is the most severe and persistent type of hereditary hyperinsulinemic hypoglycemias (9).

CHI is a genetically diverse disorder, with various underlying mutations affecting insulin regulation. Despite its heterogeneity, the unifying feature across different forms of CHI is hyperinsulinemic hypoglycemia, driven by excessive insulin secretion even in the absence of normal physiological stimuli like food intake (10, 11). As such, the hallmark of CHI is the inappropriate and excessive release of insulin by pancreatic β cells, which results in hypoglycemia accompanied by suppressed levels of ketones and free fatty acids, a reflection of the body's impaired ability to compensate for low blood sugar levels (12, 13).

Historically, terms such as "idiopathic hypoglycemia of infancy", “persistent hyperinsulinemic hypoglycemia of infancy” (PHHI), and "nesidioblastosis" were used to describe this condition, but these are now considered obsolete. Research has demonstrated that these terms were either misnomers or referred to normal pancreatic features in early infancy. In 1975, experts proposed adopting "congenital hyperinsulinism" as the preferred term, emphasizing its innate origin (8, 10)

### Outcome

If left untreated or inadequately managed, CHI is associated with a high risk of long-term neurodevelopmental complications, underscoring the critical importance of prompt diagnosis and intervention to improve long-term outcomes (12, 14). Some children may continue to experience troublesome hypoglycemia into late adolescence, reflecting the chronic nature of CHI in certain cases (13).

As many as 50% of children with CHI experience long-term neurodevelopmental impairments, with detrimental effects on patients, families, society, and healthcare systems as a whole (7, 15, 16). Patients frequently suffer from neurological disorders such as developmental delays and epilepsy due to hypoglycemic brain injury. Additionally, deficits in attention, verbal working memory, visual learning, memory, and sensorimotor functions are common in early childhood. This may result in neurodevelopmental challenges like sucking and swallowing disorders, speech, language, motor, and vision delays, lower limb weakness, as well as an increased risk of cerebral palsy (15, 17, 18).

Severe cases of CHI can lead to deep, prolonged hypoglycemia, which can result in irreversible brain damage, manifesting as coma, status epilepticus, or even death in infancy (19). The strongest associations between severe brain injury and CHI are linked to hypoglycemic seizures, blood glucose levels below 20 mg/dL (1.1 mmol/L), and a history of untreated hypoglycemia (15). Intellectual disability is more common in children with neonatal-onset CHI (11%) compared to those diagnosed later in infancy (3%) (10). There is also a risk of glucose intolerance and diabetes, particularly in patients with HNF4A gene mutations (10).

Despite advancements in diagnostic methods and treatments, rates of long-term neuro-disability remain high, with 26-48% of affected children experiencing neurodevelopmental challenges in various cohorts around the world (7, 12, 16). These complications result from the combined effects of hypoglycemia and hypoketonemia during critical stages of early brain development when neurons are most susceptible to metabolic disturbances (7). The lack of alternative brain fuels, such as ketone bodies and lactate, due to hyperinsulinism, exacerbates brain injury in CHI, as these are crucial for neuronal survival in states of glucose deficiency. Moreover, comorbidities such as status epilepticus, respiratory failure, hypoxic-ischemic injury, and infections can further increase the brain's energy demands, worsening hypoglycemic brain injury (15).

Living with CHI imposes significant psychosocial and financial burdens on families, particularly in the early years following diagnosis. Many families experience fear of hypoglycemia (20). Additionally, 48% of parents report that their physical health has suffered, while 67% note that caring for a child with CHI has negatively impacted their mental health (20). Even though some data indicate that parents’ quality of life (QoL) is high, with improved QoL as their children grow older (18, 20), a recent scoping review described that there are only four studies that investigated the health-related QoL in CHI and these studies are overall inconclusive (16).

### Epidemiology

CHI is a rare disorder, and reliable global estimates regarding its incidence and prevalence are scarce. In addition, CHI’s estimated incidence varies significantly across populations. In Western countries, the incidence is generally estimated to be between 1 in 28,000 and 1 in 50,000 live births (10, 20). However, in populations with higher rates of consanguinity, such as in Saudi Arabia, the incidence can be as high as 1 in 2,500 live births due to the increased likelihood of recessive genetic mutations being inherited (10, 20).

Although different studies have attempted to estimate the birth prevalence of hyperinsulinism (HI), varying definitions of patient populations make direct comparisons across studies challenging (11). Here are brief descriptions of five studies that have published recent incidence rates of CHI:

1. **Yau et al. (2020)**

This UK-based study used referral data from the Exeter Molecular Genetics Laboratory to estimate the minimal incidence of CHI. The study identified all referrals for genetic testing from 2007 to 2016, covering the whole of the UK. The overall incidence of CHI was calculated as 1 in 28,389 live births, with lower incidences reported in older age groups. This reflects a minimum incidence due to the high referral rate for genetic testing in the UK (21).

1. **Männistö et al. (2021)**

This Finnish study analyzed patient records from 1972 to 2015 from 19 major hospitals. The overall incidence of CHI was 1 in 11,300 live births. The incidence of persistent CHI was 1 in 25,400, but it increased significantly in the 2000–2015 period, likely due to improved diagnostics. Transient CHI had an incidence of 1 in 7,400 live births between 2000 and 2015 (22).

1. **Rozenkova et al. (2015)**

In this Czech cohort study, clinical data and DNA samples were collected from CHI patients between 1997 and 2013. The overall incidence of CHI was estimated at 1 in 44,568 live births, similar to western European rates. The study found a lower frequency of common genetic mutations, such as ABCC8/KCNJ11, compared to other populations, with a higher incidence of HNF1A mutations (23).

1. **Novoa-Medina et al. (2021)**

This study focused on CHI in Gran Canaria and Lanzarote, Spain, from 2001 to 2018. The combined incidence of CHI for these regions was 1 in 19,518 live births. Including cases without pathogenic variants detected via genetic testing, the incidence increased slightly to 1 in 15,614 live births (24).

1. **Yamada et al. (2020)**

A nationwide Japanese study conducted a survey from 2017 to 2018 to assess the incidence of CHI and other hyperinsulinemic conditions. The annual incidence of transient CHI was 1 in 13,600 births, while persistent CHI had a slightly lower incidence at 1 in 31,600 births. (25).

According to a review article by Lapidus et al (2024), the most suitable birth prevalence of persistent hyperinsulinism in populations of European ancestry comes from the UK study, which found a rate of approximately 3.5 per 100,000 live births (1 in 28,389) (11). However, this figure should be considered a minimum estimate as the study only included patients referred for genetic testing (11, 21).

The review article by Lapidus et al (2024) also highlighted several key limitations in the above studies. A major challenge is the lack of standardized, large-scale data, as most studies are case reports, single-center analyses, or specific cohort studies, which makes it difficult to combine or generalize findings. Additionally, the clinical heterogeneity of CHI overlap with other syndromes (such as Beckwith-Wiedemann or Turner syndrome). Delayed or missed diagnoses further complicate prevalence assessments (11).

The genetic diversity of populations and the varying levels of consanguinity between regions add another layer of complexity. CHI prevalence tends to be higher in populations with high rates of consanguinity, like Saudi Arabia, and may be underestimated in areas where diagnostic practices are less robust. In Yau’s cohort from the UK, consanguinity was reported in 24 individuals (8.6%) (21). There is also evidence suggesting that undiagnosed CHI might account for some unexplained neonatal deaths in these regions (11).

Specific limitations were identified in several studies. For example, the Rozenkova et al. study provided combined birth prevalence figures for transient and persistent HI, making it hard to draw separate conclusions for each form. Similarly, the Männistö et al. study from Finland is influenced by founder effects, making its prevalence data unsuitable for generalization to broader populations, especially those of European ancestry (11).

There is also a lack of data from southern European (except for the Canary Islands) and non-European populations (except for Japan), raising concerns about applying findings from the UK or other European studies to these groups. Additionally, although transient CHI seems to be more common than persistent CHI, studies that report these distinctions, such as Männistö et al. and Yamada et al., have limitations that prevent their results from being generalized to other populations (11).

Lastly, studies in specific subpopulations, such as the study by Nóvoa-Medina et al. on the Canary Islands in Spain, are limited in scope and do not represent the overall population of their respective countries. Overall, the review underscores the need for more comprehensive, standardized research to better estimate the global birth prevalence of CHI (11). Figure 1 provides an overview of birth prevalence rates from various countries/studies as provided by Lapidus et al. (2024) (11).

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Description automatically generated

Figure . Birth prevalence rates of congenital hyperinsulinism across various countries/studies (from (11))

### Clinical Manifestations

The clinical manifestations of CHI are primarily driven by hypoglycemia (10). Most infants with CHI experience hypoglycemia within the first week of life, with seizures being a common initial symptom in about half of these cases. While 60-70% of patients present within the first week of life, 20-30% are diagnosed later in their first year, and around 10% of cases are identified after the first year of life (20, 26).

In some cases, hypoglycemia may be subtle, with non-specific early signs such as jitteriness, poor feeding, lethargy, and weak crying. However, as hypoglycemia worsens, symptoms reflecting neuroglycopenia, such as apnea, seizures, irritability, coma, or status epilepticus, can develop (20, 26). Macrosomia, or being large for gestational age (LGA), is another key clinical sign of CHI (15, 26-28). In fact, approximately 30% of CHI infants need to be delivered by cesarean section due to their large size (10). In addition to being LGA, some patients present with atypical physical features such as a high forehead and a thin upper lip (19).

Hypoglycemia in CHI is persistent and occurs in both fasting and postprandial states (10). A mild hepatomegaly is also frequently observed in these patients (10). While some hormonal abnormalities, such as low cortisol or growth hormone levels, may be present during hypoglycemic episodes, these are not indicative of true deficiencies and usually resolve over time (10).

In infants diagnosed within the first year of life, seizures, drowsiness, and excitability are common presenting symptoms. After one year of age, the typical signs of hypoglycemia, such as pallor, faintness, tachycardia, sweating, and seizures, become more apparent (10). Neonatal hypoglycemia that is severe or prolonged often results in a poor neurological prognosis (10).

### Etiopathogenesis

The etiopathogenesis of CHI is rooted in a primary defect of the pancreatic β-cells, resulting in inappropriate insulin secretion. This excessive insulin production lowers plasma glucose levels by inhibiting glycogenolysis and gluconeogenesis, and by promoting glucose uptake in muscles and adipocytes (10). Under normal circumstances, β-cells suppress insulin secretion when plasma glucose levels fall below 80 mg/dL (4.4 mmol/L). However, in CHI, this suppression does not occur, leading to persistent hyperinsulinemia despite hypoglycemia (29).

The elevated insulin levels in CHI prevent the production of ketones, which would otherwise serve as an alternative energy source for the brain during periods of low glucose. This dual deficiency—low glucose and an absence of ketones—deprives brain cells of critical fuel, increasing the risk of brain damage (30). Additionally, insulin suppresses lipolysis, further reducing the ability to generate ketones to compensate for the lack of glucose (10).

In normal physiology, as blood glucose levels fall, counter-regulatory mechanisms such as glucagon secretion are activated to prevent hypoglycemia. When glucose drops to around 70 mg/dL (3.9 mmol/L), α-cells release glucagon, which promotes glycogen breakdown and gluconeogenesis. If glucose continues to decline below 65 mg/dL (3.6 mmol/L), the sympathoadrenal response triggers the release of epinephrine, and further decreases cortisol and growth hormone secretion to counteract hypoglycemia (29). In infants with CHI, these mechanisms fail to operate properly. Insulin secretion remains elevated despite low glucose levels, suppressing glucagon release, which is essential to counteract hypoglycemia. Studies have shown that both infants with diffuse and focal CHI have suppressed glucagon and epinephrine responses during hypoglycemic episodes. These impairments in glucagon secretion contribute to persistent hypoglycemia in CHI (29).

### Diagnosis

Diagnosing CHI involves assessing blood glucose levels and the body's response to insulin during episodes of hypoglycemia. A critical blood sample, taken during these episodes, is essential for evaluation. Clinical hypoglycemia is defined as a low plasma glucose level that leads to symptoms of neuroglycopenia, which can be challenging to identify in neonates and infants (7, 27, 31).

Whipple's triad, which includes low plasma glucose, hypoglycemia symptoms, and resolution of symptoms when normal glucose levels are restored, can be helpful for diagnosis, although it is not always easily applicable in young children (7).

The diagnosis of CHI is confirmed by the following criteria:

1. **Hypoglycemia**: Fasting or post-prandial hypoketotic hypoglycemia, typically defined as plasma glucose levels below 2.5–3 mmol/L (45-54 mg/dL) dependent on the patient’s age (10, 17, 32). An infants blood glucose naturally decreases within the first hour of life and then increases over the following hours and days (18)
2. **Inappropriate Insulin Levels**: Insulin levels should be detectable during hypoglycemia, whereas they are usually undetectable in healthy individuals. In CHI patients, insulin levels may not be significantly elevated, as they often fall within the normal range. (10, 17). However, insulin cannot be detected if blood sample screening is delayed due to a short half-life of around 6 minutes (31).
3. **Glycemic Response to Glucagon**: A significant increase in blood glucose (greater than 1.7 mmol/L or 30 mg/dL) within 30-40 minutes after glucagon administration suggests CHI. This is important because, in CHI, the liver retains glycogen, allowing glucagon to effectively increase blood glucose levels, which rules out other conditions like glycogen storage diseases (10, 17).
4. **Low Ketone Bodies and Free Fatty Acids**: In CHI, plasma and urine levels of ketone bodies and free fatty acids are inappropriately low, even during fasting hypoglycemia, as insulin inhibits lipolysis (10, 17).

An overview of the diagnostic features of CHI at the time of hypoglycemia according to an International Guideline for the Diagnosis and Management of Hyperinsulinism is shown in Figure 2.

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Figure 2. Diagnostic features of CHI at the time of hypoglycemia (plasma glucose <2.8 mmol/L [50 mg/dL]). From (17)

It’s worth noting that the threshold for diagnosing hypoglycemia has been debated. A previously accepted plasma glucose level of 2.6 mmol/L (47 mg/dL) lacks robust long-term outcome data, and individual responses to hypoglycemia can vary (7, 31). Some studies have suggested that the cut-off should be 2.0 mmol/L (36 mg/dL) in neonates (31).

A key diagnostic indicator is the glucose infusion rate required to maintain blood glucose above 3 mmol/L (54 mg/dL). In neonates, a glucose infusion rate exceeding 8-10 mg/kg/min suggests insulin-related hypoglycemia, while lower thresholds apply to older children and adults (10, 31).

For newborns tested for hypoglycemia within the first 72 hours of life, retesting is necessary if hypoglycemia persists, to confirm the diagnosis (17). A significant barrier to timely diagnosis is a lack of awareness about CHI among healthcare professionals. Improving education and training could help clinicians recognize and diagnose CHI more effectively (11).

After establishing a diagnosis of hyperinsulinemic hypoglycemia, further evaluations are necessary to determine the underlying cause and subtype of CHI. Genetic testing is a part of the standard diagnostic work up to determine the CHI subtype as described in the following section.

### Subtypes of CHI

CHI can be classified based on various factors, including clinical and histopathological features, etiology, and response to treatment (7, 12).

Identifying the genotype is critical for predicting the clinical phenotype, selecting appropriate treatments, and preventing the long-term neurological consequences of persistent hypoglycemia (27). CHI subtypes exhibit variation in their clinical management based on the underlying cause, and an accurate diagnosis is essential to optimize therapeutic strategies (7). However, the cause of CHI remains unidentified in up to 50% of patients, suggesting the involvement of undiscovered genetic loci and complex, multifactorial mechanisms (28)

A critical distinction is made between transient and persistent CHI. Although transient CHI typically resolves by six months, its prognosis can only be confirmed retrospectively, as no biomarkers are available to predict its course (7). Furthermore, both transient and persistent forms tend to decrease in severity over time, regardless of gene variants (7). However, neurodevelopmental abnormalities occur in a significant percentage of children ranging from 25% to 30% for transient CHI and from 26% to 48% for persistent CHI (22).

Etiologically, hyperinsulinism is divided into acquired forms, such as perinatal stress-induced hyperinsulinism (PSHI), and genetic forms, typically caused by monogenic defects affecting insulin secretion (12, 28). Acquired hyperinsulinism is often transient and commonly seen in neonates exposed to pre- or perinatal stress, such as maternal diabetes, intrauterine growth restriction (IUGR), or birth asphyxia (15). PSHI typically resolves within days or weeks but may persist for longer in severe cases (11, 17). PSHI affects approximately 1 in 1,200–1,700 newborns, with more severe forms occurring in 1 in 12,000–13,600 cases (17).

Genetic forms of hyperinsulinism are commonly caused by single-gene mutations, with the most frequent being in *ABCC8* and *KCNJ11*, which encode the ATP-dependent potassium channel (KATP). These mutations account for about 60% of identifiable cases and are typically severe (11, 18, 27). There are more than 30 other known pathogenic variants involving mutations in 11 genes including *GLUD1*, *GCK*, HADH, UCP2, SLC16A1 (MCT1), *HNF1A, HNF4A*, HK1, PMM2, FOXA2 and PGM1 (11, 15, 19). Notably, some transient forms of hyperinsulinism have genetic underpinnings with potential implications for future health, such as *HNF1A* and *HNF4A* variants, which are associated with a predisposition to maturity-onset diabetes of the young (MODY) (11).

Genetic forms of hyperinsulinism are further categorized into channelopathies and metabolopathies. Channelopathies arise from mutations in genes like *ABCC8* and *KCNJ11*, affecting ion channel function, while metabolopathies involve mutations in genes regulating glucose metabolism like *GLUD1* or *GCK* (7). Channelopathies tend to be more challenging to manage medically, while metabolopathies may respond better to diazoxide therapy. However, the complexity of medical management does not necessarily reflect better long-term outcomes, as neurological dysfunction is common in both forms (7).

Another distinction is that patients may have "isolated CHI," stemming from a primary insulin secretion disorder, or "syndromic CHI," where hyperinsulinism is one symptom of a broader condition (10, 20). Most patients with isolated CHI have no other symptoms, though some may exhibit subtle facial dysmorphisms. Syndromic forms of CHI involve complex multisystemic presentations, with hyperinsulinism often being a prominent feature (27, 28). Examples of syndromic hyperinsulinism include Beckwith-Wiedemann syndrome, Congenital Disorder of Glycosylation (CDG) syndrome types Ia and Ib, Kabuki syndrome, Costello syndrome, Turner syndrome, and others (27, 32).

Histopathologically, CHI is classified as diffuse, focal, or atypical. In diffuse CHI, all pancreatic β-cells are affected, while focal CHI involves localized areas of islet cell hyperplasia and can often be cured by surgical resection (11, 12, 18). The focal form constitutes approximately 30–40% of all CHI cases (15). Atypical CHI includes rare and complex histological patterns that do not fit neatly into either category (7).

Finally, the classification of CHI based on responsiveness to diazoxide is clinically significant. Diazoxide is the first-line treatment for controlling hypoglycemia in CHI, but in cases of diazoxide-unresponsiveness, there is a high likelihood of identifying pathogenic variants, particularly in *ABCC8* or *KCNJ11* (17). In such cases, further diagnostic measures, including genetic testing and pancreatic imaging like 18F-DOPA positron emission tomography (PET) scans, are recommended to identify potentially resectable focal lesions (17). Focal CHI accounts for 50% of diazoxide-unresponsive cases, and identifying these cases early can guide surgical intervention, as they can often be cured with targeted resection (7). Contrarily, Medical therapy is typically prioritized for diffuse forms to avoid extensive pancreatic surgery (7).

## State-of-the-Art in Medicine and Alternative Treatment Options

CHI treatment is primarily aimed at preventing hypoglycemia-related brain injury by maintaining plasma glucose levels within a safe range. Rapid diagnosis and timely management are essential to avoid severe neurological damage and lifelong intellectual disabilities (10, 11). Hypoglycemia in CHI, if left untreated or inadequately managed, can lead to irreversible neuroglycopenia, which results in common pathways of neuronal injury, regardless of the CHI subtype (7, 33).

The severity of CHI is assessed by the rate of glucose infusion necessary to maintain normoglycemia and the patient’s response to medical interventions (10). Plasma glucose below 3.0 mmol/L (54 mg/dL) is considered harmful for neuronal survival (13). As such, specialized CHI centers aim to keep plasma glucose levels above 3.5 mmol/L (63 mg/dL), though there is some variability of this level in clinical practice across various neonatal units and guidelines (7, 15, 31, 32). A recent international consensus agreement for CHI management recommended maintaining plasma glucose levels within a range of 3.9–5.6 mmol/L (70–100 mg/dL), which is in accordance with a guideline from the Pediatric Endocrine Society (PES) (17). This target is set to ensure a safe margin above the critical point at which brain damage occurs, although no specific threshold is known (7, 17, 27).

As such, of hypoglycemia management acute hypoglycemiaepisodesHowever, rof as well as fluid overload IVdextrosethusing While glucagon is effective in acute hypoglycemia management, it is unstable and tends to fibrillate in aqueous solutions, and hence requires reconstitution immediately before use to avoid occlusions (29, 31, 34, 35). Rion(34, 36-38)

Pharmaceutical companies have been developing more stable glucagon formulations that do not require reconstitution, which marks a significant improvement over traditional glucagon therapy (37). These stable, ready-to-use liquid formulations, delivered via injection devices, offer several clinical advantages, such as speed and ease of use in treating severe hypoglycemia (39). This may reduce anxiety around hypoglycemic events, which often leads to suboptimal glucose management and increases the risk of complications (34).

Dasiglucagon is one of the available glucagon analogues with promising results in clinical trials. The ready-to-use version (brand name: Zegalogue) was approved for the treatment of severe hypoglycemia by the US FDA in 2021 and EMA in 2024. It has been shown to reduce the need for intravenous glucose and decrease time spent in hypoglycemia in infants with CHI (12, 40). This glucagon analog consists of 29 amino acids, where seven of these have been substituted compared to native glucagon, providing improved chemical and physical stability, which prevents fibril formation in aqueous solutions (29, 34). Dasiglucagon was the first glucagon analogue that provided a ready-to-use aqueous glucagon formulation, requiring no reconstitution, which enhances ease of use and compliance (34, 37, 41). The potency of dasiglucagon has been reported to be higher or comparable to native glucagon when it comes to raising blood glucose levels (38, 42, 43). Both native g and dasiglucagon, and pain/erythema at the injection site (7, 37, 43-45)

However, despite its efficacy for treating acute hypoglycemia, the currently used dasiglucagon autoinjector (Zegalogue) is not suitable for long-term management of CHI, which requires consistent, prolonged administration of dasiglucagon to prevent recurrent hypoglycemic episodes (34, 46).

In sections 4.2.3 to 4.2.6, we will describe the options for long-term hypoglycemia management of CHI patients including the potential for continuous dasiglucagon infusion using a subcutaneous infusion pump as well as alternative administrative options. However, first, a historical overview of CHI management:

### Historical Aspects of CHI treatment

The history of CHI treatment has evolved significantly since the early recognition of this disorder in the early 20th century. The first known cases of hypoglycemia in children were reported in 1910 by Cobliner in Germany (8). Hypoglycemia as a human disorder was further highlighted in 1922, following the introduction of insulin therapy by Banting and Best. The symptoms of low blood sugar were observed in insulin-treated patients, linking hypoglycemia to insulin (8). By 1937, Hartmann and Jaudon described infant hypoglycemia, while in 1954, McQuarrie brought attention to the persistent nature of hypoglycemia in infants, emphasizing its potential to cause severe brain injury (8). His observations were pivotal in alerting pediatricians to the dangers of untreated CHI.

While McQuarrie’s work laid the foundation for understanding CHI, much of the early treatment involved surgical approaches. Pancreatectomy, initially used to manage hyperthyroidism by removing the thyroid gland, became a common method to treat persistent hypoglycemia thought to be caused by insulin hypersecretion (8). However, surgery only provided a cure in case of hyperinsulinism caused by insulinomas (insulin-secreting tumors) were completely removed (8). By the 1960s, pancreatectomy was regularly performed in children with persistent hypoglycemia, particularly when dietary interventions and corticosteroid therapy failed (8). In 1964, the introduction of diazoxide by Drash marked a major breakthrough in medical therapy, as it effectively treated children with “idiopathic hypoglycemia” and “leucine-sensitive hypoglycemia,” reducing the need for surgery (8, 47).

The 1970s saw further advancements in medical treatment with the introduction of native somatostatin infusions to manage blood glucose in CHI infants (8). Later, octreotide, an intermediate-acting somatostatin analogue, was introduced, allowing patients to avoid surgery (8). In the late 1990s, long-acting somatostatin analogues, such as octreotide LAR and lanreotide, were introduced, simplifying treatment by reducing the frequency of dosing to monthly injections (8).

The development of the diagnostic triad for CHI was a landmark moment in understanding the condition. In the early 1980s, David Feingold and Charles Stanley introduced a three-part diagnostic tool that remains central to CHI diagnosis today. The triad consists of (1) inappropriately high plasma insulin during hypoglycemia, (2) suppression of free fatty acids and ketones, and (3) a rise in blood glucose after glucagon administration (8). This method greatly improved diagnostic precision and established a robust framework for identifying hyperinsulinism in children.

A major advancement in the diagnosis and treatment of focal CHI came in the 1990s with the introduction of 18F-DOPA PET by Timo Otonkoski. This imaging technique allowed for the precise localization of focal lesions in the pancreas, leading to more targeted surgical interventions and curing many cases of focal CHI (8).

Despite these significant developments, challenges remain in achieving optimal long-term outcomes for children with CHI as will be described in section 4.2.3.

### Glucose Monitoring

For CHI patients, continuous and accurate glucose monitoring is essential due to the unpredictable and often severe nature of hypoglycemia (17). The standard approach for monitoring glucose levels in CHI patients involves regular point-of-care glucose testing, which is usually performed through fingerprick or heelprick methods, depending on the patient's age (31, 48). This frequent testing is particularly important during the acute inpatient phase when glucose fluctuations are more severe and frequent, often requiring testing every 1–2 hours (13, 40). At home, this may be reduced to 3-4 measurements per day (13). The CHI International Consensus Statement recommends that blood glucose should be monitored before meals and at bedtime, supplemented with additional testing as needed to detect hypoglycemia (17).

Despite the high accuracy of point-of-care testing, it may still fail to capture all hypoglycemic episodes, especially overnight or in between scheduled tests (12, 20). This is problematic because hypoglycemia in CHI is erratic and can have serious consequences if missed (40). At the time of discharge, CHI patients and caregivers are typically trained to use handheld blood glucose meters for home monitoring, which, while convenient, are not as accurate as point-of-care devices (31).

An alternative to intermittent testing is continuous glucose monitoring (CGM), which is widely used in managing diabetes but is currently considered off-label use for CHI management (7, 12). CGM devices provide real-time glucose readings every few minutes, offering detailed information about glucose trends and alerting caregivers to impending hypoglycemia, which is particularly helpful in reducing overnight hypoglycemia (41, 49). CGM systems feature active alarms and alerts, which are crucial for individuals at risk of problematic hypoglycemia, including frequent or severe episodes (50). Moreover, these devices allow remote data sharing with clinicians, caregivers, or family members, adding another layer of safety for patients (50).

The use of CGM in type 1 diabetes (T1D) is well-established and recommended by various diabetes guidelines (41, 50-52). However, unlike T1D, there is insufficient evidence to recommend CGM as the primary method for glucose monitoring in CHI (17). Despite the lack of extensive data for CHI, CGM has been shown to provide additional reassurance about glucose levels, particularly in unstable patients. It can guide clinicians in adjusting treatments and reduce the number of routine fingerprick tests needed during hospital stays (31). However, due to funding limitations, CGM devices are generally not available for home use by CHI patients unless special funding requests are approved (31). A current UK national collaborative consensus for CHI management recommends using CGM for pattern recognition only rather than for acute hypoglycemia detection, advising families to continue traditional blood glucose testing to avoid missed hypoglycemia due to CGM inaccuracies (31).

### Current Management

An algorithm for the long-term management of CHI is presented in Figure 2. The initial step in optimizing CHI treatment involves assessing the patient's response to diazoxide, which is considered the first-line therapy (12). For focal CHI, partial pancreatectomy remains the preferred treatment (7), while diffuse CHI cases may benefit from medical management before considering surgery (7). If diffuse CHI patients do not respond to diazoxide, second-line options include continuous enteral dextrose and somatostatin analogs like octreotide or lanreotide (12, 29). In severe cases of diffuse CHI where medical management fails, near-total pancreatectomy may be required, although this procedure is palliative and associated with complications like exocrine pancreatic insufficiency and post-pancreatectomy diabetes (12). Many children still struggle with hypoglycemia despite available therapies (20).

A diagram of a medical test

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Figure . Algorithm for CHI management (from (12))

#### Medical management

##### Diazoxide

Diazoxide is the first-line therapy for treating CHI and has been a cornerstone of treatment since its approval by the U.S. Food and Drug Administration (FDA) in 1976 (12, 17). Diazoxide is commonly used to stabilize blood glucose levels following initial glycemic management (12, 31). The Pediatric Endocrine Society (PES) recommends diazoxide as a first-line treatment for CHI, provided glucose levels can be maintained at a safe level (47). A review of case reports and case series from 1947-2013 found that 84% of 619 CHI patients were treated with diazoxide (53). A more recent survey from 2022 in the global registry for CHI reported that 82.7% of the 139 participating patients have been treated with diazoxide (14).

Diazoxide exerts its effect by binding to the SUR1 subunit of the KATP channels on pancreatic β-cells, which helps keep the channels open, reducing insulin secretion and preventing hypoglycemia (7, 8, 18). However, it is ineffective in patients with KATP- hyperinsulinism, who have mutations in ABCC8 or KCNJ11, as these mutations impair the drug's mechanism of action (9, 20). As such, about 60% of children with CHI do not respond to diazoxide (12). Despite this, diazoxide remains effective for patients with non-KATP forms of CHI (31, 40). Unfortunately, diazoxide is unavailable in many countries. As such, a survey by CHI International found that 64% of the enrolled clinicians reported that their patients had problems accessing diazoxide (20).

Side effects are an important consideration with diazoxide treatment. Hypertrichosis is the most frequent long-term side effect, occurring in up to 84% of patients (14). This excess body hair can be distressing for older children and may even lead to discontinuation of treatment (7). Additionally, fluid retention, a common acute side effect (25.7%), increases the risk of pulmonary hypertension, which occurs in 2.4-4.8% of treated infants (14, 15, 47). Gastrointestinal issues, including poor appetite, stomach pain, and vomiting, are also frequently reported, while rarer side effects like alteration of facial features, bone marrow suppression and anaphylaxis have been observed (7, 14, 17, 20, 47). A survey in the global registry for CHI reported that only 2.7% of participants have experienced no side-effects from diazoxide treatment (14).

##### Somatostatin analogues

Somatostatin analogues (SSAs) like octreotide, long-acting octreotide (LAR octreotide), and lanreotide are widely used as second-line treatments for CHI in patients unresponsive to diazoxide (17). These agents inhibit insulin secretion by acting on somatostatin receptors, suppressing cAMP-mediated insulin release (18, 31). SSAs have long been used off-label to manage hypoglycemia and prevent surgery (12, 30). They are especially helpful when diazoxide is contraindicated or unavailable (7), although they are not FDA-approved for this indication (8). Guidelines recommend their use in patients who are unresponsive to diazoxide or cannot tolerate its side effects (17).

Octreotide, the most commonly used short-acting SSA, has been in clinical use since the 1980s for long-term management of CHI (17). Given its short half-life of approximately 90 minutes, frequent subcutaneous injections (4-6 times per day) or continuous infusion are required to maintain efficacy (7, 31). However, its long-term use is limited by the development of tachyphylaxis and various side effects, including necrotizing enterocolitis (NEC), particularly in neonates, and liver dysfunction (17, 31, 53). Octreotide also affects other organs, such as the splanchnic circulation, potentially leading to complications like hepatitis, gallstones, and feeding issues (20, 40).

For patients requiring frequent dosing, long-acting SSAs, such as LAR octreotide and lanreotide, are available and administered as monthly injections (7, 31, 54). These formulations offer the advantage of reducing injection frequency, thus improving patient compliance and QoL, although they carry similar side effect profiles to short-acting octreotide (30, 54). Long-term safety concerns persist, especially with the occurrence of elevated liver transaminases in some patients (7, 30). Given the risk of NEC, these agents are not recommended for use in neonates (26). In rare cases, alternative SSAs like pasireotide have been used, though their efficacy remains under debate (31).

A review of case reports and case series from 1947-2013 found that 16% of 619 CHI patients were treated with SSAs (53). A more recent survey from 2022 in the global registry for CHI reported that 24.5% of the 139 participating patients have been treated with octreotide and 11.5% have been treated with lanreotide (14).

##### Alternative agents

Recently, alternative treatments have emerged for diffuse CHI unresponsive to standard therapies like diazoxide and octreotide. Sirolimus, an mTOR inhibitor, has shown promise in some cases by reducing pancreatic β-cell proliferation and insulin production, though its use is limited by severe side effects, including immunosuppression, risk of infections, and potential organ damage (9, 31, 32, 54). While sirolimus has produced favorable outcomes in certain patients, its efficacy remains inconsistent, and due to the high risk of adverse events, it is reserved for exceptional cases (7, 26).

Other agents like everolimus, another mTOR inhibitor, have been tested but have shown limited efficacy in CHI treatment (26). Nifedipine, a calcium channel blocker, has been proposed based on its ability to reduce insulin release in vitro, but its long-term safety and efficacy in CHI are not well established (26, 31, 54). A review of case reports and case series from 1947-2013 found that 4% of 619 CHI patients were treated with calcium channel blockers like Nifedipine (53). Exendin-(9-39), a GLP-1 receptor antagonist, has demonstrated significant reductions in hypoglycemia in early studies, particularly in children with KATP-HI (12, 26, 54). RZ-358, an allosteric modulator of the insulin receptor, has also shown promise in improving glycemic control in CHI patients with daily hypoglycemia (26).

#### Dietary supplementation

Dietary carbohydrate supplementation is commonly needed alongside medical treatment to prevent hypoglycemia (20). In cases where diazoxide and octreotide are ineffective, therapy may instead focus on increased carbohydrate intake, meal splitting, and enteral nutrition, including the use of uncooked corn starch (32). Moreover, for children with CHI on diazoxide therapy where frequent hypoglycemic episodes persist, regular feeds may be used to maintain stable blood sugar levels (20).

In addition to oral supplementation, intravenous glucose is often used in the initial phase of CHI management to maintain glycemic stability, especially in infants requiring high concentrations of glucose (20). While intravenous glucose support may be needed initially, prolonged use can pose risks like infection or fluid overload (20). Moreover, it requires administration via a central venous catheter (13).

Enteral feeding, via nasogastric or gastrostomy tubes, may be introduced to transition from intravenous support, with continuous infusion of glucose or carbohydrate-enriched formulas ensuring consistent glucose levels when oral feeding alone is insufficient (17, 31). Continuous intragastric glucose infusions are often necessary for children who cannot maintain stable blood sugar through oral feeds alone (17).

Parents often face anxiety over their child's feeding routines and the risk for hypoglycemia, leading to potential issues like overfeeding and eating disorders (20). In many cases, frequent feeds or continuous enteral feeding through nasogastric or gastrostomy tubes are required to manage glycemic stability. However, these methods can hinder the child’s mobility, social interactions, and participation in normal activities (20). Moreover, continuous feeding can be stressful for families and may result in food aversion and weight management challenges (7, 20, 31). As such, excessive carbohydrate supplementation from glucose-enriched formulas or slow-release carbohydrates may lead to obesity and interfere with normal feeding development (30, 31). Careful dietetic supervision is essential to ensure proper growth (20).

#### Surgical interventions

Surgical intervention for CHI is often necessary in cases where medical therapy fails, compliance is poor, or a resectable pancreatic lesion is detected (18, 33). Approximately 70% of children with homozygous or compound heterozygous KATP mutations, which cause diffuse CHI, are unresponsive to medications and require pancreatectomy (20). Pancreatectomy can be performed laparoscopically in both initial and redo procedures (31, 33).

Focal CHI, which accounts for 40-50% of cases, typically requires a partial pancreatectomy as recommended in a recent Consensus Statement (17, 19). This localized surgical excision of the focal lesion generally results in favorable outcomes and has a high cure rate achieving resolution of hypoglycemia (8, 27, 32).

For diffuse CHI, which affects the entire pancreas and is associated with autosomal mutations, near-total pancreatectomy may be necessary when medical therapy fails. This procedure involves removing about 95-98% of the pancreas (8, 27, 40). An extent of 98% was recently recommended to decrease the risk of recurrent hypoglycaemia with a need for reoperations (33). Near-total pancreatectomy is considered a last resort for severe diffuse CHI, as it carries significant risks of postoperative complications (20, 31). Diabetes mellitus is a common long-term outcome following near-total pancreatectomy as up to 91% of patients who undergo >95% resection in infancy will develop diabetes during adolescence or adulthood(13, 20). Many patients also experience pancreatic exocrine insufficiency, requiring enzyme replacement therapy (13, 31, 40). Consequently, near-total pancreatectomy should be reserved for cases unresponsive to medical management (9).

Advancements in medical therapies are crucial to reducing the need for pancreatectomy in diffuse CHI (33).

### Glucagon, dasiglucagon and other variants

, native as it counteracts the effects of insulin excess and raises blood glucose levels within 10-30 minutes (14, 31, 36, 45) However, n long-termhypoglycemia prevention (29, 31, 34, 35)

An alternative to aqueous glucagon solutions is to use intranasal glucagon in powder form (brand name: Baqsimi™), which is available for treating severe hypoglycemia episodes in children and adults with type 1 diabetes (T1D), with studies confirming its safety, efficacy, and ease of use (29, 35, 36, 39, 41). However, Baqsimi is expectedly not suitable for long-term management of CHI due to the need for recurrent and consistent administration to prevent hypoglycemic episodes, also during nighttime. Moreover, the intranasal route may not be suitable for neonates, infants, and small children.

As long-term administration of native glucagon and intranasal glucagon are not viable solutions for CHI management, various clinical trials have investigated soluble glucagon analogues that could be administered through continuous subcutaneous infusions at home, potentially providing a sustainable option for long-term CHI management in the near future (40). New glucagon formulations include chemically altered vehicles or modifications in glucagon's amino acid sequence, resulting in bioactive analogues that remain stable for longer periods (7, 29).

Most clinical trials of glucagon analogues have been focused on treatment of T1D patients, where hypoglycemia is a potential side-effect of insulin-treatment (34, 38, 39, 43, 44). However, these alternative glucagon formulations are also very relevant for other conditions, such as CHI, where hypoglycemia occurs due to a dysregulated insulin secretion. One of the available glucagon analogues with promising results in clinical trials is dasiglucagon. Dasiglucagon activates glucagon receptors in the liver similarly to native glucagon, triggering glycogen breakdown and releasing glucose to raise blood sugar levels (37). Dasiglucagon has demonstrated long-term stability in high-temperature and high-motion environments (34, 35), which makes it suitable for use in pump devices as presented in the similar device section (section 4.3.1).

Dasiglucagon infusion has been found to be effective for reducing hypoglycemia in children with CHI as shown by a two-period, open-label, randomized trial (55). This trial aimed to investigate the efficacy and safety of continuous, subcutaneous dasiglucagon infusion in reducing hypoglycemia in children with CHI. The trial included 32 children (0-17 years of age), who were randomized for either standard of care (SoC) treatment (n=16) or dasiglucagon on top of standard care (n=16) over a 4-week period. In a second 4-week period, all participants were treated with dasiglucagon plus standard care. The results from the first period showed that the percentage of time in hypoglycemia (<3.9 mmol/L) was 11.8% in the dasiglucagon group compared to 20.2% in the SoC group. For the dasiglucagon group, this was 9.91 percentage points lower than baseline. During the second period where all participants received dasiglucagon plus standard care, the percentage of time in hypoglycemia (<3.9 mmol/L) was 8.6%, which was 13.27 percentage points lower than baseline. The rate of hypoglycemia during the first period was 21.7 episodes per week in the dasiglucagon group compared to 36.9 episodes per week in the SoC group. Both rates had decreased compared to baseline. During the second period, the rate of hypoglycemia was 3.06 episodes per week. There were two serious adverse events (SAEs) in the dasiglucagon group during the first period (a localized infection and a vascular device infection), one SAE in the SoC group (a severe hypoglycemia episode), and two SAEs during the second period with dasiglucagon plus standard care (folliculitis and H1N1 influenza). Other non-serious AE episodes with dasiglucagon plus standard care were hyperglycemia (n=16), vomiting (n=12), eczema (n=6), rash (n=6), nausea (n=3), headache (n=3), rash maculopapular (n=3), dermatitis (n=2), dermatitis diaper (n=2), diarrhea (n=2), teething (n=2), developmental delay (n=2), contusion (n=2), ketosis (n=2), necrolytic migratory erythema (n=2), erythema (n=1), miliaria (n=1), urticaria (n=1), constipation (n=1), anemia (n=1), hypokalaemia (n=1), increased appetite (n=1), eye movement disorder (n=1), pericardial effusion (n=1), post-tussive vomiting (n=1), rectal haemorrhage (n=1), retching (n=1), drooling (n=1), seizure (n=1), irritability (n=1), nasal congestion (n=1), respiratory disorder (n=1), alopecia (n=1), pruritus (n=1), rash pruritic (n=1), skin discoloration (n=1), aortic dilatation (n=1), insertion site irritation (n=1), pyrexia (n=1), catheter site hemorrhage (n=1), infusion site bruising (n=1), skin laceration (n=1), muscle twitching (n=1), stoma site hypergranulation (n=1), as well as a number of infections and investigations (55).

Dasiglucagon is generally well tolerated, and the side-effects are similar to native glucagon where the most common are nausea, vomiting and headache (37). However, as with other glucagon formulations, dasiglucagon may potentially interact with certain medications, such as beta blockers, indomethacin, and warfarin, and it is contraindicated in patients with pheochromocytoma or insulinoma due to risks of elevated blood pressure or induced hypoglycemia (37, 38).

Other glucagon variants include Biochaperone Glucagon and Non-Aqueous Soluble (NAS) Glucagon (e.g., Gvoke, G-Pump™ and G-Pen Mini™). BioChaperone Glucagon incorporates polymers, oligomers, and organic compounds that form a complex with glucagon, enhancing its stability in aqueous solutions (35, 36). Preliminary studies have shown that BioChaperone Glucagon produces similar early glycemic responses in patients with T1D and hypoglycemia compared to native glucagon (GlucaGenTM) (29). NAS Glucagon formulations contain unmodified human glucagon dissolved in dimethyl sulfoxide (DMSO). This solution has demonstrated stability for up to two years and can be administered by infusion pump or syringe (26, 29, 39). It has been suggested that NAS Glucagon could be effective when used as continuous subcutaneous infusions in neonates, infants, and children with CHI (26). A downside to NAS Glucagon is that it has been associated with a higher incidence of local injection site reactions such as erythema and edema compared to GlucaGenTM (29).

### Subcutaneous Open-Loop Infusion pumps

Subcutaneous tissue in e.g., the arm, abdomen, thigh, and buttocks is an important target for drug delivery (46), e.g., for infusion of glucagon/dasiglucagon. As previously mentioned, native glucagon crystallizes over time and hence may clog infusion pumps, necessitating frequent pump changes every 12 hours to reduce blockages (26, 36). Glucagon also degrades spontaneously, further complicating its use in long-term infusion systems (36). Emerging glucagon analogues, such as dasiglucagon, offer hope for overcoming these obstacles. Dasiglucagon is chemically stable at room temperature and thus reduces the risk of infusion site blockages and improves long-term infusion reliability (26). Furthermore, there is a dasiglucagon formulation which is tailor-made for continuous infusion as it includes microbial preservatives. However, most subcutaneous infusion pumps in the EU are labelled for use in patients above 7 years of age and are therefore not available for the young CHI patients (56). As such, the use of infusion pumps for subcutaneous administration of dasiglucagon in CHI patients is seldomly described in the scientific literature, except for a few publications that are described in the similar device section (section 4.3.1). The closest analog to a dasiglucagon infusion pump is likely the continuous subcutaneous insulin infusion (CSII) pump, which has been widely used in the treatment of T1D. The following overview is therefore partly based on insulin-infusion in T1D patients.

As CHI, T1D is associated with frequent episodes of severe hypoglycemia, although being a side-effect of insulin therapy (29, 37, 41, 48, 50, 51). Patients with T1D often experience large variations in blood glucose, and even minor adjustments to insulin dosages can lead to dramatic fluctuations. Although intensive insulin therapy offers tighter glycemic control, it also increases the risk of hypoglycemia, which is linked to 4-9% of deaths in T1D patients (38, 57). Given the significant burden of hypoglycemia on T1D patients, there is an increasing focus on maintaining target glucose levels, with the goal of spending more than 70% of the time within a glucose range of 70–180 mg/dl (3.9–10 mM) (58). The lower limit of this range is the same as recommended to minimize the risk of hypoglycemia episodes for CHI (17), which makes the two diseases comparable.

Insulin may be delivered with either multiple daily injections or using an infusion pump for CSII (48). CSII therapy, introduced in the 1970s, was designed to mimic basal insulin secretion by delivering rapid-acting insulin at pre-programmed infusion rates, and its use in people with T1D has demonstrated improved glycemic control and clinical outcomes compared to multiple daily injections (49). Infusion pumps allow for personalized basal profiles, offering greater flexibility and adaptability in managing blood glucose fluctuations compared to multiple daily injections (49). insulin/ apen(56)(46)

Open-loop infusion pumps are the most basic form of infusion pumps. These pumps allow users to manually set and adjust the infusion rates according to individual’s needs, based on glucose data from fingerstick, heelprick, blood glucose meters, or CGMs. Unlike more advanced systems (see section 4.2.6.1), open-loop pumps rely on manual input to determine the correct insulin or glucagon dosage at any given time (49). These pumps have evolved significantly over time, moving from crude early models to modern, more advanced devices that allow for precise adjustments in dosing (51). Technological advancements have led to improvements in convenience, with features like programmable basal rates that help fine-tune medication delivery (50). This increased precision has contributed to improved clinical outcomes, offering better control over blood glucose levels while reducing the need for multiple injections (50).

insulin and(58)A diabetes guidelines from the UK National Institute for Health and Care Excellence (NICE) recommends using insulin pumps for patients who experience disabling hypoglycemia or have difficulty achieving target glucose levels with multiple daily injections (52). Similarly, the Endocrine Society Clinical (ESC) guidelines for diabetes recommend insulin pumps for patients who experience severe hypoglycemia despite proper management (51). The American Association of Clinical Endocrinology (AACE) recommends that all individuals using insulin pump therapy should receive comprehensive training in its use and care, e.g., to prevent issues like over-infusion or under-infusion due to pump malfunctions (50). Worth keeping in mind is that CHI treatment (e.g., dasiglucagon dose adjustment) is carried out by health care professionals, unlike insulin management which is controlled by patients/caregivers.

#### Infusion sets

Infusion sets are an essential accessory for most infusion pumps, connecting the glucagon/insulin reservoir in the pump to the infusion site. A glucagon infusion set operates much like an insulin infusion sets (IIS), transferring glucagon from the pump’s reservoir into the subcutaneous tissue of the patient. The soft, flexible plastic tubing is typically attached to a needle, either steel or Teflon, which is inserted into the subcutaneous adipose tissue. This setup allows glucagon to be delivered consistently to help manage blood glucose levels during hypoglycemia (46).

Common issues with infusion sets include kinking, leakages, occlusions, and air bubbles in the tubing, all of which can interrupt or compromise delivery. For instance, kinking occurs when the flexible tubing or the Teflon catheter becomes bent or folded, blocking the flow of glucagon/insulin. This problem was reported to affect 64.1% of insulin pump users (49). Furthermore, occlusions, which refer to blockages within the tubing or cannula, have been reported by over half of insulin pump users (49).

Another major issue is air bubbles forming in the tubing, which can lead to delayed or interrupted glucagon/insulin infusion. Air bubbles commonly result from temperature changes or pressure variations, such as when the pump is exposed to different altitudes. This can lead to gaps in glucagon delivery, which might fail to prevent hypoglycemia if the interruption lasts for an extended period (49). CHI patients require regular glucose monitoring (17), which will mitigate the risk of hypoglycemia due to issues with infusion set kinking, leakage, occlusion, and air bubbles.

Skin-related complications, such as irritation, infections, and lipohypertrophy, also represent concerns for infusion sets. These issues can occur when the catheter remains inserted for prolonged periods or due to inadequate site hygiene. The warm and humid conditions beneath the infusion set adhesive create an ideal environment for bacterial growth, making infection a potential complication (46). Furthermore, local skin reactions such as redness, swelling, and itching could affect the comfort and adherence of patients using the infusion set (46).

The FDA recommends changing infusion sets every 2-3 days to prevent blockages and skin-related complications. The need for such frequent changes of the infusion set is an annoyance to many patients, who extend the duration, sometimes keeping the infusion set in place for up to 7-10 days, which increases the risk of occlusions and infections (46).

Advancements in technology have led to the innovation of tubeless patch pumps like Omnipod®, which eliminate some of the issues related to tubing and connectors (46, 49, 50).

### Alternative Administrative Options

#### Sensor-Augmented Pumps and Closed-Loop Infusion Pumps

Alternatives to the open loop infusion pump include the sensor-augmented pump and the closed-loop infusion pump:

The **sensor-augmented pump (SAP)** system represents a more advanced stage of infusion therapy compared to the open-loop pump, as it integrates real-time CGM data with the infusion pump. While this system does not fully automate medicine delivery, users can adjust the infusion rate based on continuous glucose readings. SAP systems have been shown to improve glycemic control in T1D patients by offering real-time data to guide insulin administration (50, 57). Additionally, some SAP systems include features like low glucose suspend (LGS) and predictive low glucose suspend (PLGS) to prevent hypoglycemia in diabetic patients by halting insulin delivery when glucose levels drop below a certain threshold or are predicted to fall soon, respectively (49, 50).

The **closed-loop infusion pump**, also referred to as an "artificial pancreas" (AP) or an “automated insulin dosing” (AID) system, represent the most advanced technology in insulin delivery for diabetes treatment. These systems fully automate insulin delivery by using an algorithm that modulates infusion rates based on continuous glucose data from a CGM. The AP system aims to maintain glucose levels within a target range, minimizing both hypoglycemia and hyperglycemia without requiring significant manual intervention from the patient (45, 50, 58). Closed-loop systems consist of three primary components: a CGM, an infusion pump, and a control algorithm that processes the glucose data to determine the appropriate insulin dose (49, 58, 59). While the most common form of the artificial pancreas today is a **hybrid closed-loop** (HCL) system, which still requires the patient to manually input meal information, **fully closed-loop systems** with advanced algorithms are being developed to reduce the burden on users. These new systems aim to predict and adjust for factors like meal ingestion without manual input, using machine learning techniques to estimate glucose needs based on various physiological responses (41, 58). However, the prediction of influencing factors like meals and physical activities of the full closed-loop is currently not accurate (56). For diabetes treatment, there is also the possibility of using a **dual-hormone AP** that infuses both insulin and glucagon for more refined blood glucose control (41, 45, 49). A recent study comparing an experimental dual-hormone system using dasiglucagon with an insulin-only system found that the dual-hormone system reduced the time participants spent in hypoglycemia, though time spent within the target glucose range was similar between the two systems (58).

Closed-loop systems have been tested in clinical trials, demonstrating superiority over standard treatments in maintaining glucose within the desired range (50, 59). Additionally, closed-loop systems have been shown to be highly effective in preventing nocturnal hypoglycemia for T1D patients by automatically adjusting insulin delivery during the night (49).

Karageorgiou et al. (2019) conducted a systematic review and meta-analysis to evaluate the efficacy of closed-loop systems in the glycemic control of non-adult T1D patients (59). The meta-analysis included 25 clinical studies that compared the glycemic control of closed-loop systems (either single- or dual-hormone) with CSII in a total of 504 pediatric patients with T1D. The pairwise meta-analysis showed that the closed-loop group demonstrated a significantly higher percentage of time within the target glycemic range compared to the open-loop group (mean difference (MD): −11.97%, 95% confidence interval (CI): −18.40% to −5.54%. On average, individuals using closed-loop technology spent 67.59% (SD: 8.07) of the time in the target range, while those in the open-loop group spent 55.77% (SD: 11.73). Subgroup analyses revealed that this difference remained significant in both announced and unannounced meal or exercise conditions. Secondary analysis indicated that the open-loop group exhibited significantly higher mean glucose levels (MD: 0.75 mmol/L, 95% CI: 0.18-1.33 mmol/L), alongside a higher proportion of time spent in both hypoglycemia (MD: 0.67%, 95% CI: 0.21-1.13%) and hyperglycemia (MD: 3.01%, 95% CI: 1.68-4.34%). However, only 3 out of 9 comparisons yielded a significant benefit for the closed-loop group. Of note is that studies with closed-loop interventions lasting less than 72 hours showed a significantly smaller mean difference in hypoglycemia time and thus a stronger superiority of the closed-loop system compared to those exceeding 72 hours. The authors concluded that: “*This meta-analysis suggests that the artificial pancreas systems are superior to the standard sensor-augmented pump treatment of type 1 diabetes mellitus*” (59).

Jiao et al (2022) conducted a systematic review and meta-analysis to evaluate the effectiveness and safety for long-term treatment of T1D using a closed-loop insulin system compared to controls (CSII with blinded CGM or unblinded SAP therapy or multiple daily injections or predictive low-glucose suspend system) (57). Eleven randomized controlled trials (RCTs) with a total of 817 patients were included in the meta-analysis. The study found that the time in range (TiR; 3.9-10 mM), time below range and time above range were better with the closed-loop insulin system compared to the controls. The authors concluded that the closed loop insulin system “*is a better solution than control treatment in optimizing blood glucose management in patients with T1D*” (57).

In diabetes management, SAPs and closed-loop systems are recommended by both the NICE and AACE guidelines, particularly for patients with severe or unrecognized hypoglycemia (50, 52). Whereas SAPs, closed-loop infusion pumps and dual-hormone APs have strong relevance in the diabetes patient population, their applicability to treatment of CHI patients is limited.

The main concerns with closed-loop pumps in CHI care are related to the CGM that is integrated with the closed-loop pump. The use of CGM is not currently standard care for CHI due to accuracy issues in the hypoglycemic range, time lags, and limited evidence regarding the usefulness for this population (17, 31). Specifically, there is a time lag with these systems as it may take 10 minutes or more for the CGM to register a change in glucose levels and further 10 minutes for the absorption of the injected insulin/glucagon (38, 56). CGM devices monitor glucose levels by measuring interstitial glucose, not plasma glucose, which introduces this time lag and can lead to discrepancies between actual blood glucose levels and the CGM reading, particularly during rapid glucose fluctuations, such as after meals, during hypoglycemia, or exercise (49, 58). Moreover, CGM devices face significant challenges in terms of accuracy, which can limit their effectiveness (49). In infants and children with hyperinsulinism, CGM devices reported low positive predictive values for detecting hypoglycemia but high negative predictive values, indicating that while CGM may reliably detect normal glucose levels, it struggles to accurately identify hypoglycemia (20, 31)(7, 12). The use of CGM in especially neonates, therefore, remains limited (15). In the outpatient setting, these accuracy issues are often amplified, posing additional risks to patients who rely on them for managing conditions like CHI (31).

The risk of missed hypoglycemia due to CGM inaccuracies outweighs the potential benefits of automated glucose regulation. A UK national collaborative consensus does, therefore, not recommend the routine use of CGM as standard care for CHI patients, particularly in outpatient settings, where the potential for missed hypoglycemia is higher (31). The UK national collaborative consensus advise that any hypoglycemia detected by a CGM device should be confirmed with a point-of-care glucometer before any treatment is administered, as CGM devices are not always accurate in CHI (31). While CGM can reduce the need for frequent fingerstick tests, especially in hospitalized patients, it does not replace glucometer testing and should be used primarily for recognizing patterns in blood glucose fluctuations rather than for immediate hypoglycemia detection (31). Therefore, in CHI, clinicians should rely on intermittent blood glucose testing to guide adjustments in dasiglucagon infusion, even if CGM is used as a supplemental tool for tracking glucose patterns (17, 31).

Despite these challenges, the evolution of CGM technology continues. Emerging models show promise in better correlating with plasma glucose, particularly at the lower end of the glucose range (7). As sensor technology advances, and mathematical modeling improves, CGM devices may eventually replace traditional blood glucose testing for many patients (7).

Another significant concern with the closed-loop AP is the complexity, which leads to patients not using the device (49, 56). The success of the device is directly linked to the user’s education, capability and willingness to use them (51). HThe system is prone to cumulative failures that may arise from minor abnormalities in one or more components of the interconnected subsystems. The need for effective communication between the system's devices, which often use wireless technologies, also raises concerns around data transmission, signal dropouts, and cybersecurity threats (49). Wireless communication failures, power outages, and sensor malfunctions are commonly reported issues with closed-loop systems in both clinical and home settings. These failures can result in interruptions to insulin/glucagon delivery or erroneous dosing (49). To mitigate such issues, AP systems are often equipped with a fail-safe mode, where insulin (or glucagon) infusion reverts to a preset basal rate if the CGM signal is lost (49).

Additionally, while the controller—essentially the AP’s “brain”—aims to simplify the complex task of blood glucose regulation, incorporating more sensors and expanding system capabilities (e.g., adapting to various patient activities) increases the likelihood of systemic errors. More sensors may allow tighter glucose control but also make the system more fragile and susceptible to dangerous hazards if something goes wrong (49). For example, activity monitors might misinterpret restless sleep as wakefulness, leading the system to deliver incorrect insulin/glucagon doses based on misinterpreted signals (49).

(56)In summary, while the SAP and closed-loop AP offer significant advantages in blood glucose control, they also pose substantial risks due to their complexity, CGM time lag, low CGM accuracy in the hypoglycemic range, potential for systemic failure, and susceptibility to misinterpretations of physiological signals. Moreover, patient behavior and compliance play critical roles in the system’s effectiveness. Ramkissoon et al. described that “*As complexity increases, hazards can become more intricately woven into the system*” (49). A UK national collaborative consensus advises that any hypoglycemia detected by a CGM device (as included in the SAP and closed-loop pumps) should be confirmed with a point-of-care glucometer before any treatment is administered, as CGM devices are not always accurate in CHI (31).

#### Intravenous (IV) Infusion

An international CHI guideline suggests that continuous intravenous (IV) glucagon infusion can be used to control hypoglycemia, when the dose of dextrose needed to prevent hypoglycemia is so high that there is a risk of complications from fluid overload (17).

A study by Salomon-Estebanaz *et al.* (2020) explored the efficacy of managing CHI with dose-titrated IV glucagon infusion, focusing on its ability to stabilize glycemia and reduce glucose infusion requirements (60). The study recruited 33 patients, primarily neonates and infants diagnosed with CHI, over eight years. Patients underwent continuous IV glucagon infusion with dose escalation as needed to achieve plasma glucose levels ≥3.5 mmol/L while minimizing fluid overload. Glucagon dosing began at 5 µg/kg/h and was adjusted incrementally up to a maximum of 30 µg/kg/h. Results demonstrated that IV glucagon was effective in stabilizing blood glucose levels and reducing glucose infusion rates (GIR) in most patients. The average GIR decreased significantly from 15.6 to 13.4 mg/kg/min within 24 hours, with 56.2% of patients experiencing a reduction. This effect was observed regardless of whether patients had transient or persistent CHI or genetic mutations in ATP-sensitive potassium channels, which are often associated with CHI severity. Furthermore, glucagon enabled fluid restriction without causing SAEs. While glucagon was generally well-tolerated, one patient developed necrolytic migratory erythema during prolonged high-dose treatment, and another experienced diarrhea. The study concluded that dose-titrated IV infusion of glucagon is a valuable and safe adjunct for glycemic control in CHI (60).

#### Connected Pens

Recent advancements in injection technology have led to the development of “smart” pens, which automatically track dosing and offer decision support through built-in calculators (50). These connected pens are particularly beneficial for individuals requiring multiple daily injections, as they help optimize dosing and administration of e.g., insulin (50).

Smart pens not only simplify the injection process but also improve the accuracy of dosage calculations, making intensive therapy more manageable. They provide valuable insights into administration patterns and can be paired with monitoring systems for better overall control. Additionally, these devices often include features like missed dose alerts, notifying users if doses are not delivered within a specified timeframe, which is crucial for preventing adverse outcomes due to lapses in treatment adherence.

Furthermore, modern connected pens may integrate data on dosing, monitoring levels, and intake, facilitating communication with healthcare teams. Some models even have memory functions that recall past doses and timings, enhancing the user experience (50).

Guideline recommendations suggest that connected pens may be beneficial for individuals engaged in intensive management requiring frequent injections. These devices can assist in optimizing treatment regimens and minimizing risks associated with dosing errors (50).

While connected pens have successfully reached the market, further research is needed to evaluate their effectiveness in real-world management settings. Exploring the potential for seamless transitions between connected pens and other delivery methods may offer individuals greater flexibility and reduce their reliance on multiple devices (50). The literature searches for the present CER did not find any reports of using connected pens for CHI treatment.

### Guidelines

#### The international guideline for diagnosis and management of hyperinsulinism

In 2024, an international guideline for diagnosis and management of hyperinsulinism was created and published by a multidisciplinary committee of 17 experts in CHI management, including paediatric and adult endocrinologists, a pathologist, a genetic scientist, and a representative from an international hyperinsulinism advocacy group (17). The guideline provides a comprehensive and evidence-based framework for diagnosing, treating, and supporting individuals with hyperinsulinism. Below is a summary of the guideline recommendations:

Diagnosis of hyperinsulinism

Hyperinsulinism diagnosis is based on identifying inappropriate insulin action during hypoglycemia. Measurements include metabolic fuels (e.g., β-hydroxybutyrate, free fatty acids) and hormones (insulin, growth hormone, cortisol), alongside the glycemic response to glucagon. A high-sensitivity insulin assay is essential, as markers like suppressed ketones (BOHB) and an exaggerated glucagon response are more reliable than insulin levels in some cases (17).

Newborns with hypoglycemia during the transitional period (<72 hours of life) should be reassessed if symptoms persist. Provocative tests (e.g., with glucose or leucine) are not diagnostic but may help identify hyperinsulinism subtypes (17).

Genetic Testing for hyperinsulinism

Genetic testing is advised for all children with hyperinsulinism, excluding those with clear acquired etiologies like PSHI. Testing is particularly crucial in diazoxide-unresponsive cases to identify potential focal lesions treatable by surgery. Rapid sequencing of the ABCC8 and KCNJ11 genes is prioritized, with further testing for other hyperinsulinism-associated genes as needed (17).

Evaluation for Syndromic hyperinsulinism

Syndromic causes of hyperinsulinism, such as Beckwith-Wiedemann spectrum or mutations in genes like GLUD1 and HADH, should be evaluated, as they often involve multi-system effects (17).

Screening for Insulinomas

Children over two years old with new-onset hyperinsulinism should be screened for insulinomas, rare but potentially malignant tumours associated with conditions like multiple endocrine neoplasia type 1 (17).

Pancreatic Imaging

For diazoxide-unresponsive hyperinsulinism, imaging (e.g., 18F-DOPA PET scans) is recommended to identify focal pancreatic lesions when genetic evidence does not indicate diffuse disease. Focal lesions are highly localized with this technique, aiding surgical planning (17).

Additional Insights

The guideline emphasizes distinguishing between genetic and acquired forms of hyperinsulinism, as the etiology informs therapy and prognosis. Acquired forms, such as PSHI, are typically transient and do not require genetic testing, while persistent or diazoxide-unresponsive forms often warrant comprehensive genetic and imaging studies. This structured approach ensures precise diagnosis and tailored management, optimizing outcomes for patients with hyperinsulinism (17).

Medical Management of hyperinsulinism

Effective management of hyperinsulinism involves maintaining plasma glucose levels within the normal range of 70–100 mg/dL (3.9–5.6 mmol/L). The guideline emphasizes prompt glucose restoration, followed by individualized therapy based on the specific type of hyperinsulinism. Although achieving ideal glycemic targets may be challenging in severe cases, thresholds may be adjusted to mitigate risks of hypoglycemia and its consequences (17).

Acute Interventions:

IV glucose (dextrose) is recommended as the initial treatment to rapidly restore normal glucose levels, with continuous infusion rates adjusted based on the patient’s needs. Subcutaneous glucagon infusion is also useful for infants requiring high glucose rates, reducing the risk of fluid overload. However, this is currently unreliable due to the formation of fibrils and crystals that block infusion lines. The guideline does not address dasiglucagon infusion (17).

Long-Term Pharmacologic Management:

Diazoxide is the first-line, long-term treatment. Dosage adjustments are tailored to efficacy and side effect profiles, which include fluid retention, pulmonary hypertension, and hypertrichosis. Regular monitoring of side effects, such as through echocardiograms and lab tests, is advised (17).

For diazoxide-unresponsive patients or those with intolerable side effects, somatostatin analogs like octreotide or lanreotide are second-line therapies. These agents reduce insulin secretion but are limited by potential side effects such as gastrointestinal issues and necrotizing enterocolitis in vulnerable infants (17).

Other treatments, including nifedipine and sirolimus, lack sufficient evidence for routine use and are generally reserved for investigational protocols (17).

Nutritional Support:

In children with unstable glucose levels despite medication, continuous intragastric glucose supplementation or modified formula feedings may help maintain euglycemia. Older children may benefit from cornstarch supplements, though this approach is not universally recommended due to limited evidence (17).

The guideline underscores the complexity of managing hyperinsulinism, requiring a multifaceted approach involving pharmacological, nutritional, and potentially surgical interventions to optimize outcomes and minimize risks (17).

Surgical Management of Hyperinsulinism

Surgical management of hyperinsulinism is primarily indicated for cases with resectable focal lesions or diffuse pancreatic disease that is unresponsive to medical therapy. For focal HI, surgery is often curative, with a success rate exceeding 95% and minimal risk of subsequent diabetes if only the lesion is removed. In cases of diffuse HI, a 90–98% pancreatectomy is performed to control persistent hypoglycemia, striking a balance between achieving euglycemia and delaying the onset of diabetes, which can develop in a significant proportion of patients over time (17).

Postoperative care involves close monitoring in an intensive care setting to manage plasma glucose fluctuations and prevent complications such as neuroglycopenia or prolonged hyperglycemia. Persistent hypoglycemia or hyperglycemia may require further medical interventions, including insulin therapy or additional surgical procedures. Long-term follow-up is essential for patients, especially those who have undergone substantial pancreatic resections, as they are at risk for recurrent hypoglycemia, diabetes, and exocrine pancreatic insufficiency (17).

Discharge Planning

Effective discharge planning for children with hyperinsulinism is essential to ensure safety and continuity of care at home. This involves a fasting study to evaluate each child's ability to maintain glycemic control, guiding feeding schedules, and glucose monitoring. Children with persistent hypoglycemia may require interventions like gastrostomy tubes for emergency use or continuous feeds overnight, along with contingency plans for equipment failures, such as alarms for fluid leaks and access to glucagon therapy for rescue situations (17).

Families should be equipped with an individualized plan, including medications, glucose monitoring supplies, and an emergency management guide in the family’s primary language. Addressing medical and psychological comorbidities is critical, as caregiving burdens can affect family well-being. Psychological resources and connections to hyperinsulinism patient organizations are encouraged, along with referrals for genetic counselling when necessary (17).

Long-Term Management

Children with hyperinsulinism require ongoing follow-up to monitor glycaemic control, adjust treatments, and detect potential complications like diabetes or pancreatic insufficiency. Side effects of medications should be assessed, and regular developmental surveillance is vital due to the increased risk of neurocognitive deficits and feeding challenges. Neurodevelopmental testing and interventions, involving specialists like therapists and feeding experts, are recommended to address delays, feeding aversions, and other challenges (17).

Patients who have undergone pancreatectomy need routine screening for diabetes and pancreatic insufficiency, with treatments tailored to their evolving needs. For those with postsurgical diabetes, conventional insulin therapies may be required, while pancreatic enzyme replacement therapy should be initiated if insufficiency develops (17).

Special Considerations

Children and adolescents transitioning to adulthood with ongoing hyperinsulinism needs should have dedicated programs to ensure continuity of care, addressing neurodevelopmental, hypoglycaemia awareness, and genetic implications. Long-term support through multidisciplinary teams and peer organizations can improve outcomes and patient experience. Additionally, research efforts remain critical to develop new therapies and improve existing guidelines, particularly for areas with limited resources (17).

#### European guidelines

At present, there is no EU guideline for CHI management. However, there are national guidelines, consensus statements and position statements from European countries including the United Kingdom (31), France (32) and Germany (61).

The recommendations by these national guidelines are generally aligned with the international CHI guideline (17). The International, English and German guidelines all mention that subcutaneous glucagon infusion may be considered but is unreliable for long-term home usage due to the fibrillation of native glucagon causing occlusion of infusion lines (17, 31, 61). None of the guidelines address dasiglucagon infusion directly, although the UK consensus mentions that glucagon analogues may become available for use in the near future as there are successful investigations in clinical trials (31). Moreover, the French guideline emphasizes that it is important to monitor the benefits of developmental drugs including stable glucagon [*“glucagon en forme stable”*] for use in CHI, because some children escape conventional treatments (32).

## Hazards and complications with infusion pumps

While continuous subcutaneous infusion pumps are a promising solution for long-term dasiglucagon administration in the treatment of CHI, several potential hazards and complications need to be considered. These risks can arise from various components, including the infusion pump itself, the infusion set, or the dasiglucagon medication. The risks related to dasiglucagon and the infusion sets were discussed in sections 4.2.4 and 4.2.5.1, respectively, and are not directly relevant for the device under evaluation in the present CER. In brief, while dasiglucagon is generally well-tolerated, it may cause some side effects, such as nausea, vomiting, and rare skin reactions like necrolytic migratory erythema (NME) (17). Regarding infusion sets, risks include inflammation, skin irritation, redness, swelling, and infection at the insertion site. Prolonged or repeated use at the same site can lead to more severe reactions, such as lipohypertrophy or scarring (46, 49), which might affect the absorption of the infused medication and compromise its effectiveness (46). The potential hazards that are directly related to the infusion pump itself are covered in the following section:

### Infusion Pump-Related Hazards

1. **Pump Malfunctions (Software/Hardware Failures):** Despite technological advancements, infusion pumps are still susceptible to malfunctions in both software and hardware. Software glitches can disrupt the precise programming needed for continuous infusion, resulting in either under-delivery or over-delivery of the medication (49). Similarly, hardware components such as buttons, screens, or internal mechanics can fail, leading to unintentional interruptions or errors in delivery. For example, some pumps may stop working without warning, and without proper alerts or alarms, this can go unnoticed, compromising the treatment.
2. **Connectivity Issues:** Many modern infusion pumps rely on wireless connectivity between the pump and its controller. If the connection is lost or interrupted, the pump may default to a basal rate or stop delivery of the medication altogether, while alerting the user. Clinical studies have shown that a significant number of pump-related interruptions were due to connectivity failures. For example, over 50% of treatment interruptions have been reported to be due to the loss of communication between the pump and the controller (49). This is particularly concerning in the context of dasiglucagon therapy for CHI, where continuous and timely administration of the hormone is crucial to avoid hypoglycemia episodes.
3. **Battery-Related Issues:** Infusion pumps are powered by batteries, which require regular charging or replacement. Failures to replace or recharge the batteries in time can result in the pump ceasing to function, halting the delivery of the medication. While most pumps are designed with alerts for low battery life, human error or negligence can sometimes lead to critical treatment gaps (49).
4. **Human Error:** The reliance on patients or caregivers to operate infusion pumps introduces the potential for human error. This can include misprogramming the pump, failing to properly load medication cartridges, or not replacing components (e.g., infusion sets, batteries) as recommended. In high-stress situations, such as managing severe hypoglycemia in CHI, errors can increase, including leaving the pump disconnected or continuing infusion without recalibrating settings (49).
5. **Interruption Due to Device Maintenance:** Continuous infusion pumps require periodic maintenance, including replacing parts such as infusion sets and batteries, and recalibrating sensors. During these times, there may be interruptions in delivery of the medication, which could pose a risk, particularly if the pump is down for an extended period during maintenance or troubleshooting (49).
6. **Pump Leakage and Over-Infusion:** While rare, leakage at the pump connection or infusion set can lead to under-infusion, potentially compromising the therapeutic effect of the medication. On the other hand, over-infusion due to pump misprogramming or mechanical failure could result in the delivery of too much medication (49). These kinds of errors necessitate careful monitoring of the pump’s output and the patient’s response .
7. **Alarm Fatigue:** Alarm fatigue is a recognized risk associated with the use of infusion pumps. Frequent alerts, many of which may not require immediate action, can lead to patients or caregivers ignoring important notifications, a phenomenon known as alarm fatigue (56). This is a significant barrier to the effective use of infusion devices, as managing and responding to alarms is crucial for maintaining safe glucose levels. In fact, excessive alerts and the need for frequent calibrations are among the main reasons some patients discontinue the use of such systems (56). Therefore, efforts to minimize unnecessary alarms while retaining those essential for safety are critical for improving patient adherence and long-term success with these devices.
8. **Lack of Adherence and Body-Image Issues:** Some patients, especially children and adolescents, may find wearing an infusion pump cumbersome or embarrassing, which can lead to periods where the pump is intentionally disconnected, either for convenience or to avoid visibility in social situations. Studies have shown that CSIIs are only worn for 83% of the day or less in many cases, and some patients report removing the pump during activities like swimming, vacations, or intimate situations (20, 49). Each disconnection increases the risk of interrupted therapy.
9. **Complications During Mobility:** Infusion pumps can also be affected by environmental factors. For instance, changes in altitude or temperature can interfere with the pump's function or affect the stability of the medication inside the pump. Rapid temperature fluctuations, such as moving from cold to warm environments, can result in condensation inside the pump or air bubbles forming in the tubing, both of which may interfere with precise delivery (49).
10. **Counterfeit Products and Device Integrity:** Due to the expensiveness of infusion pump systems, there is a risk that patients may buy counterfeit components including infusion sets and batteries. The use of counterfeit products poses a significant hazard in infusion therapy. Counterfeit products may not meet safety standards, potentially leading to inaccurate delivery of the medication, reduced efficacy of treatment, or even dangerous outcomes due to faulty operation of the pump. Ensuring that all components of the infusion system are sourced from reputable manufacturers is essential to maintain the integrity of the treatment and safeguard patient health (49).
11. **Eczema or allergic reactions:** The adhesives (e.g., glue) that are used to attach the pump to the skin may cause an allergic reaction, contact dermatitis, or eczema (56).

## Benefit/risk discussion

Subcutaneous infusion pumps, like the device under evaluation, are used for continuous administration of medicinal substances like dasiglucagon to maintain recommended glucose levels and minimize the risk for hypoglycemia episodes (49, 62). The positive effect of subcutaneous infusion pumps has primarily been reported for diabetic patients but is also very relevant for hypoglycemia prevention and treatment in the rare disease, CHI. If left untreated or inadequately managed, CHI is associated with a high risk of long-term neurodevelopmental complications in primarily neonates and children due to the severe episodes of hypoglycemia that are caused by dysregulated insulin secretion (7, 8, 12).

Dasiglucagon is a ready-to-use aqueous glucagon formulation that has been reported to be effective for the treatment of hypoglycemia in both T1D and CHI patients (37, 41, 62)(55). Dasiglucagon has a comparable safety profile to native glucagon, with similar side effects like nausea, headache, and mild injection site reactions (37, 44). An autoinjector may be used to administer dasiglucagon during severe hypoglycemia episodes in T1D patients. However, the autoinjector is not suitable for long-term management of CHI, which requires consistent, prolonged administration of dasiglucagon to prevent recurrent hypoglycemic episodes (34, 46). An infusion pump may be used to provide the benefit of long-term glucose control by delivering a steady and controlled dose of dasiglucagon over time.

The use of infusion pumps is associated with some potential hazards like hardware and software malfunctions, leakages, connectivity issues, human errors, alarm fatigue, maintenance issues and environmental challenges that may affect the administration of dasiglucagon (49, 56). These risks highlight the need for regular monitoring, proper user training, and careful management to ensure the continuous and reliable delivery of dasiglucagon in CHI therapy. Most pumps also require usage of accessory infusion sets and adhesives, which are themselves associated with risks such as inflammation, skin irritation, allergic reactions, eczema, redness, swelling, and infections as well as lipohypertrophy or scarring if the infusion set is used repeatedly at the same site (46, 49, 56).

An overview of the identified benefits and risks with subcutaneous infusion pumps are listed in **Table 1**. Based on the identified benefits and risks of subcutaneous infusion pumps, it is concluded that the main benefit of a steady and controlled dasiglucagon delivery by far outweighs the risks.

Table . Benefits and risks with use of subcutaneous infusion pumps for dasiglucagon delivery in CHI patients

| **Benefits** |  | **Risks** |
| --- | --- | --- |
| Subcutaneous infusion pumps may provide a continuous, steady and controlled delivery of dasiglucagon, e.g., for prevention and treatment of hypoglycemia (46) |  | Hardware and software malfunctions may affect delivery (49) |
| Subcutaneous infusion pumps are suitable for long-term glucose control in CHI patients, unlike the autoinjector, and reduce the need for constant manual injections (46) |  | Connectivity issues between the pump and its controller may affect delivery (49) |
| The dosing with an infusion pump is 20 times finer than with a pen (≤0.025 U vs 0.5 U) (56). |  | Human error from operating somewhat complex infusion pumps (49) |
| The plasma glucose recovery time for dasiglucagon is comparable to reconstituted glucagon, which makes it effective for hypoglycemia treatment. Dasiglucagon also has a similar safety profile as native glucagon (38) |  | Environmental challenges like changes in altitude or temperature may interfere with the pump’s function (49) |
| Unlike native glucagon, preserved dasiglucagon has demonstrated long-term stability and availability in high-temperature and high-motion environments, which makes it suitable for use in pump devices (34, 35). Furthermore, the dasiglucagon formulation for CHI is tailor made for continuous infusion e.g. includes microbial preservative. |  | Maintenance issues may occur e.g., while changing the infusion set, battery or cartridge or while recalibrating sensors. Such maintenance issues may interfere with the consistent delivery of medication (49) |
|  | Frequent unimportant alerts can lead to alarm fatigue causing patients or caregivers to ignore important notifications (56) |
|  |  | Infusion sets (accessory) may cause inflammation, skin irritation, redness, swelling, and infections at the insertion site as well as lipohypertrophy or scarring (46, 49) |
|  |  | Eczema, allergic reactions or contact dermatitis may be caused by adhesives used to attach the pump to the skin (56). |

As an alternative to the open-loop infusion pump, sensor-augmented pumps (SAPs) and closed-loop infusion pumps contain a continuous glucose monitor (CGM) that offers real-time glucose data. The acquired data can then be used to adjust the insulin/glucagon delivery either manually with the SAP or automatically with the closed-loop infusion pumps. However, unlike T1D treatment, the use of CGM is not currently standard care for CHI patients because the accuracy of the CGM is poor in the lower glucose ranges, and therefore struggles to accurately identify hypoglycemia (7, 12, 20, 31). Moreover, the CGM has a time lag in detection glucose fluctuations, which makes it poor at identifying the rapidly changing glucose levels in CHI patients (15, 56). In support of this, the similar device studies that compared closed-loop pumps with other less advanced infusion pumps typically found limited evidence for improved hypoglycemia management with the closed-loop pumps, although the TiR was improved compared to the other pumps. As such, the standard approach for monitoring glucose levels in CHI patients involves regular point-of-care glucose testing (31, 48). Another drawback of the advanced pumps is that the closed-loop system is prone to issues such as complex system failures, communication issues, sensor malfunctions, and user errors due to a lack of simplicity (41, 49, 56). Two similar device publications reported that closed-loop operation was interrupted between 0.4% to 1.6% of the time (87, 88) and the CGM signal was unavailable for 5.6% of the time on average (87). Ramkissoon et al. described that, “*As complexity increases, hazards can become more intricately woven into the system*” (49).

For many CHI patients, there is an insufficiency of available treatments. Diazoxide is the current standard of care for stabilizing blood glucose levels in CHI patients (12, 17). However, approximately 60% of children with CHI do not respond to diazoxide (12). Up to 50% of children with CHI experience long-term neurodevelopmental impairments, and this is even more pronounced in cases that do not respond to diazoxide treatment (15). Second-line options like the somatostatin analogues are currently not approved for CHI treatment and are hampered by long-term safety concerns and tachyphylaxis (8, 17, 31). Native glucagon is useful for acute treatment of hypoglycemia, but tends to degrade and form fibrils in aqueous solutions, and therefore requires frequent reconstitution (every 12-24 hours) to avoid fibrillation, catheter occlusion, and inconsistent drug delivery, which limits its suitability for long-term use (7). Contrarily, dasiglucagon has demonstrated long-term stability, high potency and high tolerability, which makes it suitable for use in infusion pumps (34, 35, 42, 56). As such, subcutaneous infusion pumps for dasiglucagon delivery can be considered a state-of-the-art approach for long-term treatment of CHI patients, especially those that do not respond to diazoxide.

# Incident Reporting

## Vigilance Search Plan

The vigilance search plan is described in the LSP [ref].

## Vigilance Search Results

The vigilance search results are presented in the following sections. Details of the retrieved vigilance reports are provided in **Appendix II** including assessments of the relevance for the Dasiglucagon Delivery System.

### MHRA, United Kingdom

A review of the Medicines and Healthcare Products Regulatory Agency (MHRA) records, United Kingdom, was carried out on September 24, 2024 without date limitations. Records searched included Medical Device Alerts and Field Safety Notices.A total of 22 reports were retrieved. One of these was a duplicate. Details of the retrieved reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1 | “Infusion pump” AND “Dasiglucagon infusion” | 0 | 0 | 0 |
| 2 | Roche AND “ACCU-CHEK Spirit Combo” | 3 | 0 | 2 |
| 3 | Medtronic AND “MiniMed 770G” | 1 | 0 | 1 |
| 4 | Medtronic AND “Minimed 630G” | 0 | 0 | 0 |
| 5 | ”t:slim X2” | 2 | 0 | 2 |
| 6 | “iLet Bionic Pancreas” | 0 | 0 | 0 |
| 7 | CADD-MS3 | 12  (1 duplicate) | 0 | 6 |
| 8 | Canè AND “Crono SC” | 0 | 0 | 0 |
| 9 | Canè AND “Crono 50 SC” | 0 | 0 | 0 |
| 10 | Everaid AND “i-Jet” | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **22**  **21** | **0**  **-** | **11**  **-** |

As shown in **Appendix II**, 11 of the retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as alarms not working or inaudible, unintentional shift in the basal rate time block, incomplete battery connection, disruption of medicine delivery, under-delivery or over-delivery of medicine, weakened weld joints, unresponsive Start/Stop key, Air Detector faults, unrecoverable error codes, password errors, or tubing occlusion.

### BfArM, Germany

A review of the German federal institute for drugs and medical devices (BfArM) records was carried out on September 24, 2024 with no date limits.A total of 11 reports were retrieved. Two were removed as duplicates, and hence 9 unique records were found. Details of the retrieved unique reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1 | Infusion pump AND Dasiglucagon infusion | 0 | 0 | 0 |
| 2 | Roche ACCU-CHEK Spirit Combo | 2 | 0 | 2 |
| 3 | Medtronic MiniMed 770G | 2 | 0 | 1 |
| 4 | Medtronic Minimed 630G | 2 | 0 | 2 |
| 5 | t:slim X2 | 4  (2 duplicates) | 0 | 0 |
| 6 | iLet Bionic Pancreas | 0 | 0 | 0 |
| 7 | CADD-MS3 | 1 | 0 | 0 |
| 8 | Canè Crono SC | 0 | 0 | 0 |
| 9 | Canè Crono 50 SC | 0 | 0 | 0 |
| 10 | Everaid i-Jet | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **11**  **9** | **0**  **-** | **5**  **-** |

Five of the retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as a blockage of the pump motor function, loss of the date and time settings, lack of basal rate settings, and cybersecurity vulnerabilities.

### Health Canada

Review of the Health Canada Recalls and Safety Alerts records was carried out on September 24, 2024 with no date limits.A total of 9 reports were retrieved. Three were removed as duplicates, and hence 6 unique records were found.Details of the retrieved unique reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1 | “Infusion pump” AND “Dasiglucagon infusion” | 0 | 0 | 0 |
| 2 | “Roche ACCU-CHEK Spirit Combo” | 0 | 0 | 0 |
| 3 | Medtronic AND "MiniMed 770G" | 2 (1 duplicate) | 0 | 1 |
| 4 | Medtronic AND “Minimed 630G” | 7  (2 duplicates) | 0 | 5 |
| 5 | ”t:slim X2” | 0 | 0 | 0 |
| 6 | “iLet Bionic Pancreas” | 0 | 0 | 0 |
| 7 | CADD-MS3 | 0 | 0 | 0 |
| 8 | Canè AND “Crono SC” | 0 | 0 | 0 |
| 9 | Canè AND “Crono 50 SC” | 0 | 0 | 0 |
| 10 | Everaid i-Jet | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **9**  **6** | **0**  **-** | **6**  **-** |

All six retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as a problem with basal rate settings, incorrect instructions, a battery connection issue, a loose reservoir, a damaged retainer ring, and cybersecurity vulnerabilities.

### ANSM, France

A review of the French National Agency for Medicine and Hospital Equipment (ANSM) records was carried out on September 24, 2024 with no date limits. The searches were filtered for records concerning medical devices (dispositifs médicaux) and other (autres). Eight reports were retrieved. Three were removed as duplicates, and hence 5 unique records were found. Details of the retrieved unique reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1a | Infusion pump | 5  (1 duplicate) | 0 | 1 |
| 1b | Dasiglucagon infusion | 0 | 0 | 0 |
| 2 | Roche ACCU-CHEK Spirit Combo | 0 | 0 | 0 |
| 3 | Medtronic MiniMed 770G | 0 | 0 | 0 |
| 4 | Medtronic Minimed 630G | 0 | 0 | 0 |
| 5 | t:slim X2 | 3  (2 duplicates) | 0 | 1 |
| 6 | iLet Bionic Pancreas | 0 | 0 | 0 |
| 7 | CADD-MS3 | 0 | 0 | 0 |
| 8 | Canè Crono SC | 0 | 0 | 0 |
| 9 | Canè Crono 50 SC | 0 | 0 | 0 |
| 10 | Everaid i-Jet | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **8**  **5** | **0**  **-** | **2**  **-** |

Two of the retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The first report described that a t:slim X2 infusion pump was used on children below 6 years of age (off-label use). The second report described issues such as an infusion pump continuing to deliver fluid when an alarm should cause an infusion cessation, interrupted medicine delivery, and a freezing screen/key.

### HPRA, Ireland

A review of the Healthcare Products Regulatory Authority (HPRA) records, Ireland, was carried out on September 24, 2024 with no date limitations. The searches were filtered for records concerning medical devices.Ten reports were retrieved. Four were removed as duplicates, and hence 6 unique records were found. Details of the retrieved unique reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1a | Infusion pump | 6 | 0 | 2 |
| 1b | Dasiglucagon infusion | 0 | 0 | 0 |
| 2 | ACCU-CHEK Spirit Combo | 4  (4 duplicates) | 0 | 0 |
| 3 | MiniMed 770G | 0 | 0 | 0 |
| 4 | Minimed 630G | 0 | 0 | 0 |
| 5 | t:slim X2 | 0 | 0 | 0 |
| 6 | iLet Bionic Pancreas | 0 | 0 | 0 |
| 7 | CADD-MS3 | 0 | 0 | 0 |
| 8 | Crono SC | 0 | 0 | 0 |
| 9 | Crono 50 SC | 0 | 0 | 0 |
| 10 | i-Jet | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **10**  **6** | **0**  **-** | **2**  **-** |

Two of the retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as a display fading over time, unintended infusion stops, over-infusions, and under-infusions.

### DMA, Denmark

Review of records from the Danish Medicines Agency (DMA) was carried out on September 24, 2024 with no date limitations. Twenty reports were retrieved. Ten were removed as duplicates, and hence 10 unique records were found. Details of the retrieved unique reports are presented in **Appendix II**.

| **Search #** | **Search term(s)** | **Number of Results** | **Number of results for subject device** | **Number of relevant results for similar devices** |
| --- | --- | --- | --- | --- |
| 1a | Infusion pump | 15  (5 duplicates) | 0 | 7 |
| 1b | Dasiglucagon infusion | 0 | 0 | 0 |
| 2 | ACCU-CHEK Spirit Combo | 2  (2 duplicates) | 0 | 0 |
| 3 | MiniMed 770G | 0 | 0 | 0 |
| 4 | Minimed 630G | 0 | 0 | 0 |
| 5 | t:slim X2 | 3  (3 duplicates) | 0 | 0 |
| 6 | iLet Bionic Pancreas | 0 | 0 | 0 |
| 7 | CADD-MS3 | 0 | 0 | 0 |
| 8 | Crono SC | 0 | 0 | 0 |
| 9 | Crono 50 SC | 0 | 0 | 0 |
| 10 | Everaid i-Jet | 0 | 0 | 0 |
| 11 | Remunity | 0 | 0 | 0 |
| **Total**  **Total after de-duplication** | | **20**  **10** | **0**  **-** | **7**  **-** |

Seven of the retrieved reports were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as calibration of the force sensor shifting over time, Primary Audible Alarm (PAA) System faults, network errors, unintended infusion stops, unresponsive Start/Stop key, incorrect dose time display, under-infusion, error message cannot be removed, cracked plastic screw joint, binding of the cassette locking assembly, loose pump capsule, water damage, and prevented automatic resumption of basal delivery.

### FDA Medical Device Recalls, USA

Review of the FDA Medical Device Recalls database was carried out on September 25, 2024, for recalls between January 01, 1900 and September 24, 2024.A total of 664 recalls were retrieved for FDA product code FRN including 23 recalls for the similar devices and their components. Details of the similar device reports are presented in **Appendix II**.

| **Search Term** | **Number of Recalls** | **Number of results for subject devices****\*** | **Number of results for similar devices\*** |
| --- | --- | --- | --- |
| FRN | 664 | 0 | 23 |
| *\* Manufacturer and device names were applied for screening the exported raw data*. | | | |

Eight of the retrieved recalls were evaluated to be relevant for the clinical evaluation of the Dasiglucagon Delivery System. The relevant reports described issues such as manufacturing errors, leakages, devices powering down without an alarm, and over-infusion.

### FDA TPLC, USA

Review of the FDA total product life cycle (TPLC) database was carried out on September 25, 2004 for records since 2009 (database limit). As shown in the following table, the review of reports under FDA product code FRN resulted in more than 1.7 million device problems and more than 1.5 million associated patient problems.

| **Search Term** | **Number of Device Problems** | **Number of Patient Problems** |
| --- | --- | --- |
| FRN | 1,796,480 | 1,585,594 |

Details of the various types of device problems and patient problems are presented in **Appendix II**. The TPLC reports covered 50 different types of device problems of which 45 could potentially occur with a subcutaneous infusion pump like the subject device.The majority of device problems were related to cracks (40.8%), corrosions (11.4%) and breaks (7.4%) (see **Appendix II, Table 26**).

TPLC reported on a total of 1,585,594 patient-related Medical Device Recordings for FDA product code FRN, as detailed in **Appendix II**, of which 97.7% had no consequences to the patient or lacked further information. Only 2.2% of the reports were considered relevant for a subcutaneous dasiglucagon infusion pump like the subject device. The relevant patient problems were mainly due to hyperglycemia (1.4%; n = 22,099), hypoglycemia (0.3%, n = 4,785), and hypotension (0.1%, n = 1,390) (**Appendix II, Table 27**).

### FDA MAUDE, USA

A review of the FDA MAUDE database was carried out on September 25, 2024 for records between 01/01/1990 and September 24, 2024. As the searches in the TPLC database show that more than 1.5 million MAUDE records are available for product code FRN, and MAUDE is limited to return a maximum of 500 results per search, using “FRN” as a stand-alone search term was not feasible. Instead, MAUDE was searched for a combination of FRN and/or similar device names or manufacturer names as shown in **Table 16**. A total of 1,687 reports were retrieved. After de-duplication, 1,345 reports remained. Of these, there were 5 death reports, 504 injury reports and 830 malfunction reports, whereas 6 hits had no specified event type. As expected, none of these were associated with the use of the subject device, as it is pre-CE mark. However, 747 reports were related to the use of a similar device including5 deaths, 467 injuries and 273 malfunctions. An overview of the number of retrieved records are provided in **Table 16**.

**Table 16: Overview of received MAUDE records**

| **Search Terms** | **All records** | | **Records for subject device\*\*** | | **Records for similar devices\*\*** | |
| --- | --- | --- | --- | --- | --- | --- |
| **Number of records** | **Details** | **Number of records** | **Details** | **Number of records** | **Details** |
| FRN + Roche | 334 | Malfunctions: 322  Injuries: 12  Deaths: 0 | 0 | - | 98 | Malfunctions: 86  Injuries: 12  Deaths: 0 |
| FRN + ACCU-CHEK | 563 | Malfunctions: 535  Injuries: 26  Deaths: 0  Other: 2 | 0 | - | 121 | Malfunctions: 108  Injuries: 13  Deaths: 0  Other: 0 |
| FRN + Minimed | 20 | Malfunctions: 9  Injuries: 11  Deaths: 0 | 0 | - | 1 | Malfunctions: 0  Injuries: 1  Deaths: 0 |
| t slim X2 | 3 | Malfunctions: 0  Injuries: 3  Deaths: 0 | 0 | - | 3 | Malfunctions: 0  Injuries: 3  Deaths: 0 |
| FRN + Tandem Diabetes Care | 9 | Malfunctions: 0  Injuries: 9  Deaths: 0 | 0 | - | 3 | Malfunctions: 0  Injuries: 3  Deaths: 0 |
| iLet Bionic Pancreas | 397 | Malfunctions: 0  Injuries: 394  Deaths: 3 | 0 | - | 397 | Malfunctions: 0  Injuries: 394  Deaths: 3 |
| FRN + CADD-MS3 | 122 | Malfunctions: 116  Injuries: 4  Deaths: 1  Other: 1 | 0 | - | 25 | Malfunctions: 21  Injuries: 2  Deaths: 1  Other: 1 |
| Crono SC | 0 | - | 0 | - | 0 | - |
| Crono 50 SC | 0 | - | 0 | - | 0 | - |
| FRN + Cane | 40 | Malfunctions: 34  Injuries: 4  Deaths: 0  Other: 2 | 0 | - | 0 | Malfunctions: 0  Injuries: 0  Deaths: 0  Other: 0 |
| i-Jet | 0 | - | 0 | - | 0 | - |
| FRN + Everaid | 0 | - | 0 | - | 0 | - |
| Remunity | 199 | Malfunctions: 144  Injuries: 53  Deaths: 1  Other: 1 | 0 | - | 197 | Malfunctions: 144  Injuries: 51  Deaths: 1  Other: 1 |
| **Total after deduplication\*** | **1,345**  (1,687 before de-duplication) | **Malfunctions: 830**  **Injuries: 504**  **Deaths: 5**  **Other: 6** | **0** | **-** | **747**  (845 before de-duplication) | **Malfunctions: 273**  **Injuries: 467**  **Deaths: 5**  **Other: 2** |
| \* Deduplicated using Excel’s Remove Duplicates function  \*\* Manufacturer and device names were applied for screening the exported MAUDE raw data. | | | | | | |

Five death events were found for the similar devices. With three of the five deaths, there was insufficient information to establish the cause. However, the infusion pumps were not alleged to be directly involved in the deaths. The fourth death was associated with a hyperglycemic event as the patient failed to replace the insulin cartridge when empty despite multiple alerts. Prior to the death, a clinical diabetes specialist had expressed concerns regarding the patient's inability to independently fill the insulin cartridges, change her infusion site and CGM sensor as well as respond to alarms, especially overnight. The fifth death was related to a cardiac arrest caused by the failure of the Remunity pump to deliver Remodulin to the patient. Details of the death events are provided in **Appendix II** (**Table 28**).

Many of the 273 malfunction events with the similar devices were not relevant for the Dasiglucagon Delivery System as the MAUDE records contained insufficient information (29.3%). The relevant malfunctions were mainly due to the similar devices operating differently than expected (10.6%), display problems (9.9%), contaminations (9.9%), fail-safe problems (8.1%), inaccurate dispensing (6.2%), or mechanical problems (5.9%) (see **Appendix II, Table 29** for the complete list of malfunctions).

Of the 467 reported injury events for the similar devices, the majority (89.3%) were considered to be relevant for the Dasiglucagon Delivery System (see **Appendix II, Table 30**). The most often reported patient problems were hypoglycemia (49.7%) and hyperglycemia (33.8%). Hyperglycemia is a relevant risk for diabetes patients, whereas for CHI patients, the main concern is hypoglycemia. Hypoglycemia was frequently accompanied by a loss of consciousness and/or convulsions (24.4%). The reported injuries were typically associated with usability issues of the infusion pumps, but also with calibration problems, incorrect device messages, flow problems and leakages.

## Vigilance Search Conclusion

The FDA MAUDE, FDA TPLC and FDA Medical Device Recalls databases as well as MHRA, BfArM, Health Canada, ANSM, HPRA and DMA databases were searched for records without time limitations. No records were retrieved for the Dasiglucagon Delivery System in any of the databases, which was expected as the subject device is pre-CE mark. However, several reports were retrieved for the similar devices, which included the following device problems that are considered relevant for the Dasiglucagon Delivery System:

* Medicine delivery issues
  + Disruption of medicine delivery
  + Interrupted medicine delivery
  + Unintended infusion stops
  + Inaccurate delivery
  + Under-infusion
  + Over-infusion
* Basal rate errors
  + Unintentional shift in the basal rate time block
  + Lack of basal rate settings
  + Problem with basal rate settings
  + Prevented automatic resumption of basal delivery
* Alarm system issues
  + Defective alarm
  + Inaudible alarms
  + An infusion pump continuing to deliver fluid when an alarm should cause an infusion cessation
  + Primary Audible Alarm (PAA) System faults
  + Devices powering down without an alarm
  + False alarms
* Cassette/reservoir issues
  + A loose reservoir
  + Binding of the cassette locking assembly
* Leakages
  + Fluid leakage
  + Air leak
* Software problems
  + Unrecoverable error codes
  + Password errors
  + Error message cannot be removed
  + Device displays incorrect message
  + Application program freezes
  + Loss of the date and time settings
  + Cybersecurity vulnerabilities
* Display problem
  + No display
  + A fading display
  + Display difficult to read
  + A freezing screen/key
  + Incorrect dose time display
* Network errors
  + Communication or transmission problem
* Battery/power problems
  + Incomplete battery connection
  + A battery connection issue
  + Electrical problem
  + Premature discharge of battery
  + Failure to power up
* Calibration issues
  + Failure to calibrate
  + Calibration problem
  + Calibration of the force sensor shifting over time
* Device sensing problems
  + Failure to read input signal
  + Failure to sense
  + Air Detector faults
* Malfunctions:
  + Unresponsive Start/Stop key
  + Tubing occlusion
  + Occlusion within device
  + Obstruction of flow
  + Blockage of the pump motor function
  + A damaged retainer ring
  + Deformation due to compressive stress
  + Naturally worn
* Manufacturing errors
  + Weakened weld joints
  + Cracked plastic screw joint
  + Cracked/broken device
  + Loose pump capsule
  + Circuit failure
  + Misassembled
* Water damage
* Corrosions
* Contamination
* Labelling issues
  + Incorrect instructions
  + Off-label use on unintended patient population
  + Protective measures problem
  + Nonstandard component used with device
* Usability errors
  + The device operates differently than expected
  + Altered mechanics

Such device problems may be associated with risks to the patient including:

* Under-delivery or over-delivery of medicine
* Hypoglycemia
  + Potentially accompanied by symptoms like confusion, disorientation, dizziness, presyncope, a loss of consciousness, fall injuries, fatigue, tremors, nausea, vomiting, hot flashes, muscle weakness, blurred vision, discomfort, and pain/headache.
* Hyperglycemia
  + Potentially accompanied by symptoms like nausea, vomiting, dizziness, polydipsia, headache, abdominal pain, fatigue, presyncope, a loss of consciousness, fall injuries, discomfort, muscle weakness, frequent urination, malaise, hyperventilation, pain, emotional/cognitive changes, tremors, dysphasia, dehydration, dry mouth, polydipsia, and decreased appetite.
* Anxiety
* Diarrhea
* Infections
* Hypotension
* Hypertension
* Bradycardia
* Tachycardia
* Coma
* Seizures
* Chest pain
* Cardiac arrest
* Death (in the worst case)

DEKA’s risk management files will be reviewed as part of the clinical evaluation to assess whether the mitigation of the retrieved risks is appropriate and whether the residual risk is acceptable. This will be documented in the CER.

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Appendix I – Details of retrieved publications

The full disclosure of the literature screening with reasons for inclusions/exclusions of each article is presented by search number in the tables below.

Table : Retrieved publications from the device-specific searches

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Database Search #** | **Authors** | **Year** | **Title** | **Source** | **Selection criteria** |
| PM2 | W. Regittnig, M. Tschaikner, A. C. Tuca, A. Simic, J. Feiel, R. Schaller-Ammann, A. H. Licht, M. Jungklaus and T. R. Pieber | 2022 | Insulin induces a progressive increase in the resistance of subcutaneous tissue to fluid flow: Implications for insulin pump therapy | Diabetes Obes Metab 24 (3) 455-464 10.1111/dom.14594 | Included |
| PM2 | M. D. R. Vallejo Mora, M. Carreira, M. T. Anarte, F. Linares, G. Olveira and S. González Romero | 2017 | Bolus Calculator Reduces Hypoglycemia in the Short Term and Fear of Hypoglycemia in the Long Term in Subjects with Type 1 Diabetes (CBMDI Study) | Diabetes Technol Ther 19 (7) 402-409 10.1089/dia.2017.0019 | Excluded: NRF |
| PM2 | R. Boizel, M. Pinget, K. Lachgar, C. G. Parkin, H. Grulet, F. Guillon-Metz and J. Weissmann | 2014 | Clinical evaluation of the use of a multifunctional remotely controlled insulin pump: multicenter observational study | J Diabetes Sci Technol 8 (6) 1145-50 10.1177/1932296814545670 | Included |
| PM2 | H. Zisser, R. Wagner, S. Pleus, C. Haug, N. Jendrike, C. Parkin, M. Schweitzer and G. Freckmann | 2010 | Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison | Diabetes Technol Ther 12 (12) 955-61 10.1089/dia.2010.0064 | Excluded: NR |
| PM2 | L. G. Jahn, J. J. Capurro and B. L. Levy | 2013 | Comparative dose accuracy of durable and patch insulin infusion pumps | J Diabetes Sci Technol 7 (4) 1011-20 10.1177/193229681300700425 | Excluded: DS |
| PM2 | L. Leelarathna, H. Thabit, J. M. Allen, M. Nodale, M. E. Wilinska, K. Powell, S. Lane, M. L. Evans and R. Hovorka | 2014 | Evaluating the Performance of a Novel Embedded Closed-loop System | J Diabetes Sci Technol 8 (2) 267-272 10.1177/1932296813519882 | Included |
| PM2 | R. Ziegler, C. Rees, N. Jacobs, C. G. Parkin, M. R. Lyden, B. Petersen and R. S. Wagner | 2016 | Frequent use of an automated bolus advisor improves glycemic control in pediatric patients treated with insulin pump therapy: results of the Bolus Advisor Benefit Evaluation (BABE) study | Pediatr Diabetes 17 (5) 311-8 10.1111/pedi.12290 | Included |
| PM2 | A. Pfützner, J. Weissmann, S. Mougiakakou, E. Daskalaki, N. Weis and R. Ziegler | 2015 | Glycemic Variability Is Associated with Frequency of Blood Glucose Testing and Bolus: Post Hoc Analysis Results from the ProAct Study | Diabetes Technol Ther 17 (6) 392-7 10.1089/dia.2014.0278 | Excluded: NR |
| PM2 | R. Ziegler, C. Tubili, A. Chico, B. Guerci, E. Lundberg, M. Borchert, A. Löffler, S. Bloethner, J. Weissmann and A. Pfützner | 2013 | ProAct study: new features of insulin pumps improve diabetes management and glycemic control in patients after transition of continuous subcutaneous insulin infusion systems | Diabetes Technol Ther 15 (9) 738-43 10.1089/dia.2013.0090 | Included |
| PM2 | S. Borot, S. Franc, J. Cristante, A. Penfornis, P. Y. Benhamou, B. Guerci, H. Hanaire, E. Renard, Y. Reznik, C. Simon and G. Charpentier | 2014 | Accuracy of a new patch pump based on a microelectromechanical system (MEMS) compared to other commercially available insulin pumps: results of the first in vitro and in vivo studies | J Diabetes Sci Technol 8 (6) 1133-41 10.1177/1932296814543946 | Excluded: DS |
| PM3 | J. R. Thrasher, A. Arrieta, F. Niu, K. R. Cameron, T. L. Cordero, J. Shin, A. S. Rhinehart and R. A. Vigersky | 2024 | Early Real-World Performance of the MiniMed™ 780G Advanced Hybrid Closed-Loop System and Recommended Settings Use in the United States | Diabetes Technol Ther 26 (S3) 24-31 10.1089/dia.2023.0453 | Included |
| PM3 | T. Akiyama, T. Yamakawa, K. Orime, M. Ichikawa, M. Harada, T. Netsu, R. Akamatsu, K. Nakamura, S. Shinoda and Y. Terauchi | 2024 | Effects of hybrid closed-loop system on glycemic control and psychological aspects in persons with type 1 diabetes treated with sensor-augmented pump: A prospective single-center observational study | J Diabetes Investig 15 (2) 219-226 10.1111/jdi.14103 | Included |
| PM3 | S. Kubota, A. Sato, M. Hosokawa, Y. Okubo, S. Takayama, A. Kaneko, Y. Shimada, Y. Asano, Y. Sato, M. Yamazaki and M. Komatsu | 2024 | Improving glycemic control by transitioning from the MiniMed(TM) 640G to 770G in Japanese adults with type 1 diabetes mellitus: a prospective, single-center, observational study | Endocr J 10.1507/endocrj.EJ24-0136 | Included |
| PM3 | Y. Pei, W. Ke, J. Lu, Y. Lin, Z. Zhang, Y. Peng, Y. Bi, Y. Li, J. Hou, X. Zhang, X. Chen, Y. Treminio, S. W. Lee, J. Shin, A. S. Rhinehart, R. A. Vigersky and Y. Mu | 2023 | Safety Event Outcomes and Glycemic Control with a Hybrid Closed-Loop System Used by Chinese Adolescents and Adults with Type 1 Diabetes Mellitus | Diabetes Technol Ther 25 (10) 718-725 10.1089/dia.2023.0234 | Included |
| PM7 | A. L. Carlson, T. E. Graham, H. K. Akturk, D. R. Liljenquist, R. M. Bergenstal, B. Sulik, V. N. Shah, M. Sulik, P. Zhao, P. Briggs, R. Sassan-Katchalski and J. E. Pinsker | 2024 | Control-IQ Technology Use in Individuals With High Insulin Requirements: Results From the Multicenter Higher-IQ Trial | J Diabetes Sci Technol 19322968241234072 10.1177/19322968241234072 | Included |
| PM7 | V. N. Shah, H. K. Akturk, A. Trahan, N. Piquette, A. Wheatcroft, E. Schertz, K. Carmello, L. Mueller, K. White, L. Fu, R. Sassan-Katchalski, L. H. Messer, S. Habif, A. Constantin and J. E. Pinsker | 2024 | Safety and Feasibility Evaluation of Automated User Profile Settings Initialization and Adaptation With Control-IQ Technology | J Diabetes Sci Technol 19322968241229074 10.1177/19322968241229074 | Included |
| PM7 | L. H. Messer, E. D'Souza, G. Merchant, L. Mueller, J. Farnan, S. Habif and J. E. Pinsker | 2024 | Smartphone Bolus Feature Increases Number of Insulin Boluses in People With Low Bolus Frequency | J Diabetes Sci Technol 18 (1) 10-13 10.1177/19322968231191796 | Excluded: NR |
| PM8 | R. W. Beck, S. J. Russell, E. R. Damiano, F. H. El-Khatib, K. J. Ruedy, C. Balliro, Z. Li and P. Calhoun | 2022 | A Multicenter Randomized Trial Evaluating Fast-Acting Insulin Aspart in the Bionic Pancreas in Adults with Type 1 Diabetes | Diabetes Technol Ther 24 (10) 681-696 10.1089/dia.2022.0167 | Included |
| PM8 | D. Kruger, A. Kass, J. Lonier, J. Pettus, P. Raskin, M. Salam, S. Trikudanathan, K. Zhou, S. J. Russell, E. R. Damiano, F. H. El-Khatib, K. J. Ruedy, C. Balliro, Z. Li, M. C. Marak, P. Calhoun and R. W. Beck | 2022 | A Multicenter Randomized Trial Evaluating the Insulin-Only Configuration of the Bionic Pancreas in Adults with Type 1 Diabetes | Diabetes Technol Ther 24 (10) 697-711 10.1089/dia.2022.0200 | Included |
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| GS8 | M. Patil, N. Deshmukh, M. Patel and G. Sangle | 2020 | Glucagon-based therapy: past, present and future | <https://www.sciencedirect.com/science/article/pii/S0196978120300450> | Excluded: MA |
| GS8 | C. Martinez | 2019 | Implementation of a Multisensor Wearable Artificial Pancreas Platform: Ensuring Safety with Communication Robustness and Cyber Security | <https://search.proquest.com/openview/b2539e48e9e32b04d8d04bf820009750/1?pq-origsite=gscholar&cbl=18750&diss=y> | Excluded: CR |
| GS8 | M. Devices | 2023 | India's First DNA Test for Personalized Skin and Hair Care | https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=00196169&asa=N&AN=164118359&h=ezlUTw5lEYkp5qUXhn7pOTQD6zaWx5ME5JYnFrbxCis4Y30%2FspZu9lpU1KqdIRdp%2FS0oS7bhkItZQWZ0X76vpw%3D%3D&crl=c | Excluded: NRTA |
| GS8 | J. Kesavadev, G. Krishnan and N. Benny | 2023 | Insulin delivery: An evolution in the technology | https://link.springer.com/chapter/10.1007/978-3-031-25519-9\_69 | Excluded: MA |
| GS8 | V. R. Martínez | 2019 | Método de personalización de una bomba automática de infusión de insulina | https://oa.upm.es/id/eprint/56582 | Excluded: DP |
| GS8 | P. Phadtare, D. Patil and S. Desai | 2023 | Nanotechnology: Newer Approach in Insulin Therapy | https://www.ingentaconnect.com/content/ben/pnt/2023/00000011/00000001/art00004 | Excluded: DP |
| GS8 | G. Forlenza, I. Tabatabai and D. Lewis | 2024 | Point-Counterpoint: The Need for Do-It-Yourself (DIY) Open Source (OS) AID Systems in Type 1 Diabetes Management | https://www.liebertpub.com/doi/abs/10.1089/dia.2024.0073 | Excluded: DP |
| GS8 | R. Lal, L. Ekhlaspour, K. Hood and ... | 2019 | Realizing a closed-loop (artificial pancreas) system for the treatment of type 1 diabetes | https://academic.oup.com/edrv/article-abstract/40/6/1521/5528142 | Excluded: DP |
| GS8 | Y. Wang, T. Chen-Mayfield, Z. Li and Q. Hu | 2023 | Recent advances in self-regulated drug delivery devices | https://www.sciencedirect.com/science/article/pii/B9780323899253000125 | Excluded: MA |
| GS8 | A. Thomas and R. Kolassa | 2022 | Systeme zur automatisierten Insulinabgabe (AID-Systeme) | https://www.thieme-connect.com/products/ejournals/html/10.1055/a-1779-8174 | Excluded: DP |
| GS8 | S. Russell, C. Balliro, C. Jafri and J. Sherwood | N/A | The Bihormonal iLet™ Bionic Pancreas Feasibility Study (Study 19-002) Principal Investigator | <https://cdn.clinicaltrials.gov/large-docs/78/NCT03840278/Prot_SAP_000.pdf> | Excluded: P |
| GS8 | R. Lakshman, C. Boughton and ... | 2023 | The changing landscape of automated insulin delivery in the management of type 1 diabetes | https://ec.bioscientifica.com/view/journals/ec/12/8/EC-23-0132.xml | Excluded: DP |
| GS8 | K. Weaver and I. Hirsch | 2018 | The hybrid closed-loop system: evolution and practical applications | <https://www.liebertpub.com/doi/abs/10.1089/dia.2018.0091> | Excluded: MM |
| GS8 | S. Russell, B. C. Balliro and C. Jafri | N/A | The Monitoring Study: Evaluating the Effect of Remote Monitoring For Hypoglycemia on Bionic Pancreas Safety and Efficacy | <https://cdn.clinicaltrials.gov/large-docs/63/NCT02969863/Prot_SAP_000.pdf> | Excluded: P |
| GS8 | S. Saraf and V. Patravale | N/A | Vice-President's Message | https://pdfs.semanticscholar.org/f535/4731e76b7bc0ee534918efa42598d13f0ed1.pdf | Excluded: VLQ |
| GS9 | C. Kam and F. Ruiz | 2021 | Opportunities and challenges of pharmacotherapy for pulmonary arterial hypertension in children | <https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.25101> | Excluded: MA |
| GS9 | K. Qaiser and A. Tonelli | 2021 | Novel treatment pathways in pulmonary arterial hypertension | <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8298123/> | Excluded: MA |
| GS9 | M. Sketch, D. Sauerstrom, A. Lange and J. Diehl | 2024 | Short-term stability of diluted treprostinil sodium for subcutaneous administration | <https://www.medrxiv.org/content/10.1101/2024.04.19.24306042.abstract> | Excluded: DS |
| GS9 | M. Sketch, K. Maher and M. Broderick | 2023 | Study Design of the Decentralized EVOLVE Study Evaluating Real-world Use of Next Generation Infusion Pumps to Deliver Parenteral Treprostinil in Patients With … | https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2023.207.1\_MeetingAbstracts.A3777 | Excluded: CR |
| GS9 | J. Feldman, N. Habib, J. Fann and J. Radosevich | 2020 | Treprostinil in the treatment of pulmonary arterial hypertension | https://www.tandfonline.com/doi/abs/10.2217/fca-2020-0021 | Excluded: MA |
| GS10 | R. Sadushi-Koliçi, N. Skoro-Sajer, D. Zimmer and ... | 2012 | Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension | <https://www.sciencedirect.com/science/article/pii/S1053249812009679> | Included |
| GS10 | K. Muzevich, H. Chohan and D. Grinnan | 2014 | Management of pulmonary vasodilator therapy in patients with pulmonary arterial hypertension during critical illness | <https://link.springer.com/article/10.1186/s13054-014-0523-z> | Excluded: MA |
| GS10 | M. Kingman, M. Tankersley, S. Lombardi and ... | 2010 | Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey | <https://www.sciencedirect.com/science/article/pii/S1053249810002007> | Included |
| GS10 | R. Sadushi-Kolici, P. Jansa, G. Kopec and ... | 2019 | Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised trial | <https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30367-9/abstract> | Included |
| GS10 | N. Skoro-Sajer, C. Gerges, O. Balint, D. Kohalmi and ... | 2018 | Subcutaneous treprostinil in congenital heart disease-related pulmonary arterial hypertension | <https://heart.bmj.com/content/104/14/1195.abstract> | Excluded: NR |
| GS10 | A. Doran, S. Harris and B. Goetz | 2008 | Advances in prostanoid infusion therapy for pulmonary arterial hypertension | <https://journals.lww.com/journalofinfusionnursing/fulltext/2008/11000/advances_in_prostanoid_infusion_therapy_for.5.aspx> | Excluded: MA |
| GS10 | D. Schuller | 2013 | Clinical Overview of Pulmonary Arterial Hypertension | <https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=00185787&asa=N&AN=87923467&h=9ZIseLNszxiE3PXOE318mePKze0Hxhz74dXGYAotpuy5H5daCj5rj9CkryJk20Ez8KNuwuKDDofkx1BPzh%2FY6g%3D%3D&crl=c> | Excluded: NF |
| GS10 | R. Hanson | 2013 | Current and Emerging Therapies for Pulmonary Arterial Hypertension | <https://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=00185787&AN=87923466&h=1Zr65RcrZDlfsCJ1eRsXv8bkR7%2FgSpHr6VVtXdRshWq2kZHUIopSATONbv%2ByfRsDW%2FnzQDGjXseMmELMcxDtDQ%3D%3D&crl=c> | Excluded: NF |
| GS10 | M. R. Sadushi-Koliçi, N. Skoro-Sajer, D. Zimmer and ... | 2012 | Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension | <https://www.academia.edu/download/48194049/Long-term_treatment_tolerability_and_sur20160820-19000-4hi9hr.pdf> | Excluded: DP |
| GS10 | C. Kam and F. Ruiz | 2021 | Opportunities and challenges of pharmacotherapy for pulmonary arterial hypertension in children | https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.25101 | Excluded: DP |
| GS10 | J. Coons, M. Clarke, M. Wanek and ... | 2013 | Safe and effective use of prostacyclins to treat pulmonary arterial hypertension | https://academic.oup.com/ajhp/article-abstract/70/19/1716/5112414 | Excluded: MA |
| GS10 | J. Feldman, N. Habib, J. Fann and J. Radosevich | 2020 | Treprostinil in the treatment of pulmonary arterial hypertension | https://www.tandfonline.com/doi/abs/10.2217/fca-2020-0021 | Excluded: DP |
| GS10b | J. Radosevich, A. DeChristopher and ... | 2020 | Rapid transition from oral selexipag to parenteral treprostinil in a patient with mixed-etiology pulmonary hypertension | <https://academic.oup.com/ajhp/article-abstract/77/15/1208/5867238> | Excluded: CR |
| GS10b | M. Turbenson, J. Radosevich and ... | 2020 | Transitioning from intravenous to subcutaneous prostacyclin therapy in neonates with severe pulmonary hypertension | <https://meridian.allenpress.com/jppt/article-abstract/25/7/647/445309> | Excluded: CR |
| GS10b | A. Doran, S. Harris and B. Goetz | 2008 | Advances in prostanoid infusion therapy for pulmonary arterial hypertension | https://journals.lww.com/journalofinfusionnursing/fulltext/2008/11000/advances\_in\_prostanoid\_infusion\_therapy\_for.5.aspx | Excluded: DP |
| GS10b | K. Muzevich, H. Chohan and D. Grinnan | 2014 | Management of pulmonary vasodilator therapy in patients with pulmonary arterial hypertension during critical illness | https://link.springer.com/article/10.1186/s13054-014-0523-z | Excluded: DP |
| GS10b | C. Kam and F. Ruiz | 2021 | Opportunities and challenges of pharmacotherapy for pulmonary arterial hypertension in children | https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.25101 | Excluded: DP |
| GS10b | M. Waligóra, B. Żuławinska, M. Tomaszewski and ... | 2023 | Patient satisfaction with a dedicated infusion pump for subcutaneous Treprostinil to treat pulmonary arterial hypertension | https://www.mdpi.com/2075-4426/13/3/423 | Excluded: DP |
| GS10b | J. Coons, M. Clarke, M. Wanek and ... | 2013 | Safe and effective use of prostacyclins to treat pulmonary arterial hypertension | https://academic.oup.com/ajhp/article-abstract/70/19/1716/5112414 | Excluded: DP |
| GS10b | R. Sadushi-Kolici, P. Jansa, G. Kopec and ... | 2019 | Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised … | https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30367-9/abstract | Excluded: DP |
| GS10b | J. Feldman, N. Habib, J. Fann and J. Radosevich | 2020 | Treprostinil in the treatment of pulmonary arterial hypertension | https://www.tandfonline.com/doi/abs/10.2217/fca-2020-0021 | Excluded: DP |
| GS13 | M. Waligóra, B. Żuławinska, M. Tomaszewski and ... | 2023 | Patient satisfaction with a dedicated infusion pump for subcutaneous Treprostinil to treat pulmonary arterial hypertension | <https://www.mdpi.com/2075-4426/13/3/423> | Included |
| GS13 | A. Ari, D. Hess and J. Rau | 2009 | A Guide to Aerosol Delivery Devices | <https://www.researchgate.net/profile/Timothy-Myers-8/publication/237395883_for_Respiratory_Therapists_2nd_Edition_A_Guide_to_Aerosol_Delivery_Devices/links/0c960526dc54282bb3000000/for-Respiratory-Therapists-2nd-Edition-A-Guide-to-Aerosol-Delivery-Devices.pdf> | Excluded: NRTA |
| GS13 | D. Gardenhire, D. Hess and T. Myers | 2013 | A Guide to Aerosol Delivery Devices | <https://c.aarc.org/resources/aerosol_resources/aerosol_guide_rt.pdf> | Excluded: DP |
| GS13 | A. Ari and R. Restrepo | 2012 | Aerosol delivery device selection for spontaneously breathing patients: 2012 | https://rc.rcjournal.com/content/57/4/613.short | Excluded: NRTA |
| GS13 | R. Pleasants and D. Hess | 2018 | Aerosol delivery devices for obstructive lung diseases | https://rc.rcjournal.com/content/63/6/708.short | Excluded: NRTA |
| GS13 | D. Hess | 2008 | Aerosol delivery devices in the treatment of asthma | https://rc.rcjournal.com/content/53/6/699.short | Excluded: NRTA |
| GS13 | J. Fink and A. Ari | 2013 | Aerosol delivery to intubated patients | https://www.tandfonline.com/doi/abs/10.1517/17425247.2013.790362 | Excluded: NRTA |
| GS13 | J. Fink | 2004 | Aerosol delivery to ventilated infant and pediatric patients | https://rc.rcjournal.com/content/49/6/653.short | Excluded: NRTA |
| GS13 | F. Réminiac, L. Vecellio, N. Heuzé-Vourc'h and ... | 2016 | Aerosol therapy in adults receiving high flow nasal cannula oxygen therapy | https://www.liebertpub.com/doi/abs/10.1089/jamp.2015.1219 | Excluded: NRTA |
| GS13 | M. PALLAYOVA | 2015 | Drug Design and Therapeutic Development for Diabetes Mellitus | <https://books.google.com/books?hl=en&lr=&id=yGsoDwAAQBAJ&oi=fnd&pg=PA297&dq=ijet+everaid+%22infusion+pump%22&ots=x4OwN6ReOC&sig=kDH1I70EkuuARgc9uhwEsU4G0JU> | Excluded: MA |
| GS13 | S. Taheri, H. Zaghlool and M. Pallayova | 2015 | Drug Design and Therapeutic Development for Diabetes Mellitus | <https://books.rsc.org/books/edited-volume/532/chapter/176441> | Excluded: DP |
| GS13 | R. Dhand | 2017 | How should aerosols be delivered during invasive mechanical ventilation? | https://rc.rcjournal.com/content/62/10/1343.short | Excluded: NRTA |
| GS13 | D. Hess | 2011 | Humidity and aerosol therapy | https://books.google.com/books?hl=en&lr=&id=alzkGDNRJmEC&oi=fnd&pg=PA303&dq=ijet+everaid+%22infusion+pump%22&ots=ZQdEs3MdNx&sig=iW7zm5yak0K-3ppRxkMb6LIPvWU | Excluded: NRTA |
| GS13 | J. Lewis and R. Channick | 2011 | Idiopathic Pulmonary Arterial Hypertension | <https://link.springer.com/chapter/10.1007/978-0-387-87429-6_68> | Excluded: MA |
| GS13 | W. Sellers | 2013 | Inhaled and intravenous treatment in acute severe and life-threatening asthma | <https://academic.oup.com/bja/article-abstract/110/2/183/227690> | Excluded: MA |
| GS13 | D. Faarc | 2000 | Nebulizers: principles and performance | https://c.aarc.org/marketplace/reference\_articles/06.00.0609.pdf | Excluded: NRTA |
| GS13 | A. Ari | 2014 | Optimizing inhalation therapy in spontaneously breathing patients | https://journals.lww.com/clinpulm/fulltext/2014/01000/optimizing\_inhalation\_therapy\_in\_spontaneously.5.aspx | Excluded: NRTA |
| GS13 | H. Neufeld, A. Woods and A. Whitfield | 1987 | Proceedings of the British Cardiac Society. 66th annual general meeting. Dundee, 8-9 April 1986. Abstracts. | <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1277229/> | Excluded: CR |
| GS13 | D. Miller, T. Tarara and J. Weers | 2021 | Targeting of inhaled therapeutics to the small airways: Nanoleucine carrier formulations | https://www.mdpi.com/1999-4923/13/11/1855 | Excluded: NRTA |
| GS13 | T. Myers | 2013 | The science guiding selection of an aerosol delivery device | https://rc.rcjournal.com/content/58/11/1963.short | Excluded: NRTA |

Table : Retrieved publications from the SOTA searches

| **Database Search #** | **Authors** | **Year** | **Title** | **Source** | **Selection criteria** |
| --- | --- | --- | --- | --- | --- |
| Orphanet 1 | J. B. Arnoux, V. Verkarre, C. Saint-Martin, F. Montravers, A. Brassier, V. Valayannopoulos, F. Brunelle, J. C. Fournet, J. J. Robert, Y. Aigrain, C. Bellanne-Chantelot and P. de Lonlay | 2011 | Congenital hyperinsulinism: current trends in diagnosis and therapy | Orphanet J Rare Dis 6 (63 10.1186/1750-1172-6-63 | Excluded: DP |
| Orphanet 1 | J. B. Arnoux, V. Verkarre, C. Saint-Martin, F. Montravers, A. Brassier, V. Valayannopoulos, F. Brunelle, J. C. Fournet, J. J. Robert, Y. Aigrain, C. Bellanne-Chantelot and P. de Lonlay | 2011 | Congenital hyperinsulinism: current trends in diagnosis and therapy | Orphanet J Rare Dis 6 (63 10.1186/1750-1172-6-63 | Excluded: DP |
| Orphanet 1 | N/A | 2020 | Extraite du Protocole National de Diagnostic et de Soins (PNDS) - Hyperinsulinisme Congénital | Filières de Santé Maladies Rares G2M et Firendo | Excluded: DP |
| Orphanet 1 | N/A | 2022 | Protocole d'urgence - Hyperinsulinisme | Centré de référence | Excluded: DP |
| Orphanet 1 | J. Arnoux and K. Busiah | 2020 | Protocole National de Diagnostic et de Soins (PNDS) Hyperinsulinisme Congénital - Argumentaire | Filières de Santé Maladies Rares G2M et Firendo | Excluded: GR |
| Orphanet 1 | J. B. Arnoux, V. Verkarre, C. Saint-Martin, F. Montravers, A. Brassier, V. Valayannopoulos, F. Brunelle, J. C. Fournet, J. J. Robert, Y. Aigrain, C. Bellanne-Chantelot and P. de Lonlay | 2011 | Congenital hyperinsulinism: current trends in diagnosis and therapy | Orphanet J Rare Dis 6 (63 10.1186/1750-1172-6-63 | Included |
| Orphanet 1 | N/A | 2022 | HYPERINSULINISM | Centré de référence | Excluded: CR |
| Orphanet 1 | T. Meißner and A. Moß | 2020 | Leitlinienreport zur S1 Leitlinie: Diagnostik und Therapie des Kongenitalen Hyperinsulinismus (KHI) | Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. | Included |
| Orphanet 1 | N/A | 2022 | PROTOCOL FOR HYPOGLYCAEMIA IN A&E (No diagnosis known) | Centré de référence | Excluded: CR |
| Orphanet 1 | N/A | 2020 | Protocole National de Diagnostic et de Soins (PNDS) - Hyperinsulinisme Congénital | Filières de Santé Maladies Rares G2M et Firendo | Included |
| Orphanet 1 | N/A | 2022 | RECURRENT UNDIAGNOSED HYPOGLYCAEMIA | Centré de référence | Excluded: CR |
| Orphanet 3 | J. B. Arnoux, V. Verkarre, C. Saint-Martin, F. Montravers, A. Brassier, V. Valayannopoulos, F. Brunelle, J. C. Fournet, J. J. Robert, Y. Aigrain, C. Bellanne-Chantelot and P. de Lonlay | 2011 | Congenital hyperinsulinism: current trends in diagnosis and therapy | Orphanet J Rare Dis 6 (63 10.1186/1750-1172-6-63 | Excluded: DP |
| Orphanet 3 | N/A | 2020 | Extraite du Protocole National de Diagnostic et de Soins (PNDS) - Hyperinsulinisme Congénital | Filières de Santé Maladies Rares G2M et Firendo | Excluded: DP |
| Orphanet 3 | N/A | 2022 | HYPERINSULINISM | Centré de référence | Excluded: DP |
| Orphanet 3 | T. Meißner and A. Moß | 2020 | Leitlinienreport zur S1 Leitlinie: Diagnostik und Therapie des Kongenitalen Hyperinsulinismus (KHI) | Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. | Excluded: DP |
| Orphanet 3 | N/A | 2022 | PROTOCOL FOR HYPOGLYCAEMIA IN A&E (No diagnosis known) | Centré de référence | Excluded: DP |
| Orphanet 3 | N/A | 2022 | Protocole d'urgence - Hyperinsulinisme | Centré de référence | Excluded: DP |
| Orphanet 3 | N/A | 2020 | Protocole National de Diagnostic et de Soins (PNDS) - Hyperinsulinisme Congénital | Filières de Santé Maladies Rares G2M et Firendo | Excluded: DP |
| Orphanet 3 | J. Arnoux and K. Busiah | 2020 | Protocole National de Diagnostic et de Soins (PNDS) Hyperinsulinisme Congénital - Argumentaire | Filières de Santé Maladies Rares G2M et Firendo | Excluded: DP |
| Orphanet 3 | N/A | 2022 | RECURRENT UNDIAGNOSED HYPOGLYCAEMIA | Centré de référence | Excluded: DP |
| SOTA 1-1 | L. J. States, J. C. Davis, S. M. Hamel, S. A. Becker and H. Zhuang | 2021 | (18)F-6-Fluoro-l-Dopa PET/CT Imaging of Congenital Hyperinsulinism | J Nucl Med 62 (Suppl 2) 51s-56s 10.2967/jnumed.120.246033 | Excluded: NRTA |
| SOTA 1-1 | J. Lebl, K. Roženková and Š. Průhová | 2016 | [Congenital hyperinsulinism: Loss of B-cell self-control] | Vnitr Lek 62 (11 Suppl 4) S72-76 | Excluded: GR |
| SOTA 1-1 | L. J. States, S. Saade-Lemus and D. D. De Leon | 2020 | 18-F-L 3,4-Dihydroxyphenylalanine PET/Computed Tomography in the Management of Congenital Hyperinsulinism | PET Clin 15 (3) 349-359 10.1016/j.cpet.2020.03.004 | Excluded: NRTA |
| SOTA 1-1 | M. E. van Albada, P. Shah, T. G. J. Derks, S. Fuchs, J. J. M. Jans, V. McLin and H. P. J. van der Doef | 2023 | Abnormal glucose homeostasis and fasting intolerance in patients with congenital porto-systemic shunts | Front Endocrinol (Lausanne) 14 (1190473 10.3389/fendo.2023.1190473 | Excluded: NRTA |
| SOTA 1-1 | D. L. Stanescu and C. A. Stanley | 2022 | Advances in Understanding the Mechanism of Transitional Neonatal Hypoglycemia and Implications for Management | Clin Perinatol 49 (1) 55-72 10.1016/j.clp.2021.11.007 | Excluded: DS |
| SOTA 1-1 | C. G. Nichols, N. W. York and M. S. Remedi | 2022 | ATP-Sensitive Potassium Channels in Hyperinsulinism and Type 2 Diabetes: Inconvenient Paradox or New Paradigm? | Diabetes 71 (3) 367-375 10.2337/db21-0755 | Excluded: NRTA |
| SOTA 1-1 | T. C. Jeffery, A. B. Chang and L. S. Conwell | 2023 | Bisphosphonates for osteoporosis in people with cystic fibrosis | Cochrane Database Syst Rev 1 (1) Cd002010 10.1002/14651858.CD002010.pub5 | Excluded: NRTA |
| SOTA 1-1 | L. Bond, Z. Murrell, T. Wright and S. Bond | 2017 | Cavitron Ultrasonic Surgical Aspirator-Assisted Pancreatic Resection in Hyperinsulinism | Eur J Pediatr Surg 27 (4) 368-372 10.1055/s-0037-1603524 | Excluded: NRTA |
| SOTA 1-1 | G. Masselli, E. Casciani, C. De Angelis, S. Sollaku and G. Gualdi | 2021 | Clinical application of (18)F-DOPA PET/TC in pediatric patients | Am J Nucl Med Mol Imaging 11 (2) 64-76 | Excluded: NRTA |
| SOTA 1-1 | H. Hoermann, O. El-Rifai, M. Schebek, M. Lodefalk, K. Brusgaard, N. Bachmann, C. Bergmann, M. Roeper, A. Welters, R. Salimi Dafsari, O. Blankenstein, E. Mayatepek, H. Christesen, T. Meissner and S. Kummer | 2020 | Comparative meta-analysis of Kabuki syndrome with and without hyperinsulinaemic hypoglycaemia | Clin Endocrinol (Oxf) 93 (3) 346-354 10.1111/cen.14267 | Excluded: NRTA |
| SOTA 1-1 | T. I. Hewat, M. B. Johnson and S. E. Flanagan | 2022 | Congenital Hyperinsulinism: Current Laboratory-Based Approaches to the Genetic Diagnosis of a Heterogeneous Disease | Front Endocrinol (Lausanne) 13 (873254 10.3389/fendo.2022.873254 | Excluded: NRTA |
| SOTA 1-1 | L. J. States, S. A. Becker and D. D. De León | 2022 | Congenital hyperinsulinism: localization of a focal lesion with (18)F-FDOPA positron emission tomography | Pediatr Radiol 52 (4) 693-701 10.1007/s00247-021-05206-5 | Excluded: NRTA |
| SOTA 1-1 | B. E. Hasbaoui, A. Elyajouri, R. Abilkassem and A. Agadr | 2020 | Congenital hyperinsulinsim: case report and review of literature | Pan Afr Med J 35 (53 10.11604/pamj.2020.35.53.16604 | Excluded: CR |
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| SOTA 3 | S. Li, Y. Hu, X. Tan, D. Wang, J. Hu, P. Zou and L. Wang | 2020 | Evaluating dasiglucagon as a treatment option for hypoglycemia in diabetes | Expert Opin Pharmacother 21 (11) 1311-1318 10.1080/14656566.2020.1747432 | Excluded: GR |
| SOTA 3 | C. Schaumleffel | 2023 | Evaluating Ease of Use and Patient Safety of Dasiglucagon Hypo Pal Autoinjector for the Management of Hypoglycemia | Patient Prefer Adherence 17 (2141-2144 10.2147/ppa.S325865 | Included |
| SOTA 3 | H. Demirbilek, D. Vuralli, B. Haris and K. Hussain | 2023 | Managing Severe Hypoglycaemia in Patients with Diabetes: Current Challenges and Emerging Therapies | Diabetes Metab Syndr Obes 16 (259-273 10.2147/dmso.S313837 | Included |
| SOTA 3 | L. La Sala and A. E. Pontiroli | 2021 | New Fast Acting Glucagon for Recovery from Hypoglycemia, a Life-Threatening Situation: Nasal Powder and Injected Stable Solutions | Int J Mol Sci 22 (19) 10.3390/ijms221910643 | Included |
| SOTA 3 | M. Giménez, K. Khunti, M. Matsuhisa, S. Chenji, K. Syring and Y. Yan | 2023 | Systematic Literature Review and Indirect Treatment Comparison of Three Ready-to-Use Glucagon Treatments for Severe Hypoglycemia | Diabetes Ther 14 (11) 1757-1769 10.1007/s13300-023-01466-6 | Included |
| SOTA 4-1 | L. M. Wilson and J. R. Castle | 2018 | Stable Liquid Glucagon: Beyond Emergency Hypoglycemia Rescue | J Diabetes Sci Technol 12 (4) 847-853 10.1177/1932296818757795 | Included |
| SOTA 4-1 | T. Siegmund | 2016 | [Modern antihyperglycaemic agents--what is the patient benefit?] | MMW Fortschr Med 158 (7) 45-8 10.1007/s15006-016-8061-z | Excluded: GR |
| SOTA 4-1 | M. Puig-Domingo and S. Pellitero | 2015 | [New therapies for type 2 diabetes mellitus] | Med Clin (Barc) 144 (12) 560-5 10.1016/j.medcli.2014.03.018 | Excluded: NRTA |
| SOTA 4-1 | G. M. Ward, J. M. Walters, J. L. Gooley and R. C. Boston | 2021 | Adapting Protocols or Models for Use in Insulin-Requiring Diabetes and Islet Transplant Recipients | Front Endocrinol (Lausanne) 12 (611512 10.3389/fendo.2021.611512 | Excluded: NRTA |
| SOTA 4-1 | A. Mikłosz and A. Chabowski | 2023 | Adipose-derived Mesenchymal Stem Cells Therapy as a new Treatment Option for Diabetes Mellitus | J Clin Endocrinol Metab 108 (8) 1889-1897 10.1210/clinem/dgad142 | Excluded: NRTA |
| SOTA 4-1 | D. Lazard, P. Vardi and K. Bloch | 2016 | Anti-diabetic and neuroprotective effects of pancreatic islet transplantation into the central nervous system | Diabetes Metab Res Rev 32 (1) 11-20 10.1002/dmrr.2644 | Excluded: NRTA |
| SOTA 4-1 | D. J. Stenvers, F. Scheer, P. Schrauwen, S. E. la Fleur and A. Kalsbeek | 2019 | Circadian clocks and insulin resistance | Nat Rev Endocrinol 15 (2) 75-89 10.1038/s41574-018-0122-1 | Excluded: NRTA |
| SOTA 4-1 | S. Ganesh and V. K. Rustgi | 2016 | Current Pharmacologic Therapy for Nonalcoholic Fatty Liver Disease | Clin Liver Dis 20 (2) 351-64 10.1016/j.cld.2015.10.009 | Excluded: NRTA |
| SOTA 4-1 | S. Galcheva, S. Al-Khawaga and K. Hussain | 2018 | Diagnosis and management of hyperinsulinaemic hypoglycaemia | Best Pract Res Clin Endocrinol Metab 32 (4) 551-573 10.1016/j.beem.2018.05.014 | Excluded: DP |
| SOTA 4-1 | B. Hameed and N. Terrault | 2016 | Emerging Therapies for Nonalcoholic Fatty Liver Disease | Clin Liver Dis 20 (2) 365-85 10.1016/j.cld.2015.10.015 | Excluded: NRTA |
| SOTA 4-1 | H. M. Manukumar, J. Shiva Kumar, B. Chandrasekhar, S. Raghava and S. Umesha | 2017 | Evidences for diabetes and insulin mimetic activity of medicinal plants: Present status and future prospects | Crit Rev Food Sci Nutr 57 (12) 2712-2729 10.1080/10408398.2016.1143446 | Excluded: NRTA |
| SOTA 4-1 | P. Shah, S. A. Rahman, H. Demirbilek, M. Güemes and K. Hussain | 2017 | Hyperinsulinaemic hypoglycaemia in children and adults | Lancet Diabetes Endocrinol 5 (9) 729-742 10.1016/s2213-8587(16)30323-0 | Excluded: GR |
| SOTA 4-1 | E. Kostopoulou and P. Shah | 2019 | Hyperinsulinaemic hypoglycaemia-an overview of a complex clinical condition | Eur J Pediatr 178 (8) 1151-1160 10.1007/s00431-019-03414-8 | Excluded: DP |
| SOTA 4-1 | E. Vargas, P. Nandhakumar, S. Ding, T. Saha and J. Wang | 2023 | Insulin detection in diabetes mellitus: challenges and new prospects | Nat Rev Endocrinol 19 (8) 487-495 10.1038/s41574-023-00842-3 | Excluded: NRTA |
| SOTA 4-1 | M. Mazidi, P. P. de Caravatto, J. R. Speakman and R. V. Cohen | 2017 | Mechanisms of Action of Surgical Interventions on Weight-Related Diseases: the Potential Role of Bile Acids | Obes Surg 27 (3) 826-836 10.1007/s11695-017-2549-1 | Excluded: NRTA |
| SOTA 4-1 | J. Ampuero, Y. Sánchez-Torrijos, V. Aguilera, F. Bellido and M. Romero-Gómez | 2018 | New therapeutic perspectives in non-alcoholic steatohepatitis | Gastroenterol Hepatol 41 (2) 128-142 10.1016/j.gastrohep.2017.07.006 | Excluded: NRTA |
| SOTA 4-1 | C. Grander, F. Grabherr and H. Tilg | 2023 | Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options | Cardiovasc Res 119 (9) 1787-1798 10.1093/cvr/cvad095 | Excluded: NRTA |
| SOTA 4-1 | P. K. Prabhakar and P. M. Sivakumar | 2019 | Protein Tyrosine Phosphatase 1B Inhibitors: A Novel Therapeutic Strategy for the Management of type 2 Diabetes Mellitus | Curr Pharm Des 25 (23) 2526-2539 10.2174/1381612825666190716102901 | Excluded: NRTA |
| SOTA 4-1 | C. Douillard, A. Jannin and M. C. Vantyghem | 2020 | Rare causes of hypoglycemia in adults | Ann Endocrinol (Paris) 81 (2-3) 110-117 10.1016/j.ando.2020.04.003 | Excluded: DP |
| SOTA 4-1 | M. Danowitz and D. D. De Leon | 2022 | The Role of GLP-1 Signaling in Hypoglycemia due to Hyperinsulinism | Front Endocrinol (Lausanne) 13 (863184 10.3389/fendo.2022.863184 | Excluded: DP |
| SOTA 5-1 | N/A | 2021 | Dasiglucagon (Zegalogue) for severe hypoglycemia | Med Lett Drugs Ther 63 (1631) 132-134 | Excluded: DP |
| SOTA 5-1 | B. Xu, G. Tang and Z. Chen | 2021 | Dasiglucagon: an effective medicine for severe hypoglycemia | Eur J Clin Pharmacol 77 (12) 1783-1790 10.1007/s00228-021-03183-0 | Excluded: DP |
| SOTA 5-1 | H. A. Blair | 2021 | Dasiglucagon: First Approval | Drugs 81 (9) 1115-1120 10.1007/s40265-021-01531-z | Excluded: DP |
| SOTA 5-1 | H. Demirbilek, D. Vuralli, B. Haris and K. Hussain | 2023 | Managing Severe Hypoglycaemia in Patients with Diabetes: Current Challenges and Emerging Therapies | Diabetes Metab Syndr Obes 16 (259-273 10.2147/dmso.S313837 | Excluded: DP |
| SOTA 5-1 | L. La Sala and A. E. Pontiroli | 2021 | New Fast Acting Glucagon for Recovery from Hypoglycemia, a Life-Threatening Situation: Nasal Powder and Injected Stable Solutions | Int J Mol Sci 22 (19) 10.3390/ijms221910643 | Excluded: DP |
| SOTA 5-2 | H. Thabit, R. Lal and L. Leelarathna | 2021 | Automated insulin dosing systems: Advances after a century of insulin | Diabet Med 38 (12) e14695 10.1111/dme.14695 | Included |
| SOTA 5-2 | X. Jiao, Y. Shen and Y. Chen | 2022 | Better TIR, HbA1c, and less hypoglycemia in closed-loop insulin system in patients with type 1 diabetes: a meta-analysis | BMJ Open Diabetes Res Care 10 (2) 10.1136/bmjdrc-2021-002633 | Included |
| SOTA 5-2 | V. Karageorgiou, T. G. Papaioannou, I. Bellos, K. Alexandraki, N. Tentolouris, C. Stefanadis, G. P. Chrousos and D. Tousoulis | 2019 | Effectiveness of artificial pancreas in the non-adult population: A systematic review and network meta-analysis | Metabolism 90 (20-30 10.1016/j.metabol.2018.10.002 | Included |
| SOTA 5-2 | K. Braune, R. A. Lal, L. Petruželková, G. Scheiner, P. Winterdijk, S. Schmidt, L. Raimond, K. K. Hood, M. C. Riddell, T. C. Skinner, K. Raile and S. Hussain | 2022 | Open-source automated insulin delivery: international consensus statement and practical guidance for health-care professionals | Lancet Diabetes Endocrinol 10 (1) 58-74 10.1016/s2213-8587(21)00267-9 | Excluded: NRF |
| SOTA 5-2 | H. K. Akturk and S. Garg | 2019 | Technological advances shaping diabetes care | Curr Opin Endocrinol Diabetes Obes 26 (2) 84-89 10.1097/med.0000000000000467 | Included |
| SOTA 5-2 | T. Biester, M. Tauschmann, A. Chobot, O. Kordonouri, T. Danne, T. Kapellen and K. Dovc | 2022 | The automated pancreas: A review of technologies and clinical practice | Diabetes Obes Metab 24 Suppl 1 (43-57 10.1111/dom.14576 | Included |
| SOTA 5-2 | D. M. Lewis | 2020 | Do-It-Yourself Artificial Pancreas System and the OpenAPS Movement | Endocrinol Metab Clin North Am 49 (1) 203-213 10.1016/j.ecl.2019.10.005 | Excluded: NRTA |
| SOTA 5-2 | P. Jennings and S. Hussain | 2020 | Do-It-Yourself Artificial Pancreas Systems: A Review of the Emerging Evidence and Insights for Healthcare Professionals | J Diabetes Sci Technol 14 (5) 868-877 10.1177/1932296819894296 | Excluded: NRTA |
| SOTA 5-2 | T. T. M. Lee, C. Collett, S. Bergford, S. Hartnell, E. M. Scott, R. S. Lindsay, K. F. Hunt, D. R. McCance, K. Barnard-Kelly, D. Rankin, J. Lawton, R. M. Reynolds, E. Flanagan, M. Hammond, L. Shepstone, M. E. Wilinska, J. Sibayan, C. Kollman, R. Beck, R. Hovorka and H. R. Murphy | 2024 | Efficacy and Mechanism Evaluation | National Institute for Health and Care Research | Excluded: NRTA |
| SOTA 5-2 | D. P. Zaharieva, L. H. Messer, B. Paldus, D. N. O'Neal, D. M. Maahs and M. C. Riddell | 2020 | Glucose Control During Physical Activity and Exercise Using Closed Loop Technology in Adults and Adolescents with Type 1 Diabetes | Can J Diabetes 44 (8) 740-749 10.1016/j.jcjd.2020.06.003 | Excluded: NRTA |
| SOTA 5-2 | J. D. Morse, L. I. Cortinez and B. J. Anderson | 2021 | Pharmacokinetic concepts for dexmedetomidine target-controlled infusion pumps in children | Paediatr Anaesth 31 (9) 924-931 10.1111/pan.14235 | Excluded: NRTA |
| SOTA 5-2 | V. Chidambaran, A. Costandi and A. D'Mello | 2015 | Propofol: a review of its role in pediatric anesthesia and sedation | CNS Drugs 29 (7) 543-63 10.1007/s40263-015-0259-6 | Excluded: NRTA |
| SOTA 6-1 | C. M. Ramkissoon, B. Aufderheide, B. W. Bequette and J. Vehi | 2017 | A Review of Safety and Hazards Associated With the Artificial Pancreas | IEEE Rev Biomed Eng 10 (44-62 10.1109/rbme.2017.2749038 | Included |
| SOTA 6-1 | E. Zhang and Z. Cao | 2020 | Tissue Response to Subcutaneous Infusion Catheter | J Diabetes Sci Technol 14 (2) 226-232 10.1177/1932296819837972 | Included |
| SOTA 6-1 | E. Renard | 2023 | Automated insulin delivery systems: from early research to routine care of type 1 diabetes | Acta Diabetol 60 (2) 151-161 10.1007/s00592-022-01929-5 | Excluded: NRTA |
| SOTA 6-1 | I. Boura, N. Haliasos, A. Giannopoulou Ι, D. Karabetsos and C. Spanaki | 2021 | Combining Device-Aided Therapies in Parkinson's Disease: A Case Series and a Literature Review | Mov Disord Clin Pract 8 (5) 750-757 10.1002/mdc3.13228 | Excluded: NRTA |
| SOTA 6-1 | M. S. Jeeyavudeen, M. Crosby and J. M. Pappachan | 2024 | Continuous glucose monitoring metrics in pregnancy with type 1 diabetes mellitus | World J Methodol 14 (1) 90316 10.5662/wjm.v14.i1.90316 | Excluded: NRTA |
| SOTA 6-1 | D. Farrar, D. J. Tuffnell, J. West and H. M. West | 2016 | Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes | Cochrane Database Syst Rev 2016 (6) Cd005542 10.1002/14651858.CD005542.pub3 | Excluded: NRTA |
| SOTA 6-1 | C. A. Thiels and M. I. D'Angelica | 2020 | Hepatic artery infusion pumps | J Surg Oncol 122 (1) 70-77 10.1002/jso.25913 | Excluded: NRTA |
| SOTA 6-1 | A. Bonde, A. W. Fung, S. C. Mayo, P. Li, B. S. Walker, S. Jaganathan, N. Mallak and E. K. Korngold | 2024 | Imaging of the hepatic arterial infusion pump: Primer for radiologists | Clin Imaging 105 (110022 10.1016/j.clinimag.2023.110022 | Excluded: NRTA |
| SOTA 6-1 | C. B. Teo, P. Y. Tan, S. X. Lee, J. Khoo, J. G. Tan, S. F. Ang, S. H. Tan, T. L. Tay, E. Tan, S. C. Lim, B. O. Boehm and W. J. Loh | 2022 | Insulin Allergy to Detemir Followed by Rapid Onset of Diabetic Ketoacidosis: A Case Report and Literature Review | Front Endocrinol (Lausanne) 13 (844040 10.3389/fendo.2022.844040 | Excluded: NRTA |
| SOTA 6-1 | C. Hua, R. Bosc, E. Sbidian, N. De Prost, C. Hughes, P. Jabre, O. Chosidow and L. Le Cleach | 2018 | Interventions for necrotizing soft tissue infections in adults | Cochrane Database Syst Rev 5 (5) Cd011680 10.1002/14651858.CD011680.pub2 | Excluded: NRTA |
| SOTA 6-1 | X. Ruan, L. Ma, J. P. Couch, T. Chen and G. W. Bumgarner | 2015 | Intractable pruritus during outpatient epidural hydromorphone infusion: a case report and a focused review of the literature | J Opioid Manag 11 (2) 184-90 10.5055/jom.2015.0267 | Excluded: NRTA |
| SOTA 6-1 | M. E. Freitas, M. Ruiz-Lopez and S. H. Fox | 2016 | Novel Levodopa Formulations for Parkinson's Disease | CNS Drugs 30 (11) 1079-1095 10.1007/s40263-016-0386-8 | Excluded: NRTA |
| SOTA 6-1 | H. Quach, G. Parmar, M. V. Mateos, S. Ailawadhi and X. Leleu | 2024 | Recent Developments in Convenience of Administration of the Anti-CD38 Antibody Isatuximab: Subcutaneous Delivery and Fast Intravenous Infusion in Patients With Multiple Myeloma | Clin Lymphoma Myeloma Leuk 24 (6) 358-363 10.1016/j.clml.2024.02.004 | Excluded: NRTA |
| SOTA 6-1 | B. L. Levy, T. W. McCann, Jr. and D. A. Finan | 2016 | The Hypoglycaemia-Hyperglycaemia Minimizer System in the Management of Type 1 Diabetes | Eur Endocrinol 12 (1) 18-23 10.17925/ee.2016.12.01.18 | Excluded: NRTA |
| SOTA 7 | J. J. Robert, D. Darmaun, G. Reach and H. Lestradet | 1986 | [Artificial pancreas in diabetic children] | Presse Med 15 (43) 2159-62 | Excluded: NRTA |
| SOTA 7 | M. Bergua, I. Levy, R. Casamitjana and D. Figuerola | 1983 | [Therapeutic hyperinsulinism induced by the use of continuous insulin infusion pumps and the artificial pancreas in diabetic patients] | Med Clin (Barc) 81 (6) 243-5 | Excluded: NRTA |
| SOTA 7 | Y. Liu, D. L. Cao, L. B. Guo, S. N. Guo, J. K. Xu and H. F. Zhuang | 2013 | Amniotic stem cell transplantation therapy for type 1 diabetes: a case report | J Int Med Res 41 (4) 1370-7 10.1177/0300060513487640 | Excluded: CR |
| SOTA 7 | I. Juhan-Vague, P. Vague, C. Poisson, M. F. Aillaud, C. Mendez and D. Collen | 1984 | Effect of 24 hours of normoglycaemia on tissue-type plasminogen activator plasma levels in insulin-dependent diabetes | Thromb Haemost 51 (1) 97-8 | Excluded: NRTA |
| SOTA 7 | E. Kostopoulou and P. Shah | 2019 | Hyperinsulinaemic hypoglycaemia-an overview of a complex clinical condition | Eur J Pediatr 178 (8) 1151-1160 10.1007/s00431-019-03414-8 | Excluded: DP |
| SOTA 7 | O. Schmitz, K. G. Alberti and H. Orskov | 1984 | Insulin resistance in uraemic insulin-dependent diabetics. Effect of dialysis therapy as assessed by the artificial endocrine pancreas | Acta Endocrinol (Copenh) 105 (3) 371-8 10.1530/acta.0.1050371 | Excluded: NRTA |
| SOTA 7 | H. Gin, C. Messerchmitt, E. Brottier and J. Aubertin | 1985 | Metformin improved insulin resistance in type I, insulin-dependent, diabetic patients | Metabolism 34 (10) 923-5 10.1016/0026-0495(85)90139-8 | Excluded: NRTA |
| SOTA 7 | C. Cobelli and C. Dalla Man | 2022 | Minimal and Maximal Models to Quantitate Glucose Metabolism: Tools to Measure, to Simulate and to Run in Silico Clinical Trials | J Diabetes Sci Technol 16 (5) 1270-1298 10.1177/19322968211015268 | Excluded: DS |
| SOTA 7 | C. Guibert, L. Amoura, L. Rakotoarisoa, F. Plat, E. Sonnet, S. Lablanche, C. Tréglia, E. Sarde, V. Leca, F. Rimareix, V. Melki, F. Baucher, B. Betari, L. Meyer and L. Kessler | 2023 | MiniMed(TM) 780G Advanced Hybrid Closed-Loop System Study in Pregnant Women with Type 1 Diabetes | Diabetes Technol Ther 25 (12) 893-901 10.1089/dia.2023.0267 | Excluded: NRTA |
| SOTA 7 | A. C. Calabria, C. Li, P. R. Gallagher, C. A. Stanley and D. D. De León | 2012 | GLP-1 receptor antagonist exendin-(9-39) elevates fasting blood glucose levels in congenital hyperinsulinism owing to inactivating mutations in the ATP-sensitive K+ channel | Diabetes 61 (10) 2585-91 10.2337/db12-0166 | Excluded: NRF |

Appendix II – Details of retrieved vigilance reports

The full disclosure of the vigilance search results with evaluation of relevance for the subject device for each report is presented by search number and database in the sections below.

* 1. MHRA

**Table 19: Retrieved MHRA reports**

| **Search #** | **Date of Safety Notice** | **Reference** | **Device(s)** | **Manufacturer** | **Problem** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| 2 | 10 March 2014 | MDA/2014/008 | Accu-Chek Spirit Combo insulin pump | Roche Diagnostics Ltd. | Risk of delay to treatment.  There is an increased risk that the vibration alarm will not work, as a result of a changed component. This fault will only be detected at pump start up, when it will display an ‘E-7’ error message and give an audible signal, but will fail to start.  Roche will replace pumps that display this ‘E-7’ error message, but does not intend to replace all potentially affected pumps. | Yes |
| 2 | 18 September 2015 | 2015/004/020/701/008 | Accu-Chek Spirit Combo: 00700006863 | Roche Diagnostics | N/A | N/A |
| 2 | 25 July 2016 | MDA/2015/001 | Accu-Chek Spirit Combo | Roche Diagnostics | Interrupting the pump’s power, eg to change the battery, may reset the default date and time. If this change goes unnoticed, and the user confirms the default settings, there will be a shift in the basal rate time block and this may affect insulin delivery. Patients with impaired vision are at particular risk as they may be less likely to notice the change. | Yes |
| 3 | 30 May 2022 | 2022/005/026/599/007 | MiniMed 640G Insulin Pump (35983); MiniMed 670G Insulin Pump (35983); MiniMed 720G Insulin Pump (64889), MiniMed 740G Insulin Pump (64890); MiniMed 770G Insulin Pump (64891); MiniMed 780G Insulin Pump (64891) | Medtronic | The letter advises patients if the metal contact becomes loose or falls off from the battery cap, it can result in an incomplete battery connection, leading to no power source to the pump. When the pump detects no power source, an “Insert battery” alarm will occur, and insulin delivery will immediately stop. After 10 minutes, the alarm sound may increase to a siren, and the pump will turn off.  If the pump stops delivery of insulin due to power loss, this could lead to varying degrees of high blood sugar, including Diabetic Ketoacidosis (DKA). Serious injuries have been reported with the use of the MiniMed™ 600 series and MiniMed™ 700 series insulin pumps associated with the damaged cap | Yes |
| 5 | 20 September 2022 | 2022/009/016/599/007 | t:slim X2 Insulin Pump | Tandem Diabetes Care | Tandem have designed new software for t:slim X2 insulin pumps to mitigate the following three issues. While uncommon, each of these could result in an unexpected disruption to insulin delivery:  1. Malfunction 6 Non-Volatile Memory (NVM):  Malfunction 6 is declared when memory corruption is detected, or the memory cannot be written to or read  from. When a malfunction occurs, all insulin deliveries are stopped.  2. Inaccurate (Fluctuating) Battery Life Display:  During a high battery usage event, the pump’s displayed battery life may appear to fluctuate. If noticed, this fluctuation could create confusion for the user. If the decrease in displayed battery life occurs when the battery is very low, then following a sequence of Low Power Alerts and Alarms, the pump may stop all insulin deliveries and power off.  3. Touchscreen Staying On:  If the pump’s touchscreen senses something continuously touching the screen, the pump’s software resets the display screen timeout timer causing the screen to stay on indefinitely resulting in the battery depleting faster than expected. If the battery depletes, then following a sequence of Low Power Alerts and Alarms, the pump will eventually stop all insulin deliveries and power off.  For all three issues outlined above, the result could be an under-delivery of insulin, which may result in hyperglycemia. In severe cases of hyperglycemia, the user may experience diabetic ketoacidosis and may require hospitalization or intervention from a medical professional.  In addition, the designed new software for t:slim X2 insulin pumps mitigates a fourth issue that is related to the Control-IQ technology. While uncommon, this issue could result in an under-delivery or over-delivery of insulin:  4. Unexpected Open Loop:  Control-IQ technology could turn off unexpectedly due to a software anomaly that results in the pump entering open loop (pining mode). When Control-IQ technology turns off, the pump is no longer adjusting insulin dosing based on CGM readings and the pump reverts to the active personal profile settings. | Yes for the first 3 issues |
| 5 | 21 February 2022 | 2022/002/009/701/176 | t:slim X2 Insulin Pump | Tandem Diabetes Care | A user could inadvertently program and confirm a basal rate with an incorrectly placed decimal point. For example: The user intends to program a basal rate of 0.7 units/hour, but inadvertently enters and confirms a basal rate of 7.0 units/hour. Inputting incorrect values in your Personal Profile can lead to under-delivery or over-delivery of insulin, which could result in hyperglycemia or hypoglycemia. | Yes |
| 7 | 13 December 2022 | 5013072 | CADD Infusion System Infusion Sets for use with CADD pumps | Smiths Medical | Issue 1 – Lack of Delivery or Underdelivery related to Tubing Occlusion  Manufacturing variations may cause the green CADD Flow Stop arm to compress and partially occlude the tubing before clinical use. If this occurs, there is a potential that the occlusion does not resolve when an affected reservoir or administration set is connected to the pump, and the pump may not detect the occlusion. This may result in underdelivery or non-delivery of medication, despite the pump displaying that the infusion is running properly  Issue 2 – False “No Disposable Attached (NDA)” Alarms  There is a potential that CADD-Legacy pumps may not detect that 50 mL and 100 mL CADD Medication Cassette Reservoirs with Flow Stop are attached to the pump when the cassettes are properly attached | Yes |
| 7 | 05 September 2024 | 31747982  2024/009/002/601/020 | CADD Medication Cassette Reservoir | Smiths Medical | Certain CADD Medication Cassette Reservoirs may exhibit a weakened weld joint between the medication bag and tubing due to a production equipment malfunction. This could result in a medication leakage. | Yes |
| 7 | 26 May 2015 | 2015/005/028/071/004 | CADD® - Solis ambulatory infusion pumps | Smiths Medical | N/A | No |
| 7 | 27 March 2024 | 28607766 | CADD® - Solis ambulatory infusion pumps | Smiths Medical | Issue 1 – Upstream OcclusionThe pump may not alarm for an upstream occlusion  Issue 2 – Stop and Power Keys UnresponsiveThe Start/Stop key may become unresponsive  Issue 3 – Manual Mode Air DetectorIf the user selects a protocol from the library with the Air Detector turned off and subsequently selects to program the pump in Manual Mode, the Air Detector remains off. In Manual Mode, the Air Detector should be turned on, but in this case, it remains off.  Issue 4 – Single Bubble Air Detection  After the user clears a single bubble air alarm, primes the tubing to remove the air, and restarts the pump, the next single air bubble that should trigger a single bubble air-in-line alarm does not trigger the alarm. This behavior continues until enough air passes through the air detector to trigger an accumulated air-in-line alarm.  Issue 5 – Error Codes Not Displayed at Power Up  During the power-up sequence, if the pump detects a failure (e.g., code corruption, processor failure), it will trigger a system fault alarm indicating that an unrecoverable error may have occurred.  Issue 6 – Audible Alarm  It is possible that a defective audible alarm componentis not detected. If so, when an alarm occurs, the amber indicator light will illuminate, and the pump will display the alarm message, but the audible portion of the alarm will not sound.  Issue 7 –Low Sensitivity Air in Line Detection Threshold  Smiths Medical is reverting the Low Sensitivity Air In Line alarm threshold to the previous settings in alignment with industry standards.  Issue 8 –PharmGuard Server Password  If a user attempts to log into PharmGuard Server using LDAP and their password contains any of the HTML special characters [ “ ‘ < > ], an error occurs. | Yes |
| 7 | 24 May 2016 | MDA/2016/006 | CADD® administration sets | Smiths Medical | Risk of under-infusion. | Yes |
| 7 | January 2018 | 2017/010/012/701/035 | CADD® Medication Cassette Reservoir | Smiths Medical | N/A | N/A |
| 7 | 18 March 2020 | 2020/003/025/487/001 | Pump Kit, CADD SOLIS VIP MDL 2120 | Smiths Medical | If an AILD (Air in Line Detector) does not sufficiently discern fluid from air in line, an air in line event may not be recognized by the pump and may not alarm to notify the clinician. | Yes |
| 7 | 20 June 2018 | MDA/2018/020 | CADD Non Flow-Stop Medication Cassette Reservoirs | Smiths Medical | CADD Non Flow-Stop Medication Cassette Reservoirs may have been manufactured with an incorrect pressure plate which could cause partial or total occlusion of the tubing with no alarm | Yes |
| 7 | 2 February 2015 | 2015/001/029/071/001 | CADD® Medication Cassette Reservoir | Smiths Medical International | N/A | N/A |
| 7 | 4 May 2016 | 2016/004/022/299/002 | CADD® Administration Sets with Flow Stop Free-Flow Protection | Smiths Medical | N/A | N/A |
| 7 | 17 August 2017 | MDA/2017/022 | DePuy Synthes Impactor for PFNA Blade (P/N 03.010.410) | Depuy Synthes GmbH | In December 2016 DePuy Synthes issued a Field Safety Notice (FSN) informing clinicians of the possibility of breakage of the PFNA Blade impactor handle. If the breakage goes unnoticed, any body fluids that get into the handle during use would pose a risk of cross-contamination to other patients. | No |

* 1. BfArM

**Table 20: Retrieved BfArM reports**

| **Search #** | **Date of Safety Notice** | **Reference** | **Device(s)** | **Manufacturer** | **Problem** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| 2 | 12. May 2015 | 02218/15 | Accu-Chek Spirit Combo\_ Accu Chek Spirit | Roche Diabetes Care | We became aware that some customers using the Accu-Chek Combo system are experiencing an increase of mechanical errors with their insulin pumps showing E6 and E10 error messages.  If users do not follow the cartridge change process step-by-step as described in the attached training leaflet, there is a potential risk of small insulin amounts to drip into the cartridge compartment. Such small insulin amounts would reside in the compartment and result in a damage of the piston rod over time, so that the piston rod will not properly move and potentially limit or cause a blockage of the insulin pump motor function. Eventually, this may result in the insulin not being delivered as intended. | Yes |
| 2 | 02. October 2014 | 06264/14 | Accu-Chek Spirit Combo | Roche Diabetes Care | Patients may experience a loss of the date and time settings. This issue may occur if the pump capacitor fails to function properly due to a leakage.  The user might overlook the change. As a result a shift of the basal rate time block would occur, which could potentially contribute to hyper- hypoglycemic events. | Yes |
| 3 | 12. August 2024 | 12658/22 | Minimed Insulin Pumps | MedTronic Minimed | We are pleased to inform you that we have developed a new battery cap for these specific pumps, which addresses the potential issues with the previous battery cap (model ACC-1527).  We have attempted to send you a new battery cap, ACC-1529, along with instructions to replace your battery cap with the new cap provided. However, we have not received your acknowledgment. | No |
| 3 | 04. February 2022 | 02004/22 | MiniMed 600- und 700 serie | Medtronic | The pump your patient received was NOT pre-programmed with their basal rates or other verified settings (i.e., bolus wizard settings, sensor settings, etc.), which must be set up and saved on their pump prior to use.  Serious injuries have been reported with the use of the MiniMed™ 600 series and MiniMed™ 700 series insulin pumps which may be directly attributed to not setting basal rates. | Yes |
| 4 | 11. July 2019 | 08471/19 | MiniMed™ Paradigm™ Series and MiniMedTM 508 Insulin Pumps | Medtronic | Security researchers have identified potential cybersecurity vulnerabilities related to these insulin pumps. An unauthorized person with special technical skills and equipment could potentially send RF signals to a nearby insulin pump to change settings and control insulin delivery. This could lead to hypoglycaemia (if additional insulin is delivered) or hyperglycaemia and diabetic ketoacidosis (If not enough insulin is delivered). | Yes |
| 4 | 20. August 2018 | 10052/18 | MiniMed™ remote controller (MMT-500 or MMT-503) | Medtronic | An external security researcher has identified a potential vulnerability related to the MiniMed™ Paradigm™ family of insulin pumps and corresponding remote controller. The researcher’s report states that an unauthorized individual in close proximity of an insulin pump user could potentially copy the wireless radio frequency (RF) signals from the user’s remote controller (while they are in the process of delivering a remote bolus) and play those back later to deliver an involuntary bolus of insulin to the pump user. This could lead to potential health risks such as hypoglycemia if additional insulin is delivered beyond the user’s insulin requirements. | Yes |
| 5 | 11. September 2012 | 04013/12 | FreeSpan™ Traverse and FreeSpan Ultra Twin™ Traverse | Liko AB | *Not relevant device* | No |
| 5 | 17. March 2017 | 02596/17 | sterile endoprosthetics products and cancellous screw VariaCup | aap Implantate AG | *Not relevant device* | No |
| 7 | 16. March 2017 | 7620/16 | Life-Point AEDs | METsis Medikal Ltd. Sti. | *Not relevant device* | No |

* 1. Health Canada

**Table 21: Health Canada reports**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Search #** | **Date** | **Reference** | **Manufacturer** | **Devices** | **Problem** | **Relevance for subject device** |
| 3 | 2022-02-10 | RA-63906 | Medtronic Minimed | Minimed 630g, Minimed 670g, Minimed 770g | A Minimed 630g insulin pump user who was hospitalized with hyperglycemia and DKA (diabetic ketoacidosis). Medtronic medical safety personnel noticed that the basal rates on the pump were still set to 0.0 units (factory default).  The team identified the following three (3) reasons why basal insulin may not be programmed on the pump when it is recommended by users' hcp or intended/desired:  1. General unawareness that user settings must be manually entered prior to use of the pump.  2. 24hr technical support was unaware that the one (1) user failed to press "save" after reviewing the new basal profile.  3. The design of the user interface (UI) of the NGP pump was not intuitive to users that receive the pumps. | Yes |
| 4 | March 5, 2020 | RA-72763 | Medtronic Minimed | Minimed 630g | Instructions to confirm rise alerts are disabled, were incorrect on the release note. The rise alerts are disabled from factory and do no directly affect insulin therapy. However, it was identified that the instructions on the release note were incorrect and users were potentially not able to confirm the rise alert is disabled. | Yes |
| 4 | May 1, 2020 | RA-73121 | Medtronic Minimed | MiniMed 630G & 670G Insulin Pump | The MiniMed 600 Series insulin pump uses an AA battery for power. Recently, manufacturer identified a batch of pumps with an issue on the battery connection that does not meet quality specifications. If power is interrupted on a patient's insulin pump, then insulin is suspended which may lead to hyperglycemia (high blood sugar). There have been no reported complaints from customers as a result of this issue | Yes |
| 4 | November 21, 2019 | RA-71818 | Medtronic Minimed | MiniMed 630G & 670G Insulin Pump | There have been reported incidents of a loose reservoir that can no longer be locked into the pump. The reservoir can become loose due to a broken or missing retainer ring that prevents a proper lock. The retainer ring can be broken, for example as a result of dropping or bumping pump on a hard surface.  If the reservoir is not properly locked into the pump, it could lead to over or under delivery of insulin, which could then result in hypoglycemia or hyperglycemia. | Yes |
| 4 | October 5, 2021 | RA-76665 | Medtronic Minimed | MiniMed 630G & 670G | Medtronic initiated a recall of Minimed 600 Series insulin pumps with a damaged clear retainer ring in November 2019 due to reported incidents of a loose reservoir that can no longer be locked into the pump.  Medtronic is updating this recall to replace any Minimed 600 series insulin pump that has a clear retainer ring with a Minimed 600 series insulin pump that has the updated black retainer ring design. | Yes |
| 4 | 2022-10-07 | RA-64595 | Medtronic Minimed | MiniMed 630G & 670G | Communication between the components of the MINIMED 600 Series Pump System could be compromised by unauthorized access. | Yes |

* 1. ANSM

**Table 22: ANSM reports**

| **Search #** | **Date of Safety Notice** | **Reference** | **Manufacturer** | **Relevant Devices** | **Problem** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| 1a | 09/21/2021 | R2116668 / R2116847 | BD/Caesarea Medical Electronics Ltd | Systèmes de pompe à perfusion CME/BD BodyGuard™ | Previously, in accordance with Field Safety Notice MMS-21-4135, BD updated the following default settings and labeled it as a temporary measure:   * The maximum flow rate has been limited to 800 mL/h in continuous mode. * The maximum bolus delivery rate has been limited to 300 mL/h   BD has decided to make these features permanent for the CME/BD BodyGuard™ infusion pumps. This is because a change in the technical design has proven to be impractical. | No |
| 1a | 07/12/2023 | R2327926 | Smiths Medical ASD Inc | Pompe pousse seringue Medfusion™ modèle 3500 | Issue 1 – Delivering during High Priority Alarm Motor Not Running  There is a rare scenario in which the pump may continue to deliver fluid when the high priority alarm condition Motor Not Running should stop delivering fluid.  Issue 2 – Infusion restarted with incorrect parameters  An infusion may be restarted using the Continue Same Infusion feature with incorrect concentration values ​​if the concentration units are changed after exiting the infusion programming screens.  Issue 3 – Screen Lock  The pump may lock on a screen other than the infusion screen. Once this occurs, all buttons are locked, making it impossible to unlock the pump.  Issue 4 – Bolus or Loading Dose Delivery Interrupted  If the user presses the power button while a bolus or loading dose is being delivered, the pump will stop delivering the bolus or loading dose and return to normal infusion delivery. The pump will prompt the user to confirm that they want to turn the pump off.  Issue 5 – Pump Displays Incorrect Bolus or Loading Dose  There is a scenario where the Bolus/Loading Dose screens may display incorrect values.  Issue 6 – Loading Dose/Bolus Below Minimum Recommended Rate  A loading dose or bolus may be delivered below the low limit without notification to the user. Due to a calculation error, the pump may display a low limit that is too low for a given therapy.  Issue 7 – Motor Flow ​​Error  A motor flow error alarm will occur after approximately 27 minutes of delivery if the pump is used with a 3 mL Terumo or Monojet syringe and the delivery rate is 0.01 mL/hr. A motor flow error alarm indicates that the motor is not operating at the programmed rate.  Issue 8 – Incorrect recall of last settings  When recalling a completed DOSE/KG/TIME or DOSE/M2/TIME infusion, the DOSE value may be recalled incorrectly. If the user navigates past the Enter Dose screen and then returns to the screen, the pump may use the default dose value from the configuration instead of the dose from the last infusion.  Issue 9 – Corrupted Configuration  When a new configuration is loaded into the pump that is larger than the old configuration, the history log can potentially overwrite the configuration. If this issue occurs, the pump may display empty strings, font size changes, or other unexpected behavior. This issue may also cause the pump to display a Watchdog Failsafe alarm. Smiths Medical recommends always powering off the pump after loading a configuration.  Issue 10 – Auto Lock  If the user performs an infusion with an auto lock timer set, presses START, waits for the auto lock to expire, and then presses the OPTIONS softkey after the auto lock time expires, the pump will go to the OPTIONS screen and freeze.  Issue 11 – Loading Dose Time Values ​​Toolbox Configuration  Medfusion Model 3500 pumps can read a configuration from a pump into PharmGuard Toolbox v1.5. If the pump configuration to be read contains a loading dose time (lower hard limit, lower soft limit, initial value, upper soft limit, or upper hard limit) greater than one hour, PharmGuard Toolbox v1.5 truncates the time so that only minutes remain. None of the other loading dose programming parameters are affected. | Yes for issues 1 and 3 |
| 1a | 30/11/2023 | R2324772 / R2324432 | BD Switzerland Sàrl | Tubulures pour pompe, tubulures de perfusion par gravité et  prolongateurs de tubulure BD Alaris | BD has internally identified that the infusion sets listed in Appendix 1 contain di(2-ethylhexyl) phthalate (DEHP) and have not been labeled accordingly. The infusion sets contain DEHP by design and their content has remained unchanged since the product was first marketed. | No |
| 1a | 03/22/2022 | N/A | Smiths Medical ASD, Inc. | CADD, Snuggle Warm, Portex, BCI, Medex, Jelco, Bivona | As a result of this acquisition, we are conducting a thorough compliance assessment of all Smiths Medical Class I devices. Out of an abundance of caution, and effective immediately, we are proactively implementing a temporary freeze on shipments of all Smiths Medical Class I products to all customers in countries that require CE marking. | No |
| 5 | 18/01/2022 | R2200611 | Tandem Diabetes Care | t:slim X2 | Cases of severe hypoglycemia have been observed in young children under 6 years of age following unwanted bolus administration that can lead to loss of consciousness and potentially cause the death of the patient. These prescriptions made to children under 6 years of age go against the manufacturer's recommendations. Incidents have also been observed in children over 6 years of age due to inappropriate handling of the pump. The purpose of this safety notice is therefore to provide a reminder of the minimum age for prescribing the Tandem t:slim X2™ insulin pump and to remind people of good practices for using the pump in young patients. The Tandem t:slim X2™ insulin pump should not be prescribed to children under 6 years of age. | Yes |

* 1. HPRA

**Table 23: HPRA reports**

| **Search #** | **Date of Safety Notice** | **Reference** | **Manufacturer** | **Relevant Devices** | **Problem** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| 1a | 04/08/2015 | SN2015(20) | Animas Corporation | Animas Vibe Insulin Infusion Pump | Animas has advised that the display on the Animas Vibe pump may fade over time, making it difficult to read the information on the screen. | Yes |
| 1a | 15/05/2015 | IN2015(03) | Medtronic | Medtronic Synchromed II Implantable Infusion Pump Systems | *Not relevant device* | No |
| 1a | 24/04/2014 | SN2014(20) | Medtronic | Paradigm Insulin Infusion Pump. | Medtronic has received a number of reports regarding users who have accidentally programmed the pump to deliver the maximum bolus amount, including one incident that resulted in severe hypoglycaemia.  All insulin delivery programmed through the Main Menu will allow the down arrow button to scroll from 0.0 units to the programmed maximum bolus insulin dose. | No |
| 1a | 08/04/2014 | SN2014(17) | B.Braun Melsungen AG | BBraun Perfusor Space Infusion Pump | The Irish Medicines Board (IMB) wishes to remind users of a field safety notice (FSN) issued by B. Braun in December 2013. B. Braun has identified a risk that when the Perfusor Space pump is used with an aged battery, that the pump may not have sufficient current to perform a syringe change, despite the battery indicator on the pump showing full charge.  The issue can only occur when the pump is not connected to the mains and presents a risk when the pump is used on battery only. | No |
| 1a | 29/04/2014 | SN2014(21) | B.Braun Melsungen AG | B.Braun Infusomat & Perfusor Space Infusion Pumps & Pole Clamps | Risk of delay or interruption to therapy.  Issue 1: The Irish Medicines Board (IMB) has received an increased number of complaints in relation to breakage of the anti free-flow clip catch located inside the door of the B. Braun Infusomat Space infusion pump.  Issue 2: The IMB has received a number of complaints of pump detachment involving the B. Braun Pole Clamp when used to mount Infusomat and Perfusor Space pumps. | No |
| 1a | 30/04/2014 | SN2014(22) | Smiths Medical | Graseby Syringe Drivers (MS16A & MS26) | The incidents include the following:  • Pump stopped infusing  • Medication Infused too fast (Over-infusion)  • Medication infused too slow (Under-infusion) | Yes |

* 1. DMA

**Table 24: DMA reports**

| **Search #** | **Date of Safety Notice** | **Reference** | **Manufacturer** | **Devices** | **Problem** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| 1a | 30. august 2023 | 2023085216 | Smiths Medical | Medfusion™ Model 3500 and Model 4000 Syringe Infusion Pumps | The calibration of the force sensor used to detect occlusions may shift over time. If the force sensor calibration shift is large enough, the pump will display a System Failure Alarm (including Force Sensor BGND Test, Force Sensor Bridge Test, or Force Sensor Test). If the calibration shift is not large enough to trigger a System Failure Alarm, there may be a slight increase in the threshold to detect an occlusion. Although shifts in the force sensor calibration may occur over time with any device, an increased potential for such shifts has been reported in devices produced before April 2022 due to mechanical interference between parts of the plunger head assembly. Out of an abundance of caution, we are notifying all customers of this potential issue. | Yes |
| 1a | 1. april 2022 | 2023085216 | Smiths Medical | Medfusion™ Model 3500 and Model 4000 Syringe Infusion Pumps | Issue 1 - Primary Audible Alarm (PAA)  Under certain conditions, the pump may falsely detect a Primary Audible Alarm (PAA) System Fault.  Issue 2 – Unanticipated Depleted Battery Alarms  Under certain conditions with excessive wireless network activity, the pump may enter a state where the smart battery cannot provide its status to the pump.  Issue 3 – Time Base Alarm  A specific set of Medfusion pumps may contain a circuit board found to exhibit abnormal behavior in an internal clock. If the abnormal behavior of these boards occurs during infusion, the pump stops the infusion.  Issue 4 – Intermittent Volume Over Time (IVOT) - Infusion Continues after System Failure  If a System Failure alarm occurs during the small window of time when the pump is transitioning from IVOT delay to IVOT delivery, the pump may continue to run without the ability to terminate infusion via the Stop or Power keys.  Issue 5 – Clearing of Program Volume Delivered (PVD)  When two different syringe sizes or brands are used during the same volume-limited infusion, the PVD will be reset to zero during the syringe change. The volume of fluid delivered with the first syringe will not be accounted for in the PVD.  Issue 6 – False Alarm for Rate Below Recommended Minimum for Syringe Size  Under certain conditions, the pump may display a false “Rate Below Recommended Minimum for Syringe Size” alarm.  Issue 7 – Incorrect Bolus or Loading Dose Time Display  In rare situations, the pump may display an incorrect value for the time remaining during a Bolus Dose or Loading Dose infusion. If this issue occurs, the pump will infuse correctly to the intended infusion time even though the displayed time remaining is incorrect.  Issue 8 – Domain Name Server (DNS) Port 1001  If a Medfusion 4000 pump is configured to use a Domain Name Server (DNS) and the wireless network is configured to disallow DNS communications over port 1001, the Medfusion 4000 pump will not communicate with the PharmGuard Server (PGS). | Yes for issue 1, 2, 3, and 4 |
| 1a | 23. august 2021 | 2021082673 | Caesarea Medical Electronics Limited | BodyGuard™ Infusion Pumps Systems | BD has identified potential flow rate issues. An investigation showed an increased risk of underinfusion when using the pump system at high flow rate settings in both continuous and an intermittent infusion as PCA mode. Deviations from nominal accuracy (5-7%) were detected above 500 mL/h and were most prevalent and significant (>-20%) when running infusions at flow rates ≥ 800 mL/h in continuous mode. Likewise, when PCA bolus (intermittent) is delivered at rates ≥ 500 ml/h in combination with low basal rates. | Yes |
| 1a | 23. februar 2018 | 2018023876 | Fresenius Kabi | Volumat Infusion Pump Lines | Fresenius Kabi has received feedback from users who point out that some Volumat Agilia pumps display the error message "Error 24 (Er24)" when setting the pump.  The situation occurs when the Occlusion Check System (OCS) test is successful (the anti-free flow clamp is found to be closed) and the pump tries to open the anti-free flow clamp but cannot because sometimes there is too much resistance.  This error message cannot be removed from the display, no matter which button is pressed. It is necessary to switch off and restart the pump. After this, the pump setting process will normally expect the door to be opened and the Volumat infusion set installation process to repeat. | Yes |
| 1a | 26. september 2017 | 2017093639 | Shenzhen Shenke Medical Instrument Technical Development Co. , Ltd. | BeneFusion VP1, BeneFusion VP3 infusion pump | Shenke Medical has identified a potential issue with the BeneFusion infusion pump (BeneFusion VP1, BeneFusion VP3), which the plastic screw Joint used to fasten the pump body may crack under certain circumstance. The internal aging test revealed that, although in a rare case, the crack of the plastic screw Joint may lead to the abnormal infusion flow control. In some circumstances, this may result in over infusion. | Yes |
| 1a | 10. juni 2015 | 2015061133 | Smiths Medical ASD, Inc | CADD-Solis Ambulatory Infusion Pumps | Smiths Medical has become aware of an issue with an intermittent occurrence of binding of the locking assembly on some CADD®-Solis pumps. Binding of the Cassette/ Keypad Lock can occur after latching the CADD®-Solis Medication Cassette Reservoir or Administration Set “disposable” to the pump. When binding occurs, it can prevent the key from fully rotating the Cassette/ Keypad Lock to the locked (engaged) position. | Yes |
| 1a | 26. marts 2014 | 2014033353 | Medtronic, Inc. | SynchroMed II Implantable Drug Infusion Pump | *Not relevant device* | No |
| 1a | 1. maj 2013 | 2013040498 | Medtronic | Paradigm Insulin Infusion Pump | 1. LOOSE CAPSULE  The insulin pump capsule holds the pump motor in place and allows the motor piston to push against the reservoir to deliver insulin. Some customers have experienced that the capsule is loose and that in rare cases the capsule can protrude from the bottom of the chamber into the reservoir.  2. WATER DAMAGE  As explained in the pump's user manual, exposure to water can result in a pump alarm or damage to the pump's internal electronics or cause the buttons to stop working.  3. SENSOR CURVE TIMEOUT  If Sensor Curve Timeout is set to “ZERO”, it may prevent automatic resumption of basal delivery 2 hours after a Stop Low Glucose event, which may result in elevated blood glucose values. | Yes |
| 1a | 20. november 2012 | LMST-2012111463 | Medtronic, Inc. | SynchroMed Implantable Infusion Pump | *Not relevant device* | No |
| 1a | 29. marts 2012 | LMST-2012031834 | Medtronic | SynchroMed II Implantable Drug Infusion Pump | *Not relevant device* | No |

* 1. FDA Medical Device Recalls

Table : FDA Recalls for similar devices

| **Recall Number** | **Product Description** | **Trade Name** | **Termination Date** | **Recalling Manufacturer** | **Recall Reason** | **Relevance for subject device** |
| --- | --- | --- | --- | --- | --- | --- |
| Z-0061-2018 | For use with CADD(R) pumps (except CADD-Micro(TM), CADD-MS(R) 3 and CADD-TPN(R) pumps). | CADD(TM) Medication Cassette Reservoir | 2020-08-07 9:20:32 | Smiths Medical ASD Inc. | Smiths Medical became aware that certain Non Flow-Stop CADD(R) Medication Cassette Reservoirs may have been manufactured with an incorrect pressure plate. | Yes |
| Z-0062-2018 | For use with CADD(R) pumps (except CADD-Micro(TM), CADD-MS(R) 3 and CADD-TPN(R) pumps). | CADD(TM) Medication Cassette Reservoir | 2020-08-07 9:20:32 | Smiths Medical ASD Inc. | Smiths Medical became aware that certain Non Flow-Stop CADD(R) Medication Cassette Reservoirs may have been manufactured with an incorrect pressure plate. | No. Duplicate |
| Z-0060-2018 | For use with CADD(R) pumps (except CADD-Micro(TM), CADD-MS(R) 3 and CADD-TPN(R) pumps). | CADD(TM) Medication Cassette Reservoir | 2020-08-07 9:20:32 | Smiths Medical ASD Inc. | Smiths Medical became aware that certain Non Flow-Stop CADD(R) Medication Cassette Reservoirs may have been manufactured with an incorrect pressure plate. | No. Duplicate |
| Z-2260-2015 | MiniMed NGP 640G | Medtronic MiniMed | 2015-10-02 | Medtronic MiniMed Inc. | Medtronic MiniMed is recalling the MiniMed 620G and 640G insulin pumps because there are certain scenarios where the set Bolus screen will not timeout, which could cause confusion by showing a bolus amount that is no longer appropriate. | No |
| Z-1986-2013 | Medtronic MiniMed Paradigm Reservoirs  The model MMT-326A and MMT-332A are syringe type insulin reservoirs intended for use with Medtronic Paradigm series insulin infusion pumps. | Medtronic MiniMed Paradigm Reservoirs | 2014-01-16 | Medtronic MiniMed | Medtronic is recalling certain lots of Medtronic MiniMed Paradigm Reservoirs MMT-326A (1.8mL) and MMT-332A (3.0mL) used with Medtronic Paradigm insulin pumps because they may have increased risk for leaking. A leak in the reservoir may result in delivery of less insulin than intended. In addition, if there is a leaky reservoir and an insulin blockage occurs in the infusion set, the pump may not | Yes |
| Z-1491-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No |
| Z-1480-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1485-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1487-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1492-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1488-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1489-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1484-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1481-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1482-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1483-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1486-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1490-2011 | An infusion set for the subcutaneous infusion of insulin administered with micro dosage insulin pumps. | ACCU-CHEK FlexLink Plus | 2011-07-27 | Roche Insulin Delivery Systems Inc. | There is the potential to kink or bend the cannula when inserting the ACCU-CHEK FlexLink Plus infusion set. This can lead to under delivery and elevation of blood glucose levels. | No. Duplicate |
| Z-1641-2008 | The device is designed for subcutaneous, intravenous, epidural and intrathecal infusion of medication. | CADD-MS"3 Ambulatory Infusion Pumps | 2011-01-11 | Smiths Medical MD, Inc. | Smiths Medical has received reports that the device powers down without an alarm. Investigation concluded that if the battery cap is not fully tightened, the pump may power down and a brief "chirp" will sound. This may occur if the user has not sufficiently tightened the battery cap or if the battery cap is damaged. | Yes |
| Z-1621-2008 | Electromechanical pumps used for general drug delivery infusion therapies. Used mainly by home care patients but can also used in health care facilities. | CADD-MS¿ 3 Ambulatory Infusion Pump | 2011-12-17 | Smiths Medical MD, Inc. | Smiths Medical discovered an issue with a motor component in specific serial numbers of the CADD-MS ¿3 Ambulatory Infusion Pump. This issue affects motor operation and may cause an over-delivery of medication which could result in injury to the user. | Yes |
| Z-0876-2008 | Smiths CADD Medication Cassette Reservoirs with Clamp and Female Luer, 50 ml. | CADD Medication Cassette Reservoirs | 2011-01-11 | Smiths Medical MD, Inc. | Leakage associated with the CADD Medication Cassette Reservoirs for use with the CADD Ambulatory Infusion Pumps | Yes |
| Z-0877-2008 | Smiths CADD Medication Cassette Reservoirs with Clamp and Female Luer, 100 ml. | CADD Medication Cassette Reservoirs | 2011-01-11 | Smiths Medical MD, Inc. | Leakage associated with the CADD Medication Cassette Reservoirs for use with the CADD Ambulatory Infusion Pumps | Yes |
| Z-0878-2008 | Smiths CADD Yellow Medication Cassette Reservoirs with Clamp and Female Luer, 100 ml | CADD Medication Cassette Reservoirs | 2011-01-11 | Smiths Medical MD, Inc. | Leakage associated with the CADD Medication Cassette Reservoirs for use with the CADD Ambulatory Infusion Pumps | Yes |

* 1. FDA TPLC

Device problems

Table . TPLC Device Problems for FDA product code FRN

| **Device Problems** | **Number of events** | **Proportion of total (%)** | **Relevance for subject device** | **Cumulative relevance  (%)** |
| --- | --- | --- | --- | --- |
| Crack | 732323 | 40.8% | Yes | 40.8% |
| Corroded | 203951 | 11.4% | Yes | 52.1% |
| Break | 132449 | 7.4% | Yes | 59.5% |
| Device Displays Incorrect Message | 106449 | 5.9% | Yes | 65.4% |
| Display Difficult to Read | 90134 | 5.0% | Yes | 70.4% |
| Device Sensing Problem | 53212 | 3.0% | Yes | 73.4% |
| Failure to Read Input Signal | 52621 | 2.9% | Yes | 76.3% |
| Device Alarm System | 35199 | 2.0% | Yes | 78.3% |
| Contamination | 33019 | 1.8% | Yes | 80.1% |
| No Apparent Adverse Event | 23721 | 1.3% | N/A | 80.1% |
| Physical Resistance/Sticking | 20136 | 1.1% | No | 80.1% |
| Display or Visual Feedback Problem | 18680 | 1.0% | Yes | 81.2% |
| Appropriate Term/Code Not Available | 16587 | 0.9% | N/A | 81.2% |
| Failure to Calibrate | 15797 | 0.9% | Yes | 82.0% |
| Battery Problem | 15422 | 0.9% | Yes | 82.9% |
| Circuit Failure | 14397 | 0.8% | Yes | 83.7% |
| Electrical /Electronic Property Problem | 14209 | 0.8% | Yes | 84.5% |
| Insufficient Information | 14021 | 0.8% | N/A | 84.5% |
| No Display/Image | 12353 | 0.7% | Yes | 85.2% |
| Excess Flow or Over-Infusion | 11562 | 0.6% | Yes | 85.8% |
| Failure to Align | 10500 | 0.6% | No | 85.8% |
| Insufficient Flow or Under Infusion | 9873 | 0.5% | Yes | 86.4% |
| Premature Discharge of Battery | 9833 | 0.5% | Yes | 86.9% |
| False Alarm | 9762 | 0.5% | Yes | 87.5% |
| Computer Software Problem | 8716 | 0.5% | Yes | 87.9% |
| Communication or Transmission Problem | 8378 | 0.5% | Yes | 88.4% |
| Misassembled | 7612 | 0.4% | Yes | 88.8% |
| Air Leak | 7221 | 0.4% | Yes | 89.2% |
| Failure to Sense | 7138 | 0.4% | Yes | 89.6% |
| Protective Measures Problem | 6940 | 0.4% | Yes | 90.0% |
| Nonstandard Device | 6575 | 0.4% | Yes | 90.4% |
| Occlusion Within Device | 5705 | 0.3% | Yes | 90.7% |
| Improper Flow or Infusion | 5684 | 0.3% | Yes | 91.0% |
| Deformation Due to Compressive Stress | 5494 | 0.3% | Yes | 91.3% |
| Device Operates Differently Than Expected | 5488 | 0.3% | Yes | 91.6% |
| Naturally Worn | 5484 | 0.3% | Yes | 91.9% |
| Fluid/Blood Leak | 5328 | 0.3% | Yes | 92.2% |
| Mechanics Altered | 5315 | 0.3% | Yes | 92.5% |
| Peeled/Delaminated | 5032 | 0.3% | Yes | 92.8% |
| Device Contamination with Chemical or Other Material | 4686 | 0.3% | Yes | 93.1% |
| Infusion or Flow Problem | 4457 | 0.2% | Yes | 93.3% |
| Application Program Freezes, Becomes Nonfunctional | 4409 | 0.2% | Yes | 93.6% |
| Inaccurate Delivery | 4353 | 0.2% | Yes | 93.8% |
| Obstruction of Flow | 4317 | 0.2% | Yes | 94.0% |
| Failure to Deliver | 4247 | 0.2% | Yes | 94.3% |
| Failure to Power Up | 3858 | 0.2% | Yes | 94.5% |
| Output Problem | 3820 | 0.2% | Yes | 94.7% |
| Mechanical Problem | 3396 | 0.2% | Yes | 94.9% |
| Defective Alarm | 3316 | 0.2% | Yes | 95.1% |
| Calibration Problem | 3301 | 0.2% | Yes | 95.3% |
| **Total** | **1796480** | **100%** | - | **95.3%** |

Patient Problems

Table . TPLC Patient Problems for FDA product code FRN

| **Patient Problems** | **Number of events** | **Proportion of total (%)** | **Relevance for subject device** | **Cumulative relevance  (%)** |
| --- | --- | --- | --- | --- |
| Insufficient Information | 651566 | 41.1% | N/A | - |
| No Clinical Signs, Symptoms or Conditions | 615226 | 38.8% | N/A | - |
| No Patient Involvement | 148810 | 9.4% | N/A | - |
| No Known Impact Or Consequence To Patient | 93648 | 5.9% | N/A | - |
| No Consequences Or Impact To Patient | 30183 | 1.9% | N/A | - |
| Hyperglycemia | 22099 | 1.4% | Yes | 1.4% |
| No Information | 8881 | 0.6% | N/A | - |
| Hypoglycemia | 4785 | 0.3% | Yes | 1.7% |
| Low Blood Pressure/ Hypotension | 1390 | 0.1% | Yes | 1.8% |
| Diabetic Ketoacidosis | 1003 | 0.1% | No | - |
| Nausea | 614 | 0.0% | Yes | 1.9% |
| Death | 565 | 0.0% | Yes | 1.9% |
| Vomiting | 515 | 0.0% | Yes | 2.0% |
| Underdose | 478 | 0.0% | Yes | 2.0% |
| Overdose | 417 | 0.0% | Yes | 2.0% |
| High Blood Pressure/ Hypertension | 394 | 0.0% | Yes | 2.0% |
| No Code Available | 327 | 0.0% | N/A | - |
| Cardiac Arrest | 320 | 0.0% | Yes | 2.1% |
| Aneurysm | 301 | 0.0% | No | - |
| Loss of consciousness | 284 | 0.0% | Yes | 2.1% |
| Dyspnea | 279 | 0.0% | No | - |
| Not Applicable | 266 | 0.0% | N/A | - |
| Headache | 256 | 0.0% | Yes | 2.1% |
| Pain | 256 | 0.0% | Yes | 2.1% |
| Abdominal Pain | 205 | 0.0% | Yes | 2.1% |
| Blood Loss | 185 | 0.0% | No | - |
| Bradycardia | 163 | 0.0% | Yes | 2.1% |
| Therapeutic Response, Increased | 160 | 0.0% | No | - |
| Appropriate Clinical Signs, Symptoms, Conditions Term / Code Not Available | 159 | 0.0% | N/A | 2.1% |
| Fatigue | 159 | 0.0% | Yes | 2.1% |
| Tachycardia | 152 | 0.0% | Yes | 2.1% |
| Dizziness | 134 | 0.0% | Yes | 2.2% |
| Polydipsia | 101 | 0.0% | Yes | 2.2% |
| Complaint, Ill-Defined | 95 | 0.0% | N/A | - |
| Chest Pain | 93 | 0.0% | Yes | 2.2% |
| Chemical Exposure | 88 | 0.0% | No | - |
| Confusion/ Disorientation | 85 | 0.0% | Yes | 2.2% |
| Therapeutic Response, Decreased | 84 | 0.0% | No | - |
| Low Oxygen Saturation | 84 | 0.0% | No | - |
| Diarrhea | 80 | 0.0% | Yes | 2.2% |
| Shaking/Tremors | 79 | 0.0% | Yes | 2.2% |
| Anxiety | 78 | 0.0% | Yes | 2.2% |
| Discomfort | 78 | 0.0% | Yes | 2.2% |
| Coma | 78 | 0.0% | Yes | 2.2% |
| Oversedation | 75 | 0.0% | No | - |
| Hemorrhage/Bleeding | 70 | 0.0% | No | - |
| Seizures | 66 | 0.0% | Yes | 2.2% |
| Unspecified Infection | 62 | 0.0% | Yes | 2.2% |
| Cardiopulmonary Arrest | 59 | 0.0% | No | - |
| Injury | 59 | 0.0% | Yes | 2.2% |
| **Total** | **1585594** | **100%** |  | **2.2%** |

* 1. FDA MAUDE

Deaths

**Table 28: Details on retrieved MAUDE reports on event type “Death”**

| **Report Number** | **Event Date** | **Manufacturer** | **Brand Name** | **Event text** |
| --- | --- | --- | --- | --- |
| 3019004087-2024-00375 | 2024-07-08 4:00:00 | BETA BIONICS | ILET BIONIC PANCREAS | Event description: on 7/30/24 a beta bionics clinical diabetes specialist (cds) became aware that an ilet user had passed away. The date of death was not initially reported but is estimated to have occurred on (b)(6) 2024. At the time of this report, attempts by beta bionics to determine if the user was on the ilet at the time of the event as well as cause of death have been unsuccessful. The cds did report the user was 65 years old and had and was receiving treatment for advanced breast cancer with liver and pancreas metastases.  Manufacturer narrative: no product was returned for evaluation. Data uploads from the ilet were not completed after (b)(6) 2024, prior to the presumed event date; cgm glucose data were therefore not available to confirm the event, and ilet performance during the event could not be evaluated. No product performance issues can be identified. If the product is received at a later date, or the ilet data is uploaded, the complaint will be reopened and investigated accordingly. The device history record (dhr) review was completed, and this device passed all manufacturing release criteria for distribution. There were no issues identified that would have impacted this event. Review of the available device data showed the ilet was operating as intended at that time. Without more specific information including the event date, cause of death, and if the user was wearing the ilet at the time, and up to date device data, the performance of the device during this event cannot be evaluated and the cause of the event cannot be determined. It is likely the user's death was related to their cancer diagnosis. |
| 3019004087-2024-00198 | 2024-05-05 4:00:00 | BETA BIONICS | ILET BIONIC PANCREAS | Event description: on 5/14/24 a beta bionics clinical diabetes specialist (cds) was notified that an ilet user had passed away on (b)(6) 2024. The user's family notified the cds that the user died in her sleep and that the user's blood glucose (bg) levels at the time were unknown. The user's ilet mobile app was never activated. As a result, the ilet data reports were not accessible. Multiple attempts by beta bionics to have the ilet mobile app activated by the user's family have been unsuccessful. At the time of this report the ilet has not been returned to beta bionics.  Manufacturer narrative: no product was returned for evaluation. Ilet device logs only contain a record of the ilet being paired to the beta bionics employee's smartphone app and the ilet's software update being completed. There is no record of the device being paired to the user's app, being initialized, or dosing any insulin, and therefore no data available to review on the reported event date of 5/5/24. Notes in the user's record indicate the user completed ilet training on (b)(6) 2024 and a follow-up visit on (b)(6) 2024, where it was documented that the user was doing well. Without device data from the reported event date, it is not possible to determine if the user was still wearing the ilet on the day of their passing, (b)(6) 2024. No product performance issues can be identified. If the product is received at a later date, or the ilet data is uploaded, the complaint will be reopened and investigated accordingly. The device history record (dhr) review was completed, and this device passed all manufacturing release criteria for distribution. There were no issues identified that would have impacted this event. Without device data from the date of the event, performance of the ilet during the event cannot be assessed and without any additional information from the user's next of kin, a cause of the event cannot be determined. Review of the case notes showed the user was 70 years old and had several cardiometabolic risk factors that may have contributed to their death. |
| 3019004087-2024-00086 | 2024-03-22 4:00:00 | BETA BIONICS | ILET BIONIC PANCREAS | Event description: on 3/22/24 a beta bionics clinical diabetes specialist (cds) was notified by an assisted living facility that an ilet user was found deceased that morning. The user was still wearing the ilet at the time of their death. The user was trained on 3/8/2024. The cds followed-up with the user on 3/18/2024. The user stated she would like additional training and support. Additional follow up with the assisted living director revealed that the clinic staff at the assisted living had been supporting the user with completing ilet tasks including changing the insulin cartridge, infusion set and cgm sensor. They would also help the user respond to alarms. The cds notified the user's hcp about their request for additional training. The cds expressed concern regarding the user's inability to independently fill the insulin cartridges, change her infusion site and cgm sensor as well as respond to alarms, especially overnight. The cds has discussed the use of the fiasp pumpcart (insulin aspart in 1.6 ml pre-filled cartridge) and also recommended switching the user to the contact detach infusion set (steel cannula). When the cds contacted assisted living facility and hcp to coordinate additional training with clinic staff and the user, she was informed they had been found deceased. The assisted living director reported that the user had a history of poor glucose control prior to using the ilet and also had several serious medical conditions. The ilet was prescribed to help the user achieve better glucose control, which she believed it did. Prior to this event the user did have a previous episode where the ilet ran out of insulin on (b)(6) 2024 and the user had to ask the clinic staff for help determining the cause of why her ilet was alarming. The day prior (3/21/2024) to the user's death, the user was observed going about her usual daily activities including eating lunch in the cafeteria, circulating in the common areas and playing games late into the evening with fellow residents. She was noted to be in good spirits. At 2:00am on 3/22/2024, staff checked in on the user and she was noted to be sleeping in her recliner and chose not to disturb her. The next morning around 10:00am, the user was found deceased. The cause of death was not determined as an autopsy was declined per the user's previously expressed wishes.  Manufacturer narrative: at the time of this report no product was returned for evaluation. The ilet logs were reviewed by beta bionics failure investigation department. No instances of malfunction alerts were found in the device engineering logs. No factory reset was found in the logs. Audio setting and all cgm alerts were not changed from factory defaults (all on/high). Body weight was not changed after initial setup on (b)(6) 2024. Unless otherwise stated, no motor errors were seen to indicate inaccurate dosing relative to delivery requests for insulin. Logs contain no instances of meal bolus requests being made. All insulin requests in this log review are basal or correction requests made by the ilet. Review of the ilet report shows a prolonged period of hyperglycemia on (b)(6) 2024 that continued into the morning hours on (b)(6) 2024. On (b)(6) 2024, the cgm glucose rises above 180 mg/dl at 12:13pm and is above 300 mg/dl by 2:03pm. The cgm glucose remains above 300 mg/dl for 5 hours and is above 400 mg/dl by 7:00pm and remains above 400 mg/dl until the morning on (b)(6) 2024 when the data ends. The ilet is shown dosing insulin appropriately in response to the cgm glucose until dosing stops at 3:08pm on (b)(6) 2024, when the cartridge is empty, and does not resume. The cgm does not report glucose data after 2:58am on (b)(6) 2024 and the device is powered off before 9:00am on (b)(6) 2024. No evidence of device malfunction was found through the engineering logs. The ilet had triggered warning alerts for low insulin before triggering the alert for empty insulin cartridge the afternoon on (b)(6) 2024 prior to the high glucose events (cgm glucose over 300mg/dl). None of the alerts were ever acknowledged by the user. The cartridge is never replaced. Because of this the ilet was unable to dose insulin. During periods where cgm glucose was over 300mg/dl for at least 90 minutes, the high glucose alert was seen being triggered consistently. On (b)(6) 2024, alerts for cgm transmitter issues were triggered before the cgm transmitter failed altogether. After the cgm transmitter failure, the ilet entered bg-run mode but was unable provide basal insulin dosing as the cartridge was empty. The logs end at 6:38am on (b)(6) 2024. A similar pattern of prolonged hyperglycemia related to an empty insulin cartridge was noted in the ilet report and device logs on (b)(6) 2024. No product performance issues were identified. If the product is received at a later date, the complaint will be reopened and investigated accordingly. No anomalies were observed. The device history record (dhr) review was completed, and this device passed all manufacturing release criteria for distribution. There were no issues identified that would have impacted this event. Based on the review of the case notes, ilet report and device logs, it was determined that the ilet operated as intended. The assignable cause to the hyperglycemic event was failure to replace the insulin cartridge promptly when empty which resulted in several hours without insulin delivery. An assignable cause for death cannot be determined as an autopsy was not performed. The ilet device is in the process of being returned to beta bionics and if additional information about this event is obtained the complaint will be reopened. |
| 3012307300-2021-09555 | 2021-09-07 | SMITHS MEDICAL ASD, INC. | CADD-MS3 AMBULATORY INFUSION PUMP | Event description: the reporter (drug manufacturer) stated the prescribing pharmacy called to report a homecare patient expired. The patient was being treated with subcutaneous infusion of remodulin for treatment of pulmonary arterial hypertension. The reporter did not allege a problem with the drug or the device. The cause of death has not been provided at this time. Additional information will be requested regarding any product fault alleged, cause of death, patient's course of treatment and prognosis. A follow up mdr report will be filed if further information is provided or if device is returned for analysis. |
| 3016798778-2023-00060 | 2023-10-26 | MILLYARD ADVANCED MEDICAL PRODUCTS, LLC | REMUNITY PUMP FOR REMODULIN (TREPROSTINIL) INJECTION | Event description: an initial report of cardiac arrest was received by united therapeutics on 26-sep-2023 and forwarded to millyard advanced medical products, llc on 03-oct-2023. A follow up report from united therapeutics was received by millyard advanced medical products, llc on 13-oct-2023 in which it stated the patient was deceased. The patient was started on remodulin in (b)(6) 2023 using a different manufacturer's pump. The patient was switched to remunity therapy on an unreported date. On (b)(6) 2023, the patient experienced disease worsening including a large increase in bnp from their baseline. It was unclear whether there were alarms or any malfunction. A nurse from the physician's office reported to the specialty pharmacy on (b)(6) 2023 that their patient was currently hospitalized for cardiac arrest. The nurse stated the cardiac arrest was believed to be associated with the failure of her remunity pump. On an unreported date, the patient's disease progressed and the patient expired. The cause of death was pulmonary arterial hypertension. It is unknown if an autopsy was performed. No components or additional information associated with the reported event have been made available to the manufacturer for further evaluation despite multiple requests. |

Malfunctions

Table . Malfunctions in MAUDE database

| **Malfunctions** | **Number of malfunctions** | **Proportion of total (%)** | **Relevant for subject device** | **Cumulative relevance  (%)** |
| --- | --- | --- | --- | --- |
| Insufficient Information / Adverse Event Without Identified Device or Use Problem | 80 | 29.3% | No | - |
| Device Operates Differently Than Expected | 29 | 10.6% | Yes | 10.6% |
| Device Display Problems | 27 | 9.9% | Yes | 20.5% |
| Device Contamination | 27 | 9.9% | Yes | 30.4% |
| Fail-Safe Problem | 22 | 8.1% | Yes | 38.5% |
| Inaccurate Dispensing/Delivery or Pumping Problem | 17 | 6.2% | Yes | 44.7% |
| Mechanical Problem | 16 | 5.9% | Yes | 50.5% |
| Insufficient Flow or Under Infusion | 11 | 4.0% | Yes | 54.6% |
| Defective Alarm or Volume Accuracy Problem | 10 | 3.7% | Yes | 58.2% |
| Use of Device Problem | 9 | 3.3% | Yes | 61.5% |
| Delivery System Failure | 6 | 2.2% | Yes | 63.7% |
| Break or Fluid/Blood Leak | 4 | 1.5% | Yes | 65.2% |
| Device Displays Incorrect Message | 3 | 1.1% | Yes | 66.3% |
| Connection Problem; Wireless Communication Problem | 3 | 1.1% | Yes | 67.4% |
| Loss of Power | 2 | 0.7% | Yes | 68.1% |
| Application Program Problem or Battery Problem | 2 | 0.7% | Yes | 68.9% |
| Failure to Deliver | 2 | 0.7% | Yes | 69.6% |
| Reset Problem | 1 | 0.4% | Yes | 70.0% |
| Communication or Transmission Problem | 1 | 0.4% | Yes | 70.3% |
| Optical Distortion | 1 | 0.4% | No | 70.3% |
| **Total** | **273** | **100%** | **-** | **70.3%** |

Injuries

Table . Injuries and associated device problems in MAUDE database

| **Patient Problem** | **Associated Device Problem(s)** | **Number of Patient Problems** | **Proportion of total (%)** | **Relevant** | **Cumulative relevance  (%)** |
| --- | --- | --- | --- | --- | --- |
| Hypoglycemia\* & Loss of Consciousness and/or Convulsions and Seizures | Adverse Event Without Identified Device or Use Problem | 114 | 24.4% | Yes | 24.4% |
| Calibration Problem |
| Insufficient Information |
| Use of Device Problem |
| Hypoglycemia\* | Adverse Event Without Identified Device or Use Problem | 110 | 23.6% | Yes | 48.0% |
| Calibration Problem |
| Excess Flow or Over-Infusion |
| Insufficient Information |
| Obstruction of Flow |
| Use of Device Problem |
| Hyperglycemia\*\* & Diabetic Ketoacidosis | Adverse Event Without Identified Device or Use Problem | 88 | 18.8% | No | - |
| Calibration Problem |
| Device Displays Incorrect Message |
| Fluid/Blood Leak |
| Insufficient Information |
| Obstruction of Flow |
| Use of Device Problem |
| Hyperglycemia\*\* | Adverse Event Without Identified Device or Use Problem | 58 | 12.4% | Yes | 60.4% |
| Fluid/Blood Leak |
| Insufficient Information |
| Obstruction of Flow |
| Use of Device Problem |
| No Known Impact Or Consequence To Patient; Insufficient Information; No Clinical Signs, Symptoms or Conditions; Appropriate Clinical Signs, Symptoms, Conditions Term / Code Not Available | Break; Poor Quality Image | 24 | 5.1% | No | - |
| Compatibility Problem |
| Packaging Problem; Physical Property Issue |
| Defective Device; Infusion or Flow Problem |
| Break |
| Failure to Charge; Environmental Compatibility Problem |
| Use of Device Problem |
| Aneurysm | Insufficient Flow or Under Infusion | 11 | 2.4% | No | - |
| Adverse Event Without Identified Device or Use Problem |
| Fail-Safe Problem |
| Device Operational Issue |
| Delivery System Failure |
| Leak/Splash |
| Dyspnea/Hypoxia | Fluid/Blood Leak | 8 | 1.7% | No | - |
| No Audible Alarm |
| Pumping Problem |
| Detachment of Device or Device Component |
| Communication or Transmission Problem |
| Insufficient Information |
| Hyperglycemia\*\* & Loss of consciousness and/or Convulsions | Fluid/Blood Leak | 7 | 1.5% | Yes | 61.9% |
| Insufficient Information |
| Obstruction of Flow |
| Use of Device Problem |
| Hypoglycemia\* & Fainting & Bone Fracture(s) or Laceration(s) or Head Injury | Use of Device Problem | 6 | 1.3% | Yes | 63.2% |
| Diarrhea; Nausea; Vomiting; Dizziness; Diaphoresis | Defective Device | 6 | 1.3% | Yes | 64.5% |
| Pumping Stopped |
| Fluid/Blood Leak |
| Product Quality Problem |
| Device Displays Incorrect Message |
| Hyperglycemia\*\* & Skin Infection/Inflammation or Sepsis | Obstruction of Flow | 5 | 1.1% | Yes | 65.6% |
| Use of Device Problem |
| Use of Device Problem; Obstruction of Flow; Intermittent Communication Failure |
| Loss of consciousness; Respiratory Failure | Insufficient Information | 5 | 1.1% | Yes | 66.7% |
| Diabetic Ketoacidosis | Failure to Calibrate | 4 | 0.9% | No | - |
| Insufficient Information |
| Pulmonary Hypertension; Pulmonary Dysfunction | Patient Device Interaction Problem | 4 | 0.9% | No | - |
| Insufficient Information |
| Erythema; Swelling/ Edema; hypervolemia | Infusion or Flow Problem | 4 | 0.9% | Yes | 67.6% |
| Headache; Pain | Patient Device Interaction Problem | 3 | 0.6% | Yes | 68.2% |
| Unspecified Infection | N/A | 2 | 0.4% | Yes | 68.6% |
| Hyperglycemia\*\* / Hypoglycemia\* | Failure to Deliver; Communication or Transmission Problem; Therapeutic or Diagnostic Output Failure | 2 | 0.4% | Yes | 69% |
| Use of Device Problem |
| Hypoglycemia\* & Memory Loss/Impairment | Use of Device Problem | 1 | 0.2% | Yes | 69.2% |
| Hypoglycemia\* & Coma | Insufficient Information | 1 | 0.2% | Yes | 69.4% |
| Bruise/Contusion | N/A | 1 | 0.2% | Yes | 69.6% |
| Presyncope; Renal Impairment; Cramp(s) /Muscle Spasm(s) | Insufficient Information | 1 | 0.2% | No | - |
| Electrolyte Imbalance | N/A | 1 | 0.2% | No | - |
| Sleep Dysfunction | Low Audible Alarm; Incorrect Or Inadequate Test Results | 1 | 0.2% | No | - |
| **Grand Total** | | **416** | **100.0%** | - | **69.6%** |
| \* Sometimes accompanied by symptoms like confusion, disorientation, dizziness, presyncope, fatigue, tremors, nausea, vomiting, hot flashes, muscle weakness, blurred vision, discomfort, and pain/headache.  \*\* Sometimes accompanied by symptoms like nausea, vomiting, dizziness, polydipsia, headache, abdominal pain, fatigue, presyncope, discomfort, muscle weakness, frequent urination, malaise, hyperventilation, pain, dehydration, emotional/cognitive changes, tremors, dysphasia, dry mouth, and decreased appetite. | | | | | |