EVALUATION OF THE VARIABILITY IN THE RATES OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS ASSOCIATED TO INSULIN PUMPS IN CONTROLLED CLINICAL TRIALS VS POST APPROVAL OBSERVATIONAL STUDIES.

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Abstract:

Background – Diabetes is on the rise (1). People with type 1 diabetes have two primary options, multiple daily injections (MDI) or the use of an insulin infusion pump/insulin pump. Insulin pumps are the medical device with the most adverse events among registered devices (2) and their use is on the rise (3). Since these medical devices pass through a rigorous regulatory process, why is there such a discrepancy? Devices get approved based upon pre-marketing clinical trials and post-marketing clinical trials should reflect data used to approve it. This study is to perform a systematic literature review comparing the adverse events and serious adverse events between pre-marketing clinical trials and post-marketing clinical trials.

Hypothesis - Pre-marketing and post-marketing clinical trial studies have a statistically different ratio of Adverse Events (AE) and Serious Adverse Events (SAE). ($\alpha < 0.05$)

Experimental approach – Data will be derived from published literature. Adverse events and serious adverse events will be collected and analyzed as a group and as subgroups of individual types of events. Data will be presented and compared in incidence per patient years accompanied by a 95% confidence interval.

Results – The data presented a high level of variability and no adverse event or serious adverse event demonstrated a statistically significant difference between pre-marketing and post-marketing clinical trials. The data did demonstrate clinically relevant trends that went in the opposite direction of the hypothesis. There were 3-fold more adverse events in the pre-marketing data. However, the all the serious adverse events and subgroup analysis of adverse

events in pediatrics data had clinically relevant trends that followed the hypothesis. It demonstrated a minimum of 1.5-fold increase in post-marketing clinical trials.
Conclusion – This study did not demonstrate any statistically significant difference between adverse event and serious adverse events obtained between pre-marketing and post-marketing clinical trials.

Résumé scientifique:

Contexte - Le diabète est en hausse (1). Les personnes atteintes de diabète de type 1 ont deux options principales, des injections quotidiennes multiples (MDI) ou l'utilisation d'une pompe à perfusion d'insuline / pompe à insuline. Les pompes à insuline sont le dispositif médical présentant le plus d'événements indésirables parmi les dispositif médical enregistre (2) et leur utilisation est en hausse (3). Puisque ces dispositifs médicaux passent par un processus réglementaire rigoureux, pourquoi y a-t-il une telle divergence? Cette étude consiste à effectuer une revue systématique de la littérature comparant les événements indésirables et les événements indésirables graves entre les essais cliniques pré-commercialisation et les essais cliniques post-commercialisation.

Hypothèse - Les études cliniques pré-commercialisation et post-commercialisation ont un ratio statistiquement différent d'événements indésirables et d'événements indésirables graves. (α <0,05)

Méthode - Les données seront tirées de la littérature publiée. Les événements indésirables et les événements indésirables graves seront collectés et analysés en tant que groupe et en tant que sous-groupes d'événements individuels. Les données seront présentées et comparées en incidence par année de patient accompagnées d'un intervalle de confiance à 95%.

Résultats - Les données ont présenté un niveau élevé de variabilité et aucun événement indésirable ou événement indésirable grave n'a démontré une différence statistiquement significative entre les essais cliniques pré-commercialisation et post-commercialisation. Les données ont démontré des tendances cliniquement pertinentes qui allaient dans la direction opposée de l'hypothèse. Il y avait 3 fois plus d'événements indésirables dans les données de pré-commercialisation. Cependant, l'ensemble des événements indésirables graves et l'analyse des sous-groupes d'événements indésirables dans les données pédiatriques présentaient des tendances cliniquement pertinentes qui suivaient l'hypothèse. Il y avait 1.5 fois plus d'événements dans les essais cliniques post-commercialisation.

Conclusion - Cette étude n'a pas démontré de différences statistiquement significatives entre les événements indésirables et les événements indésirables graves entre les essais cliniques pré-commercialisation et post-commercialisation.

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Finally, my three daughters and girlfriend, Ginger, Summer, Smiley and Melanie, who supported me not just academically but personally. Your patience and understanding was unbelievable.

Contribution to original knowledge:

Contribution to original knowledge is limited in terms of innovative and novel, as the hypothesis failed. However, this study does eliminate the research question: is there a difference in adverse events and serious adverse events incidence between pre-marketing and post-

marketing clinical trials? Making way to new research questions and hypothesis to be researched.

Contribution of Authors:

This entire paper was generated and written by Richard Lebrun Trachy and reviewed by Dr. John S. Sampalis.

Introduction:

According to the Centers for Disease Control and Prevention (CDC) in the United States the prevalence and incidence of diabetes and prediabetes is on the rise (1). The Prevalence of Diabetes is currently demonstrating a significantly increasing trend among adults aged 18 years or older. The Newly Diagnosed Diabetes, i.e. Incidence of Diabetes, is also on the rise, with the most significant trends in children. Type 1 diabetes children and adolescents younger than age 20 years are on the rise and type 2 diabetes for children and adolescents age 10 to 19 years are on the rise. This rising trend in prevalence and incidence is increasing the risk factors for complications, acute and long-term complications, deaths and costs (1).

Diabetes can arise in two main form; Type 1 diabetes and type 2 diabetes. Type 1 diabetes is an autoimmune reaction that results in the inability to produce insulin and accounts for 5 to 10 percent of the total diabetes cases (1). Type 2 diabetes the body does produce insulin, but the body fails to use it properly. Type 2 diabetes accounts for 90 to 95 percent of the total diabetes

cases (1). Diabetes is diagnosed with the HbA1c test, which measures the percentage of red blood cells that have sugar coated hemoglobin. A normal HbA1c is less than 5.7%, prediabetes has a HbA1C between 5.7% to 6.4% and diabetes has a HbA1C above 6.4%. the higher the HbA1c levels the more at risk you are for having a diabetic related complications (4). Insulin is produced by the pancreas and released into the bloodstream when there is a high blood glucose level (>140mg/dL), also referred to Hyperglycemia. The Insulin then stimulates the liver to convert the glucose from the bloodstream to glycogen. The glycogen is stored as energy for when the body will need a quick boost of energy. This process returns the blood glucose level to normal, between 90mg/dL to 100 mg/dL. When the blood glucose levels are low (<70 mg/dL), also referred to hypoglycemia, the pancreas will produce glucagon and release it into the bloodstream. The Glucagon then stimulates the liver to convert glycogen to glucose and increase the blood glucose levels back to normal. This study will focus on type 1.

The primary adverse events associated to type 1 diabetes are hypoglycemia, severe hypoglycemia, hyperglycemia, diabetic ketoacidosis and Infections. These adverse events can lead to other more severe adverse events such as major cardiovascular disease, vision loss, kidney disease, coma and death.

Hypoglycemia and severe hypoglycemia occur when blood glucose is too low. Early symptoms of Hypoglycemia trigger the production of epinephrine. The early symptoms are a thumping heart and sweating. Moderate symptoms are blurred vision, confusion and trouble

concentrating. Severe symptoms are seizure, coma and death. The severe cases occur as the glucose is so low that the brain itself starves.

Hyperglycemia occurs when the blood glucose is too high. The sugar-coated hemoglobin slows the flow resulting in higher blood pressure. Counting Carbohydrates is a fundamental component for preventing Hyperglycemia. Two hours after a meal hyperglycemia of 180 mg/dL is frequently observed in a diabetic patient. A non-diabetic person would have a blood sugar level of 140 mg/dL. Overeating, poor diet or miscounting could lead to more severe complications. Stress and illness also play a role in hyperglycemia as both naturally reduce insulin and increase the blood-glucose level. Early symptom is more frequent urinations. Moderate symptoms are sweet smelling and tasting urine. Hyperglycemia may result in damaged nerves, blood vessels and organs.

Diabetic ketoacidosis is the accumulation of ketones in the blood. This occurs when you have a prolonged hyperglycemia or severe spike in hyperglycemia. The body needs energy quickly and breaks down fat instead glycogen. The absence of insulin results in glucose unable to be converted to glycogen by the liver. The converting of fat to energy produces ketones in the blood. The kidneys try to eliminate the ketone, however if there are too many ketones it will poison the person. This leads to a diabetic coma and/or death.

Infections are very common for diabetic patients as the high blood glucose make the white blood cells slow. Body produces cortisol and adrenaline, both of which will affect the insulin

levels, further increasing the blood glucose levels. This hinders the healing any can lead to more serious adverse events, such as amputation and death.

In the past 25 years, patients with type 1 diabetes can check their blood glucose levels multiple times a day and perform multiple daily injections (MDI) or seek treatment via insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII). The insulin pump therapy can also be coupled to a continuous glucose monitors (CGM).

An insulin infusion pump is a small, computerized devices that replicates the way the human pancreas Delivers small doses of short acting insulin continuously (basal rate) and delivers variable amounts of insulin when a meal is eaten (bolus).

The basic insulin pumps consist of primarily three 3 parts.

- The programable electronic device including an electronic processor, a dose controlling worm drive, user interface and battery.
- The primary pump device with a small container that hold the insulin.
- An infusion set consisting of a cannula and tubing, generally replaced every 2 to 3 days. The tubing can be 30cm, 60cm, 80cm, 110cm in length.
    - Some insulin pumps have no tubing (Omnipod®) and pump is directly attached to cannula.

The entire device is about the size of a small smart phone or deck of cards. It delivers insulin through a catheter, connected to a thin cannula, placed into the layer of fat under your skin, typically around your stomach area. It contains a reservoir or cartridge that holds the insulin. There is a microcomputer built into the pump so that it may be programmed to deliver insulin when needed. A very small motor inside the pump delivers the insulin via a screw gear and worm drive. The screw gear and worm drive allow a very small and precise volume to be dispensed. Insulin is transferred from the reservoir/cartridge to a flexible tubing fitted with either a small fixed metal cannula or a small flexible Teflon cannula. The flexible Teflon cannula is inserted with a removable fixed needle. Both types of cannula are inserted subcutaneously. The cannula is held in place by a special adhesive tape. The flexible tubing and cannula are generally referred to as the infusion set. The infusion site could be placed on the abdomen, thighs, buttocks, hips, upper arms and either side of the lower back. Preferably a site on the body with a good layer of fat under the skin. An insulin pump delivers insulin continuously, also known as basal dose, and on demand, also known as bolus dose, to account for carbohydrates in meals or high blood glucose levels.

The basal insulin is the insulin that your body needs continuously for its basic daily metabolism. It ensures that the blood glucose levels remain stable (90mg/dL to 100 mg/dL) in the absence of food. The pump delivers basal insulin automatically and continuously, generally every 3 minutes during the entire day. The basal rate is programmed in units per hour and can have many preprogrammed settings depending of the daily activities the Patient will perform. These preprogrammed rates are calculated by a diabetes educator or endocrinologist. A bolus is a

dose of insulin that is administered when requested. A bolus dose is manually requested by the patient and matches the amount of carbohydrates in a meal to be eaten. The exact amount is calculated by the pump's insulin-to-carbohydrate ratio set by the patient's diabetes educator or endocrinologist. The ideal amount of insulin delivered as a bolus dose should return the blood glucose to the desired range within two to three hours of eating. Hence, the primary benefit of insulin pump therapy is its flexible basal and bolus dosing that can be personalized to reflect the patients' personal requirements, allows the patient to have multiple settings of different basal rates to adjust to everyday life and bolus doses can be administered depending on the carbohydrates in the diet. Insulin delivery via a pump is more consistent and precise than multiple daily injections by syringe or pen (6).

Technology has progressed significantly the advancement of insulin pumps. They have become more efficient, reliable (5), user-friendly and smaller. Modern pumps are the size of a deck of card and can weigh less than 115 grams.

These technological advancements include;

1) Insulin pumps with integrated Bolus calculator. An insulin-to-carbohydrate ratio such as 1 unit of insulin per 15 g of carbohydrate is programmed into the pump. The patient programs the number of carbs that will be eaten, and the pump will administer the bolus insulin.
2) Insulin Pumps with a programable insulin correction. Where the patient tests their blood sugar level, and the glucose level is corrected automatically with 1 unit of insulin

for every 50 mg/dL glucose >100 mg/dL. Taking into consideration any recent adjust to the bolus amount based the amount of insulin still in the patient's system from a previous bolus.

3) Insulin Pumps with alarms can be set to remind the patient if a bolus was missed, if a daily glucose test was missed, if the battery is low, or if any other personalized patient parameters fail.
4) Insulin pumps with a wireless glucose meter.
    - Some insulin pumps facilitate direct communication between the patient's glucose meter and insulin pump. This allows the pump to use glucose measurements to:
        - communicate glucose readings to the pump
        - calculate boluses
        - used to control the pump itself
5) Continuous Glucose Monitoring (CGM) and a closed loop system/artificial pancreas

A continuous glucose monitoring system coupled to an insulin pumps is a way of measuring glucose levels continuously and predicting patterns and trends in glucose levels throughout the day and night. A continuous glucose monitoring system is a separate sensor inserted subcutaneously at a different location from the pump. The continuous glucose monitor measures the level of glucose in the interstitial fluid in real time, once every few minutes. The subcutaneous fluid reflects the glucose levels in the serum. A wireless communication occurs between the continuous glucose monitor and the insulin pump. The continuous glucose monitoring system has a sensor to monitor glucose levels and a transmitter to communicate

the information to the insulin pump via radio frequency. Resulting in a real time display of the blood glucose levels and its rate of change. Alarms can be triggered if hyperglycemic or hypoglycemic reading are obtained.

In the last 5 years technological advancements have introduced electronics with complex algorithms to maintain insulin bolus doses needed to obtain a desired pre-set range of blood glucose levels by the continuous glucose monitor. This technology is known as a closed loop system or an artificial pancreas. It automatically senses blood glucose level and adjusts insulin dosing accordingly. the closed-loop insulin delivery system relies on the continuous glucose monitor. Closed-loop systems were shown to reduce the risk of nocturnal hypoglycemia in children and adolescents with type 1 diabetes and improved overall glycemic control (6, 7).

Insulin pumps linked to personal computers and electronic devices can be used to manage the pump, analyze the pump data, assist physician to manage diabetes remotely.

Insulin pumps are used to avoid or prevent complications associated with insulin injections, such as frequent hyperglycemia or hypoglycemia. However, this is not a full proof method and patients still become hyperglycemic or hypoglycemic when using an insulin pump. Insulin pumps have their own complications.

Multiple studies have demonstrated that insulin infusion pumps decrease the occurrences of severe hypoglycemic adverse events when compared to multiple daily insulin injections. This

has been demonstrated in randomized control clinical trials (8-10). The elimination of using long- or intermediate-acting insulins coupled to predicting calorie predictions is the cause of this reduction. Intermediate-acting insulin is a potential issue overnight, as its effectiveness peaks when the patient is sleeping and not eating.

Hypoglycemia may still occur on an insulin pump. If the patient is calculating too many carbohydrates and gives too much bolus or the wrong preprogrammed basal rate is selected. In addition to human error, there may be a device malfunction the administers too much insulin to the patient, also known as pump runaway.

Studies have also shown improved glycemic control and reductions in Hyperglycemia and diabetic ketoacidosis for patients using insulin pumps compared with patients using multiple daily insulin injections (10, 11). Predawn and nocturnal glycemic control is better for insulin pump therapy, as hourly preprogrammed basal rate changes facilitated by the insulin pump assist in responding to prebreakfast blood glucose rise that are not easily assessed with injection therapy (12).

Even if insulin pump therapy has shown an improvement, they also have the occurrence of adverse events such as Hyperglycemia and DKA. This can occur due to human error or by a device malfunction. Using the infusion set greater than the recommended time, human negligence, creating occlusions in the cannula (13).The most common device related adverse

events are: depleted insulin, dead battery, occlusion of the cannula, pinched tubing or pump failure.

Another source of complication is irritation and infection at the infusion site. Manufacturers of insulin pumps state to change infusion sets and infusion sites every 2 to 3 days. This is recommended as a prevention measure to avoid unnecessary irritation or infection at the infusion site. Wearing an infusion set for an extended period increases the risk of an adverse event, such as; infection at the site, contact dermatitis, swelling and erythema at the infusion site, cannula occlusions, and hyperglycemia (13).

A newer complication that is starting to arise is insulin pump discontinuation, but is still rare (14). The reasons reported for discontinuing insulin pump therapy included interference with lifestyle, lack of improvement in glycemic control, discomfort/infection at the infusion site and social/psychological factors (15).

The primary insulin pump manufactures approved in Canada are Medtronic, Omnipod, Tandem, Ypsopump and Accu-Check. Medtronic, Omnipod and Tandem are approved in the United States of America.

It is very important to note that the acquisition and use of all these pumps comes with a very elaborate and complete training guide, video tutorials and telephone hotline. Their trainings cover filling the reservoir, priming the pump tubing, selecting an infusion site, changing an

infusion set, disconnecting the device, programming and calculating the basal and bolus doses, trouble shooting, backup plan and diabetic ketoacidosis prevention.

Background:

In an article published by the journal of Diabetes Care, Louisa van den Boom 2019 (3), they investigated progressive trends and current use of insulin pump therapy, with and without the use of a continuous glucose monitor. Their research concluded that the percentage of people who have adopted the use of an insulin pump therapy increased from 1% in 1995 to 53% in 2017. The table below demonstrates the increasing percentage as the age group gets younger (3).

Table 1. Percentage that use insulin pump per age group. Data from Vanden Boom 2019 (3)

Age-group	Percentage that use insulin pump therapy
Adults	37%
Adolescents aged ≥15	46%
Adolescents aged <15 years	56%
Children	74%
Preschoolers	92%

Insulin pump clinical trials in humans' have been performed since the later part of the 1970s (4). Clinical trials for Medical device involve only patients with the condition which the device is designed to treat. Exploratory or Feasibility Study are performed to establish preliminary safety and effectiveness of the device. Then Pivotal studies are performed to demonstrate the device is safe and effective and gain regulatory approval to market the device. Post-market Study are performed to better understand long-term effectiveness of the device and potential adverse

events associated with the use of the device. Bringing a medical device to market takes an average of 3 to 7 years, compared with an average of 12 years for drugs. The FDA classifies insulin infusion pumps as class II device for the basic pumps and a class III devices for the predefined diabetes management system. Class III is the highest risk attributed by the FDA. Health Canada classifies insulin infusion pumps as class II or III for the central primary insulin pump device and Class IV device for the complete diabetes management system. Class IV is the highest risk attributed by Health Canada.

In June of 1993, the food and drug administration (FDA) of the united states created the Manufacturer and User Facility Device Experience (MAUDE) data. The purpose of MAUDE was to receive and collect adverse event data files for medical devices. These data files submitted to the FDA were submitted as voluntary reports. In August of 1996 the reports for adverse events involving medical devices we now required to be submitted by the manufacturers. The FDA receives several hundred thousand medical device reports on a yearly basis (2). These medical device reports are of suspected device-associated deaths, serious injuries and malfunctions. The medical device reports are also used to monitor performance, detect potential safety issues and assist in evaluating the benefit-risk assessments of the devices. The MAUDE database contains reports submitted by manufacturers, importers, device user facilities, health care professionals, patients and consumers. The MAUDE database is a great source of information but remains unverified. This may lead to inaccurate and/or incomplete data. Due to this, the MAUDE database is not to be used as scientific statistical data.

According to the FDA's Manufacturing and Used Facility Device Experiment (MAUDE) there has been 695 self reported deaths and 46 550 injuries since it was created in 2010, for insulin infusion pumps (2). This is the highest among medical devices in the MAUDE database. It is important to note that even if the MAUDE database can not be used statistically for scientific purposes. It does confirm that there is a pool of real-world evidence pointing to a number of deaths, serious injury and malfunctions with insulin infusion pumps.

The 12th of February 2020, the insulin pump manufacturer Medtronic publicly announced it recalled two models of their MiniMed™ (Medtronic Inc. Minneapolis, Minnesota) insulin pumps due to 26 421 complaints and 2 175 injuries and 1 death (16). Medtronic privately started recalling their devices on the 21st of November 2019, over three months prior to the public announcement. The FDA identified this recall of the most serious type, a Class I recall. Since the use of these devices may cause serious injuries or death. The recall was sparked due to a missing or broken retainer ring in the insulin pump which helps to lock the insulin cartridge into place in the pump's reservoir compartment. A loose cartridge in the reservoir may administer too much or not enough insulin. This can result in hypoglycemia or hyperglycemia. Loss of consciousness, seizure, and death may incur from severe hyperglycemia. This recall was for 481 875 insulin pumps units (16).

Research Question

All the insulin pumps medical devices that are available to be purchased have been rigorously evaluated by multiple regulatory agencies around the globe. Why is there a significant amount

of complications and death associated to the Insulin pumps? Why is there a wide gap between early phase clinical trials and real-world data? The results from late phase /post-marketing studies are conducted in a real-world setting. Is there a gap in the regulatory process? Is there a possible gap is the clinical trial process? This research attempted to answer or shed light onto some of these questions.

There have been 48 Meta-Analysis performed for Insulin Pumps. Only 3 relate to adverse events. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis (17), Clinical review: insulin pump-associated adverse events in adults and children (18) and Drug-related risk of severe hypoglycaemia in observational studies: a systematic review and meta-analysis (19).
The first, Yeh et al. 2012, observes AE associated to various methods you can deliver Insulin and various methods of monitoring. The second, Czech et al. 2015, is a qualitative review.
The third, Ross et al. 2015, only looked at severe Hypoglycaemia and the associated risk.
This study was a novel study in the sense that this relationship has not been looked at.
Hypothesis - Pre-marketing and post-marketing clinical trial studies have a statistically different ratio of Adverse Events (AE) and Serious Adverse Events (SAE). ($\alpha < 0.05$)

Objective

The objective was to perform a literary search and meta-analysis. The primary aim was to investigate and quantify the adverse events and serious adverse events for Clinical trials conducted with Insulin pumps. Then use that data to compare the incidence of AE and SAE in

pre-marketing (phase I, II, III) clinical trials versus post-marketing (Phase IV) clinical trials. To subgroup and compare the incidence of specific AE and SAE of hypoglycemia, hyperglycemia, severe hypoglycemia, diabetic ketoacidosis and any other AE or SAE that has data that has a noticeable number of incidents. To demonstrate a statistically different outcome between pre- and post- marketing studies. ($\alpha < 0.05$). A secondary objective is to develop new research questions based on the outcome of the primary objectives.

Methods and Analysis

Data will be derived from published literature. This would be through an extensive search of PubMed, ScienceDirect, Google Scholar databases using the following key words: Insulin Pump, insulin infusion pump, adverse events, safety, efficacy, effectiveness, compliant, tolerability. Filters will be language and publications in the last 20 years. Randomized clinical trials and non-interventional observational studies will be included.

The search was performed online. Two criteria were selected in every search. The first was Insulin pump or insulin infusion pump. The second was adverse events, safety, efficacy, effectiveness, compliant or tolerability. That lead to 12 different searched on three scientific journal databases. The “title and abstract view” was selected to be able to read the overview of every article. Articles that involved random clinical trials or observational studies were further investigated to see if they reported the adverse events or serious adverse events. All articles that did report quantifiable data for the adverse events and serious adverse events were then catalogues in EndNote X9. EndNote X9, currently produced by Clarivate Analytics, is a

software used to manage references and bibliographies. The journal articles will be accessed through the McGill library.

Each source had to be published in a peer reviewed journal and was evaluated. Was the author an expert in the field? Was the author's data supported by empirical evidence? Was the author's data or perspective biased?

Once the articles were deemed acceptable. A working table on a Microsoft® Excel worksheet was created. This table kept track of the title, primary author, year of publication, electronic ID, clinical trial ID, pre or post marketing classification, duration of clinical trial, total number of subjects, number of cohorts, number of subjects in each cohort, number of insulin pump patients, number of patients that did not use an insulin pump, minimum age, maximum age, years with diabetes, years of experience with an insulin pump and all adverse events and serious adverse events individually organized by event.

The Identification of adverse events and serious adverse events will be identified as follows. An adverse event any untoward medical occurrence associated with the use of a drug or medical device in humans, whether or not considered drug related. A Serious adverse event is an adverse event that results in Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

A pre-marketing clinical trial in the context of this research, is a clinical trial performed using an insulin pump with or without an infusion set or a continuous glucose monitor with the aim of

demonstrating safety and efficacy in type 1 diabetes prior to its approval by the regulatory agency. A post marketing clinical trial in the context of this research, is a clinical trial performed using an insulin pump with or without an infusion set or a continuous glucose monitor with the aim of demonstrating safety and/or efficacy for type 1 diabetes in a different setting/ parameter/ timeframe or for a different type of insulin after the insulin pump has been approval by the regulatory agency.

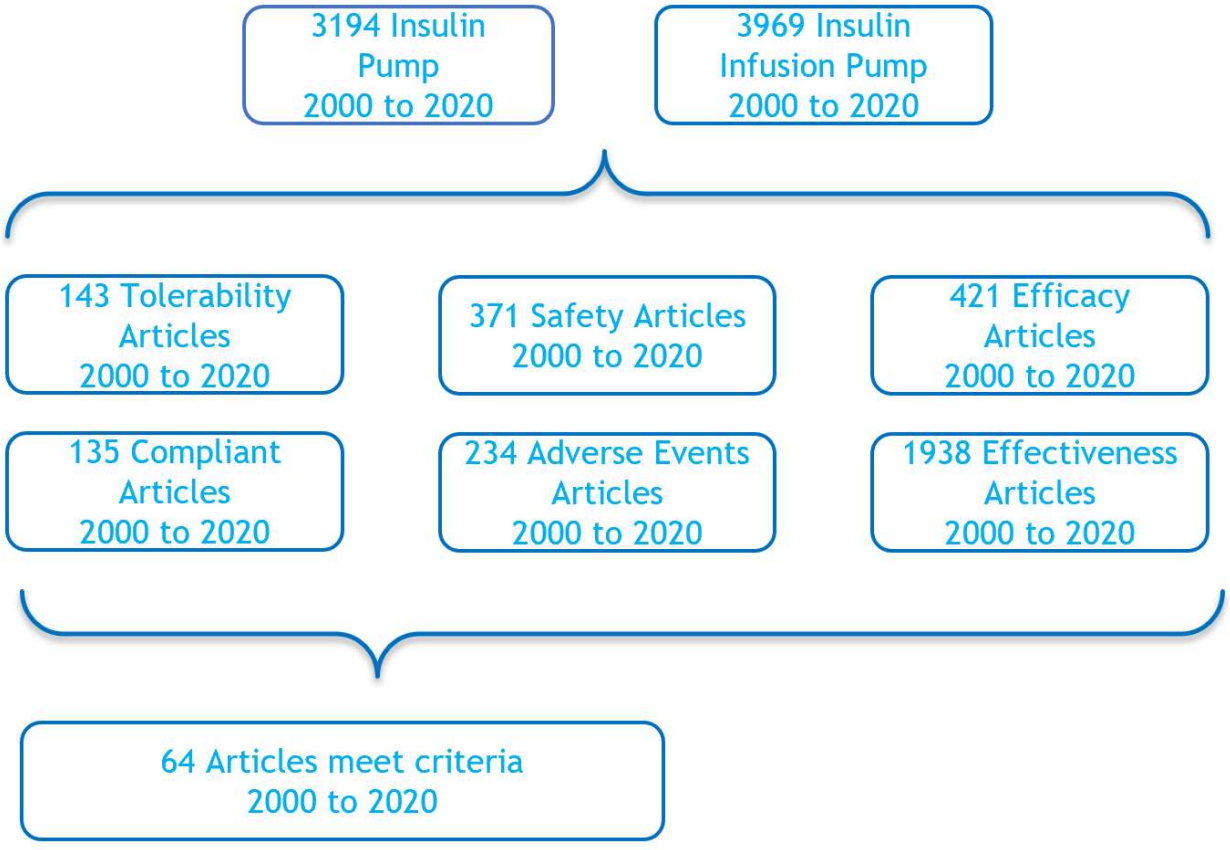
To be able to adequately compare all the adverse events and serious adverse events among all the different types of clinical trials a "total amount of patient years" was calculated for every study. This would also serve as weight in the statistical calculation, i.e. smaller pool of patients or duration of trials would have a lower "total amount of patient years". The adverse events and serious adverse events were then quantified by incidence per patient years.

The incidence per patient years for the adverse events and serious adverse events were then statistically compared. The subgroups of adverse events and serious adverse events were also compared. Each group and subgroup of pre-marketing clinical trials were evaluated for their Mean, Standard Error, Median, Mode, Standard Deviation, Sample Variance, Kurtosis, Skewness, Range, Minimum, Maximum, Sum, Count and Confidence Level (95.0%). The 95.0% confidence level was used to reflect the 95% confidence interval of the mean. The Mean and 95.0% confidence interval were then used to compare the pre-marketing clinical trials to the post-marketing clinical trials. Sensitivity analysis was conducted to assist the impact of individual studies with outliers' estimates.

Results

The literary search though PubMed, ScienceDirect, Google Scholar databases resulted in 3194 Insulin pump and 3969 Insulin Infusion Pump scientific articles. These articles were further filtered to obtain 143 Tolerability, 371 Safety, 421 Efficacy, 135 Compliant, 234 Adverse Events and 1938 Effectiveness articles. The title and abstract for these articles were all read. A total of 215 scientific articles were retained and read in their entirety. A total of 64 articles properly identified their adverse events and serious adverse events obtained during the clinical trials.

Table 2. scientific literary search presented by quantities identified between 2000 to September 30th, 2020.



The 64 articles we separated into pre-marketing clinical trials and post-marketing clinical trials. There was a total of 24 articles with pre-marketing clinical trial adverse event and serious

adverse event data (9, 20-42). The article by Thabit 2015 was split into two, Thabit 2015a and Thabit 2015b, as they performed two studies in parallel and properly distinguished their results (41). They were registered as NCT01961622 and NCT01778348 on clinicaltrial.gov. There was a total of 40 articles with post-marketing clinical trial adverse event and serious adverse event data (10, 43-82).

Once separated into Pre-Marketing and Post-Marketing, they were classified by primary author and year. Direct data from the articles were added: the duration of the clinical trials in months, number of insulin pump patients (CSII patients), minimum patient age that could participate, maximum patient age that could participate, minimum time patient has diabetes and minimum experience patient has with CSII. The data for total patient years was derived as described in the Methodology sections. If the data was not provided in the article the corresponding cell in the table was left empty. Refer to tables 3 and 4 below.

Table 3. Pre-Marketing Clinical Trials Authors, Year Published and Data

Author and year	Pre or Post Marketing Clinical	Duration of Clinical Trial in Months	CSII patients	Total Patient years	minimum patient age	maximum patient age	diabetic experience (years)	CSII Experience (years)
Ahern 2002	Pre	24.00	161	322.00	1.5	18	1	
Bergenstal 2010	Pre	12.00	244	244.00	7	70		
Bergenstal 2013	Pre	3.00	247	61.75	16	70	2	0.50
Bosi 2019	Pre	6.00	153	76.50	24	75	10	0.50
Brown 2019	Pre	6.00	168	84.00	14	71	1	
Buckingham 2017	Pre	0.03	69	0.19	14	75		
Buckingham 2018	Pre	0.30	58	1.45	6	65	1	0.50
Christiansen 2020	Pre	0.40	20	0.67	18	65	2	0.50
Dassau 2017	Pre	3.25	30	8.13	21	65	1	0.50
Ekhlaspour 2019	Pre	0.13	48	0.53	6	18	1	0.25
Hoogma 2005	Pre	16.00	223	297.33	18	65	0.5	0.00
Kovatchev 2017	Pre	5.00	14	5.83	34	51	1	0.50
Kropff 2015	Pre	2.00	32	5.33	18	69	0.5	0.25
Leelarathna 2014	Pre	0.02	8	0.01	18		1	
Logtenberg 2009	Pre	0.75	12	0.75	18			
Ly 2012	Pre	3.00	24	6.00	4	50		0.50
Nimri 2013	Pre	0.75	15	0.94	10	65	1	0.25
Nimri 2014	Pre	3.00	21	5.25	12	65	1	0.25
Nimri 2020	Pre	6.00	122	61.00	10	21	1	0.33
Plotnick 2003	Pre	120.00	95	950.00	4	18	0	
Slover 2018	Pre	0.25	158	3.29	2	18	1	
Spaic 2017	Pre	1.40	30	3.50	15	45	1	0.50
Thabit 2014	Pre	3.00	24	6.00	18	65		0.25
Thabit 2015a	Pre	8.30	33	22.83	18			0.50
Thabit 2015b	Pre	8.30	25	17.29	6	18		0.25

Table 4.Post-Marketing Clinical Trials Authors, Year Published and Data

Author and year	Pre or Post Marketing Clinical	Duration of Clinical Trial in Months	CSII patients	Total Patient years	minimum patient age	maximum patient age	diabetic experience (years)	CSII Experience (years)
Bally 2017	Post	5.00	28	11.67	18			0.50
Battelino 2012	Post	16.00	153	204.00	6	70	1	0.50
Blair 2019	Post	12.00	144	144.00	0.6	15	0	
Bode 2001	Post	2.25	29	5.44	20	56	2	0.25
Bode 2020	Post	3.50	46	13.42	18		1	0.50
Bolli 2009	Post	6.75	24	13.50	18	70	1	0.00
Brorsson 2014	Post	24.00	216	432.00	1.1	17	0	
Castle 2016	Post	0.03	19	0.05	18	65	2	
DeBoer 2017	Post	0.20	12	0.20	5	8	1	0.50
Deeb 2019	Post	6.00	43	21.50	6	30	0	
Dejgaard 2019	Post	6.50	44	23.83	18	70	1	
DeVries 2002	Post	4.00	32	10.67	18	70	0.5	
Fox 2005	Post	6.00	11	5.50	1	6	0.5	0.00
Freckmann 2017	Post	2.00	73	12.17	18			0.25
Garg 2014	Post	6.00	41	20.50	18	65	2	0.25
Haymond 2017	Post	4.25	16	5.67	18	65	2	0.50
Hirsch 2008	Post	6.00	138	69.00	12	72	1	0.50
Hoogma 2006	Post	2.50	59	12.29	33	59	1	0.50
Jankovec 2010	Post	36.00	784	2352.00	21	67		
Jeha 2005	Post	7.25	10	6.04	2	5	0.5	
Kovatchev 2020	Post	10.00	80	66.67	18	70	1	0.50
Lebenthal 2012	Post	6.00	29	14.50	18	35	1	1.00
Li 2015	Post	0.57	134	6.33	18	70	0.08	
Ly 2013	Post	6.00	95	47.50	4	50	1	0.50
Mianowska 2015	Post	9.00	3	2.25	1.3	3.8		0.50
Norgaard 2015	Post	0.50	45	1.88	18			0.25
Nuboer 2008	Post	14.00	19	22.17	4	16	1	0.00
Pinhas-Hamiel 2010	Post	60.00	56	280.00	10		2	1.00
Raskin 2001	Post	6.00	58	29.00	13	60		0.50
Raskin 2003	Post	6.00	60	30.00	35			0.50
Raz 2009	Post	0.67	26	1.45	18	65		
Reznik 2014	Post	6.00	168	84.00	30	75		
Riddle 2018	Post	1.00	32	2.67	18	70	1	
Shehadeh 2004	Post	12.00	14	14.00	1	6	0.5	0.00
Szypowska 2008	Post	12.00	53	53.00	0.9	6	0.17	
Thrasher 2018	Post	2.50	27	5.63	18	75	1	0.50
Thrasher 2020	Post	2.50	43	8.96	18		1	0.50
Tumminia 2015	Post	14.00	20	23.33	18	60	1	1.00
von Bon 2011	Post	9.25	256	197.33	18	75	2	0.50
Weintrob 2002	Post	8.00	23	15.33	8	14	2	
Wilson 2005	Post	12.00	9	9.00	1.7	6.1	0.5	0.00

The 64 articles contained a total of 5206 continuous subcutaneous insulin injection (CSII) patients, i.e. insulin pump therapy. There was a total of 2034 CSII patients from the pre-

marketing clinical trial. There was a total of 3172 CSII patients from the post-marketing clinical trial. The 64 articles contained a total of 6462.0 total patient years of insulin pump used. There was a total of 2184.6 total patient years of insulin pump used in pre-marketing clinical trials. There was a total of 4278.4 total patient years of insulin pump used in post-marketing clinical trials.

The total count in these 64 studies was 2587 adverse events and 434 serious adverse events. There was 645 adverse events and 170 serious adverse events among the pre-marketing studies. There was 1942 adverse events and 275 serious adverse events among the post-marketing studies.

During the collection of data, it was noticed that 22 of the 64 articles selected contained data for pediatric clinical trials. Nine of these articles were pre-marketing and 13 of these articles post-approval. This led to the addition of ten additional statistical analysis.

Twenty-six statistical comparisons were made. Sixteen statistical comparison involved all the data and ten involved pediatric data. For each statistical analysis the number of adverse events was tabulated by article, in addition to the incidence per patient years. Tables were generated for pre-marketing and post-marketing. A series of statistical calculations was then performed as per methodology and tabulated for each pre-marketing and post-marketing. Finally, the direct comparison between the pre-marketing and post-marketing incidence per patient years was performed.

The total number of adverse events and serious adverse events obtained from all 64 articles generated a 7.92 incidence per patient years in the pre-marketing studies compared to 2.18 incidence per patient years in the post-marketing studies. Refer to tables 5 to 8 below.

Table 5. Pre-Marketing Total Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Adverse Events (AE+SAE)	Incidence per Patient years for Total Adverse Events (AE+SAE)
Ahern 2002	pre	24.00	161	322.00	41	0.13
Bergenstal 2010	Pre	12.00	244	244.00	36	0.15
Bergenstal 2013	Pre	3.00	247	61.75	120	1.94
Bosi 2019	Pre	6.00	153	76.50	34	0.44
Brown 2019	Pre	6.00	168	84.00	19	0.23
Buckingham 2017	pre	0.03	69	0.19	5	26.11
Buckingham 2018	Pre	0.30	58	1.45	61	42.07
Christiansen 2020	pre	0.40	20	0.67	11	16.50
Dassau 2017	pre	3.25	30	8.13	24	2.95
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Hoogma 2005	pre	16.00	223	297.33	33	0.11
Kovatchev 2017	pre	5.00	14	5.83	2	0.34
Kropff 2015	pre	2.00	32	5.33	14	2.63
Logtenberg 2009	pre	0.75	12	0.75	3	4.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	43	45.87
Nimri 2014	pre	3.00	21	5.25	14	2.67
Nimri 2020	pre	6.00	122	61.00	127	2.08
Plotnick 2003	pre	120.00	95	950.00	41	0.04
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	10	1.67
Thabit 2015a	pre	8.30	33	22.83	41	1.80
Thabit 2015b	pre	8.30	25	17.29	10	0.58
Slover 2018	pre	0.25	158	3.29	124	37.67

Table 6. Post-Marketing Total Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Adverse Events (AE+SAE)	Incidence per Patient years for Total Adverse Events (AE+SAE)
Bally 2017	Post	5.00	28	11.67	8	0.69
Battelino 2012	Post	16.00	153	204.00	190	0.93
Blair 2019	Post	12.00	144	144.00	68	0.47
Bode 2001	Post	2.25	29	5.44	10	1.84
Bode 2020	Post	3.50	46	13.42	34	2.53
Bolli 2009	Post	6.75	24	13.50	59	4.37
Brorsson 2014	Post	24.00	216	432.00	53	0.12
DeBoer 2017	Post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	43	21.50	2	0.09
Dejgaard 2019	Post	6.50	44	23.83	67	2.81
DeVries 2002	Post	4.00	32	10.67	4	0.38
Fox 2005	Post	6.00	11	5.50	6	1.09
Freckmann 2017	Post	2.00	73	12.17	17	1.40
Garg 2014	Post	6.00	41	20.50	17	0.83
Haymond 2017	Post	4.25	16	5.67	3	0.53
Hirsch 2008	Post	6.00	138	69.00	17	0.25
Hoogma 2006	Post	2.50	59	12.29	43	3.50
Jankovec 2010	Post	36.00	784	2352.00	987	0.42
Jeha 2005	Post	7.25	10	6.04	1	0.17
Kovatchev 2020	Post	10.00	80	66.67	38	0.57
Lebenthal 2012	Post	6.00	29	14.50	53	3.66
Li 2015	Post	0.57	134	6.33	12	1.90
Ly 2013	Post	6.00	95	47.50	13	0.27
Mianowska 2015	Post	9.00	3	2.25	0	0.00
Norgaard 2015	Post	0.50	45	1.88	44	23.47
Nuboer 2008	Post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	Post	60.00	56	280.00	29	0.10
Raskin 2001	Post	6.00	58	29.00	8	0.28
Raskin 2003	Post	6.00	60	30.00	51	1.70
Raz 2009	Post	0.67	26	1.45	3	2.08
Reznik 2014	Post	6.00	168	84.00	42	0.50
Riddle 2018	Post	1.00	32	2.67	41	15.38
Shehadeh 2004	Post	12.00	14	14.00	5	0.36
Szypowska 2008	Post	12.00	53	53.00	2	0.04
Thrasher 2018	Post	2.50	27	5.63	23	4.09
Thrasher 2020	Post	2.50	43	8.96	16	1.79
Tumminia 2015	Post	14.00	20	23.33	1	0.04
von Bon 2011	Post	9.25	256	197.33	58	0.29
Weintrob 2002	Post	8.00	23	15.33	119	7.76
Wilson 2005	Post	12.00	9	9.00	1	0.11

Table 7. Statistics for Total Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Total Adverse Events (AE+SAE) in Pre-Maketing Clinical Trials	
Mean	7.92
Standard Error	2.95
Median	1.73
Mode	0.00
Standard Deviation	14.44
Sample Variance	208.55
Kurtosis	2.25
Skewness	1.91
Range	45.87
Minimum	0.00
Maximum	45.87
Sum	189.97
Count	24
Confidence Level (95.0%)	6.10

Incidence per Patient Years for Total Adverse Events (AE+SAE) in Post-Maketing Clinical Trials	
Mean	2.18
Standard Error	0.70
Median	0.55
Mode	0.00
Standard Deviation	4.41
Sample Variance	19.42
Kurtosis	15.54
Skewness	3.78
Range	23.47
Minimum	0.00
Maximum	23.47
Sum	87.23
Count	40
Confidence Level (95.0%)	1.41

Table 8. Incidence per Patient Years for Total Adverse Event Data

	Incidence per Patient Years	95% CI
Total AE Pre-Marketing	7.92	1.82 to 14.01
Total AE Post-Marketing	2.18	0.77 to 3.59

The total number of treatment related adverse events and treatment related serious adverse events obtained from all 64 articles generated a 6.52 incidence per patient years in the pre-marketing studies compared to 1.67 incidence per patient years in the post-marketing studies. Refer to tables 9 to 12 below.

Table 9. Pre-Marketing Total Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Treatment Related Adverse Events (AE+SAE)	Incidence per Patient years for Total Treatment Related Adverse Events (AE+SAE)
Ahern 2002	pre	24.00	161	322.00	40	0.12
Bergenstal 2010	Pre	12.00	244	244.00	35	0.14
Bergenstal 2013	Pre	3.00	247	61.75	25	0.40
Bosi 2019	Pre	6.00	153	76.50	26	0.34
Brown 2019	Pre	6.00	168	84.00	16	0.19
Buckingham 2017	pre	0.03	69	0.19	1	5.22
Buckingham 2018	Pre	0.30	58	1.45	61	42.07
Christiansen 2020	pre	0.40	20	0.67	8	12.00
Dassau 2017	pre	3.25	30	8.13	7	0.86
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Hoogma 2005	pre	16.00	223	297.33	31	0.10
Kovatchev 2017	pre	5.00	14	5.83	2	0.34
Kropff 2015	pre	2.00	32	5.33	4	0.75
Logtenberg 2009	pre	0.75	12	0.75	3	4.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	42	44.80
Nimri 2014	pre	3.00	21	5.25	14	2.67
Nimri 2020	pre	6.00	122	61.00	91	1.49
Plotnick 2003	pre	120.00	95	950.00	41	0.04
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	9	1.50
Thabit 2015a	pre	8.30	33	22.83	34	1.49
Thabit 2015b	pre	8.30	25	17.29	6	0.35
Slover 2018	pre	0.25	158	3.29	124	37.67

Table 10. Post-Marketing Total Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Treatment Related Adverse Events (AE+SAE)	Incidence per Patient years for Total Treatment Related Adverse Events (AE+SAE)
Bally 2017	post	5.00	28	11.67	6	0.51
Battelino 2012	post	16.00	153	204.00	190	0.93
Blair 2019	Post	12.00	144	144.00	33	0.23
Bode 2001	Post	2.25	29	5.44	10	1.84
Bode 2020	Post	3.50	46	13.42	34	2.53
Bolli 2009	Post	6.75	24	13.50	59	4.37
Brorsson 2014	Post	24.00	216	432.00	53	0.12
DeBoer 2017	Post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	43	21.50	2	0.09
Dejgaard 2019	Post	6.50	44	23.83	1	0.04
DeVries 2002	Post	4.00	32	10.67	3	0.28
Fox 2005	Post	6.00	11	5.50	6	1.09
Freckmann 2017	Post	2.00	73	12.17	17	1.40
Garg 2014	Post	6.00	41	20.50	12	0.59
Haymond 2017	Post	4.25	16	5.67	1	0.18
Hirsch 2008	Post	6.00	138	69.00	15	0.22
Hoogma 2006	Post	2.50	59	12.29	43	3.50
Jankovec 2010	Post	36.00	784	2352.00	943	0.40
Jeha 2005	Post	7.25	10	6.04	0	0.00
Kovatchev 2020	Post	10.00	80	66.67	10	0.15
Lebenthal 2012	Post	6.00	29	14.50	50	3.45
Li 2015	Post	0.57	134	6.33	12	1.90
Ly 2013	Post	6.00	95	47.50	13	0.27
Mianowska 2015	Post	9.00	3	2.25	0	0.00
Norgaard 2015	Post	0.50	45	1.88	44	23.47
Nuboer 2008	Post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	Post	60.00	56	280.00	29	0.10
Raskin 2001	Post	6.00	58	29.00	7	0.24
Raskin 2003	Post	6.00	60	30.00	51	1.70
Raz 2009	Post	0.67	26	1.45	3	2.08
Reznik 2014	Post	6.00	168	84.00	42	0.50
Riddle 2018	Post	1.00	32	2.67	15	5.63
Shehadeh 2004	Post	12.00	14	14.00	5	0.36
Szypowska 2008	Post	12.00	53	53.00	2	0.04
Thrasher 2018	Post	2.50	27	5.63	10	1.78
Thrasher 2020	Post	2.50	43	8.96	12	1.34
Tumminia 2015	Post	14.00	20	23.33	1	0.04
von Bon 2011	Post	9.25	256	197.33	58	0.29
Weintrob 2002	Post	8.00	23	15.33	71	4.63
Wilson 2005	Post	12.00	9	9.00	1	0.11
Castle 2016	Post	0.03	19	0.05	62	1175.91

Table 11. Statistics for Total Treatment Related Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Total Treatment Related Adverse Events (AE+SAE) in Pre-Maketing Clinical Trials	
Mean	6.52
Standard Error	2.82
Median	0.58
Mode	0.00
Standard Deviation	13.80
Sample Variance	190.33
Kurtosis	3.90
Skewness	2.30
Range	44.80
Minimum	0.00
Maximum	44.80
Sum	156.56
Count	24
Confidence Level (95.0%)	5.83

Incidence per Patient Years for Total Treatment Related Adverse Events (AE+SAE) in Post-Maketing Clinical Trials	
Mean	1.67
Standard Error	0.60
Median	0.43
Mode	0.00
Standard Deviation	3.81
Sample Variance	14.53
Kurtosis	28.79
Skewness	5.07
Range	23.47
Minimum	0.00
Maximum	23.47
Sum	66.85
Count	40
Confidence Level (95.0%)	1.22

Table 12. Incidence per Patient Years for Total Treatment Related Adverse Event Data

	Incidence per Patient Years	95% CI
Total Treatment Related AE Pre-Marketing	6.52	0.70 to 12.35
Total Treatment Related AE Post-Marketing	1.67	0.45 to 2.89

The total number of pediatric adverse events and pediatric serious adverse events obtained from all 64 articles generated a 0.50 incidence per patient years in the pre-marketing studies compared to 0.84 incidence per patient years in the post-marketing studies. Refer to tables 13 to 16 below.

Table 13. Pre-Marketing Total Pediatric Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Pediatric Adverse Events (AE+SAE)	Incidence per Patient years for Total Pediatric Adverse Events (AE+SAE)
Ahern 2002	pre	24.00	161	322.00	41	0.13
Bergenstal 2010	Pre	12.00	78	78.00	11	0.14
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Nimri 2020	pre	6.00	122	61.00	127	2.08
Plotnick 2003	pre	120.00	95	950.00	41	0.04
Thabit 2015b	pre	8.30	25	17.29	10	0.58

Table 14. Post-Marketing Total Pediatric Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Pediatric Adverse Events (AE+SAE)	Incidence per Patient years for Total Pediatric Adverse Events (AE+SAE)
Blair 2019	Post	12.00	144	144.00	68	0.47
Brorsson 2014	post	24.00	216	432.00	53	0.12
DeBoer 2017	post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	14	7.00	2	0.29
Fox 2005	post	6.00	11	5.50	6	1.09
Jeha 2005	post	7.25	10	6.04	1	0.17
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	post	60.00	56	280.00	29	0.10
Shehadeh 2004	Post	12.00	14	14.00	5	0.36
Szypowska 2008	post	12.00	53	53.00	2	0.04
Weintrob 2002	post	8.00	23	15.33	119	7.76
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 15. Statistics for Total Pediatric Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient years for Total Pediatric Adverse Events (AE+SAE) in Pre-Maketing Clinical Trials	
Mean	0.50
Standard Error	0.33
Median	0.13
Mode	#N/A
Standard Deviation	0.80
Sample Variance	0.65
Kurtosis	4.58
Skewness	2.13
Range	2.08
Minimum	0.00
Maximum	2.08
Sum	2.97
Count	6
Confidence Level (95.0%)	0.84

Incidence per Patient Years for Total Pediatric Adverse Events (AE+SAE) in Post-Maketing Clinical Trials	
Mean	0.84
Standard Error	0.58
Median	0.17
Mode	0.00
Standard Deviation	2.10
Sample Variance	4.41
Kurtosis	12.35
Skewness	3.49
Range	7.76
Minimum	0.00
Maximum	7.76
Sum	10.96
Count	13
Confidence Level (95.0%)	1.27

Table 16. Incidence per Patient Years for Total Pediatric Adverse Event Data

	Incidence per Patient Years	95% CI
Total Pediatric AE Pre-Marketing	0.50	-0.35 to 1.34
Total Pediatric AE Post-Marketing	0.84	-0.43 to 2.11

The total number of treatment related pediatric adverse events and treatment related pediatric serious adverse events obtained from all 64 articles generated a 0.36 incidence per patient

years in the pre-marketing studies compared to 0.84 incidence per patient years in the post-marketing studies. Refer to tables 17 to 20 below.

Table 17. Pre-Marketing Total Pediatric Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Pediatric Treatment Related Adverse Events (AE+SAE)	Incidence per Patient years for Total Pediatric Treatment Related Adverse Events (AE+SAE)
Ahern 2002	pre	24.00	161	322.00	40	0.12
Bergenstal 2010	Pre	12.00	78	78.00	10	0.13
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Nimri 2020	pre	6.00	122	61.00	91	1.49
Plotnick 2003	pre	120.00	95	950.00	37	0.04
Thabit 2015b	pre	8.30	25	17.29	6	0.35

Table 18. Post-Marketing Total Pediatric Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Pediatric Treatment Related Adverse Events (AE+SAE)	Incidence per Patient years for Total Pediatric Treatment Related Adverse Events (AE+SAE)
Blair 2019	Post	12.00	144	144.00	68	0.47
Brorsson 2014	post	24.00	216	432.00	53	0.12
DeBoer 2017	post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	14	7.00	2	0.29
Fox 2005	post	6.00	11	5.50	6	1.09
Jeha 2005	post	7.25	10	6.04	1	0.17
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	post	60.00	56	280.00	29	0.10
Shehadeh 2004	Post	12.00	14	14.00	5	0.36
Szypowska 2008	post	12.00	53	53.00	2	0.04
Weintrob 2002	post	8.00	23	15.33	119	7.76
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 19. Statistics for Total Pediatric Treatment Related Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Total Pediatric Treatment Related Adverse Events (AE+SAE) in Pre-Maketing Clinical Trials	
Mean	0.36
Standard Error	0.23
Median	0.13
Mode	#N/A
Standard Deviation	0.57
Sample Variance	0.32
Kurtosis	5.05
Skewness	2.22
Range	1.49
Minimum	0.00
Maximum	1.49
Sum	2.13
Count	6
Confidence Level (95.0%)	0.60

Incidence per Patient Years for Total Pediatric Treatment Related Adverse Events (AE+SAE) in Post-Maketing Clinical Trials	
Mean	0.84
Standard Error	0.58
Median	0.17
Mode	0.00
Standard Deviation	2.10
Sample Variance	4.41
Kurtosis	12.35
Skewness	3.49
Range	7.76
Minimum	0.00
Maximum	7.76
Sum	10.96
Count	13
Confidence Level (95.0%)	1.27

Table 20. Incidence per Patient Years for Total Pediatric Treatment Related Adverse Event Data

	Incidence per Patient Years	95% CI
Total Pediatric Treatment Related AE Pre-Marketing	0.36	-0.24 to 0.95
Total Pediatric Treatment Related AE Post-Marketing	0.84	-0.43 to 2.11

The number of adverse events obtained from all 64 articles generated an 8.69 incidence per patient years in the pre-marketing studies compared to 2.76 incidence per patient years in the post-marketing studies. Refer to tables 21 to 24 below.

Table 21. Pre-Marketing Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Adverse Events	Incidence per Patient years for Adverse Events
Bergenstal 2013	Pre	3.0	247	61.8	118	1.9
Bosi 2019	Pre	6.0	153	76.5	25	0.3
Brown 2019	Pre	6.0	168	84.0	15	0.2
Buckingham 2017	pre	0.0	69	0.2	5	26.1
Buckingham 2018	Pre	0.3	58	1.5	61	42.1
Christiansen 2020	pre	0.4	20	0.7	11	16.5
Kovatchev 2017	pre	5.0	14	5.8	2	0.3
Kropff 2015	pre	2.0	32	5.3	14	2.6
Logtenberg 2009	pre	0.8	12	0.8	3	4.0
Nimri 2013	pre	0.8	15	0.9	43	45.9
Nimri 2014	pre	3.0	21	5.3	13	2.5
Nimri 2020	pre	6.0	122	61.0	121	2.0
Plotnick 2003	pre	120.0	95	950.0	36	0.0
Spaic 2017	pre	1.4	30	3.5	0	0.0
Thabit 2014	pre	3.0	24	6.0	8	1.3
Thabit 2015a	pre	8.3	33	22.8	37	1.6
Thabit 2015b	pre	8.3	25	17.3	7	0.4
Slover 2018	pre	0.3	158	3.3	124	37.7
Leelarathna 2014	pre	0.0	8	0.0	2	180.0

Table 22. Post-Marketing Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Adverse Events	Incidence per Patient years for Adverse Events
Bally 2017	post	5.0	28	11.7	8	0.7
Battelino 2012	post	16.0	153	204.0	178	0.9
Blair 2019	Post	12.0	144	144.0	54	0.4
Bode 2001	pre	2.3	29	5.4	9	1.7
Bode 2020	pre	3.5	46	13.4	32	2.4
Bolli 2009	post	6.8	24	13.5	59	4.4
DeBoer 2017	post	0.2	12	0.2	0	0.0
Deeb 2019	Post	6.0	43	21.5	0	0.0
Dejgaard 2019	pre	6.5	44	23.8	64	2.7
Freckmann 2017	post	2.0	73	12.2	15	1.2
Garg 2014	pre	6.0	41	20.5	7	0.3
Haymond 2017	pre	4.3	16	5.7	3	0.5
Hoogma 2006	post	2.5	59	12.3	34	2.8
Jankovec 2010	post	36.0	784	2352.0	987	0.4
Kovatchev 2020	post	10.0	80	66.7	35	0.5
Lebenthal 2012	post	6.0	29	14.5	52	3.6
Li 2015	Post	0.6	134	6.3	12	1.9
Ly 2013	Post	6.0	95	47.5	2	0.0
Mianowska 2015	post	9.0	3	2.3	0	0.0
Norgaard 2015	post	0.5	45	1.9	44	23.5
Raskin 2001	pre	6.0	58	29.0	0	0.0
Raskin 2003	post	6.0	60	30.0	51	1.7
Raz 2009	pre	0.7	26	1.4	3	2.1
Reznik 2014	Post	6.0	168	84.0	40	0.5
Riddle 2018	Pre	1.0	32	2.7	41	15.4
Shehadeh 2004	Post	12.0	14	14.0	1	0.1
Thrasher 2018	Pre	2.5	27	5.6	17	3.0
Thrasher 2020	pre	2.5	43	9.0	16	1.8
Weintrob 2002	post	8.0	23	15.3	116	7.6
Castle 2016	pre	0.0	19	0.1	62	1175.9

Table 23. Statistics for Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Adverse Events in Pre-Maketing Clinical Trials	
Mean	8.69
Standard Error	3.63
Median	1.91
Mode	#N/A
Standard Deviation	14.97
Sample Variance	224.02
Kurtosis	2.31
Skewness	1.87
Range	45.87
Minimum	0.00
Maximum	45.87
Sum	147.79
Count	17
Confidence Level (95.0%)	7.70

Incidence per Patient Years for Adverse Events in Post-Maketing Clinical Trials	
Mean	2.76
Standard Error	0.93
Median	1.23
Mode	0.00
Standard Deviation	5.02
Sample Variance	25.23
Kurtosis	11.28
Skewness	3.27
Range	23.47
Minimum	0.00
Maximum	23.47
Sum	79.91
Count	29
Confidence Level (95.0%)	1.91

Table 24. Incidence per Patient Years for Adverse Event Data

	Incidence per Patient Years	95% CI
AE Pre-Marketing	8.69	1.00 to 16.39
AE Post-Marketing	2.76	0.84 to 4.67

The number of treatment related adverse events obtained from all 64 articles generated a 6.87 incidence per patient years in the pre-marketing studies compared to 1.98 incidence per patient years in the post-marketing studies. Refer to tables 25 to 28 below.

Table 25. Pre-Marketing Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Treatment Related Adverse Events	Incidence per Patient years for Treatment Related Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	23	0.37
Bosi 2019	Pre	6.00	153	76.50	25	0.33
Brown 2019	Pre	6.00	168	84.00	15	0.18
Buckingham 2017	pre	0.03	69	0.19	1	5.22
Buckingham 2018	Pre	0.30	58	1.45	61	42.07
Christiansen 2020	pre	0.40	20	0.67	8	12.00
Kovatchev 2017	pre	5.00	14	5.83	2	0.34
Kropff 2015	pre	2.00	32	5.33	4	0.75
Logtenberg 2009	pre	0.75	12	0.75	3	4.00
Nimri 2013	pre	0.75	15	0.94	42	44.80
Nimri 2014	pre	3.00	21	5.25	13	2.48
Nimri 2020	pre	6.00	122	61.00	88	1.44
Plotnick 2003	pre	120.00	95	950.00	36	0.04
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	7	1.17
Thabit 2015a	pre	8.30	33	22.83	33	1.45
Thabit 2015b	pre	8.30	25	17.29	4	0.23

Table 26. Post-Marketing Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Treatment Related Adverse Events	Incidence per Patient years for Treatment Related Adverse Events
Bally 2017	post	5.00	28	11.67	6	0.51
Battelino 2012	post	16.00	153	204.00	178	0.87
Blair 2019	Post	12.00	144	144.00	20	0.14
Bode 2001	Post	2.25	29	5.44	9	1.66
Bode 2020	Post	3.50	46	13.42	32	2.39
Bolli 2009	Post	6.75	24	13.50	59	4.37
Castle 2016	Post	0.03	19	0.05	0	0.00
DeBoer 2017	Post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	43	21.50	0	0.00
Dejgaard 2019	Post	6.50	44	23.83	0	0.00
Freckmann 2017	Post	2.00	73	12.17	15	1.23
Garg 2014	Post	6.00	41	20.50	7	0.34
Haymond 2017	Post	4.25	16	5.67	1	0.18
Hoogma 2006	Post	2.50	59	12.29	34	2.77
Jankovec 2010	Post	36.00	784	2352.00	943	0.40
Kovatchev 2020	Post	10.00	80	66.67	10	0.15
Lebenthal 2012	Post	6.00	29	14.50	50	3.45
Li 2015	Post	0.57	134	6.33	12	1.90
Ly 2013	Post	6.00	95	47.50	2	0.04
Mianowska 2015	Post	9.00	3	2.25	0	0.00
Norgaard 2015	Post	0.50	45	1.88	44	23.47
Raskin 2001	Post	6.00	58	29.00	0	0.00
Raskin 2003	Post	6.00	60	30.00	51	1.70
Raz 2009	Post	0.67	26	1.45	3	2.08
Reznik 2014	Post	6.00	168	84.00	40	0.48
Riddle 2018	Post	1.00	32	2.67	15	5.63
Shehadeh 2004	Post	12.00	14	14.00	1	0.07
Thrasher 2018	Post	2.50	27	5.63	10	1.78
Thrasher 2020	Post	2.50	43	8.96	12	1.34
Weintrob 2002	Post	8.00	23	15.33	70	4.57
Wilson 2005	Post	12.00	9	9.00	0	0.00

Table 27. Statistics for Treatment Related Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Treatment Related Adverse Events in Pre-Maketing Clinical Trials	
Mean	6.87
Standard Error	3.42
Median	1.17
Mode	#N/A
Standard Deviation	14.08
Sample Variance	198.34
Kurtosis	4.73
Skewness	2.42
Range	44.80
Minimum	0.00
Maximum	44.80
Sum	116.86
Count	17
Confidence Level (95.0%)	7.24

Incidence per Patient Years for Treatment Related Adverse Events in Post-Maketing Clinical Trials	
Mean	1.98
Standard Error	0.77
Median	0.51
Mode	0.00
Standard Deviation	4.27
Sample Variance	18.24
Kurtosis	22.81
Skewness	4.53
Range	23.47
Minimum	0.00
Maximum	23.47
Sum	61.49
Count	31
Confidence Level (95.0%)	1.57

Table 28. Incidence per Patient Years for Treatment Related Adverse Event Data

	Incidence per Patient Years	95% CI
Treatment Related AE Pre-Marketing	6.87	-0.37 to 14.12
Treatment Related AE Post-Marketing	1.98	0.42 to 3.55

The number of pediatric adverse events obtained from all 64 articles generated a 0.81 incidence per patient years in the pre-marketing studies compared to 1.34 incidence per patient years in the post-marketing studies. Refer to tables 29 to 32 below.

Table 29. Pre-Marketing Pediatric Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Adverse Events	Incidence per Patient years for Pediatric Adverse Events
Nimri 2020	pre	122.00	6	61.00	121	1.98
Plotnick 2003	pre	95.00	120	950.00	36	0.04
Thabit 2015b	pre	25.00	8.3	17.29	7	0.40

Table 30. Post-Marketing Pediatric Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Adverse Events	Incidence per Patient years for Pediatric Adverse Events
Blair 2019	Post	144.00	12	144.00	54	0.38
DeBoer 2017	post	12.00	0.2	0.20	0	0.00
Deeb 2019	Post	14.00	6	7.00	0	0.00
Mianowska 2015	post	3.00	9	2.25	0	0.00
Shehadeh 2004	Post	14.00	12	14.00	1	0.07
Weintrob 2002	post	23.00	8	15.33	116	7.57

Table 31. Statistics for Pediatric Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.81
Standard Error	0.60
Median	0.40
Mode	#N/A
Standard Deviation	1.03
Sample Variance	1.07
Kurtosis	#DIV/0!
Skewness	1.49
Range	1.95
Minimum	0.04
Maximum	1.98
Sum	2.43
Count	3
Confidence Level (95.0%)	2.57

Incidence per Patient Years for Pediatric Adverse Events in Post-Maketing Clinical Trials	
Mean	1.34
Standard Error	1.25
Median	0.04
Mode	0.00
Standard Deviation	3.06
Sample Variance	9.34
Kurtosis	5.95
Skewness	2.44
Range	7.57
Minimum	0.00
Maximum	7.57
Sum	8.01
Count	6
Confidence Level (95.0%)	3.21

Table 32. Incidence per Patient Years for Pediatric Adverse Event Data

	Incidence per Patient Years	95% CI
Pediatric AE Pre-Marketing	0.81	-1.76 to 3.38
Pediatric AE Post-Marketing	1.34	-1.87 to 4.54

The number of treatment related pediatric adverse events obtained from all 64 articles generated a 0.57 incidence per patient years in the pre-marketing studies compared to 0.80 incidence per patient years in the post-marketing studies. Refer to tables 33 to 36 below.

Table 33. Pre-Marketing Pediatric Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Treatment Related Adverse Events	Incidence per Patient years for Pediatric Treatment Related Adverse Events
Nimri 2020	pre	6.00	122	61.00	88	1.44
Plotnick 2003	pre	120.00	95	950.00	36	0.04
Thabit 2015b	pre	8.30	25	17.29	4	0.23

Table 34. Post-Marketing Pediatric Treatment Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Treatment Related Adverse Events	Incidence per Patient years for Pediatric Treatment Related Adverse Events
Blair 2019	Post	12.00	144	144.00	20	0.14
DeBoer 2017	post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	14	7.00	0	0.00
Mianowska 2015	post	9.00	3	2.25	0	0.00
Shehadeh 2004	Post	12.00	14	14.00	1	0.07
Weintrob 2002	post	8.00	23	15.33	70	4.57

Table 35. Statistics for Pediatric Treatment Related Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Treatment Related Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.57
Standard Error	0.44
Median	0.23
Mode	#N/A
Standard Deviation	0.76
Sample Variance	0.58
Kurtosis	#DIV/0!
Skewness	1.61
Range	1.40
Minimum	0.04
Maximum	1.44
Sum	1.71
Count	3
Confidence Level (95.0%)	1.89

Incidence per Patient Years for Pediatric Treatment Related Adverse Events in Post-Maketing Clinical Trials	
Mean	0.80
Standard Error	0.75
Median	0.04
Mode	0.00
Standard Deviation	1.85
Sample Variance	3.41
Kurtosis	5.98
Skewness	2.44
Range	4.57
Minimum	0.00
Maximum	4.57
Sum	4.78
Count	6
Confidence Level (95.0%)	1.94

Table 36. Incidence per Patient Years for Pediatric Treatment Related Adverse Event Data

	Incidence per Patient Years	95% CI
Pediatric Treatment Related AE Pre-Marketing	0.57	-1.32 to 2.46
Pediatric Treatment Related AE Post-Marketing	0.80	-1.14 to 2.73

The number of serious adverse events obtained from all 64 articles generated a 0.20 incidence per patient years in the pre-marketing studies compared to 0.22 incidence per patient years in the post-marketing studies. Refer to tables 37 to 40 below.

Table 37. Pre-Marketing Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Serious Adverse Events	Incidence per Patient years for Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	41	0.13
Bergenstal 2010	Pre	12.00	244	244.00	36	0.15
Bergenstal 2013	Pre	3.00	247	61.75	2	0.03
Bosi 2019	Pre	6.00	153	76.50	9	0.12
Brown 2019	Pre	6.00	168	84.00	4	0.05
Buckingham 2017	pre	0.03	69	0.19	0	0.00
Buckingham 2018	Pre	0.30	58	1.45	0	0.00
Christiansen 2020	pre	0.40	20	0.67	0	0.00
Dassau 2017	pre	3.25	30	8.13	24	2.95
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Hoogma 2005	pre	16.00	223	297.33	33	0.11
Kropff 2015	pre	2.00	32	5.33	0	0.00
Logtenberg 2009	pre	0.75	12	0.75	0	0.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	0	0.00
Nimri 2014	pre	3.00	21	5.25	1	0.19
Nimri 2020	pre	6.00	122	61.00	6	0.10
Plotnick 2003	pre	120.00	95	950.00	5	0.01
Slover 2018	pre	0.25	158	3.29	0	0.00
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	2	0.33
Thabit 2015a	pre	8.30	33	22.83	4	0.18
Thabit 2015b	pre	8.30	25	17.29	3	0.17

Table 38. Post-Marketing Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Serious Adverse Events	Incidence per Patient years for Serious Adverse Events
Battelino 2012	post	16.00	153	204.00	12	0.06
Blair 2019	Post	12.00	144	144.00	14	0.10
Bode 2001	Post	2.25	29	5.44	1	0.18
Bode 2020	Post	3.50	46	13.42	2	0.15
Brorsson 2014	Post	24.00	216	432.00	53	0.12
Castle 2016	Post	0.03	19	0.05	0	0.00
DeBoer 2017	Post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	43	21.50	2	0.09
Dejgaard 2019	Post	6.50	44	23.83	3	0.13
DeVries 2002	Post	4.00	32	10.67	4	0.38
Fox 2005	Post	6.00	11	5.50	6	1.09
Freckmann 2017	Post	2.00	73	12.17	2	0.16
Garg 2014	Post	6.00	41	20.50	10	0.49
Hirsch 2008	Post	6.00	138	69.00	17	0.25
Hoogma 2006	Post	2.50	59	12.29	9	0.73
Jeha 2005	Post	7.25	10	6.04	1	0.17
Kovatchev 2020	Post	10.00	80	66.67	3	0.05
Lebenthal 2012	Post	6.00	29	14.50	1	0.07
Li 2015	Post	0.57	134	6.33	0	0.00
Ly 2013	Post	6.00	95	47.50	11	0.23
Mianowska 2015	Post	9.00	3	2.25	0	0.00
Nuboer 2008	Post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	Post	60.00	56	280.00	29	0.10
Raskin 2001	Post	6.00	58	29.00	8	0.28
Raz 2009	Post	0.67	26	1.45	0	0.00
Reznik 2014	Post	6.00	168	84.00	2	0.02
Riddle 2018	Post	1.00	32	2.67	0	0.00
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	Post	12.00	53	53.00	2	0.04
Thrasher 2018	Post	2.50	27	5.63	6	1.07
Tumminia 2015	Post	14.00	20	23.33	1	0.04
von Bon 2011	Post	9.25	256	197.33	58	0.29
Weintrob 2002	Post	8.00	23	15.33	3	0.20
Wilson 2005	Post	12.00	9	9.00	1	0.11

Table 39. Statistics for Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.20
Standard Error	0.13
Median	0.03
Mode	0.00
Standard Deviation	0.61
Sample Variance	0.37
Kurtosis	21.88
Skewness	4.63
Range	2.95
Minimum	0.00
Maximum	2.95
Sum	4.51
Count	23
Confidence Level (95.0%)	0.26

Incidence per Patient Years for Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.22
Standard Error	0.05
Median	0.12
Mode	0.00
Standard Deviation	0.27
Sample Variance	0.07
Kurtosis	4.63
Skewness	2.16
Range	1.09
Minimum	0.00
Maximum	1.09
Sum	7.33
Count	34
Confidence Level (95.0%)	0.10

Table 40. Incidence per Patient Years for Serious Adverse Event Data

	Incidence per Patient Years	95% CI
SAE Pre-Marketing	0.20	-0.07 to 0.46
SAE Post-Marketing	0.22	0.12 to 0.31

The number of treatment related serious adverse events obtained from all 64 articles generated a 0.085 incidence per patient years in the pre-marketing studies compared to 0.16 incidence per patient years in the post-marketing studies. Refer to tables 41 to 44 below.

Table 41. Pre-Marketing Treatment Related Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Treatment Related Serious Adverse Events	Incidence per Patient years for Treatment Related Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	40	0.12
Bergenstal 2010	Pre	12.00	244	244.00	35	0.14
Bergenstal 2013	Pre	3.00	247	61.75	2	0.03
Bosi 2019	Pre	6.00	153	76.50	1	0.01
Brown 2019	Pre	6.00	168	84.00	1	0.01
Buckingham 2017	pre	0.03	69	0.19	0	0.00
Buckingham 2018	Pre	0.30	58	1.45	0	0.00
Christiansen 2020	pre	0.40	20	0.67	0	0.00
Dassau 2017	pre	3.25	30	8.13	7	0.86
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Hoogma 2005	pre	16.00	223	297.33	33	0.11
Kropff 2015	pre	2.00	32	5.33	0	0.00
Logtenberg 2009	pre	0.75	12	0.75	0	0.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	0	0.00
Nimri 2014	pre	3.00	21	5.25	1	0.19
Nimri 2020	pre	6.00	122	61.00	3	0.05
Phillip 2013	pre	0.07	54	0.30	0	0.00
Plotnick 2003	pre	120.00	95	950.00	5	0.01
Slover 2018	pre	0.25	158	3.29	0	0.00
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	2	0.33
Thabit 2015a	pre	8.30	33	22.83	1	0.04
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 42. Post-Marketing Treatment Related Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Treatment Related Serious Adverse Events	Incidence per Patient years for Treatment Related Serious Adverse Events
Battelino 2012	post	16.00	153	204.00	12	0.06
Blair 2019	Post	12.00	144	144.00	14	0.10
Bode 2001	Post	2.25	29	5.44	1	0.18
Bode 2020	Post	3.50	46	13.42	2	0.15
Brorsson 2014	Post	24.00	216	432.00	53	0.12
Castle 2016	Post	0.03	19	0.05	0	0.00
DeBoer 2017	Post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	43	21.50	2	0.09
Dejgaard 2019	Post	6.50	44	23.83	1	0.04
DeVries 2002	Post	4.00	32	10.67	3	0.28
Fox 2005	Post	6.00	11	5.50	6	1.09
Freckmann 2017	Post	2.00	73	12.17	2	0.16
Garg 2014	Post	6.00	41	20.50	5	0.24
Hirsch 2008	Post	6.00	138	69.00	15	0.22
Hoogma 2006	Post	2.50	59	12.29	9	0.73
Jeha 2005	Post	7.25	10	6.04	0	0.00
Kovatchev 2020	Post	10.00	80	66.67	0	0.00
Lebenthal 2012	Post	6.00	29	14.50	0	0.00
Li 2015	Post	0.57	134	6.33	0	0.00
Ly 2013	Post	6.00	95	47.50	11	0.23
Mianowska 2015	Post	9.00	3	2.25	0	0.00
Nuboer 2008	Post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	Post	60.00	56	280.00	29	0.10
Raskin 2001	Post	6.00	58	29.00	7	0.24
Raz 2009	Post	0.67	26	1.45	0	0.00
Reznik 2014	Post	6.00	168	84.00	2	0.02
Riddle 2018	Post	1.00	32	2.67	0	0.00
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	Post	12.00	53	53.00	2	0.04
Thrasher 2018	Post	2.50	27	5.63	0	0.00
Tumminia 2015	Post	14.00	20	23.33	1	0.04
von Bon 2011	Post	9.25	256	197.33	58	0.29
Weintrob 2002	Post	8.00	23	15.33	1	0.07
Wilson 2005	Post	12.00	9	9.00	1	0.11

Table 43. Statistics for Treatment Related Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Treatment Related Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.08
Standard Error	0.04
Median	0.01
Mode	0.00
Standard Deviation	0.18
Sample Variance	0.03
Kurtosis	14.46
Skewness	3.59
Range	0.86
Minimum	0.00
Maximum	0.86
Sum	2.04
Count	24
Confidence Level (95.0%)	0.08

Incidence per Patient Years for Treatment Related Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.16
Standard Error	0.04
Median	0.10
Mode	0.00
Standard Deviation	0.23
Sample Variance	0.05
Kurtosis	8.78
Skewness	2.71
Range	1.09
Minimum	0.00
Maximum	1.09
Sum	5.36
Count	34
Confidence Level (95.0%)	0.08

Table 44. Incidence per Patient Years for Treatment Related Serious Adverse Event Data

	Incidence per Patient Years	95% CI
Treatment Related SAE Pre-Marketing	0.08	0.01 to 0.16
Treatment Related SAE Post-Marketing	0.16	0.08 to 0.24

The number of pediatric serious adverse events obtained from all 64 articles generated a 0.068 incidence per patient years in the pre-marketing studies compared to 0.23 incidence per patient years in the post-marketing studies. Refer to tables 45 to 48 below.

Table 45. Pre-Marketing Pediatric Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Serious Adverse Events	Incidence per Patient years for Pediatric Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	41	0.13
Bergenstal 2010	Pre	12.00	78	78.00	11	0.14
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Nimri 2020	pre	6.00	122	61.00	6	0.10
Plotnick 2003	pre	120.00	95	950.00	5	0.01
Thabit 2015b	pre	8.30	25	17.29	3	0.17
Buckingham 2018	Pre	0.30	24	0.60	0	0.00
Slover 2018	pre	0.25	158	3.29	0	0.00

Table 46. Post-Marketing Pediatric Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Serious Adverse Events	Incidence per Patient years for Pediatric Serious Adverse Events
Blair 2019	Post	12.00	144	144.00	14	0.10
Brorsson 2014	post	24.00	216	432.00	53	0.12
DeBoer 2017	post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	14	7.00	2	0.29
Fox 2005	post	6.00	11	5.50	6	1.09
Jeha 2005	post	7.25	10	6.04	1	0.17
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	post	60.00	56	280.00	29	0.10
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	2	0.04
Weintrob 2002	post	8.00	23	15.33	3	0.20
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 47. Statistics for Pediatric Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.07
Standard Error	0.03
Median	0.05
Mode	0.00
Standard Deviation	0.07
Sample Variance	0.01
Kurtosis	-2.16
Skewness	0.27
Range	0.17
Minimum	0.00
Maximum	0.17
Sum	0.55
Count	8
Confidence Level (95.0%)	0.06

Incidence per Patient Years for Pediatric Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.23
Standard Error	0.08
Median	0.12
Mode	0.00
Standard Deviation	0.29
Sample Variance	0.08
Kurtosis	7.27
Skewness	2.53
Range	1.09
Minimum	0.00
Maximum	1.09
Sum	2.95
Count	13
Confidence Level (95.0%)	0.17

Table 48. Incidence per Patient Years for Pediatric Serious Adverse Event Data

	Incidence per Patient Years	95% CI
Pediatric SAE Pre-Marketing	0.07	0.01 to 0.13
Pediatric SAE Post-Marketing	0.23	0.05 to 0.40

The number of treatment related pediatric serious adverse events obtained from all 64 articles generated a 0.054 incidence per patient years in the pre-marketing studies compared to 0.20 incidence per patient years in the post-marketing studies. Refer to tables 49 to 52 below.

Table 49. Pre-Marketing Pediatric Treatment Related Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Treatment Related Serious Adverse Events	Incidence per Patient years for Pediatric Treatment Related Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	40	0.12
Bergenstal 2010	Pre	12.00	78	78.00	11	0.14
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.00
Nimri 2020	pre	6.00	122	61.00	3	0.05
Plotnick 2003	pre	120.00	95	950.00	5	0.01
Thabit 2015b	pre	8.30	25	17.29	2	0.12
Buckingham 2018	Pre	0.30	24	0.60	0	0.00
Slover 2018	pre	0.25	158	3.29	0	0.00

Table 50. Post-Marketing Pediatric Treatment Related Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Pediatric Treatment Related Serious Adverse Events	Incidence per Patient years for Pediatric Treatment Related Serious Adverse Events
Blair 2019	Post	12.00	144	144.00	14	0.10
Brorsson 2014	post	24.00	216	432.00	53	0.12
DeBoer 2017	post	0.20	12	0.20	0	0.00
Deeb 2019	Post	6.00	14	7.00	2	0.29
Fox 2005	post	6.00	11	5.50	6	1.09
Jeha 2005	post	7.25	10	6.04	0	0.00
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	10	0.45
Pinhas-Hamiel 2010	post	60.00	56	280.00	29	0.10
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	2	0.04
Weintrob 2002	post	8.00	23	15.33	1	0.07
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 51. Statistics for Pediatric Treatment Related Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Treatment Related Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.05
Standard Error	0.02
Median	0.03
Mode	0.00
Standard Deviation	0.06
Sample Variance	0.00
Kurtosis	-2.09
Skewness	0.48
Range	0.14
Minimum	0.00
Maximum	0.14
Sum	0.44
Count	8
Confidence Level (95.0%)	0.05

Incidence per Patient Years for Pediatric Treatment Related Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.20
Standard Error	0.08
Median	0.10
Mode	0.00
Standard Deviation	0.30
Sample Variance	0.09
Kurtosis	7.00
Skewness	2.51
Range	1.09
Minimum	0.00
Maximum	1.09
Sum	2.65
Count	13
Confidence Level (95.0%)	0.18

Table 52. Incidence per Patient Years for Pediatric Treatment Related Serious Adverse Event Data

	Incidence per Patient Years	95% CI		
Pediatric Treatment Related SAE Pre-Marketing	0.05	0.00	to	0.11
Pediatric Treatment Related SAE Post-Marketing	0.20	0.02	to	0.38

The total number of all hypoglycemic adverse events and serious adverse events obtained from all 64 articles generated a 4.21 incidence per patient years in the pre-marketing studies compared to 0.32 incidence per patient years in the post-marketing studies. Refer to tables 53 to 56 below.

Table 53. Pre-Marketing All Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Hypoglycemic Adverse Events	Incidence per Patient years for All Hypoglycemic Adverse Events
Ahern 2002	pre	24.00	161	322.00	38	0.12
Bergenstal 2010	Pre	12.00	244	244.00	32	0.13
Bergenstal 2013	Pre	3.00	247	61.75	5	0.08
Bosi 2019	Pre	6.00	153	76.50	14	0.18
Brown 2019	Pre	6.00	168	84.00	0	0.00
Buckingham 2018	Pre	0.30	58	1.45	45	31.03
Christiansen 2020	pre	0.40	20	0.67	8	12.00
Dassau 2017	pre	3.25	30	8.13	1	0.12
Hoogma 2005	pre	16.00	223	297.33	13	0.04
Kropff 2015	pre	2.00	32	5.33	0	0.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	37	39.47
Nimri 2014	pre	3.00	21	5.25	1	0.19
Nimri 2020	pre	6.00	122	61.00	7	0.11
Plotnick 2003	pre	120.00	95	950.00	18	0.02
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	2	0.33
Thabit 2015a	pre	8.30	33	22.83	1	0.04
Thabit 2015b	pre	8.30	25	17.29	2	0.12
Slover 2018	pre	0.25	158	3.29	1	0.30

Table 54. Post-Marketing All Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Hypoglycemic Adverse Events	Incidence per Patient years for All Hypoglycemic Adverse Events
Bally 2017	post	5.00	28	11.67	0	0.00
Battelino 2012	post	16.00	153	204.00	6	0.03
Blair 2019	post	12.00	144	144.00	7	0.05
Bode 2001	post	2.25	29	5.44	1	0.18
Bode 2020	post	3.50	46	13.42	2	0.15
Bolli 2009	post	6.75	24	13.50	2	0.15
Brorsson 2014	post	24.00	216	432.00	13	0.03
Deeb 2019	post	6.00	43	21.50	1	0.05
Dejgaard 2019	post	6.50	44	23.83	1	0.04
DeVries 2002	post	4.00	32	10.67	3	0.28
Fox 2005	post	6.00	11	5.50	2	0.36
Garg 2014	post	6.00	41	20.50	5	0.24
Hirsch 2008	post	6.00	138	69.00	14	0.20
Hoogma 2006	post	2.50	59	12.29	4	0.33
Jankovec 2010	post	36.00	784	2352.00	243	0.10
Jeha 2005	post	7.25	10	6.04	1	0.17
Kovatchev 2020	post	10.00	80	66.67	5	0.08
Lebenthal 2012	post	6.00	29	14.50	2	0.14
Ly 2013	post	6.00	95	47.50	11	0.23
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	8	0.36
Pinhas-Hamiel 2010	post	60.00	56	280.00	22	0.08
Raskin 2001	post	6.00	58	29.00	6	0.21
Raskin 2003	post	6.00	60	30.00	0	0.00
Reznik 2014	post	6.00	168	84.00	0	0.00
Riddle 2018	post	1.00	32	2.67	15	5.63
Shehadeh 2004	post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	1	0.02
Thrasher 2020	post	2.50	43	8.96	4	0.45
von Bon 2011	post	9.25	256	197.33	45	0.23
Weintrob 2002	post	8.00	23	15.33	1	0.07
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 55. Statistics for All Hypoglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Hypoglycemic Adverse Events in Pre-Maketing Clinical Trials	
Mean	4.22
Standard Error	2.47
Median	0.12
Mode	0.00
Standard Deviation	11.03
Sample Variance	121.57
Kurtosis	6.58
Skewness	2.72
Range	39.47
Minimum	0.00
Maximum	39.47
Sum	84.30
Count	20
Confidence Level (95.0%)	5.16

Incidence per Patient Years for All Hypoglycemic Adverse Events in Post-Maketing Clinical Trials	
Mean	0.32
Standard Error	0.17
Median	0.14
Mode	0.00
Standard Deviation	0.98
Sample Variance	0.95
Kurtosis	30.90
Skewness	5.52
Range	5.63
Minimum	0.00
Maximum	5.63
Sum	10.23
Count	32
Confidence Level (95.0%)	0.35

Table 56. Incidence per Patient Years for All Hypoglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
ALL Hypoglysimic AE Pre-Marketing	4.22	-0.95 to 9.38
ALL Hypoglysimic AE Post-Marketing	0.32	-0.03 to 0.67

The number of hypoglycemic adverse events obtained from all 64 articles generated a 6.51 incidence per patient years in the pre-marketing studies compared to 1.27 incidence per patient years in the post-marketing studies. Refer to tables 57 to 60 below.

Table 57. Pre-Marketing Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Hypoglycemic Adverse Events	Incidence per Patient years for Hypoglycemic Adverse Events
Bergenstal 2013	Pre	247.00	3	61.75	4	0.06
Bosi 2019	Pre	153.00	6	76.50	13	0.17
Christiansen 2020	pre	20.00	0.4	0.67	8	12.00
Hoogma 2005	pre	223.00	16	297.33	0	0.00
Nimri 2013	pre	15.00	0.75	0.94	37	39.47
Nimri 2020	pre	122.00	6	61.00	5	0.08
Plotnick 2003	pre	95.00	120	950.00	18	0.02
Slover 2018	pre	158.00	0.25	3.29	1	0.30

Table 58. Post-Marketing Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Hypoglycemic Adverse Events	Incidence per Patient years for Hypoglycemic Adverse Events
Blair 2019	Post	144.00	12	144.00	6	0.04
Kovatchev 2020	Post	80.00	10	66.67	5	0.08
Lebenthal 2012	Post	29.00	6	14.50	2	0.14
Riddle 2018	Post	32.00	1	2.67	15	5.63
Thrasher 2020	Post	43.00	2.5	8.96	4	0.45

Table 59. Statistics for Hypoglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Hypoglycemic Adverse Events in Pre-Maketing Clinical Trials	
Mean	6.51
Standard Error	4.93
Median	0.13
Mode	#N/A
Standard Deviation	13.95
Sample Variance	194.62
Kurtosis	5.87
Skewness	2.41
Range	39.47
Minimum	0.00
Maximum	39.47
Sum	52.11
Count	8
Confidence Level (95.0%)	11.66

Incidence per Patient Years for Hypoglycemic Adverse Events in Post-Maketing Clinical Trials	
Mean	1.27
Standard Error	1.09
Median	0.14
Mode	#N/A
Standard Deviation	2.44
Sample Variance	5.97
Kurtosis	4.91
Skewness	2.21
Range	5.58
Minimum	0.04
Maximum	5.63
Sum	6.33
Count	5
Confidence Level (95.0%)	3.03

Table 60. Incidence per Patient Years for Hypoglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
Hypoglysimic AE Pre-Marketing	6.51	-5.15 to 18.18
Hypoglysimic AE Post-Marketing	1.27	-1.77 to 4.30

The number of hypoglycemic serious adverse events obtained from all 64 articles generated a 0.068 incidence per patient years in the pre-marketing studies compared to 0.13 incidence per patient years in the post-marketing studies. Refer to tables 61 to 64 below.

Table 61. Pre-Marketing Severe Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Severe Hypoglycemia Adverse Events	Incidence per Patient years for Severe Hypoglycemia Adverse Events
Ahern 2002	pre	24.00	161	322.00	38	0.12
Bergenstal 2010	Pre	12.00	244	244.00	32	0.13
Bergenstal 2013	Pre	3.00	247	61.75	1	0.02
Bosi 2019	Pre	6.00	153	76.50	1	0.01
Brown 2019	Pre	6.00	168	84.00	0	0.00
Christiansen 2020	pre	0.40	20	0.67	0	0.00
Dassau 2017	pre	3.25	30	8.13	1	0.12
Hoogma 2005	pre	16.00	223	297.33	13	0.04
Kropff 2015	pre	2.00	32	5.33	0	0.00
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2013	pre	0.75	15	0.94	0	0.00
Nimri 2014	pre	3.00	21	5.25	1	0.19
Nimri 2020	pre	6.00	122	61.00	2	0.03
Spaic 2017	pre	1.40	30	3.50	0	0.00
Thabit 2014	pre	3.00	24	6.00	2	0.33
Thabit 2015a	pre	8.30	33	22.83	1	0.04
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 62. Post-Marketing Severe Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Severe Hypoglycemia Adverse Events	Incidence per Patient years for Severe Hypoglycemia Adverse Events
Bally 2017	post	5.00	28	11.67	0	0.00
Battelino 2012	post	16.00	153	204.00	6	0.03
Blair 2019	Post	12.00	144	144.00	1	0.01
Bode 2001	pre	2.25	29	5.44	1	0.18
Bode 2020	pre	3.50	46	13.42	2	0.15
Bolli 2009	post	6.75	24	13.50	2	0.15
Brorsson 2014	post	24.00	216	432.00	13	0.03
Deeb 2019	Post	6.00	43	21.50	1	0.05
Dejgaard 2019	pre	6.50	44	23.83	1	0.04
DeVries 2002	post	4.00	32	10.67	3	0.28
Fox 2005	post	6.00	11	5.50	2	0.36
Garg 2014	pre	6.00	41	20.50	5	0.24
Hirsch 2008	post	6.00	138	69.00	14	0.20
Hoogma 2006	post	2.50	59	12.29	4	0.33
Jankovec 2010	post	36.00	784	2352.00	243	0.10
Jeha 2005	post	7.25	10	6.04	1	0.17
Ly 2013	Post	6.00	95	47.50	11	0.23
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	8	0.36
Pinhas-Hamiel 2010	post	60.00	56	280.00	22	0.08
Raskin 2001	pre	6.00	58	29.00	6	0.21
Raskin 2003	post	6.00	60	30.00	0	0.00
Reznik 2014	Post	6.00	168	84.00	0	0.00
Riddle 2018	Pre	1.00	32	2.67	0	0.00
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	1	0.02
von Bon 2011	post	9.25	256	197.33	45	0.23
Weintrob 2002	post	8.00	23	15.33	1	0.07
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 63. Statistics for Severe Hypoglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Severe Hypoglycemia Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.07
Standard Error	0.02
Median	0.03
Mode	0.00
Standard Deviation	0.09
Sample Variance	0.01
Kurtosis	3.38
Skewness	1.75
Range	0.33
Minimum	0.00
Maximum	0.33
Sum	1.16
Count	17
Confidence Level (95.0%)	0.05

Incidence per Patient Years for Severe Hypoglycemia Adverse Events in Post-Maketing Clinical Trials	
Mean	0.13
Standard Error	0.02
Median	0.11
Mode	0.00
Standard Deviation	0.12
Sample Variance	0.01
Kurtosis	-1.02
Skewness	0.47
Range	0.36
Minimum	0.00
Maximum	0.36
Sum	3.91
Count	29
Confidence Level (95.0%)	0.05

Table 64. Incidence per Patient Years for Severe Hypoglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
Severe Hypoglycemia SAE Pre-Marketing	0.07	0.02 to 0.12
Severe Hypoglycemia SAE Post-Marketing	0.13	0.09 to 0.18

The total number of all pediatric hypoglycemic adverse events and serious adverse events obtained from all 64 articles generated a 0.13 incidence per patient years in the pre-marketing studies compared to 0.14 incidence per patient years in the post-marketing studies. Refer to tables 65 to 68 below.

Table 65. Pre-Marketing All Pediatric Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pediatric Hypoglycemic Adverse Events	Incidence per Patient years for All Pediatric Hypoglycemic Adverse Events
Ahern 2002	pre	24.00	161	322.00	38	0.12
Bergenstal 2010	Pre	12.00	78	78.00	7	0.09
Nimri 2020	pre	6.00	122	61.00	7	0.11
Plotnick 2003	pre	120.00	95	950.00	18	0.02
Slover 2018	pre	0.25	158	3.29	1	0.30
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 66. Post-Marketing All Pediatric Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pediatric Hypoglycemic Adverse Events	Incidence per Patient years for All Pediatric Hypoglycemic Adverse Events
Blair 2019	Post	12.00	144	144.00	7	0.05
Brorsson 2014	post	24.00	216	432.00	13	0.03
Deeb 2019	Post	6.00	15	7.50	1	0.13
Fox 2005	post	6.00	11	5.50	2	0.36
Jeha 2005	post	7.25	10	6.04	1	0.17
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	8	0.36
Pinhas-Hamiel 2010	post	60.00	56	280.00	22	0.08
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	1	0.02
Weintrob 2002	post	8.00	23	15.33	1	0.07
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 67. Statistics for All Pediatric Hypoglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Pediatric Hypoglycemic Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.13
Standard Error	0.04
Median	0.12
Mode	#N/A
Standard Deviation	0.09
Sample Variance	0.01
Kurtosis	3.55
Skewness	1.50
Range	0.28
Minimum	0.02
Maximum	0.30
Sum	0.76
Count	6
Confidence Level (95.0%)	0.10

Incidence per Patient Years for All Pediatric Hypoglycemic Adverse Events in Post-Maketing Clinical Trials	
Mean	0.14
Standard Error	0.04
Median	0.09
Mode	#N/A
Standard Deviation	0.13
Sample Variance	0.02
Kurtosis	-0.54
Skewness	0.93
Range	0.36
Minimum	0.00
Maximum	0.36
Sum	1.66
Count	12
Confidence Level (95.0%)	0.08

Table 68. Incidence per Patient Years for All Pediatric Hypoglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
ALL Pediatric Hypoglysimic AE Pre-Marketing	0.13	0.03 to 0.23
ALL Pediatric Hypoglysimic AE Post-Marketing	0.14	0.06 to 0.22

The number of pediatric serious hypoglycemic adverse events obtained from all 64 articles generated a 0.089 incidence per patient years in the pre-marketing studies compared to 0.13 incidence per patient years in the post-marketing studies. Refer to tables 69 to 72 below.

Table 69. Pre-Marketing Pediatric Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Severe Hypoglycemia Adverse Events	Incidence per Patient years for Pediatric Severe Hypoglycemia Adverse Events
Ahern 2002	pre	24.00	161	322.00	38	0.12
Bergenstal 2010	Pre	12.00	78	78.00	7	0.09
Nimri 2020	pre	6.00	122	61.00	2	0.03
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 70. Post-Marketing Pediatric Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Severe Hypoglycemia Adverse Events	Incidence per Patient years for Pediatric Severe Hypoglycemia Adverse Events
Blair 2019	Post	12.00	144	144.00	1	0.01
Brorsson 2014	post	24.00	216	432.00	13	0.03
Deeb 2019	Post	6.00	15	7.50	1	0.13
Fox 2005	post	6.00	11	5.50	2	0.36
Jeha 2005	post	7.25	10	6.04	1	0.17
Mianowska 2015	post	9.00	3	2.25	0	0.00
Nuboer 2008	post	14.00	19	22.17	8	0.36
Pinhas-Hamiel 2010	post	60.00	56	280.00	22	0.08
Shehadeh 2004	Post	12.00	14	14.00	4	0.29
Szypowska 2008	post	12.00	53	53.00	1	0.02
Weintrob 2002	post	8.00	23	15.33	1	0.07
Wilson 2005	post	12.00	9	9.00	1	0.11

Table 71. Statistics for Pediatric Hypoglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Severe Hypoglycemia Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.09
Standard Error	0.02
Median	0.10
Mode	#N/A
Standard Deviation	0.04
Sample Variance	0.00
Kurtosis	1.66
Skewness	-1.45
Range	0.09
Minimum	0.03
Maximum	0.12
Sum	0.36
Count	4
Confidence Level (95.0%)	0.06

Incidence per Patient Years for Pediatric Severe Hypoglycemia Adverse Events in Post-Maketing Clinical Trials	
Mean	0.13
Standard Error	0.04
Median	0.09
Mode	#N/A
Standard Deviation	0.13
Sample Variance	0.02
Kurtosis	-0.62
Skewness	0.89
Range	0.36
Minimum	0.00
Maximum	0.36
Sum	1.62
Count	12
Confidence Level (95.0%)	0.08

Table 72. Incidence per Patient Years for Pediatric Hypoglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
Pediatric Severe Hypoglycemia SAE Pre-Marketing	0.09	0.03 to 0.15
Pediatric Severe Hypoglycemia SAE Post-Marketing	0.13	0.05 to 0.22

The number of diabetic ketoacidosis serious adverse events obtained from all 64 articles generated a 0.0036 incidence per patient years in the pre-marketing studies compared to 0.049 incidence per patient years in the post-marketing studies. Refer to tables 73 to 76 below.

Table 73. Pre-Marketing Diabetic Ketoacidosis Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Diabetic Ketoacidosis Serious Adverse Events	Incidence per Patient years for Diabetic Ketoacidosis Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	2	0.006
Bergenstal 2010	Pre	12.00	244	244.00	3	0.012
Bergenstal 2013	Pre	3.00	247	61.75	0	0.000
Bosi 2019	Pre	6.00	153	76.50	0	0.000
Brown 2019	Pre	6.00	168	84.00	1	0.012
Christiansen 2020	pre	0.40	20	0.67	0	0.000
Dassau 2017	pre	3.25	30	8.13	0	0.000
Hoogma 2005	pre	16.00	223	297.33	4	0.013
Kropff 2015	pre	2.00	32	5.33	0	0.000
Ly 2012	pre	3.00	24	6.00	0	0.000
Nimri 2013	pre	0.75	15	0.94	0	0.000
Nimri 2014	pre	3.00	21	5.25	0	0.000
Nimri 2020	pre	6.00	122	61.00	1	0.016
Plotnick 2003	pre	120.00	95	950.00	1	0.001
Slover 2018	pre	0.25	158	3.29	0	0.000
Spaic 2017	pre	1.40	30	3.50	0	0.000
Thabit 2014	pre	3.00	24	6.00	0	0.000

Table 74. Post-Marketing Diabetic Ketoacidosis Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Diabetic Ketoacidosis Serious Adverse Events	Incidence per Patient years for Diabetic Ketoacidosis Serious Adverse Events
Bally 2017	post	5.00	28	11.67	0	0.000
Battelino 2012	post	16.00	153	204.00	6	0.029
Blair 2019	Post	12.00	144	144.00	2	0.014
Bode 2020	Post	3.50	46	13.42	0	0.000
Brorsson 2014	Post	24.00	216	432.00	12	0.028
Deeb 2019	Post	6.00	43	21.50	1	0.047
DeVries 2002	Post	4.00	32	10.67	1	0.094
Fox 2005	Post	6.00	11	5.50	4	0.727
Freckmann 2017	Post	2.00	73	12.17	1	0.082
Hirsch 2008	Post	6.00	138	69.00	1	0.014
Hoogma 2006	Post	2.50	59	12.29	0	0.000
Jankovec 2010	Post	36.00	784	2352.00	142	0.060
Jeha 2005	Post	7.25	10	6.04	0	0.000
Ly 2013	Post	6.00	95	47.50	0	0.000
Mianowska 2015	Post	9.00	3	2.25	0	0.000
Nuboer 2008	Post	14.00	19	22.17	2	0.090
Pinhas-Hamiel 2010	Post	60.00	56	280.00	7	0.025
Raskin 2001	Post	6.00	58	29.00	1	0.034
Reznik 2014	Post	6.00	168	84.00	0	0.000
Riddle 2018	Post	1.00	32	2.67	0	0.000
Shehadeh 2004	Post	12.00	14	14.00	0	0.000
Szypowska 2008	Post	12.00	53	53.00	1	0.019
Thrasher 2018	Post	2.50	27	5.63	0	0.000
Thrasher 2020	Post	2.50	43	8.96	0	0.000
Tumminia 2015	post	14.00	20	23.33	1	0.043
von Bon 2011	post	9.25	256	197.33	1	0.005
Wilson 2005	post	12.00	9	9.00	0	0.000

Table 75. Statistics for Diabetic Ketoacidosis Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Diabetic Ketoacidosis Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.004
Standard Error	0.001
Median	0.000
Mode	0.000
Standard Deviation	0.006
Sample Variance	0.000
Kurtosis	-0.065
Skewness	1.281
Range	0.016
Minimum	0.000
Maximum	0.016
Sum	0.061
Count	17
Confidence Level (95.0%)	0.003

Incidence per Patient Years for Diabetic Ketoacidosis Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.049
Standard Error	0.027
Median	0.014
Mode	0.000
Standard Deviation	0.139
Sample Variance	0.019
Kurtosis	24.351
Skewness	4.837
Range	0.727
Minimum	0.000
Maximum	0.727
Sum	1.312
Count	27
Confidence Level (95.0%)	0.055

Table 76. Incidence per Patient Years for Diabetic Ketoacidosis Serious Adverse Event Data

	Incidence per Patient Years	95% CI
DKA SAE Pre-Marketing	0.004	0.00 to 0.01
DKA SAE Post-Marketing	0.049	-0.01 to 0.10

The number of pediatric diabetic ketoacidosis serious adverse events obtained from all 64 articles generated a 0.008 incidence per patient years in the pre-marketing studies compared to 0.080 incidence per patient years in the post-marketing studies. Refer to tables 77 to 80 below.

Table 77. Pre-Marketing Pediatric Diabetic Ketoacidosis Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Diabetic Ketoacidosis Serious Adverse Events	Incidence per Patient years for Pediatric Diabetic Ketoacidosis Serious Adverse Events
Ahern 2002	pre	24.00	161	322.00	2	0.006
Bergenstal 2010	Pre	12.00	78	78.00	3	0.038
Buckingham 2018	Pre	0.30	24	0.60	0	0.000
Ekhlaspour 2019	Pre	0.13	48	0.53	0	0.000
Nimri 2020	pre	6.00	122	61.00	1	0.016
Plotnick 2003	pre	120.00	95	950.00	1	0.001
Slover 2018	pre	0.25	158	3.29	0	0.000
Thabit 2015b	pre	8.30	25	17.29	0	0.000

Table 78. Post-Marketing Pediatric Diabetic Ketoacidosis Serious Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Pediatric Diabetic Ketoacidosis Serious Adverse Events	Incidence per Patient years for Pediatric Diabetic Ketoacidosis Serious Adverse Events
Blair 2019	Post	12.00	144	144.00	2	0.014
Brorsson 2014	post	24.00	216	432.00	12	0.028
DeBoer 2017	post	0.20	12	0.20	0	0.000
Deeb 2019	Post	6.00	14	7.00	1	0.143
Fox 2005	post	6.00	11	5.50	4	0.727
Jeha 2005	post	7.25	10	6.04	0	0.000
Mianowska 2015	post	9.00	3	2.25	0	0.000
Nuboer 2008	post	14.00	19	22.17	2	0.090
Pinhas-Hamiel 2010	post	60.00	56	280.00	7	0.025
Shehadeh 2004	Post	12.00	14	14.00	0	0.000
Szypowska 2008	post	12.00	53	53.00	1	0.019
Weintrob 2002	post	8.00	23	15.33	0	0.000
Wilson 2005	post	12.00	9	9.00	0	0.000

Table 79. Statistics for Pediatric Diabetic Ketoacidosis Serious Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Pediatric Diabetic Ketoacidosis Serious Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.008
Standard Error	0.005
Median	0.001
Mode	0.000
Standard Deviation	0.014
Sample Variance	0.000
Kurtosis	4.072
Skewness	2.049
Range	0.038
Minimum	0.000
Maximum	0.038
Sum	0.062
Count	8
Confidence Level (95.0%)	0.011

Incidence per Patient Years for Pediatric Diabetic Ketoacidosis Serious Adverse Events in Post-Maketing Clinical Trials	
Mean	0.080
Standard Error	0.055
Median	0.014
Mode	0.000
Standard Deviation	0.199
Sample Variance	0.040
Kurtosis	11.486
Skewness	3.335
Range	0.727
Minimum	0.000
Maximum	0.727
Sum	1.046
Count	13
Confidence Level (95.0%)	0.120

Table 80. Incidence per Patient Years for Pediatric Diabetic Ketoacidosis Serious Adverse Event Data

	Incidence per Patient Years	95% CI
Pediatric DKA Pre-Marketing	0.008	0.00 to 0.02
Pediatric DKA Post-Marketing	0.080	-0.04 to 0.20

The total number of all hyperglycemic adverse events and serious adverse events obtained from all 64 articles generated a 0.34 incidence per patient years in the pre-marketing studies compared to 0.08 incidence per patient years in the post-marketing studies. Refer to tables 81 to 84 below.

Table 81. Pre-Marketing All Hyperglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Hyperglycemic Adverse Events	Incidence per Patient years for All Hyperglycemic Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	3	0.05
Bosi 2019	Pre	6.00	153	76.50	12	0.16
Brown 2019	Pre	6.00	168	84.00	14	0.17
Kovatchev 2017	pre	5.00	14	5.83	2	0.34
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2014	pre	3.00	21	5.25	9	1.71
Nimri 2020	pre	6.00	122	61.00	5	0.08
Thabit 2015a	pre	8.30	33	22.83	10	0.44
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 82. Post-Marketing All Hyperglycemic Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Hyperglycemic Adverse Events	Incidence per Patient years for All Hyperglycemic Adverse Events
Blair 2019	Post	12.00	144	144.00	2	0.01
Freckmann 2017	post	2.00	73	12.17	2	0.16
Kovatchev 2020	post	10.00	80	66.67	3	0.05
Mianowska 2015	post	9.00	3	2.25	0	0.00
Raskin 2003	post	6.00	60	30.00	6	0.20
Reznik 2014	Post	6.00	168	84.00	7	0.08

Table 83. Statistics for All Hyperglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Hyperglycemic Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.34
Standard Error	0.18
Median	0.16
Mode	#N/A
Standard Deviation	0.53
Sample Variance	0.28
Kurtosis	7.28
Skewness	2.63
Range	1.71
Minimum	0.00
Maximum	1.71
Sum	3.07
Count	9
Confidence Level (95.0%)	0.41

Incidence per Patient Years for All Hyperglycemic Adverse Events in Post-Maketing Clinical Trials	
Mean	0.08
Standard Error	0.03
Median	0.06
Mode	#N/A
Standard Deviation	0.08
Sample Variance	0.01
Kurtosis	-1.59
Skewness	0.57
Range	0.20
Minimum	0.00
Maximum	0.20
Sum	0.51
Count	6
Confidence Level (95.0%)	0.09

Table 84. Incidence per Patient Years for All Hyperglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
All Hyperglycemic AE Pre-Marketing	0.34	-0.07 to 0.75
All Hyperglycemic AE Post-Marketing	0.08	0.00 to 0.17

The number of hyperglycemic adverse events obtained from all 64 articles generated a 0.34 incidence per patient years in the pre-marketing studies compared to 0.10 incidence per patient years in the post-marketing studies. Refer to tables 85 to 88 below.

Table 85. Pre-Marketing Hyperglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Hyperglycemic Adverse Events	Incidence per Patient years for Hyperglycemic Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	3	0.05
Bosi 2019	Pre	6.00	153	76.50	12	0.16
Brown 2019	Pre	6.00	168	84.00	14	0.17
Ly 2012	pre	3.00	24	6.00	0	0.00
Nimri 2014	pre	3.00	21	5.25	9	1.71
Nimri 2020	pre	6.00	122	61.00	5	0.08
Thabit 2015a	pre	8.30	33	22.83	10	0.44
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 86. Post-Marketing Hyperglycemic Hypoglycemic Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Hyperglycemic Adverse Events	Incidence per Patient years for Hyperglycemic Adverse Events
Blair 2019	Post	12.00	144	144.00	2	0.01
Freckmann 2017	post	2.00	73	12.17	2	0.16
Kovatchev 2020	post	10.00	80	66.67	3	0.05
Raskin 2003	post	6.00	60	30.00	6	0.20
Reznik 2014	Post	6.00	168	84.00	5	0.06

Table 87. Statistics for Hyperglycemic Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Hyperglycemic Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.34
Standard Error	0.20
Median	0.14
Mode	#N/A
Standard Deviation	0.57
Sample Variance	0.33
Kurtosis	6.72
Skewness	2.55
Range	1.71
Minimum	0.00
Maximum	1.71
Sum	2.72
Count	8
Confidence Level (95.0%)	0.48

Incidence per Patient Years for Hyperglycemic Adverse Events in Post-Maketing Clinical Trials	
Mean	0.10
Standard Error	0.04
Median	0.06
Mode	#N/A
Standard Deviation	0.08
Sample Variance	0.01
Kurtosis	-2.41
Skewness	0.52
Range	0.19
Minimum	0.01
Maximum	0.20
Sum	0.48
Count	5
Confidence Level (95.0%)	0.10

Table 88. Incidence per Patient Years for Hyperglycemic Adverse Event Data

	Incidence per Patient Years	95% CI
Hyperglycemic AE Pre-Marketing	0.34	-0.14 to 0.82
Hyperglycemic AE Post-Marketing	0.10	0.00 to 0.20

The total number of pump related adverse events and serious adverse events obtained from all 64 articles generated a 0.56 incidence per patient years in the pre-marketing studies compared to 2.07 incidence per patient years in the post-marketing studies. Refer to tables 89 to 92 below.

Table 89. Pre-Marketing All Pump Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pump Related Adverse Events	Incidence per Patient years for All Pump Related Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	16	0.26
Brown 2019	Pre	6.00	168	84.00	1	0.01
Hoogma 2005	pre	16.00	223	297.33	28	0.09
Nimri 2013	pre	0.75	15	0.94	3	3.20
Nimri 2020	pre	6.00	122	61.00	5	0.08
Slover 2018	pre	0.25	158	3.29	1	0.30
Thabit 2015a	pre	8.30	33	22.83	6	0.26
Thabit 2015b	pre	8.30	25	17.29	1	0.06
Dassau 2017	pre	3.25	30	8.13	6	0.74

Table 90. Post-Marketing All Pump Related Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pump Related Adverse Events	Incidence per Patient years for All Pump Related Adverse Events
Bally 2017	post	5.000	28	11.667	4	0.343
Blair 2019	Post	12.000	144	144.000	4	0.028
Bode 2020	Post	3.500	46	13.417	5	0.373
Bolli 2009	Post	6.750	24	13.500	20	1.481
Deeb 2019	Post	6.000	43	21.500	0	0.000
Freckmann 2017	Post	2.000	73	12.167	1	0.082
Jankovec 2010	Post	36.000	784	2352.000	655	0.278
Jeha 2005	Post	7.250	10	6.042	0	0.000
Kovatchev 2020	Post	10.000	80	66.667	2	0.030
Lebenthal 2012	Post	6.000	29	14.500	47	3.241
Ly 2013	Post	6.000	95	47.500	2	0.042
Norgaard 2015	Post	0.500	45	1.875	43	22.933
Reznik 2014	Post	6.000	168	84.000	35	0.417
Shehadeh 2004	Post	12.000	14	14.000	0	0.000
Thrasher 2018	Post	2.500	27	5.625	10	1.778
Weintrob 2002	Post	8.000	23	15.333	58	3.783
Hoogma 2006	post	2.500	59	12.292	5	0.407

Table 91. Statistics for All Pump Related Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Pump Related Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.56
Standard Error	0.34
Median	0.26
Mode	#N/A
Standard Deviation	1.02
Sample Variance	1.03
Kurtosis	7.81
Skewness	2.75
Range	3.19
Minimum	0.01
Maximum	3.20
Sum	5.01
Count	9
Confidence Level (95.0%)	0.78

Incidence per Patient Years for All Pump Related Adverse Events in Post-Maketing Clinical Trials	
Mean	2.07
Standard Error	1.33
Median	0.34
Mode	0.00
Standard Deviation	5.50
Sample Variance	30.24
Kurtosis	15.22
Skewness	3.83
Range	22.93
Minimum	0.00
Maximum	22.93
Sum	35.22
Count	17
Confidence Level (95.0%)	2.83

Table 92. Incidence per Patient Years for All Pump Related Adverse Event Data

	Incidence per Patient Years	95% CI
Total Pump Related AE Pre-Marketing	0.56	-0.22 to 1.34
Total Pump Related AE Post-Marketing	2.07	-0.76 to 4.90

The number of device related adverse events obtained from all 64 articles generated a 0.61 incidence per patient years in the pre-marketing studies compared to 0.82 incidence per patient years in the post-marketing studies. Refer to tables 93 to 96 below.

Table 93. Pre-Marketing Device Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Device Adverse Events	Incidence per Patient years for Device Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	16	0.26
Brown 2019	Pre	6.00	168	84.00	1	0.01
Hoogma 2005	pre	16.00	223	297.33	28	0.09
Nimri 2013	pre	0.75	15	0.94	3	3.20
Slover 2018	pre	0.25	158	3.29	1	0.30
Thabit 2015a	pre	8.30	33	22.83	6	0.26
Thabit 2015b	pre	8.30	25	17.29	1	0.06
Dassau 2017	pre	3.25	30	8.13	6	0.74

Table 94. Post-Marketing Device Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Device Adverse Events	Incidence per Patient years for Device Adverse Events
Bally 2017	post	5.00	28	11.67	4	0.34
Bolli 2009	post	6.75	24	13.50	20	1.48
Freckmann 2017	post	2.00	73	12.17	1	0.08
Jankovec 2010	post	36.00	784	2352.00	457	0.19
Jeha 2005	post	7.25	10	6.04	0	0.00
Kovatchev 2020	post	10.00	80	66.67	2	0.03
Lebenthal 2012	post	6.00	29	14.50	31	2.14
Ly 2013	Post	6.00	95	47.50	2	0.04
Reznik 2014	Post	6.00	168	84.00	35	0.42
Shehadeh 2004	Post	12.00	14	14.00	0	0.00
Thrasher 2018	Post	2.50	27	5.63	10	1.78
Weintrob 2002	Post	8.00	23	15.33	58	3.78
Hoogma 2006	post	2.50	59	12.29	5	0.41

Table 95. Statistics for Device Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Device Adverse Events in Pre-Maketing Clinical Trials	
Mean	0.62
Standard Error	0.38
Median	0.26
Mode	#N/A
Standard Deviation	1.07
Sample Variance	1.14
Kurtosis	6.92
Skewness	2.59
Range	3.19
Minimum	0.01
Maximum	3.20
Sum	4.93
Count	8
Confidence Level (95.0%)	0.89

Incidence per Patient Years for Device Adverse Events in Post-Maketing Clinical Trials	
Mean	0.82
Standard Error	0.32
Median	0.34
Mode	0.00
Standard Deviation	1.15
Sample Variance	1.33
Kurtosis	2.56
Skewness	1.70
Range	3.78
Minimum	0.00
Maximum	3.78
Sum	10.69
Count	13
Confidence Level (95.0%)	0.70

Table 96. Incidence per Patient Years for Device Adverse Event Data

	Incidence per Patient Years	95% CI
Device AE Pre-Marketing	0.62	-0.28 to 1.51
Device AE Post-Marketing	0.82	0.13 to 1.52

The total number of infection adverse events and serious adverse events obtained from all 64 articles generated a 0.96 incidence per patient years in the pre-marketing studies compared to 0.44 incidence per patient years in the post-marketing studies. Refer to tables 97 to 100 below.

Table 97. Pre-Marketing All Infection Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Infection Adverse Events	Incidence per Patient years All Infections Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	2	0.03
Brown 2019	Pre	6.00	168	84.00	1	0.01
Buckingham 2017	pre	0.03	69	0.19	1	5.22
Dassau 2017	pre	3.25	30	8.13	5	0.62
Hoogma 2005	pre	16.00	223	297.33	3	0.01
Kropff 2015	pre	2.00	32	5.33	4	0.75
Nimri 2013	pre	0.75	15	0.94	2	2.13
Nimri 2014	pre	3.00	21	5.25	1	0.19
Nimri 2020	pre	6.00	122	61.00	74	1.21
Plotnick 2003	pre	120.00	95	950.00	12	0.01
Thabit 2014	pre	3.00	24	6.00	8	1.33
Thabit 2015a	pre	8.30	33	22.83	18	0.79
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 98. Post-Marketing All Infection Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Infection Adverse Events	Incidence per Patient years All Infections Adverse Events
Bally 2017	post	5.00	28	11.67	2	0.17
Blair 2019	Post	12.00	144	144.00	9	0.06
Bode 2001	Post	2.25	29	5.44	9	1.66
Bolli 2009	Post	6.75	24	13.50	1	0.07
Dejgaard 2019	Post	6.50	44	23.83	3	0.13
Haymond 2017	Post	4.25	16	5.67	1	0.18
Hirsch 2008	Post	6.00	138	69.00	2	0.03
Norgaard 2015	Post	0.50	45	1.88	1	0.53
Shehadeh 2004	Post	12.00	14	14.00	1	0.07
Thrasher 2018	Post	2.50	27	5.63	3	0.53
Thrasher 2020	Post	2.50	43	8.96	8	0.89
Weintrob 2002	Post	8.00	23	15.33	14	0.91

Table 99. Statistics for All Infection Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Infections Events in Pre-Maketing Clinical Trials	
Mean	0.96
Standard Error	0.40
Median	0.62
Mode	#N/A
Standard Deviation	1.44
Sample Variance	2.07
Kurtosis	6.95
Skewness	2.48
Range	5.21
Minimum	0.01
Maximum	5.22
Sum	12.43
Count	13
Confidence Level (95.0%)	0.87

Incidence per Patient Years for All Infections Events in Post-Maketing Clinical Trials	
Mean	0.44
Standard Error	0.14
Median	0.17
Mode	0.53
Standard Deviation	0.50
Sample Variance	0.25
Kurtosis	2.05
Skewness	1.52
Range	1.63
Minimum	0.03
Maximum	1.66
Sum	5.24
Count	12
Confidence Level (95.0%)	0.32

Table 100. Incidence per Patient Years for All Infection Adverse Event Data

	Incidence per Patient Years	95% CI
All Infections AE Pre-Marketing	0.96	0.09 to 1.82
All Infections AE Post-Marketing	0.44	0.12 to 0.75

The total number of pediatric infection adverse events and serious adverse events obtained from all 64 articles generated a 0.34 incidence per patient years in the pre-marketing studies compared to 0.21 incidence per patient years in the post-marketing studies. Refer to tables 101 to 104 below.

Table 101. Pre-Marketing All Pediatric Infection Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pediatric Infection Adverse Events	Incidence per Patient years All Pediatric Infections Adverse Events
Bergenstal 2010	Pre	12.00	78	78.00	1	0.01
Nimri 2020	pre	6.00	122	61.00	74	1.21
Plotnick 2003	pre	120.00	95	950.00	12	0.01
Thabit 2015b	pre	8.30	25	17.29	2	0.12

Table 102. Post-Marketing All Pediatric Infection Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Total Number of Pediatric Infection Adverse Events	Incidence per Patient years All Pediatric Infections Adverse Events
Blair 2019	Post	12.00	144	144.00	9	0.06
Fox 2005	post	6.00	11	5.50	0	0.00
Jeha 2005	post	7.25	10	6.04	0	0.00
Shehadeh 2004	Post	12.00	14	14.00	1	0.07
Weintrob 2002	post	8.00	23	15.33	14	0.91

Table 103. Statistics for All Pediatric Infection Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for All Pediatric Infections Events in Pre-Maketing Clinical Trials	
Mean	0.34
Standard Error	0.29
Median	0.06
Mode	#N/A
Standard Deviation	0.59
Sample Variance	0.34
Kurtosis	3.86
Skewness	1.96
Range	1.20
Minimum	0.01
Maximum	1.21
Sum	1.35
Count	4
Confidence Level (95.0%)	0.93

Incidence per Patient Years for All Pediatric Infections Events in Post-Maketing Clinical Trials	
Mean	0.21
Standard Error	0.18
Median	0.06
Mode	0.00
Standard Deviation	0.39
Sample Variance	0.16
Kurtosis	4.86
Skewness	2.20
Range	0.91
Minimum	0.00
Maximum	0.91
Sum	1.05
Count	5
Confidence Level (95.0%)	0.49

Table 104. Incidence per Patient Years for All Pediatric Infection Adverse Event Data

	Incidence per Patient Years	95% CI
All Pediatric Infections AE Pre-Marketing	0.34	-0.59 to 1.27
All Pediatric Infections AE Post-Marketing	0.21	-0.28 to 0.70

The number of respiratory infection adverse events obtained from all 64 articles generated a 0.91 incidence per patient years in the pre-marketing studies compared to 0.53 incidence per patient years in the post-marketing studies. Refer to tables 105 to 108 below.

Table 105. Pre-Marketing Respiratory Track Infections Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Respiratory Track Infection Adverse Events	Incidence per Patient years Respiratory Track Infections Adverse Events
Bergenstal 2013	Pre	3.00	247	61.75	1	0.02
Buckingham 2017	pre	0.03	69	0.19	1	5.22
Hoogma 2005	pre	16.00	223	297.33	1	0.00
Kropff 2015	pre	2.00	32	5.33	3	0.56
Nimri 2020	pre	6.00	122	61.00	2	0.03
Thabit 2014	pre	3.00	24	6.00	5	0.83
Thabit 2015a	pre	8.30	33	22.83	12	0.53
Thabit 2015b	pre	8.30	25	17.29	1	0.06

Table 106. Post-Marketing Respiratory Track Infections Adverse Event Data

Author and Year	Pre or Post Marketing Clinical Trial	Duration of Clinical Trial in Months	CSII Patients	Total Patient Years	Number of Respiratory Track Infection Adverse Events	Incidence per Patient years Respiratory Track Infections Adverse Events
Bally 2017	post	5.00	28	11.67	2	0.17
Bode 2001	post	2.25	29	5.44	9	1.66
Dejgaard 2019	post	6.50	44	23.83	3	0.13
Haymond 2017	post	4.25	16	5.67	1	0.18
Thrasher 2018	post	2.50	27	5.63	3	0.53

Table 107. Statistics for Respiratory Track Infections Adverse Event Pre-marketing and Post Marketing Data

Incidence per Patient Years for Respiratory Track Infections Events in Pre-Maketing Clinical Trials	
Mean	0.91
Standard Error	0.63
Median	0.29
Mode	#N/A
Standard Deviation	1.77
Sample Variance	3.14
Kurtosis	7.24
Skewness	2.65
Range	5.22
Minimum	0.00
Maximum	5.22
Sum	7.25
Count	8
Confidence Level (95.0%)	1.48

Incidence per Patient Years for Respiratory Track Infections Events in Post-Maketing Clinical Trials	
Mean	0.53
Standard Error	0.29
Median	0.18
Mode	#N/A
Standard Deviation	0.65
Sample Variance	0.42
Kurtosis	3.65
Skewness	1.92
Range	1.53
Minimum	0.13
Maximum	1.66
Sum	2.66
Count	5
Confidence Level (95.0%)	0.81

Table 108. Incidence per Patient Years for Respiratory Track Infections Adverse Event Data

	Incidence per Patient Years	95% CI
Respiratory track infection AE Pre-Marketing	0.91	-0.57 to 2.39
Respiratory track infection AE Post-Marketing	0.53	-0.27 to 1.34

Discussion

The hypothesis was; Pre-approval and post-approval clinical trial studies have a statistically different ratio of Adverse Events and Serious Adverse Events ($\alpha < 0.05$). This was not achieved as all the data fell within the statistical parameters. The 95% confidence interval lead to the conclusion that 100% of the data confirmed. This, however, is not entirely representative of the data. The variability from study to study of the adverse events and serious adverse events was very high. The variability was investigated. Multiple studies had many adverse events and serious adverse events that were specific to just one study or a few incidences but with a smaller patient pool in a study of short duration. Slover 2018 which had 122 redness/rash adverse event at the injection site out of 158 injection pump patients (38). Leelarathna 2014 which had 2 hypoglycemic adverse events in 8 patients for a 1 period overnight study of 12 hours (31). Riddle 2018 which had 15 GI adverse events out of 32 injection pump patients (75). No single study could be identified as an outlier and all studies met criteria for inclusion into the analysis. Data from table 3e is an example of what was observed through the study. The total adverse event for Pre-Marketing demonstrated a 7.92 incidence per patient year with a 95.0% confidence interval that ranges from 1.82 to 14.01 and the total adverse event for Post-Marketing demonstrated a 2.18 incidence per patient year with a 95.0% confidence interval that ranges from 0.77 to 3.59. Even if the pre-marketing incidence per year was 3.6 times higher that the post-marketing incidence per year it was deemed not statistically significant as both values fit comfortably into the 95% confidence intervals of one another. However, even if the data is not statistically significant, a common trend was observed that was consistent throughout the group and subgroup analysis that is deemed clinically relevant. As

demonstrated in the article by Allen et al. 2017, clinical relevance or clinical significance can be analyzed even when there is no statistical significance (83).

The adverse events were between 3.1 to 3.9 times higher in the pre-marketing studies compared to the post-marketing studies for the;

- total cumulative adverse events and serious adverse events (3.6 times higher)
- total cumulative treatment related adverse events and serious adverse events (3.9 times higher)
- total adverse events (3.1 times higher)
- total treatment related adverse events (3.5 times higher)
- Hyperglycaemia (3.5 times higher)

The pediatric specific adverse events showed between 1.4 to 2.4 times higher in the post-marketing studies compared to the pre-marketing studies for:

- total cumulative pediatric adverse events and serious adverse events (1.7 times higher)
- total cumulative pediatric treatment related adverse events and serious adverse events (2.4 times higher)
- total pediatric adverse events (1.7 times higher)
- Pediatric Treatment related AE as well (2.4 times higher)
- total pediatric treatment related adverse events (1.4 times higher)

Thus, the data for the adverse events as a whole is demonstrating clinically relevant data that goes opposite to the initial hypothesis and the pediatric adverse event data is providing information that is in line with the initial hypothesis. The rational behind the pre-marketing data having more adverse events than the post-marketing is believed to be due to early phase clinical trials being more in a controlled environment than late phase clinical trials. Early phase trials are often conducted in a research facility with a full staff keeping a continuous monitoring of the patients. Late phase trials are conducted by phone, through home-based surveys, during hospital visits and are generally not as rigorously monitored. In addition, adverse events may not be self reported by the patients as they are minor or judge not significant. However, the rational behind the post-marketing data having more adverse events than the pre-marketing studies in pediatrics is due to a more rigorous involvement by the parent or caregiver of the child. Early phase pediatric studies are also conducted in a research facility with a full staff keeping a continuous monitoring of the pediatric patients. Late phase pediatric trials are also conducted by phone, through home-based surveys, during hospital visits but do have parents or guardians that are potentially more attentive and provide a more accurate record of adverse events. There could be a valid argument made that adolescence, 14 to 17 years of age, do not follow this trend due to a potential rebellious nature. This could not be evaluated as there was not enough data that segregated the pediatric adverse events.

The only adverse event that had a very different outcome compared to all the other adverse events was the total Hypoglycaemia. It demonstrated a much larger incidence rate per patient years for pre-marketing clinical trials with an incidence per patient years 13.6 times higher than

post-marketing studies. This difference could be attributed to the complexity of counting carbohydrates and the bolus dose. Miscounting carbohydrates or eating a different quantity could result in an adverse event. The new technologies with continuous glucose monitoring and the closed loop system are currently trying to integrate artificial intelligence to reduce the human variable. The upcoming and future technologies should close this GAP.

Furthermore, the purpose of Early phase clinical trials is to test novel drugs and devices. It is completely justifiable that some of the early phase, i.e. pre-marketing trials, were conducting pilot studies to test and refine their device. The device could have demonstrated flaws in these early trials giving a lot of very specific adverse events that was then rectified in future designs. Ultimately the core fundamental of early phase design is to test the safety. Some early phase data collected in this research may have been from devices that were not yet optimized resulting in a higher instance of adverse events and serious adverse events.

Serious adverse events demonstrated different results from the adverse events. Serious adverse events had an increase incidence rate in the post-marketing studies. There was a 0.20 incidence per patient years in pre-marketing versus 0.22 incidence per patient years in post-marketing, showing an increase rate of incidence per patient years of 10% for serious adverse events in pos-marketing studies. The other sub categorises of serious adverse events further demonstrated this by having an increase rate of incidence per patient years ranging from 1.5 times higher to 13.5 times higher.

- Treatment related serious adverse events (1.9 times higher)
- Pediatric serious adverse events (3.3 times higher)
- Pediatric treatment related serious adverse events (3.7 times higher)
- Severe hypoglycemia (2.0 times higher)
- Pediatric severe hypoglycemia (1.5 times higher)
- Diabetic ketoacidosis (13.5 times higher)
- Pediatric diabetic ketoacidosis (10.4 times higher)

Unlike the adverse event data, the serious adverse event data was trending in the same direction as our initial hypothesis. Once again, the confidence interval was to large that none of these results are statistically significant, nevertheless all the serious adverse event data does contain clinically relevant information. Treatment related serious adverse events and severe hypoglycemia showed a two-fold increase rate of incidence. The pediatric serious adverse events, pediatric treatment related serious adverse events showed over a three-fold increase. The most significant increase was for the diabetic ketoacidosis and pediatric ketoacidosis with an increase of 13.5 and 10.4 times higher in post-marketing studies. The only results that were not as significant was the pediatric severe hypoglycemia. It was still 1.5 times higher in the post-marketing studies.

The data shows the adverse events being more dominate in the pre-marketing trials and the serious adverse events being more dominate in the post-marketing trials. The rational believed to be a cause of this discrepancy is that adverse events are not always documented and when it is documented, it is at the discretion of the device manufacture to report it. The Manufacturer

and User Facility Device Experience (MAUDE) data was created in the united states and does contain a significant number of adverse events and serious adverse event for insulin pump, however there is a disclaimer that the data can not be used for scientific purposes (2). In addition, the entries made were with little follow-up and can't directly confirm if the adverse event is directly linked to the device. Therefore, adverse events for insulin pumps do get overviewed post-marketing. Serious adverse events, however, are documented more rigorously as it implies the assistance of a second person to intervene. These events due to the more serious nature can be recollected more easily and communicated to their physician. This created a concrete record in a medical database that can then be scientifically interpreted in a post-marketing retrospective study. Another partial explanation is that there were a number of post-marketing studies that specifically looked into nocturnal insulin control with insulin pumps. As patients are sleeping, they are less aware of their blood glucose levels and can not sense early symptoms of potential adverse events.

There was a notable discrepancy between diabetic ketoacidosis serious adverse events and all other forms of serious adverse events. They were over 10-fold higher in post-marketing studies for both the general population and for pediatrics. All the other serious adverse events were between 1.5 to 3.7 times higher. Diabetic ketoacidosis is a serious adverse event that requires the patient to go to the hospital, whereas severe hypoglycemia requires the assistance of a second person to get your blood sugar levels back up. All the hospitalizations are recorded for diabetic ketoacidosis and provide a more representative outcome. Diabetic ketoacidosis is tested by checking if you have ketones in your urine. If you do have ketones in your urine you

go to the hospital. Hypoglycemia is identified as a blood glucose level below 70mg/dL, but severe hypoglycemia is different for everyone as it requires assistance form a second person. Severe hypoglycemia does not have a concentration associated to it. In addition, the notion of "assistance of a second person" is subjective to the patient. what is the minimum intervention to be considered assistance form a second person? It is believed that the notable difference in the much higher rate of incidence per patient years for post-marketing diabetic ketoacidosis is due to these observations.

Deaths also fall within the serious adverse events and are the only adverse events investigated. Autopsies are generally performed, but not always, when a person dies without a doctor present or if the death is suspicious. According to the United States Centers for Disease Control and Prevention, In 2017 there were 83,564 death certificates in which diabetes was identified as the underlying cause of death in addition to 270,702 death certificates with diabetes identified as the underlying or contributing cause of death (1). The total number of deaths self-reported by the manufacturers in 2017 in the MAUDE database was thirty-five. The total number of deaths with diabetes as the underlying or contributing cause reported by the CDC does not specify identify how many patients were using an insulin pump, but it is safe to assume it was more than 35. The MAUDE database was created to keep track of all the adverse events and serious adverse events acknowledged by the manufacturer, weather it was related to the device or not. A potential GAP for future study. A major source of inconsistency between the post-marketing clinical data and what the manufactures of the insulin pumps is likely to be the way manufacture report their data. As demonstrated by the MAUDE database, the events are not

present, not reported or potentially withheld. I more rigorous and transparent process would be required to try and have both sets of data reflect each other.

There were two deaths in the 64 articles reviewed. A 57-year-old female in a Post-Approval study who suffered a cardiorespiratory arrest, hypoglycemia, and accidental overdose. One patient who was on a Control Multiple daily injection arm (i.e. no insulin pump). Hence death as a serious adverse event was not an issue in both pre-marketing and post marketing studies. There were only 4 cardiovascular serious adverse events, including one in pediatrics. This was expected as cardiovascular disease is mainly associated with type 2 diabetes (84).
Upper Respiratory Infection was the most common AE outside the main core with 39 occurrences. The immune system is deeply affected by high blood sugar levels that make it difficult fort he white blood cells to travel to the infection site. Would healing also has the same impact but was not present in any form in the adverse events.

It was observed that there were 9 of 24 pre-marketing studies that used a large pool of pediatric patients for their analysis (2 adults: 1 child). The articles did not mention the rational behind having so many pediatric patients. Type 1 diabetes is diagnosed in children as it is a condition the patient is born with. However, there are significantly less adverse events in children as diabetes is a degenerative disease. Pediatric adverse events and serious adverse event were lower across the board except for diabetic ketoacidosis, which was marginally higher. Even if the aim of the study was comparing the pre-marketing adverse events versus the post-marketing adverse events, there was one statistic that was statistically significant even if it

was out of scope of this study. The total adverse event for pre-marketing studies was 7.92 incidence per patient years with a confidence interval of 1.82% to 14.01%. The total pediatric adverse event for pre-marketing studies was 0.50 incidence per patient years with a confidence interval of -0.35% to 1.34%. Hence, there was a significant difference in the pre-marketing adverse events for these two categories. This reinforces the notion that pediatric data does assist in lowering the overall adverse event impact on an early phase clinical trial. This could be a potential point of future interest; is the use of pediatric data in early phase clinical trials helping the medical device, insulin pump, in obtaining regulatory approval. A potential approach would be using only adult patients transferring from multiple daily injections to insulin pumps and eliminating pediatric patients. As demonstrated by van den Boom 2019, the rise of percentage of people using insulin pumps is continuously increasing as the technology is getting better (3).

There were Additional factors that could not be quantified in this study but deserve to be mentioned. These were viewed as limitations. Insulin pumps are complex medical device that requires to be adequately trained. The manufactures have set up very elaborate and complete training programmes. Short-term and long-term adherence to these programs could potentially impact the post-marketing data. The education level of the insulin pump patient was not documented in any of the articles. Due to the complexity of the medical device and the rigorous training program, it is feasible to think that the educational level of the patient may have a potential impact on the incidence of adverse events. This may also have an impact but could not be address in this study.

Conclusion

In Conclusion the Hypothesis has failed and no statistical difference is observed between pre-marketing and post-marketing clinical trials. This was due to the high variability. The data did have clinically relevant data demonstrating that there were more incidence of adverse events per patient years in pre-marketing than post-marketing and in serious adverse events the inverse was observed as there are more incidences in patient years for post-marketing clinical trials. This discrepancy may be due to way adverse events and serious adverse events are reported by the patients and manufactures. Pediatric studies were in line with the hypothesis demonstrating more post-marketing adverse events and serious adverse events but were not statistically significant as well.

Including very early phase pre-marketing clinical trials is a potential limiting factor in the design of this thesis as the theory behind these studies is to test the safety. More adverse events are expected for very early phase clinical trials that are conducted and potentially did not meet criteria.

Contribution to the Advancement of Knowledge - This study did not confirm the discrepancy observed between serious adverse events and adverse events obtained during clinical trials and real-world settings. It did not identify a potential GAP in the clinical trial process or in the regulatory process. The results can be used to guide towards new hypothesis for future studies to demonstrate the expected benefits and risks of the insulin infusion pump in the real-world setting or to determine benchmark assessments for cost-effectiveness assessments.

Through this research the patient as the end user does not gain direct answers or additional health benefits. They must remain vigilant, maintain a healthy lifestyle, count carbohydrates appropriately and stay up to date with the proper use of their device.

The study has brought to light a potential new question. Usually, pediatric studies are performed after the new device is approved. Type II diabetes starts at early childhood and this patient population is included in the initial pre-approval clinical trials. Diabetes being degenerative, there is a time effect. Evaluating pediatrics and adults in the same clinical trial, does the use of pediatrics patients in an early phase clinical trial adds a bias in the safety and efficacy evaluation in the approval process of a medical device such as an insulin pump? As a statistically significant difference was observed between pre-marketing adverse events and pediatric pre-marketing adverse events.

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