Official Title: PRO Solo**:** Patient-Reported Outcomes with the Accu-Chek® Solo micropump system vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in Patients with Type 1 Diabetes

NCT Number: NCT03478969

Document Date: Protocol Version 4: 21 Jun 2018

CONFIDENTIAL

Study Protocol RD002718

Version 4.0 21.Jun.2018

Short Title: PRO Solo Study

Patient-Reported Outcomes with the Accu-Chek® Solo Micropump System vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in Patients with Type 1 Diabetes

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SUMMARY OF REVISION HISTORY

Version	Date of issue (dd mmm yyyy)	Reason for change
1.0	18 Sep 2017	Initial version
2.0	13 Mar 2018	Changed: • Group B (MDI): use Accu-Chek Aviva/Performa Connect instead of Accu-Chek Aviva/Performa Nano outside of Poland • Use of Accu-Chek SoftClix instead of Accu-Chek FastClix in Austria Added: • Details on central lab • Details on CI Poland • Details on Safety Reporting • Primary endpoint: hierarchical testing of Accu-Chek Solo® vs. mylife Omnipod® Clarifications: • Randomization during V1 • Initial questionnaires before randomization • Timing of initial pump training and hand-out of material • Return of used materials • Statement of compliance Minor editorial changes
3.0	20 Mar 2018	Clarification: • t-test in Synopsis corrected to ANCOVA Minor editorial changes

Version	Date of issue (dd mmm yyyy)	Reason for change
4.0	21 Jun 2018	Changed: • Exclusion criteria regarding hypoglycemia unawareness and history of recent hospitalizations adapted Added: • Possibility to use material with CE mark • Details on collection of materials regarding CE mark • Interim Analysis at V5 Clarifications • Study device version numbers added • Insulin pump training at V4 • Need to link replacement devices to subject profile in Accu-Chek Smart Pix • Update of Reporting of Protocol Deviations incl. definition Minor editorial changes

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RESPONSIBILITIES OF THE COORDINATING INVESTIGATOR(s)

The Coordinating Investigators from each participating country are appointed by the Sponsor to coordinate work in a multicenter clinical study. During the conduct of the clinical study the Coordinating Investigators will provide scientific advice and support the Sponsor in writing study publications.
In addition, the Sponsor may request that the Coordinating Investigator coordinate the work for this study and support the submission process to the Ethics Committee/ Institutional Review Board and/or Regulatory Authorities.

PRINCIPAL INVESTIGATORs

The Sponsor shall maintain an updated list of Principal Investigators, study sites, and institutions. This list can be kept separately from the protocol and provided to Principal Investigators. The definitive list shall be provided with the clinical study report. The Principal Investigator is the qualified person for conducting the clinical study at a site.

SIGNATURE SHEET FOR INVESTIGATORS

Principal Investigator	City	Country

Study Protocol RD002718 (Version 4.0)

Patient-Reported Outcomes with the Accu-Chek® Solo Micropump System vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in Patients with Type 1 Diabetes

I have thoroughly read and reviewed the above study protocol, and I agree that it contains all necessary details for carrying out this study.

I agree to conduct the study as specified in this study protocol and in accordance with the principles of the Guidelines of the International Council of Harmonization (ICH) on Good Clinical Practice (GCP) where it can be applied to medical devices, with the Declaration of Helsinki, harmonized European standards (ISO 14155:2011(E), the European Medical Device Directive [e.g. 93/42/EEC]) and FDA 21 CFR Parts 11, 50, 54, 56, 99, 312, 803, 812, 814 and 820.30; as applicable, with all local laws and regulations and with the regulatory requirements for source data verification.

I fully understand that any changes instituted by the Investigator(s) without previous discussion with the appropriate Sponsor personnel would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well–being of the subjects).

I will discuss this material with subjects to ensure they are fully informed regarding the investigational device and the conduct of the study. I will use only the Informed Consent Form approved by the Sponsor and will fulfil all responsibilities for submitting pertinent information to the EC/IRB responsible for this study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Roche Diabetes Care.

I agree that the Study Monitor/Clinical Research Associate (CRA), and/or other Sponsor representatives shall have access to any source data from which case report form information may have been generated.

To be signed by the Principal Investigator and Sub- or Co-Investigator (as appropriate).

Please sign and date next to your printed name:

PRINTED NAME	Signature	Date (dd-mmm-yyyy)

If more space is needed, please use a second copy of this page.

Protocol Outline

For comprehensive details, please refer to the respective sections.

Study Title:	Patient-Reported Outcomes with the Accu-Chek® Solo Micropump System vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in People with Type 1 Diabetes
Short Name	PRO Solo Study
Investigational Device:	Accu-Chek® Solo micropump system
Other Study Devices:	- Intensified therapy with multiple daily injections (MDI) - mylife™ OmniPod® Insulin Management System (Insulet Corporation)
Research Question/ Working Hypothesis:	Assessment of treatment satisfaction in patients with type 1 diabetes comparing Accu-Chek® Solo to standard therapy via MDI and to mylife™ OmniPod®. First Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and MDI. First Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with MDI. Second Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and mylife™ OmniPod®. Second Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with mylife™ OmniPod®.
Primary Objective:	To compare treatment satisfaction with Accu-Chek® Solo versus MDI and versus mylife™ OmniPod® assessed by Diabetes Technology Questionnaire (DTQ).
Secondary Objectives:	To evaluate • Mean HbA_{1c} change difference between treatment groups at end of study • Therapy relevant examination and diary parameters • The answers of additional questionnaires measuring psychological parameters relevant in diabetes therapy • Therapy relevant parameters from data download from BG-meter or respective patch pump, e.g. bolus frequency • Device parameters
Indication	Type 1 diabetes mellitus
Target Population	Age ≥18 years
Number of Subjects	180 subjects, 60 subjects in each treatment group
Number of Sites	10-20
Countries	Austria, Germany, Poland, and UK
Study Design:	Prospective, multinational study where adults ≥ 18 years will be randomly allocated (1:1:1 ratio) to **Group A:** Continuous subcutaneous insulin infusion (CSII) with Accu-Chek® Solo micropump system for 26 weeks. or

	Group B: Multiple daily injections (MDI) for 26 weeks. or **Group C**: Continuous subcutaneous insulin infusion (CSII) with the mylife™ OmniPod® therapy system for 26 weeks. **Follow Up:** From Week 26 until Week 39, all Groups will be using the Accu-Chek® Solo micropump system for CSII therapy.
Study Duration:	40 weeks
Study Visits	• Visit 1 – Screening (-14 to 0 days) • Visit 2 – Baseline (day 1) • Visit 3 – Middle of parallel phase (week 13) • Visit 4 – End of parallel phase (week 26) • Visit 5 - Final Visit (week 39) • Follow-up call (week 40)
Main Inclusion Criteria:	• Signed written Informed Consent • Diagnosed type 1 diabetes mellitus • At least 6 months experience with MDI therapy • Age ≥18 years and age ≤ 65 • Able to perform carbohydrate counting • Clinically suitable for CSII including willingness to measure blood glucose at least 4 times per day or to use flash or real-time continuous glucose monitoring consistently • HbA1c between 7.5% (58 mmol/mol) and 9.0% (75 mmol/mol) (determined within the last 2 months) • Ability and willingness to read and understand study materials (subject information, data protection and written consent form, all questionnaires etc.) and to comply with study procedures • Ability and willingness to use investigational devices independently and respond to alarms after training and run-in phase • Using a BG-meter or real-time continuous glucose monitoring device that can be downloaded to the eCRF or willing to use a compatible meter that will be provided for the duration of the study
Main Exclusion Criteria:	• Prior insulin pump use • Relevantly impaired hypoglycemia awareness • History of >1 hospitalization due to severe hypoglycemia within the previous 3 months • History of >1 hospitalization due to diabetic ketoacidosis within the last 3 months • Significant manifestation of diabetes-related late complications • Pregnant or planning to become pregnant or breastfeeding • Known allergic reactions to plaster adhesive

	• Chronic use of
	  o steroids in adrenal suppressive doses,
	  o immunosuppressive medication, or
	  o chemotherapy
	• Serious or unstable chronic medical or psychological condition(s)
	• Addiction to alcohol or other substance(s) of abuse as determined by the investigator
	• Psychological condition rendering the subject unable to understand the nature and the scope of the study
	  • Plans for relocation or extensive travel
	  • Participation in another clinical study within 4 weeks prior to the screening visit
	• Dependency on Sponsor or Investigator (e.g. co-worker or family member)

Sample Size Calculation:	Sample size calculation is based on the expected difference and variability in the DTQ score in the Accu-Chek® Solo and the MDI group. An anticipated mean score of 90 in the MDI group and of 110 in the Solo group and a standard deviation of 30 is used for sample size calculation. A sample size of 49 subjects per group will have a 90% power to detect a significant difference at a two sided alpha level of 0.05. To adjust for a maximum drop-out rate of 18%, 60 subjects will be enrolled in every treatment arm. To allow for comparison with the mylife™ OmniPod® pump, the same number of subjects will be enrolled in group C. No assumptions on the difference between treatment satisfaction in the Accu-Chek® Solo and in the mylife™ OmniPod® groups and thus no sample size adjustments are made. The comparisons between Accu-Chek® Solo and MDI (H_1) and between Accu-Chek® Solo and mylife™ OmniPod® (H_2) will be performed hierarchically, first H_1 and only if H_1 can be rejected H_2. Therefore, no multiplicity correction and thus no sample size adjustment is required.
Statistical Methods:	**Analysis populations** 1. The safety population is defined as all enrolled patients with data documented at least one - of the visits 1 to 5. 2. The full analysis set (FAS) will conform to the intention to treat principle. All randomized subjects will be included according to the group allocated at randomization. 3. The per-protocol (PP) set will include all subjects that completed the study. Subjects that do not complete the study and subjects with protocol deviations that may affect the data will be excluded from the PP set. **Primary efficacy endpoints**

	The primary goal of the study is to assess, if treatment satisfaction in the Accu-Chek® Solo group (Group A) increases more than in the group using MDI (Group B) and in the mylife™ OmniPod® group (Group C). Change in treatment satisfaction will be assessed by the blue (right) answers to the questions of the Technology Questionnaire (DTQ). Every individual of these answer has a score between 1 (much worse) and 5 (much better). The sum of all 30 individual answers is calculated for each subject and analyzed with an ANCOVA with group as independent variable and the pink (right) answers of the DTQ and the site as covariates. The comparisons between the Accu-Chek® Solo group and MDI and between the Accu-Chek® Solo group and the mylife™ OmniPod group will be performed hierarchically. Only if the comparison between the Accu-Chek® Solo and the MDI group will show a statistically significant difference, the comparison between the Accu-Chek® Solo and the mylife™ OmniPod® group will also be performed. Details of the statistical analyses will be described in the statistical analysis plan (SAP).

Schedule of Assessments

Procedure \ Visits	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Phone Follow up[1]
Time point		day 1	week 13	week 26	week 39	
Time window (+/- days)		0 to +14 days to Visit 1	±14 days	±14 days	±14 days	2-5 days >Visit 5
Informed consent	X[2]					
Eligibility check (inclusion/exclusion criteria)	X					
Pregnancy test (ß-HCG urine)[3]	X	X[9]	X[9]	X[9]	X[9]	
HbA_{1c} in central lab	X[4]	X	X	X	X	
Demographic data and other Baseline data	X[5]					
Diabetes & diabetes treatment history	X	X[6]				
Diabetes medication	X	X[6]	X[6]	X[6]	X[6]	
Diabetes-associated diseases and treatment	X	X[6]	X[6]	X[6]	X[6]	
Other diseases and medications	X	X[6]	X[6]	X[6]	X[6]	
Hypoglycemic events (severe, mild)		X	X	X	X	
Time of absence from work or school		X	X	X	X	
Height & weight		X	X[7]	X[7]	X[7]	
Skin reactions		X	X	X	X	
Subject questionnaires	X		X	X	X	
Randomization	X					
Distribution of devices and other study material		X	X	X		
Pump training		X[8]		X[10]		
Carbohydrate Counting Training		X				
Device data download			X	X	X	
A(D)Es/SA(D)Es		X	X	X	X	X[1]
Malfunctions			X	X	X	
Collect study devices and other study material				X	X	

1 If ongoing A(D)E/SA(D)E at visit 5
2 Written informed consent must be obtained prior to any study related procedure
3 If applicable

4 Performed in local lab
5 Year of birth, gender, race; handedness, highest level of education, employment status, family status
6 If any changes
7 Weight only
8 For group A and C
9 if applicable by local law (e.g. in Austria)
10 For group B and C

Abbreviations

ADE	Adverse device effect
AE	Adverse events
BG	Blood Glucose
BMI	Body Mass Index
CE	Conformité Européene (European conformity)
CFR	Code of Federal Regulations
CIP	Clinical investigation plan; synonym for protocol
CRA	Clinical research associate
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical Study Report
DTQ	Diabetes Technology Questionnaire
DKA	Diabetic ketoacidosis
EC	Ethics Committee
eCRF	electronic case report form
GCP	Good clinical practice
HbA1c	Glycated Hemoglobin
ICH	International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISO	International Organization for Standardization
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Regulatory Activities
MPSV	Medizinprodukte Sicherheitsverordnung
PAID	Problem Areas In Diabetes questionnaire
PP	Per protocol
Protocol	Synonym for CIP
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SDV	Source Data Verification
SMBG	Self-monitored blood glucose
TBD	Total Daily Basal Insulin Dose
TDD	Total Daily Insulin Dose

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1 Introduction

1.1 Introduction and Background

Continuous subcutaneous insulin infusion, CSII, often called insulin pump therapy, was introduced in the late 1970s as a way to achieve and maintain tight control of blood glucose concentrations in people with insulin dependent diabetes. A programmable insulin infusion pump with a reservoir of short-acting insulin is connected via thin tubing to a cannula inserted through the skin. The pump is set to deliver insulin at slow rates appropriate to patients' insulin demand throughout the day. This basal rate can be adjusted by the user e.g. to accommodate reduced insulin needs during and after exercise. Additional boosts in the insulin dose (boluses) can be activated to administer insulin for food intake (meal bolus) and/or for correction of high blood glucose values (correction bolus). The clinical benefits of CSII therapy have been confirmed by systematic reviews and meta-analyses [1-4].

So far, CSII has mainly been performed with so called durable pumps. These systems consist of the actual pump and an infusion set which provides means for reliable insulin delivery from the pump into the subcutaneous tissue. Some durable pumps offer the option of being controlled via a remote control. These remote controls may even include a blood glucose meter and offer increased flexibility and discreteness.

Since the introduction of the mylife™ OmniPod® Insulin Management System (Insulet Corporation) a new type of CSII devices is available which has been termed patch pumps. While based on the same principles as durable pumps, these small devices are attached directly to the infusion site and thus eliminate the need for additional tubing. This is thought to provide more comfort, discreteness and less stigma and subsequently improve therapy adherence with improved outcome.

mylife™ OmniPod® is designed as a single use device. After it is applied to the body, it can deliver insulin for up to 3 days. After this, the whole pump is discarded. This system is therefore very convenient, but accumulates a considerable amount of electronic waste.

The Accu-Chek® Solo micropump system seeks to amend this issue by using a modular design: Even though the pump is miniaturized, so it can be worn directly on the body, the electronic and electro-mechanical components can be used for several months. Only the insulin reservoir and the infusion cannula setup are replaced every few days. This approach allows for manufacturing of higher quality components and reduces waste for a more sustainable solution. On the other hand, the system requires more handling steps which may affect user acceptance.

1.2 Intended Use of Study Device

The Accu-Chek® Solo micropump system is a medical device for subcutaneous delivery of insulin. The Accu-Chek® Solo system is made up of two main parts which work together wirelessly, the micropump and the Diabetes Manager. The system delivers insulin in a personalized way and provides status information to users via the Remote Control.

The Accu-Chek® Solo micropump consists of a disposable 2ml (200 IU) insulin reservoir attached to a pump base, which is usable for 120 days. The Accu-Chek® Solo pump base contains the electronics, memory, pump engine, bolus buttons and a buzzer that will let the user know if there is a safety issue, so it has the key functions of a traditional insulin pump – just in a smaller form factor. The two bolus buttons featured on the pump allow users to program a bolus on demand – without the use of the Diabetes Manager. These bolus buttons can be deactivated and activated again by the Diabetes Manager menu.

The Accu-Chek® Solo Diabetes Manager operates the micropump wirelessly. It is needed to program and operate the micropump with personalized parameters, such as basal rate profiles and parameters of insulin action. The Diabetes Manager also features an integrated blood glucose monitoring system using the Accu-Chek® Aviva/Performa strips and a bolus advisor supporting the user in calculating meal and correction boluses.

The Accu-Chek® Solo Diabetes Manager features a touch screen based graphical user interface. The workflows/menus are based on the Accu-Chek® Aviva/Performa Insight Diabetes Manager (for Accu-Chek® Insight).

The micropump is attached to the body via the Accu-Chek® Solo infusion assembly that carries the micropump and allows insulin delivery through a soft, flexible (6 or 9 mm) cannula. The special design allows users to connect to and disconnect the micropump from the infusion assembly during certain activities. An inserter is required to apply the soft cannula into the subcutaneous fat tissue.

1.3 Study Rationale

This study aims for the first larger comparison of patch pump based CSII therapy versus injection based intensified insulin therapy. In addition to the relatively large number of subjects included, the study will also compare the Accu-Chek® Solo micropump System to mylife™ Omnipod® system as the only patch pump in the market and which is currently defining the new class of insulin pumps.

Even though the Diabetes Control and Complications trial showed a strong correlation between HbA_{1c} and diabetes complications, HbA_{1c} was not chosen as the primary objective. Instead the primary objective is a measure of device and treatment satisfaction. The main reason for this is the fact that therapy adherence strongly influences therapy success. Thus, factors that are suitable to improve therapy adherence over a long time may predict clinical outcome concerning complications even better than HbA_{1c}. In order to provide comparability with other studies, HbA_{1c} has been kept as secondary objective.

The Accu-Chek® Solo micropump system will not have CE marking when the study starts. Still, the system's development will have reached an advanced stage and all essential requirements will be met.

The Sponsor of this study is convinced that patch pumps can significantly improve the life of patients with diabetes by reducing the therapy associated burden. Learnings that can be derived from this study will be used to further improve the system. Especially aspects that result from system handling, user interface and usability can strongly affect acceptance of the system and thus therapy adherence and results.

This clinical study will provide additional insights into user interactions and user preferences in a home use setting and therefore collects valuable data for possible differences with regards to therapy compliance between patch pumps and standard of care.

In addition to the above, data from this study will be used to support internal development projects.

Teaching cases may be developed from the data to teach health care professionals techniques.

2 Study Design and Duration

2.1 Study Design Overview

This is a multinational randomized, three arm interventional study.
Subjects will be randomized to one of the following treatments:

- **Group A**: Accu-Chek® Solo micropump system for 39 weeks
- **Group B**: MDI for 26 weeks, then Accu-Chek® Solo micropump system for 13 weeks
- **Group C**: mylife™ OmniPod® for 26 weeks, then Accu-Chek® Solo micropump system for 13 weeks

Total duration is 40 weeks, during which all subjects switch from MDI to tubeless CSII at a time point determined by their allocated group. After 26 weeks, all subjects will use Accu-Chek® Solo micropump system.

In the case that mylife™ OmniPod® should not be commercially available in a country; no subjects will be randomized into Group C at the respective sites.

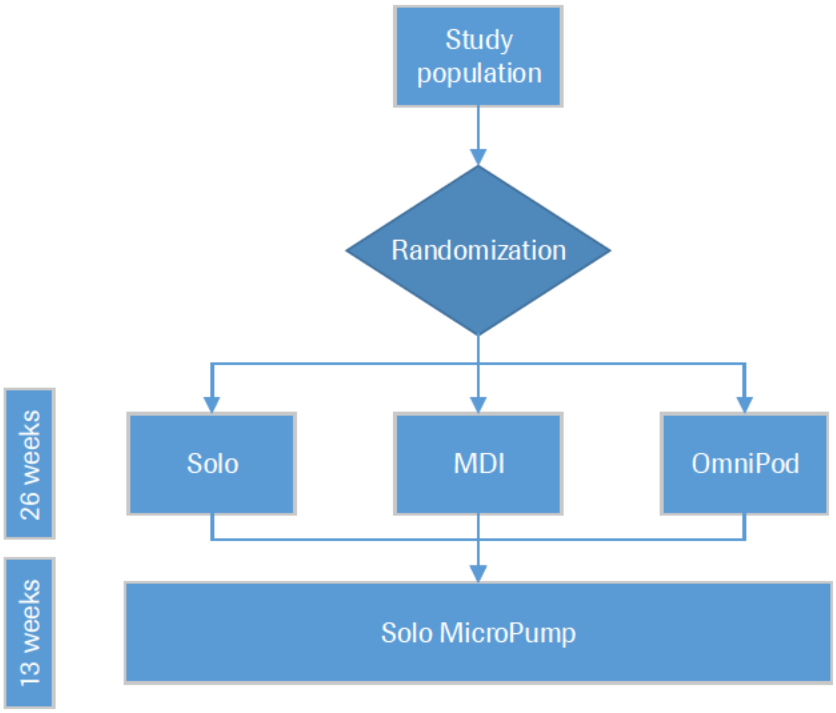


Figure 1: Study design overview

2.2 Rationale for the Study Design

During more than 20 years of diabetes therapy history with CSII, this form of therapy has been shown to be a safe and effective option for the treatment of T1D. Most of the available data was acquired during the use of durable pumps, but there now also is considerable experience in the use of patch pumps. Safety and effectiveness of CSII in general and of tubeless pumps in specific are therefore not the main focus of this study. Still, respective data will be collected and evaluated.

A rigid risk management process according to DIN EN ISO 14971 is part of Roche's quality system. During this process, no safety concerns outside the range of normal therapeutic risks of CSII have been identified for the Accu-Chek® Solo system. Therefore,

- formal study results are not required prior to CE marking,
- safety is not a primary endpoint of this study.

The study will start before CE marking has been obtained. This will give the Sponsor of the Accu-Chek® Solo micropump system the chance to optimize the product until launch and thus provide patients with a device that supports user satisfaction and therapy adherence. This advantage has been weighed against potential effects from the use of a device without CE marking. However, essential requirements of the device are met and it is safe and effective for use in this study. Possible hazards due to the product being in a state before CE marking are discussed in a separate risk document. The resulting risks are small and acceptable.

In order to produce high quality data that is relevant for a maximum number of potential users, the following decision concerning the study design has been taken:

- Data quality may be affected when subjects without previous insulin pump experience are mixed with subjects with insulin pump experience. Therefore, criteria to control previous therapy experience have been established.
- Instable metabolic conditions as well as medications that affect insulin sensitivity may have negative effects on data quality. Therefore criteria to exclude subjects suffering from such conditions were established. As relevant metabolic changes that require multiple therapy adoptions within a short time frame happen during pregnancy, pregnancy and planned pregnancy were also defined as an exclusion criterion.
- A 3-arm study design has been chosen where two tubeless pump systems are compared with the standard therapy (MDI). This maximizes information gain while minimizing subjects numbers.
- HbA_{1c} was not chosen as the primary objective. Instead the primary objective is a measure of device satisfaction. The main reason for this is the fact that therapy adherence strongly influences therapy success. Thus, factors that are suitable to improve therapy adherence over a long time may predict clinical outcome concerning complications even better than HbA_{1c}.
- In order to provide comparability with other studies, HbA_{1c} has been kept as secondary objective.
- Finally, in order to minimize effects of subject's or investigator's preferences, subjects will be randomly allocated to their treatment group (A, B or C respectively A or B*). (*at sites in countries where mylife™ OmniPod® is not commercially available)

3 Study Device(s)

3.1 Identification and Description of the Investigational Device: Accu-Chek® Solo micropump system

The Accu-Chek® Solo micropump system is a medical device for subcutaneous delivery of insulin in a personalized way. It is characterized by a high degree of miniaturization and modularity. The Accu-Chek® Solo micropump system consists of two main parts: the Accu-Chek® Solo micropump and Accu-Chek® Aviva/Performa Solo Diabetes Manager that integrates all therapy data and acts as remote control of the actual micropump.

Figure 2: Accu-Chek® Solo Aviva Diabetes Manager (left) and Accu-Chek® Solo micropump (right)

The Diabetes Manager is a key component of the system that communicates with the micropump via Bluetooth Low Energy. It controls the pump and displays all operational information from the pump. All interaction with the pump except the final confirmation of insulin doses is done via the Diabetes Manager's interactive touch screen. The Diabetes Manager features a hardware button that is used specifically to confirm insulin doses. In addition, it includes an Accu-Chek® Aviva/Performa blood glucose meter with integrated bolus advisor functionality.

The Accu-Chek® Solo micropump delivers insulin as programmed via the Diabetes Manager. Furthermore, it features two buttons directly on the micropump, enabling users to program a bolus on demand without the Diabetes Manager. The pump stores parameters such as the activated basal rate profile and the bolus button increment. Therefore, basic basal-bolus therapy is available even when the Diabetes Manager is not present or when communication between the devices is not available.

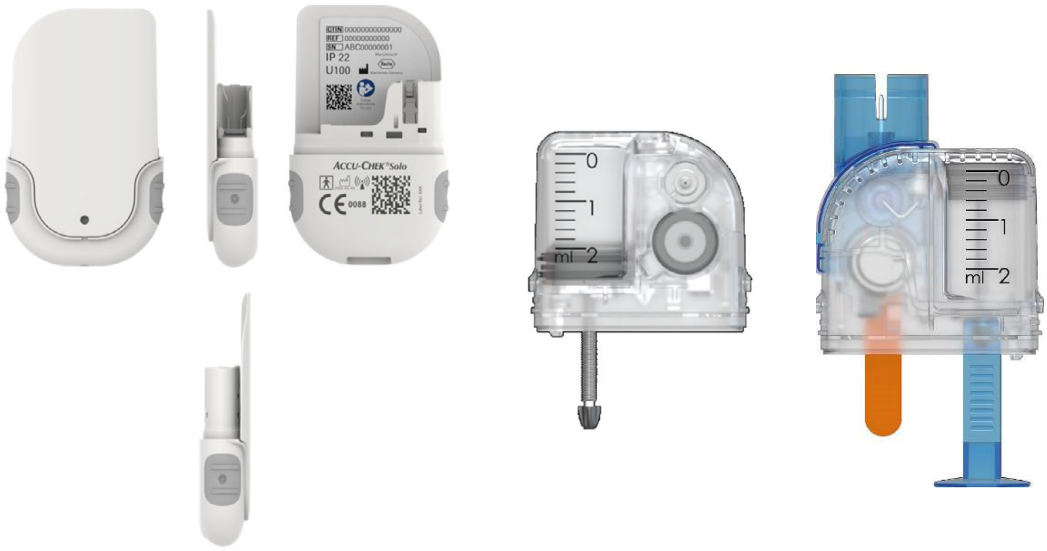


Figure 3: Accu-Chek® Solo pump base (left), Accu-Chek® Solo reservoir (middle), Accu-Chek® Solo reservoir assembly

The micropump actually consists of a pump base, and a disposable reservoir:

The pump base (Accu-Chek® micropump base) has a lifetime of 120 days and contains electronics, memory, pump engine, bolus buttons as well as a buzzer to inform the user in case of pump events.

The disposable reservoir integrates a button cell and an insulin compartment holding up to 2 ml of insulin (i.e. 200 units of U100 insulin) with a minimum filling amount of corresponding to 80 units. The reservoir is provided as part of a reservoir assembly that enables the user to fill the insulin compartment directly from 10 ml vials. The filling aid is not reusable.

Battery lifetime is at least 4 days under normal use conditions. Insulin compatibility has been shown to for up to 6 days.

Figure 4: Accu-Chek® micropump clicking into the infusion assembly (left) and Accu-Chek® Solo insertion device

Micropump connection to the body is provided by the Accu-Chek® Solo infusion assembly (pump holder plus cannula): the pump holder is stuck to the user's skin by an adhesive tape. It anchors the cannula securely in position in the subcutaneous tissue and enables the attachment of the

pump to the body. By design, the system enables the user to detach and reattach the micropump from the pump holder.

Insertion of the cannula is done via the Accu-Chek® Solo insertion device. As with other Teflon infusion sets used with durable insulin pumps, the cannula and pump holder should be replaced every 2-3 days.

Accu-Chek® Solo micropump system as well as all needed consumables will be provided during the course of the study.

3.2 Comparator Devices: mylife™ OmniPod® Insulin Management System and Other Study Devices

3.2.1 Multiple daily injection therapy

Intensified therapy, either MDI or CSII, strongly depends on multiple self-monitored blood glucose values. Both the mylife™ OmniPod® and the Accu-Chek® Solo micropump system offer an integrated blood glucose meter. Accordingly, subjects on CSII therapy will use the meter integrated into the respective pump system. Subjects in the MDI control arm will use either a blood glucosemeter of their own choice, if this is listed as a compatible meter with Accu-Chek® Smart Pix or will switch to a provided Accu-Chek® Aviva/Performa Connect or Accu-Chek® Aviva/Performa Nano as blood glucose meter for the duration of the study. No effect is expected by the specific brand or model of blood glucose meter.

Figure 5: Accu-Chek® blood glucose meters

Subjects s in group A will use either a Smart Pix compatible blood glucosemeter of their own choice or the depicted device (Accu-Chek® Aviva/Performa Connect, left or Accu-Chek® Aviva/Performa Nano, right) for 26 weeks.

MDI therapy has been chosen as comparator, as it is standard of care.

3.2.2 mylife™ OmniPod® Insulin Management System

The mylife™ OmniPod® Insulin Management System is a patch pump system designed by Insulet Corporation. It was first brought to the US market and is available worldwide (including UK and Germany) since 2010 under the brand name mylife™ OmniPod®.

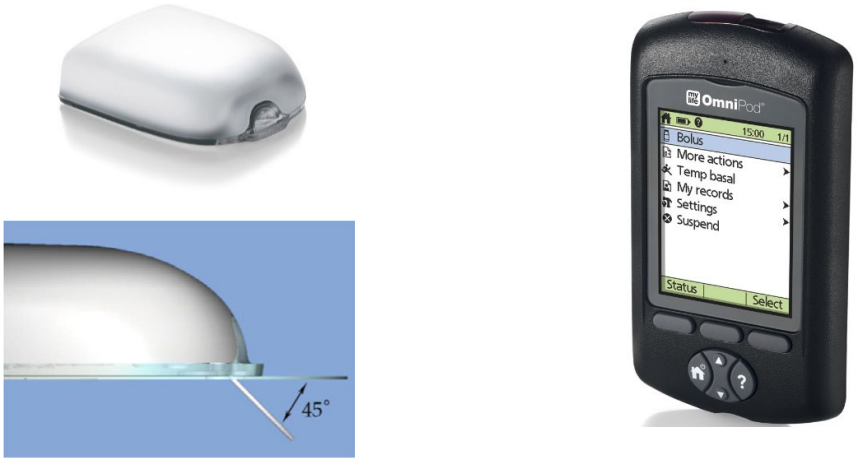


Figure 6: mylife™ Omnipod® Pod (left top), mylife™ Omnipod® infusion set (left bottom) and mylife™ Omnipod® Personal Diabetes Manager (right)

The mylife™ OmniPod® Insulin Management System is comprised of two components: the actual Pod and a Personal Diabetes Manger (PDM) that serves as remote control of the pod.

The Pod is single-use disposable, microprocessor-controlled infusion pump that is worn directly on the body. The adhesive on the base of the Pod keeps it in place for the typical wear times of 48 to 72 hours.

The PDM is a hand-held, battery-powered device integrating a blood glucose (BG) meter that remotely controls the insulin delivery of the pod. BG and insulin therapy data are stored and can be displayed directly on the PDM. In addition, the PDM provides further information on audio alarms, alerts, and reminders related to insulin delivery, reservoir level, Pod functioning, and battery life.

The Pod incorporates an insulin reservoir holding up to 2 ml (i.e. 200 units of U100 insulin) which has to be filled by the user with equipment provided with each Pod (fill syringe and needle). A separate infusion set or reservoir is not needed. Insulin is delivered through a soft cannula integrated in the Pod and inserted automatically into the subcutaneous tissue at an angle of 45°.

All components of the mylife™ OmniPod® diabetes management system used in the study will have CE marking.

Subjects in group C will use this device for 26 weeks.

This device has been chosen as comparator, as it is the only patch pump available on the market so far and therefore defines the class of patch pumps.

For the time of mylife™ OmniPod® use during the study, the Sponsor will cover the costs for the mylife™ OmniPod® Insulin Management System.

3.2.3 Other devices

Subjects using a flash or real-time continuous blood glucose measuring device may continue to use it.

Apart from the devices described above, all subjects using a blood glucosemeter will need a lancing device. As no effect on the study results is expected from the specific type of lancing device used, subjects may use the lancing device they prefer. The Accu-Chek® FastClix lancing device is included in the starter packed of the Accu-Chek® Solo system.

For purposes of downloading BG data, data from mylife™ Omnipod®, or data from the Accu-Chek® Solo micropump system, the Accu-Chek® Smart Pix software and corresponding Smart Pix device reader will be used by the study sites.

The Sponsor will provide the following materials to all investigators and participating centers:

- IEC approved study protocol
- Electronic Case Report Form (eCRF)
- IEC approved informed consent
- Investigator site file (ISF)
- Investigator/hospital contract
- Electronic subject questionnaires
- Accu-Chek® Smart Pix Software and Smart Pix Device Reader

3.3 Status of Documentation of Study Device(s)

The Accu-Chek® Solo micropump system will not have CE marking when the study starts. A manufacturer's declaration will be provided. CE marking is expected to be available before the end of the study. On availability of CE mark, CE marked material will be usable in the study and will be handed out to the study subjects as appropriate. As the differences to the non-CE marked material are minor (mainly bug fixes), the effects on study outcomes are negligible.

All other devices have CE marking and marketed in countries of the European Union.

Table 1: Regulatory status of the study devices

Device Name	CE marking at study start
Accu-Chek® Solo Aviva/Performa Diabetes Manager (Version PPB 2/FC 2.3)	No
Accu-Chek® Solo pump base (Version PPB 1/V 1.00 and PPB 2/V 1.02	No
Accu-Chek® Solo insulin reservoir (Version PPB G3)	No
Accu-Chek® Solo infusion set assembly (Version PPB G3)	No
Accu-Chek® Solo inserter (Version PPB 2)	No
mylife™ OmniPod®	Yes
Accu-Chek® Aviva/Performa Connect[1]	Yes
Accu-Chek® Aviva/Performa Nano[2]	Yes

[1] Not in Poland
[2] In Poland only

Accu-Chek® FastClix lancing device[3]	Yes
Accu-Chek® SoftClix lancing device[4]	Yes

[3] Not in Austria
[4] In Austria only

4 Study Objectives

4.1 Primary Objective

The primary objective of this study is to compare treatment satisfaction with Accu-Chek® Solo system vs. MDI and versus mylife™ OmniPod®, measured by the difference in the Diabetes Technology Questionnaire (DTQ) change score after 26 weeks.

The two comparisons will be performed using a hierarchical procedure. First, the comparison between the Accu-Chek® Solo system vs. MDI will be performed and only if the corresponding Null hypothesis of no difference between both systems can be rejected, the second comparison between Accu-Chek® Solo system and versus mylife™ OmniPod® will also be performed.

4.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- Psychological parameters that describe or affect therapy:
  - Diabetes-related Emotional Distress assessed by PAID-5.
  - Device satisfaction
  - Device and Treatment Preference
- Physical parameters that describe therapy changes or success:
  - HbA_{1c}
  - Change in weight and BMI
  - glycemic variability
- Therapy parameters that describe therapy changes or may affect the results
  - Indication for commencement of CSII
  - Type of insulin used
  - Total daily insulin dose (TDD)
  - Total daily basal insulin dose (TBD)
  - Average number of SMBGs per day
  - Frequency of hypoglycemic events
  - Frequency of hyperglycemia
  - Frequency of consultations between scheduled visits, emergency and call center calls, hospitalizations and absenteeism from work/school
- Device specific parameters that may affect user acceptance
  - number of pods/ infusion assemblies falling off prematurely
  - average infusion assembly usage time
  - number, type and intensity of skin reactions
- Parameters that may affect socio-economic acceptance
  - Insulin amount left in device at reservoir change / device discard

- Amount of waste, inferred by total material consumption

5 Subject Selection

Subjects will be identified and recruited from the Investigator's established subject population or from respective group practices using the inclusion/exclusion criteria; see Section 6.1 and Section 6.2.

If a subject agrees to consider participation in the study, he/she shall be informed (verbally and in writing by means of the Subject Information Leaflet) and given the possibility to ask questions to authorized study staff. If a subject decides to participate, he/she shall sign the current Ethics Committee (EC) approved Subject Informed Consent Form before any study-related procedures; see Section 12.2.

During the Screening and Baseline Visits, the subject will be interviewed to obtain demographic information and diabetes and other medical history to determine if he/she meets all of the inclusion, but none of the exclusion criteria.

6 Study Population

A total of 180 adult patients with type 1 diabetes suitable for CSII therapy will be included, if they comply with the following inclusion and exclusion criteria.

6.1 Inclusion Criteria

To be eligible to participate in this clinical study, subjects must meet **ALL** of the following criteria:

- Signed written Informed Consent
- Diagnosed type 1 diabetes mellitus
- At least 6 months experience with MDI therapy
- Age ≥18 years and age ≤ 65
- Able to perform carbohydrate counting
- Clinically suitable for CSII including willingness to measure blood glucose at least 4 times per day or to use flash or real-time continuous glucose monitoring consistently
- HbA_{1c} between 7.5% (58 mmol/mol) and 9.0% (75 mmol/mol) (determined within the last 2 months)
- Ability and willingness to read and understand study materials (subject information, data protection and written consent form, all questionnaires etc.) and to comply with study procedures
- Ability and willingness to use investigational devices independently and respond to alarms after training and run-in phase
- Using a BG-meter or real-time continuous glucose monitoring device that can be downloaded via Accu-Chek® Smart Pix or willingness to use a compatible meter that will be provided for the duration of the study

6.2 Exclusion Criteria

Subjects may not participate in this clinical study if they meet **ANY** of the following criteria:

- Prior insulin pump use
- Relevantly impaired hypoglycemia awareness
- History of >1 hospitalization due to severe hypoglycemia within the previous 3 months
- History of >1 hospitalization due diabetic ketoacidosis within the last 3 months
- Significant manifestation of diabetes-related late complications
- Pregnant or planning to become pregnant or breastfeeding
- Known allergic reactions to plaster adhesive
- Chronic use (therapy lasting for more than 3 months) of
    - steroids in adrenal suppressive doses,
    - immunosuppressive medication, or
    - chemotherapy
- Serious or unstable chronic medical or psychological condition(s)
- Addiction to alcohol or other substance(s) of abuse as determined by the investigator
- Psychological condition rendering the subject unable to understand the nature and the scope of the study
- Plans for relocation or extensive travel
- Participation in another clinical study within 4 weeks prior to the screening visit
- Dependency on Sponsor or Investigator (e.g. co-worker or family member)

6.3 Point of Enrolment and Withdrawal

A subject is considered enrolled in the study:

- as soon as he/she has signed the Subject Informed Consent Form and has been deemed eligible according to above inclusion/exclusion criteria.

A subject is considered withdrawn if he/she was first enrolled, and thereafter one or more of the following occurs:

- Withdrawal of consent to participate in the study.
- Non-compliance with the protocol procedures e.g., subject missed two consecutive study visits and/or one period with the study device(s).
- Subject requires chronic steroid in adrenal suppressive doses, other immuno-modulatory medication or chemotherapy being determined after having been enrolled.
- Subject becomes pregnant (self-reported).
- Investigator determines it is not in the best interest of the subject to continue participation in the study.

If any of the above occurs, the Investigator will:

- Ask the subject to present at site in order to ensure complete documentation (eCRF and electronic questionnaires), and to return all study materials.
- Complete the Study Completion Form in the eCRF including the date of and reason for early discontinuation.

If withdrawal occurs after completion of visit 2:

- Ask the subject to perform visit 5 as early termination visit

6.4 Replacements

Subjects that withdraw form this study will not be replaced.

7 Visit Schedule, Study Procedures, Training and Data Collection

7.1 Visit Schedule

Subjects will be invited to the clinic for the following visits:

- Visit 1 – Screening
- Visit 2 – Baseline Day 1 (0 to +14 days to Visit 1)
- Visit 3 – Middle of parallel phase (week 13)
- Visit 4 – End of parallel phase (week 26)
- Visit 5 - Final Visit (week 39)
- Follow-up call (+2 to +5 days) if needed

Please refer to the overall Schedule of Assessments and the below details for each study visit.

7.2 Visit 1 – Screening

No study-specific procedures must be performed before informed consent has been obtained.

Study procedures include the following assessments:

- Provide information to subject – orally as well as presented in the written Subject Information Leaflet – and ensure possibility to ask questions, see section 12.2
- Obtain written Informed Consent
- Allocate subject ID number (via the eCRF-system) to each subject who has signed the informed consent form; see section 13.1.1 for details
- Assess all applicable inclusion and exclusion criteria and confirm subjects s' eligibility
- Obtain and record demographics, including age, gender, race
- Obtain and record handedness, highest level of education as well as current employment status and family status
- Obtain and record diabetes background and history including insulin therapy and diabetes complications
- Obtain and record diabetes medication including but not limited to brand name(s) of insulin used, total daily dose, total basal and bolus doses, sensitivity factors, etc.
- Obtain and record relevant previous and ongoing concomitant medications
- Obtain and record relevant medical history of diseases other than diabetes
- Obtain indication for CSII
- Record HbA_{1c} value, taken less than 2 months prior to this visit based on routine clinic practice (local laboratory)
- Perform urine pregnancy test if applicable (i.e. women of child bearing potential only. Post-menopausal status and surgical sterility to be reported as medical history)
- Record all relevant data in the eCRF
- Have subject complete questionnaires
- Randomization (in the eCRF-system) to one of the three study groups
  - Group A: Accu-Chek® Solo micropump system for 39 weeks
  - Group B: MDI for 26 weeks, then Accu-Chek® Solo micropump system for 13 weeks
- Group C: mylife™ OmniPod® for 26 weeks then Accu-Chek® Solo micropump system for 13 weeks Make appointment for next visit

Remind the subjects to bring the blood glucose meter currently used with them to the next visit.

7.3 Visit 2 – Baseline Day 1 (0 to +14 days to Visit 1)

The baseline visit must take place not later than 14 days after the screening visit, and can be combined with the screening visit.

Study procedures include the following assessments:

- Obtain and record any changes in concomitant medications
- Obtain and record diabetes background and history including insulin therapy and diabetes complications
- Assess and record any AE/SAEs
- Obtain information on hypoglycemic events and time of absence from work or school due to diabetes complications
- Obtain and record weight and height
- Draw blood sample for determination of HbA_{1c} (in central laboratory)
- Perform urine pregnancy test in women of child bearing potential (only if applicable by local law, e.g. in Austria)
- Examine insertion sites and record signs of redness, swelling, heat, pain and itching according to the categories as listed (none, minor, moderate, severe)
- Perform and document training of study devices and procedures, see section 7.9
- Perform carbohydrate counting training
- Hand-out and register study material:
  - Study device(s), consumables and other supplies[5]
  - Create subjects' profile in Accu-Chek® Smart Pix and link assigned study device(s) with subject profile
- Provide instructions with regard to:
  - Handling of any malfunctions and contact to local Call Center (handing out call center card)
- Make appointment for the following visit
- Remind the subjects to bring all devices currently used (i.e. Accu-Chek® Solo system, mylife™ OmniPod® system, Accu-Chek® blood glucose meter /Accu-Chek® Smart Pix compatible meter) with them to the next visit
- Record all relevant data in the eCRF

7.4 Visit 3 – Middle of parallel phase (week 13 [± 14 days])

Study procedures include the following assessments:

- Record any changes in diabetes medication
- Record any changes in diabetes-associated diseases and treatment

[5] Study devices may be handed-out prior visit 2 if this is required for training purposes.

- Record any changes in concomitant medications
- Record any malfunctions /incidents
- Assess and record any new AE/SAEs and/or changes in ongoing AE/SAEs since the previous visit
- Obtain information on hypoglycemic events and time of absence from work or school due to diabetes complications
- Have subjects complete questionnaires
- Obtain and record weight
- Draw blood sample for determination of HbA_{1c} (in central laboratory)
- Perform urine pregnancy test in women of child bearing potential (only if applicable by local law, e.g. in Austria)
- Examine insertion sites and record signs of redness, swelling, heat, pain and itching according to the categories as listed (none, minor, moderate, severe)
- Download data from the devices used since previous visit
- Hand-out new study material, collect used study material and register study material accordingly:
  - consumables and other supplies
- Make appointment for the next visit
- Remind the subjects to bring all devices currently used (e.g. Accu-Chek® Solo system, mylife™ OmniPod® system, Accu-Chek® blood glucose meter /Accu-Chek® Smart Pix compatible meter) with them to the next visit
- Record all relevant data in the eCRF

7.5 Visit 4 – End of parallel phase (week 26 [± 14 days])

Study procedures include the following assessments:

- Record any changes in diabetes medication
- Record any changes in diabetes-associated diseases and treatment
- Record any changes in concomitant medications
- Record any malfunctions /incidents
- Assess and record any new AE/SAEs and/or changes in ongoing AE/SAEs since the previous visit.
- Obtain information on hypoglycemic events and time of absence from work or school due to diabetes complications
- Have subjects complete questionnaires
- Obtain and record weight
- Draw blood sample for determination of HbA_{1c} (in central laboratory)
- Perform urine pregnancy test in women of child bearing potential (only if applicable by local law, e.g. in Austria)
- Examine insertion sites and record signs of redness, swelling, heat, pain and itching according to the categories as listed (none, minor, moderate, severe), if applicable
- Download data from the devices used since previous visit
- Perform and document training for the Accu-Chek® Solo micropump system study devices and procedures, see section 7.9

- Collect and register study materials and return to Sponsor:
  - Group A: Study device if previously using non-CE marked device
  - Group B: Study device, remaining consumables and other supplies
  - Group C: Study device, remaining consumables and other supplies
- Hand-out new study material and register study material accordingly:
  - New study device(s), consumables and other supplies[6]
- Provide instructions with regard to:
  - Handling of any malfunctions and contact to local Call Center (hand out call center card)
- Make appointment for the next visit
- Remind the subjects to bring all devices currently used (Accu-Chek® Solo micropump system) with them to the next visit
- Record all relevant data in the eCRF

7.6 Visit 5 – Final Visit (week 39 [± 14 days]) or Early Termination Visit

Study procedures include the following assessments:

- Record any changes in diabetes medication
- Record any changes to other medications
- Record any malfunctions /incidents
- Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit
- Obtain information in hypoglycemic events and time of absence from work or school due to diabetes complications
- Have subject complete questionnaires
- Obtain and record weight
- Draw blood sample for determination of HbA_{1c} (in central laboratory)
- Perform urine pregnancy test in women of child bearing potential (only if applicable by local law, e.g. in Austria)
- Examine insertion sites and record signs of redness, swelling, heat, pain and itching according to the categories as listed (none, minor, moderate, severe), if applicable
- Download data from the devices used since previous visit
- Collect and register study material and return to sponsor:
  - Study device(s), remaining consumables and other supplies[7]
- Record all relevant data in the eCRF

[6] Study devices may be handed-out prior visit 4 if this is required for training purposes.

[7] All non-CE marked material must be collected. In case the subject was using CE-marked material, is willing to continue therapy with Accu-Chek Solo and proper medical support can be assumed, only used Accu-Chek Solo pump bases must be collected.

7.7 Follow-up Call

This follow-up phone call takes place 2-5 days after visit 5 if ongoing AEs or SAEs including but not limited to skin reactions have been recorded at this visit. Record all relevant data obtained at the follow up call in the source data and the eCRF.

7.8 Unscheduled Study Visits or Phone Calls

During the course of the study, subjects may require additional (unscheduled) visits with their physicians (Investigators) for any number of reasons including, but not limited to the following:

- Routine visits according to local practice
- Medication adjustment for diabetes and/or other diseases
- Adverse Events/Severe Adverse Events

Full documentation of the visit including any assessments or examinations performed should be maintained in the source documents.

7.9 Training of Subjects

In order to prepare subjects for their study procedures, they will be trained in the following:

- All subjects will receive general diabetes training including carbohydrate counting at visit 2 – Baseline Visit
- All subjects will receive general insulin pump training when switching from MDI to CSII (groups A & C at visit 2 - Baseline, group B at visit 4 - End of parallel phase).
- All subjects switching therapy will receive pump therapy optimization during a run-in phase of up to 2 weeks after switching from MDI to CSII.
- Subjects will receive training for the Accu-Chek® Solo micropump system when switching to this pump system (group A at visit 2 - Baseline, groups B & C at visit 4, End of parallel phase).
- Subjects will receive training for mylife™ OmniPod® when switching to this pump system (group C at visit 2 - Baseline).

All trainings will be done according to the established standard for pump therapy of the respective site.

Both carbohydrate count training (for all groups) and insulin pump trainings (for groups A & C) required during visit 2 – Baseline may be started after randomization at visit 1 – Screening.Insulin pump training required during visit 4 – End of parallel phase (for group B) may be started up to one week prior to this visit and must be completed at the end of the run-in phase.

The sites will be trained in the use of the Accu-Chek® Solo micropump system by the Sponsor. Training for subjects will be according to local routine.

The sites will use their own, established mylife™ OmniPod® training for subjects in group C.

Both planned ambulant contacts and planned hospitalizations for training purposes will be considered non-captured adverse events.

7.10 Subject Questionnaires (to be completed at the site)

Subjects will be asked to complete several questionnaires at each visit. These questionnaires will be presented electronically. Thus, study staff will open subject´s file in the eCRF-system, open the questionnaires, and hand over to the subject with a short explanation as to completion.
When the subject has finished he/she should "save" and close the document.
Hereafter, neither Investigator nor study staff will be able to see the subject´s entries, and thus, confidentiality is ensured.

Study questionnaires can be grouped thematically:

- Questionnaires regarding the subject's psychological situation,
- Questionnaires assessing device parameters,
- Questionnaires assessing training.

The following table lists the timing of the subject questionnaires as per their treatment group (A, B, or C):

Visits / Questionnaire	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5
DTQ, Initial	A, B, C				
DTQ, Difference			A, B, C,	A, B, C	A, B, C
PAID-5	A, B, C		A, B, C	A, B, C	A, B, C
Roche-Specific			A	A	A, B, C
Roche-Specific without questions 8&9			C	C	

7.11 Subject Diaries

No study specific diary for will be required.

7.12 Laboratories

7.12.1 Local Laboratories

Blood samples must be drawn for the determination of the following parameters at the site's local laboratory according to local practice:

- HbA_{1c}

Please note that a previous result may be used if less than 2 months prior to Visit 1.

The following urine tests will be performed at the site's local laboratory at Visit 1- Screening:

- Pregnancy test, if applicable and at every visit if required by local law, e.g. Austria. The pregnancy tests will be provided by the Central Laboratory

7.12.2 Central Laboratory

Blood samples must be drawn for the central determination of:

- HbA_{1c} at Visits 2 – Baseline, 3 – Middle of parallel phase, 4 – End of parallel phase, and 5 –Final visit

For details regarding tubes, labelling, packaging, dispatch to central laboratory, please refer to the Central Laboratory Handbook.

Name of Central Laboratory	Q Squared Solutions Ltd.
Address	The Alba Campus, Rosebank
	Livingston, EH54 7EG
	United Kingdom

7.13 Data Collection

A **Subject Identification Log** will be completed for all subjects who have provided their informed consent i.e., signed the Subject Informed Consent Form.

eCRF

An eCRF has been set up for this study.

For each subject who has signed the Subject Informed Consent Form, the Investigator must allocate a **subject ID number** via the eCRF-system of two digits for the site and three digits for the subject: **SS-XXX**.

For each enrolled subject, an eCRF must be completed (throughout the study) and electronically signed by the Principal Investigator or Sub-/ Co-Investigator (at the end of the subject's participation in the study).

Upon training, Investigators and authorized study staff will enter subject data during or shortly after the respective visits.

Data Discrepancy Management

Subsequently, the entered data will be systematically checked:

- by means of pre-defined computerized validation checks (as outlined in the Data Management Plan)
- by data review by the Sponsor including but not limited to the Data Manager, Monitor and Study Manager.

All data discrepancies will result in data queries within the eCRF-system, which must be addressed (data confirmed or changed) by the study site staff and closed by the originator.

In addition, protocol deviations must be recorded throughout the study and documented further, as applicable (see section 14).

If a subject withdraws from the study, the reason must be recorded on the eCRF.

Subject Questionnaires

Subjects will be asked to complete a set of questionnaires at each visit, see section 7.10. These questionnaires will be presented electronically.

Upon completion of the questionnaires, the subject will press “Save” and close the document. This enables entries to be saved (in the eCRF). This will generate a notification to (named) study staff that the questionnaires have been completed/saved.

For the sake of confidentiality, neither the Investigator nor other study staff will be able to read the subject’s entries.

Database Closure

Quality control of the database will be made throughout the study conduct in order to prepare the database closure. After the database has been declared clean (i.e. complete and accurate), the database will be locked.

Any changes to the database after that time can only be made by joint written agreement between the Study Manager and the Statistician.

7.14 Medical Care after Study Participation

Upon the subject´s planned termination in the clinical study, it is up to the subject him/herself, preferably in agreement with the treating physician, for the future treatment

- to return to the device used prior to the study or
- to continue with the investigational device, if CE-mark has been obtained or
- to use any other suitable device available on the market.

8 Risk/Benefit Analysis of the Investigational Device and Clinical Investigation

8.1 Potential Risks

During participation in this clinical study, subjects may encounter the following known potential risks of insulin pump therapy:

- Possible hypoglycemia.
- Possible hyperglycemia which might progress to ketosis and diabetic ketoacidosis (DKA)
- Infusion site reactions (bleeding, bruising, inflammation, infection, etc.)

The above risks are an integral part of intensive insulin therapy and applied in daily practice. It has to be underlined that subjects face the same risks as listed during their routine therapy. The likelihood of serious events occurring is considered uncommon.

8.2 Minimization of Risks

The Sponsor has minimized the potential of the above risks to occur by:

- Selection of qualified investigators consulting study subjects during the scheduled visits including an inspection of infusion sites.
- Selection of subjects experienced in MDI therapy lacking any serious problems regarding the risks mentioned above.
- Selecting subjects adhering to the minimum number of 4 blood glucose measurements per day recommended for MDI therapy.
- Design of the clinical study, including individualized training which will include the precautions for pump systems e.g., to measure blood glucose 1-3 hours after insertion device / cannula (see instructions for use), if applicable.
- Subjects are advised not to change their current diabetes therapy without consulting their physician (Investigator), if applicable.

Furthermore, a risk analysis was performed, resulting measures have been implemented and none of the remaining risks is outside the acceptable region (Reference: Risk Management, Roche on file).

8.3 Potential Benefits

The study subjects may experience the following potential benefits while participating in this study:

- mylife™ OmniPod® system and the Accu-Chek® Solo micropump system will be provided at no charge to subjects.
- Screening and study visits (as well as scheduled telephone calls) will be provided at no charge to subjects.
- Study subjects will gain additional attention by their physician.
- Subjects may be motivated to learn more about diabetes and to have better discussions of potential issues with their health care providers.
- Subjects may gain personal satisfaction from participating in this study.
- Subjects may experience improved treatment satisfaction from participating in this study, which might increase therapy adherence and thus reduce their HbA_{1c}.

9 Adverse Events Recording and Reporting

The definitions are based on ISO 14155:2011(E) and respective sections CFR Title 21 for Medical Device Studies.

9.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

In addition, this definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

9.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that fulfils at least one of the following criteria:

- Led to death.
- Led to a serious deterioration in the health of a subject resulting in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - An in-patient or prolonged hospitalization, or
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Fetal distress, fetal death or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition, or a procedure required by the study procedure, without serious deterioration in health, is not considered an SAE.

Applicable for Germany only:

Serious Adverse Event (SAE) definition according to MPSV:

A serious adverse event is defined by German Ordinance on the Medical Device Safety Plan (MPSV) as any untoward medical event in a clinical trial or performance evaluation, which is subject to approval, that directly or indirectly led, could have led or could lead to death, or resulted, could have resulted or could result in a serious deterioration of health status or death of a subject, user or another person, whether or not related to the investigational medical device.

9.1.3 Adverse Device Effects

An Adverse Device Effect (ADE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons related to the use of an investigational medical device (including consumables).

NOTE: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

9.1.4 Serious Adverse Device Effects

A Serious Adverse Device Effect (SADE) is any adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

9.2 Definition of Hypoglycemia, Hyperglycemia Episodes and Diabetic Ketoacidosis

Hypoglycemia and hyperglycemia can be symptomatic or asymptomatic and are subset of AEs occurring within Diabetes studies.

Any hypoglycemia or hyperglycemia episode which occurs during the course of the study will be documented by the subject him-/herself in his/her individual Subject Diary, if applicable, or will be defined specifically by the study procedure e.g. in the visit description of this study protocol.

9.2.1 Asymptomatic Hypoglycemic Episode

An asymptomatic hypoglycemic episode is defined as a low blood glucose reading below 70 mg/dL (3.9 mmol/L) without symptoms and is considered as a non-captured expected AE described in Section 9.3.1.2.

9.2.2 Symptomatic Hypoglycemia Episode

A symptomatic hypoglycemia episode is defined as an AE with symptoms consistent with hypoglycemia and may be confirmed by blood glucose readings below 70 mg/dL (3.9 mmol/L).

Symptoms might include but are not limited to: sweating, dizziness, light-headedness, tremors, nervousness, hunger, headaches, weakness or tiredness.

Symptomatic hypoglycemia will be recorded by the subject in their Subject Diary, if applicable, and transferred to the AE Form in the eCRF by the Investigator or authorized site staff and is considered an expected and captured AE, as described in Section 9.3.1.1.

9.2.3 Severe Hypoglycemia Episode

A severe hypoglycemia episode is defined as symptoms in loss of consciousness and/or seizures resolving upon administration of glucose or glucagon by another person (only third-party assistance). A blood glucose value below 36 mg/dL (2.0 mmol/L) might be available, but is not mandatory (if no assistance, then not considered Severe Hypoglycemia).

Such episodes are defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or be faxed).

9.2.4 Hyperglycemic Episode

Hyperglycemia is defined as high blood glucose readings, a recommended threshold to intervene could be defined as values above 250 mg/dL (13.9 mmol/L). However, investigators should consider the condition of the individual subject.

Only hyperglycemia episodes in combination with medical intervention or additional diagnostic procedures have to be documented as AE in the eCRF, as described in Section 9.3.1.1.

9.2.5 Diabetic Ketoacidosis

Diabetic Ketoacidosis is defined as any symptoms such as polydipsia, polyphagia, polyuria, nausea, or vomiting; and presence of serum ketones, or moderate or high urinary ketones; and either arterial blood pH <7.3 or serum bicarbonate <15 mg/L and treated as directed by the subject's physician.

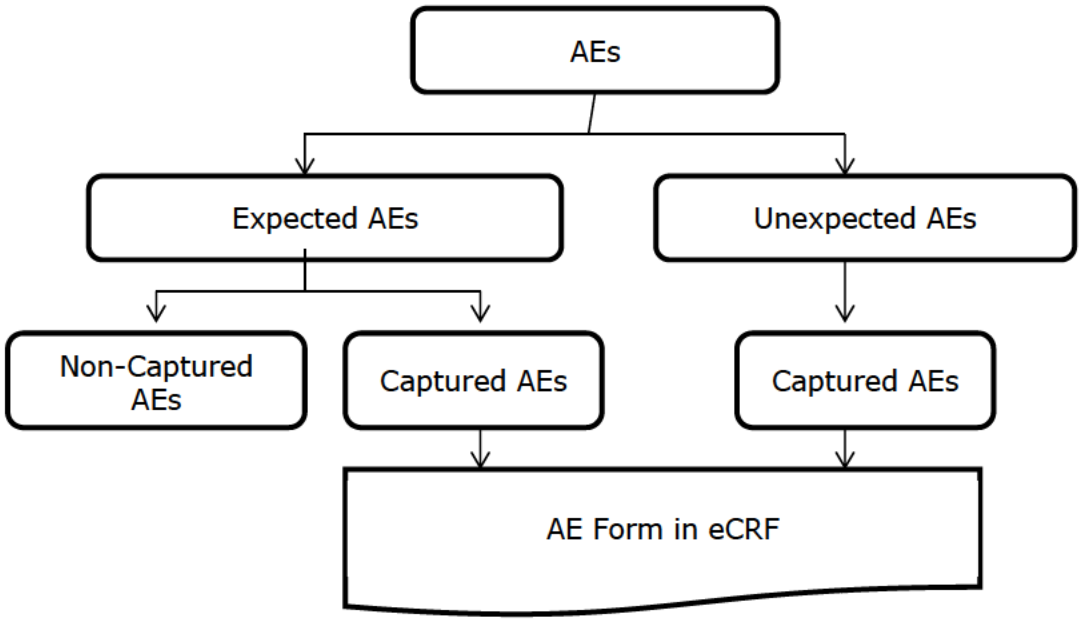
Such episodes are also defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or be faxed).

9.3 Expectedness Classification of Adverse Events

An AE will be classified as either expected or unexpected (see Figure 5).

For the purpose of this study, expected AEs will be divided into non-captured and captured AEs. These distinctions were made based on the frequency of occurrence, severity of event, and risk to subject. All captured AEs will be documented in the eCRF.

Figure 5 Expectedness Classification of Adverse Events



Abbreviations: AE = adverse event; eCRF = electronic Case Report Form.

9.3.1 Expected Adverse Events

9.3.1.1 Captured Expected Adverse Events

The following expected AEs may occur at any time in the course of managing diabetes. Immediate or short-term risks to subjects from some of these expected AEs are higher than those identified under Non-Captured Expected AEs.

Therefore, for the purposes of this study, the following expected AEs will be considered captured expected AEs and the AE Form in the eCRF needs to be completed:

- Symptomatic hypoglycemia episodes (see Section 9.2.2).

- Hyperglycemia in combination with medical intervention.
- Hyperglycemia in combination with medical intervention or suspected by the site staff to be caused by insulin leakage or infusion set occlusion.
- Infusion site infection and abscesses, if applicable.
- Unintentional needle stick injury with the guiding needle of the infusion set, if applicable.
- Plaster reactions to the infusion set, if applicable.
- Generalized hypersensitivity reactions.
- Ketosis and ketoacidosis.

These captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values or otherwise as instructed by the Investigator.

9.3.1.2 Non-Captured Expected Adverse Events

Non-Captured expected AEs may occur at any time in the normal course of managing diabetes. For the purpose of this study, they will be considered as non-captured expected AEs and will not be documented in the eCRF, these include:

- Asymptomatic hypoglycemia episode (see Section 9.2.1).
- Hyperglycemia without medical intervention.
- Hyperglycemia with a suspected cause other than infusion set leakage or occlusion and without medical intervention.
- In the event of a sore finger, subjects will be advised to avoid taking self-monitoring blood glucose samples from that finger.
- In the event of a mild infection at a lancing site, the study subject will be reminded to wash hands before all blood tests and encouraged to consult their nurse or physician on the management of an infection.
- Minor skin damage due to plaster removal which disappears within a few hours.
- Minor bleeding into the infusion set plaster or into the catheter or tubing, if applicable.
- Mild discomfort by plaster or cannula that may result into replacement decision by the subject.
- Also, both planned ambulant contacts and planned hospitalizations for training purposes will be considered non-captured adverse events.

Since these non-captured expected Adverse Events identified above are common as well as expected and pose minimal immediate risk to the subjects, they will not be tracked and logged as AEs during the course of the study. Investigators may log reports of these non-captured expected AEs as is customary within their practice.

These non-captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values as well as for minor skin damage, minor bleeding and mild discomfort.

9.3.2 Unexpected Adverse Events

All AEs which do not meet the criteria mentioned under expected AEs (Section 9.3.1) are considered as unexpected AEs and will be documented in an AE Form in the eCRF.

9.4 Assessment of Causality in Relationship to Device

9.4.1 Related

An AE is deemed related with a device if **ALL** of the following criteria apply:

- There is a reasonable temporal sequence between AE and use of the device.
- It follows a known or expected response pattern of the device.
- It cannot be reasonably explained by the known characteristics of subject's clinical state.

Adverse events resulting from insufficiencies and/or inadequacies in the instructions for use or the deployment of the device will be classified as related.

Adverse events resulting from a user error will be classified as related.

9.4.2 Possibly Related

An AE is deemed possibly related if:

- There is a reasonable temporal relationship between the AE and use of the device; and
- It follows a known or expected response pattern of the device but could have been easily produced by a number of other etiologies.

9.4.3 Unrelated

When there is no reasonable temporal association between the device and the AE or the event was related to the subject's clinical state or concomitant treatment(s).

9.4.4 Not Assessable

When there is not sufficient information to assess a relationship.

9.5 Period of Observation

All AEs ongoing at the time of study termination – irrespective their severity – should be followed up – via telephone – for a maximum of 5 days after the subject's last visit to the site. A medical statement should be included in the AE Form in the eCRF for all ongoing AEs after the Period of Observation.

9.6 Investigators' Responsibility to Report Serious Adverse Events/Serious Adverse Device Effects

Investigators must immediately report all SAEs/SADEs on the SAE Report Form which has been integrated in the eCRF – irrespective of expectedness or relationship to study procedures or study devices.

For reported deaths, the Investigator should provide any additional information, as requested and required, such as autopsy reports or terminal medical reports.

The Investigator should complete and (electronically) sign the form, and send it (electronically, within the eCRF system) to:

- **Study Safety Officer:** mannheim.dcas_medical_safety@roche.com

In case, the eCRF system is not functioning, a paper version of the form should be completed by hand, signed and sent as described above (faxed or e-mailed).

If SAE/SADE information is unsatisfactory and essential data is missing, the Investigator is requested to conduct the necessary follow-up actions and/or to provide additional information as soon as possible.

9.7 Sponsor's Responsibility to Report Serious Adverse Events/Serious Adverse Device Effects

The below **Study Safety Officer** is responsible for all safety related topics of the study:

Name: [redacted]
E-mail: [redacted]
Phone: [redacted]
Fax: [redacted]

Upon receipt of an SAE Report Form, the Study Safety Officer will:

- Review the SAE Report Form for completeness and make a medical assessment.
- Ensure that additional (initially, follow-up and final) information is obtained and communicated, as applicable.

After Safety Assessment the SAE/SADE is reported, as applicable, via the following internal lines:

Roche Q-Function is responsible for reporting of initial, follow-up and final SAE reports to:

- Regulatory Authorities.

Study Manager or designee is responsible for reporting to:

- Ethics Committees
- Other Investigators

10 Malfunction and Incidents

The CE-marked medical devices observed in this study are used within the Intended Use.

The documentation and reporting of the incidents and indirect harms will follow the guidance provided in Medical Devices (MEDDEV) 2.12.-1 rev. 8 (January 2013) and local regulations and guidelines.

10.1 Definitions

10.1.1 Definition of Device Deficiency

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE Device deficiencies include malfunctions, use errors and inadequate labelling.

10.1.2 Definition of Malfunction

A malfunction is a failure of a study device to perform in accordance with its intended purpose by users, operators or other users without any medical impact on subject.

10.1.3 Definition of Incidents

An incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or user or of other persons or to a serious deterioration in their state of health.

An indirect harm may occur as a consequence of the medical decision, action taken/not taken on the basis of information or result(s) provided by the device. Examples include:

- Misdiagnosis
- Delayed diagnosis
- Delayed treatment
- Inappropriate treatment

10.2 Incident Reporting

The Investigators should identify incidents with direct and indirect harms of devices with CE-mark used within Intended Use (as defined in the beginning of this section), and report such on the **Incidents Report** (integrated into the eCRF) which should be sent to the Sponsor immediately.

Even if the requested information is not yet complete, it is required to submit the report immediately.

Respective contact details can be found in the Investigator site file and in the Incident Report in the eCRF.

Subjects will report such incidents to the respective Call Centre, as usual for these products or inform their Investigator. Contact details will be noted on subject´s identification card.

In case of doubt on the duty to report an incident, there should be a pre-disposition to report rather than not to report - as a general principle

Incidents with devices from other manufacturers should be reported directly to the respective manufacturer.

Identified malfunctions will be submitted to the Sponsor – either via the eCRF or by means of a separate **Malfunction Report**.

In addition, all incidents and indirect harms are also to be documented in the source data. The following details should be provided:

- Description of event/incident
- Start date
- Resolution date
- Action taken
- Outcome

11 Statistical Considerations and Data Analysis

The primary and secondary analysis as defined in this study protocol will be described in the Statistical Analysis Plan (SAP) and summarized in the final Clinical Study Report (CSR). All additional exploratory analyses required for publications or requested for different needs will be included in a separate Appendix e.g. Publication Analysis Plan (PAP). This might include any ad-hoc additional analyses not defined in the final version of the study protocol/amendment and the SAP.

11.1 Null Hypotheses and Sample Size Calculation

Assessment of treatment satisfaction in patients with type 1 diabetes comparing standard therapy via MDI to patch pumps.

First Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and MDI.

First Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with MDI.

Second Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and mylife™ OmniPod.

Second Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with mylife™ OmniPod.

The first and second Null hypothesis are tested using a hierarchical procedure. Only if the first Null hypothesis of no difference in treatment satisfaction between Accu-Chek® Solo and MDI can be rejected, the second Null hypothesis of no difference in treatment satisfaction between Accu-Chek® Solo and mylife™ OmniPod will also be tested.

Sample size calculation is based on the expected difference and variability in the DTQ change score between the Accu-Chek® Solo and the MDI group. An anticipated mean score of 90 in the MDI group and of 110 in the Solo group and a standard deviation of 30 is used for sample size calculation.

A sample size of 49 subjects per group will have a 90% power to detect a significant difference at a two sided alpha level of 0.05. To adjust for a maximum drop-out rate of up to 18%, 60 subjects will be enrolled in every treatment arm.

To allow for comparison between the Accu-Chek® Solo and the mylife™ OmniPod, the same number of subjects as in groups A and B will be enrolled in group C. No assumptions on the difference in change of treatment satisfaction between the Accu-Chek® Solo and in the mylife™ OmniPod groups are made and thus, sample size is not adjusted for this comparison. Also, since testing of the first and the second Null hypothesis will be performed using a hierarchical procedure, no multiplicity correction and thus no sample size adjustment is necessary.

11.2 Populations for Analysis

The safety population consists of all subjects enrolled.

The primary analysis population will be the Full Analysis Set (FAS). The FAS is defined as all randomized subjects.

The per protocol population (PP) consists of all subjects who have completed all visits according to the protocol. Detailed criteria for assignment to the PP population will be described in the SAP.

11.3 Handling of subject withdrawals and missing values

As described in 11.2, all randomized subjects will be part of the FAS group and thus be utilized for primary analysis. The pink (left) part of the DTQ will be assessed before randomization. This will guarantee that no bias will be introduced by a possible preference of subjects for a particular group, resulting in a possible withdrawal of individual subjects right after randomization.

For subjects that answered DTQ during Visit 4, these answers will be used for the primary analysis.

The following steps are planned to avoid missing data:

- In case of withdrawal, subjects will be asked to answer the DTQ questionnaire during the End of Study visit.
- If it will not be possible to get questionnaire results at the End of Study visit but questionnaire results are available from week 13 (visit 3), these results will be used, i.e. a LOCF procedure will be applied.
- If there will be no results from week 13, e.g. because a subject will withdraw before week 13, a value of 3 ("Same") will be imputed as the answer to every individual question. This will results in a total score of 90 (30 times 3), which corresponds to the assumed mean result for the MDI group and thus represents a conservative imputation (the anticipated mean score for the Accu-Chek® Solo group is 110).

11.4 Missing values for scores other than the primary endpoint will be imputed using a LOCF approach, where applicable. Details will be specified in the SAP. Subject Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by study group:

- Gender, age and race.
- Height, weight, body mass index, blood pressure and pulse rate.
- Handedness.
- Highest level of education.
- Current employment status and family status.
- Diabetes Background and History
- Diabetes Medication.
- Baseline HbA_{1c}.
- Medical History - diseases other than Diabetes
- Previous Medications for diseases other than Diabetes.

All subject characteristic variables will be summarized descriptively. Continuous variables will be summarized in terms of descriptive statistics including the number of subjects (N) without missing values, mean, median, standard deviation, and range

Categorical variables will be summarized in terms of absolute frequencies and percentages. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population, unless otherwise specified.

11.5 Primary Objective Analysis

The primary objective of this study is to assess the change in treatment satisfaction between start of study and the end of its parallel phase. Change in treatment satisfaction will be assessed by the change in answers to the questions of the Diabetes Technology Questionnaire (DTQ). These answers range from "Much worse" (score 1) over "Same" (score 3) to "Much better" (score 5). In the MDI group, participation in this study results in no treatment change and therefore the mean anticipated score per question is 3, while a significantly higher score is anticipated for the Solo group.

The primary analysis consists of two individual comparisons, firstly the comparison between the between the Accu-Chek® Solo and MDI and secondly between Accu-Chek® Solo and mylife™ OmniPod®. The two comparisons will be performed using a hierarchical procedure.

First, the results from the Accu-Chek® Solo group will be compared to those of the MDI group. Only if the Null hypothesis of no difference in treatment satisfaction between Accu-Chek® Solo and MDI can be rejected, Accu-Chek® Solo will also be compared to mylife™ OmniPod®.

The comparisons will be performed using an ANCOVA with the DTQ score as dependent variable and treatment arm, baseline DTQ score, and site as covariates.

Details of the statistical analyses will be described in the SAP.

11.6 Secondary Objective(s) Analysis

For subjects from groups B (starting with MDI) and C (starting with mylife™ OmniPod®), who will all use the Accu-Chek® Solo micropump after week 26, the change in DTQ score between week 26 and week 39 will be analyzed.

Additionally, the following parameters will be tested. More parameters may be specified in the statistical analysis plan (SAP). Both pairwise tests (Accu-Chek® Solo versus MDI and Accu-Chek® Solo versus mylife™ OmniPod®) and simultaneous analyses of all three treatment alternatives will be performed where applicable, e.g. using an Ancova with treatment arm as independent variable. Baseline adjustment will be performed where applicable. Details will be specified in the SAP.

- Psychological parameters that describe or affect therapy:
    - Treatment satisfaction with Accu-Chek® Solo system vs. mylife™ OmniPod®, measured by the difference in the Diabetes Technology Questionnaire (DTQ) change score after 26 weeks.
    - Diabetes-related Emotional Distress assessed by PAID-5.
    - Device satisfaction
    - Device and Treatment Preference
- Physical parameters that describe therapy changes or success:
    - HbA_{1c}
    - Change in weight and BMI
    - Glycemic variability
- Therapy parameters that describe therapy changes or may affect the results
    - Indication for commencement of CSII
    - Type of insulin used
    - Total daily insulin dose (TDD)

  - Total daily basal insulin dose (TBD)
  - Average number of SMBGs per day
  - Frequency of hypoglycemic events
  - Frequency of hyperglycemia
  - Frequency of consultations between scheduled visits, emergency and call center calls, hospitalizations and absenteeism from work/school
- Device specific parameters that may affect user acceptance
  - Number of pods/ infusion assemblies falling off prematurely
  - Average infusion assembly usage time
  - Number, type and intensity of skin reactions
- Parameters that may affect socio-economic acceptance
  - Insulin amount left in device at reservoir change / device discard
  - Amount of waste, inferred by total material consumption
- Subject withdrawal
  - It will be tested whether there is a bias in the fraction of subject withdrawal among the different treatment arms
- Descriptive evaluation:
  - Accu-Chek® Solo micropump system: Training Satisfaction

11.7 Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only AEs occurring after the start of the treatment with either MDI, mylife™ Omnipod® or Accu-Chek® Solo micropump system will be included in the AEs tables.

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System Organ Class and Preferred Term will be prepared. Such summaries will be displayed for all AEs, AEs by maximum severity, AEs by strongest causality to study device (and any associated pump devices), and AEs leading to withdrawal of study device.

Deaths, other SAEs and AEs leading to withdrawal will be listed separately.

In addition, the sub-group of ADEs and SADEs will also be summarized by MedDRA System Organ Class and Preferred Term including summaries by study device.

Episodes (numbers) of the following AEs will be summarized:

- Symptomatic hypoglycemia
- Severe hypoglycemia (SAEs)
- Diabetic Ketoacidosis (SAEs)

The following ADEs are of particular interest:

- ADEs leading to replacement of device.

Incidence rates of all ADEs and of these ADEs and AEs of special interest (as captured on the AE Form in the eCRF) per 100 patient years will be calculated together with exact two-sided 95% CIs assuming that the number of special AEs observed in the study is Poisson distributed.

11.8 Concomitant Medication

Previous and concomitant medications (separated for diabetes and for other indications) will be listed by subject.

11.9 Interim Analysis

An interim analysis will be conducted when all patients have either passed visit 4 (End of parallel phase) or withdrawn from the study, i.e. when all data for performing the primary analysis and the majority of the secondary analyses will be available No changes on the study protocol will be made due to the results of this interim analysis.

12 Ethical and Legal Considerations

12.1 Statement of Compliance

The study will be performed in accordance with the principles stated in the World Medical Association's Declaration of Helsinki "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects" (Fortaleza, 2013), that are consistent with the principles outlined in the ICH Guideline on GCP E6 (R2) (November 9, 2016 where it applies to medical devices and the applicable national regulations for medical device law and applicable ordinances, for the provisions of ISO 14155:2011(E), the European Medical Device Directive (e.g. 93/42/EEC), FDA 21 CFR Parts 11, 50, 54, 56, 99, 312, 803, 812, 814 and 820.30, as applicable in each participating country.

12.2 Subject Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Subject informed consent – before any study procedures - from each subject considering participation in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study – orally as well as presented in the written Subject Information Leaflet.

The Investigator or designee (if applicable) must also explain that the subject is completely free to refuse to enter the study or to withdraw from the study at any time, for any reason and could return to standard care.

The Investigator or authorized staff must document the date of each subject´s informed consent in the respective eCRF.

Furthermore, in case that Screening and Baseline Visits are combined, the time point of the Subject inform consent must be documented.

If any new safety information results in significant changes in the risk/benefit assessment, the Subject Information Leaflet and/or the Informed Consent Form should be reviewed, updated and re-submitted to the EC/IRB for approval.

Subjects already participating in the study should be informed of the new information, and asked to give their written inform consent to continue in the study.

New subjects shall only receive the updated documents.

All subjects will be given a copy of the signed Subject Informed Consent Form(s).

12.3 Confidentiality of Study Documents and Subject Records

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by a unique study identification code, i.e. Subject ID (Number).

The Investigator will keep a **Subject Identification Log** linking study identification codes, and subject contact information. The Investigator will maintain these study documents e.g. subjects' written inform consent forms, in strict confidence and as part of the Investigator's Site File.

Any data obtained from subjects participating in the study may be used to build case studies for educational purposes and all identifying data will be completely removed or blacked-out for these purposes.

12.4 Data Protection

The subject will be informed of his/her right of access, objection and correction of the data recorded during this study, and that this right may be exercised at any time through his/her physician.

Information relating to participating physicians will be declared and the physicians will be informed – within the framework of their agreement – of their right to access, object to and correct this information.

12.5 Independent Ethics Committee

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising used or compensation given to the subject, will be submitted by the Sponsor to an EC. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Sponsor specifying the date on which the committee met and granted the approval. Any modifications made to the protocol after receipt of the EC approval must be re-submitted by the Sponsor to the Committee in accordance with local procedures and regulatory requirements.

When no local committee exists, the Sponsor will submit the protocol to a regional committee. If no regional committee exists, the Sponsor will submit the protocol to the European Ethics Review Committee.

12.6 Regulatory Authorities

Submissions and/or notification to Regulatory Authorities will be performed as required by local legislation in each participating country for this type of study.

12.7 Amendments to the Clinical Study Protocol

Study protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the Investigator. These modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the appropriate representatives of the Sponsor and Statistician.

All study protocol modifications must be submitted to the appropriate EC for approval in accordance with local procedures, and Competent/Regulatory Authorities as required. Approval must be granted in writing before any changes can be implemented, except for those changes necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the study (e.g. change in Monitor, change of telephone number). Note: these changes will be re-submitted for EC/IRB review and approval as soon as possible.

12.8 Suspension or Premature Termination of the Clinical Study

Both the Sponsor and the Investigator reserve the right to terminate the clinical study at any time. Should this be necessary, the parties will arrange the procedures on an individual basis after review and consultation. The only reason for early termination of the study by the Sponsor would be the occurrence of unexpected safety or ethical consideration for the protection of the subject's interests. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests.

12.9 Record Retention

In order to comply with Roche Diabetes Care's requirements, Investigators must maintain all required essential documents – in the Investigator Site File - at the site **for at least 15 years after the study ends**.

Essential study documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced – stored before during and after the study conduct in the Investigator´s Site File. They include but are not limited to, those pertaining to subject files and other source data (e.g. hospital files, consultation records, laboratory reports, etc). The Investigator should ensure that the Investigator Site File is stored in a secure location and should take measures to prevent accidental or premature destruction of any documents.

The Investigator must contact the Sponsor for approval prior to discarding any study-related documents, even if retention requirements have been met.

If the Investigator leaves the clinical site at which the study has been conducted, he/she or current representative must contact the Sponsor to make suitable arrangements to ensure that the study records, including a copy of the **Subject Identification Log** are retained as specified above and to provide for the continuing access to the records by Sponsor representatives and Regulatory Authorities.

12.10 Reimbursement, Indemnity and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement agreed upon by the parties.

12.11 Publication of Data and Protection of Trade Secrets

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to Roche Diabetes Care prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Any formal publication of the study in which input of Roche Diabetes Care personnel exceeds that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Roche Diabetes Care personnel. Authorship will be determined by mutual agreement.

13 Clinical Conduct, Study Material and Accountability

13.1 Material and Procedures

13.1.1 Numbering of Subjects

As soon as a subject has signed the Informed Consent Form, the Investigator or authorized study staff will allocate a subject ID number via the eCRF-system.

The subject ID number consists of 2 digits for the site and 3 digits for the subject: **SS-XXX**.

13.1.2 Supply of Study Material to Study Sites

The Investigator will receive all of the materials needed to initiate and conduct the clinical study. The materials include, but are not limited to:

- Study protocol, final approved version.
- Patient Information and Informed Consent Form
- Electronic CRF, available on-line.
- Investigator Site File including all relevant documents.
- Investigational devices
- Packaging material for return of study devices

13.1.3 Dispensing of Study Devices

The site will be responsible for maintaining a supply inventory log recording receipt and disposition of all the devices with serial or batch numbers and supply materials, if applicable.

For this purpose, a study specific **Supplies Dispense & Return** shall be completed for each subject.

When a study device is replaced either according to the protocol or as a result of malfunction, the new device needs to be linked to the subject's profile in Accu-Chek Smart Pix.

13.1.4 Return of Study Devices

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

1. Subject identification.
2. Date on which the investigational device was returned/explanted from subject, if applicable.
3. The date or return of unused, expired or defective investigational devices, if applicable.

Note: Written procedures may be required by national regulations.

Subjects are asked to return all study devices (used, unused, expired or malfunctioning) at the following visit. To ensure safe transportation, subjects will receive appropriate packing material, if applicable.

For this purpose, a study-specific **Supplies Dispense & Return Form** shall be completed for each subject.

13.1.5 Destruction of Study Devices

Reusable components of the Accu-Chek® Solo micropump system shall be returned to the Sponsor for after-use-inspection.

If devices are not to be returned to the Sponsor, destruction (of used and unused devices including comparative devices) is only allowed upon written permission from the Sponsor.

13.2 Site Selection

Sites will be selected for participation in this clinical study by the Sponsor. These sites must have qualified personnel and must be equipped with the appropriate medical facilities to fulfil the study requirements. The clinical sites must be associated with and under the guidance of an Ethics Committee which satisfies all Regulatory Authority requirements and conducts meetings on a regular basis. These sites must also have an adequate subject population to meet the study requirements.

Sites will be approved for participation by the Study Manager.

13.3 Responsibilities of the Site Principal Investigator(s)

The site Principal Investigator(s) shall be responsible for the day-to-day conduct of the clinical study as well as for the safety and well-being of the study subjects.

The site Principal Investigator(s) must satisfy the following requirements:

- Have adequate knowledge and experience in diabetes care management as documented in the Investigator's Curriculum Vitae.
- Have the resources and time to comply with the requirements of this clinical study.
- Have access to an appropriate medical facility and equipment necessary for the conduct of this clinical study.
- Have primary responsibility for the accuracy, legibility and security of all study data.
- Have an adequate subject population to meet the requirements of the study.
- Observe confidentiality at all times throughout the study.
- Ensure only eligible subjects, per the approved study protocol, are enrolled into the study and that written informed consent is obtained from each subject.
- Follow protocol procedures and provide accurate data in a timely manner.

13.4 Study Monitoring and Auditing

13.4.1 Study Monitoring and Source Data Verification

It is understood that the responsible Roche Diabetes Care Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. It will be the Monitor's responsibility to review the eCRFs at regular intervals throughout the study, to verify protocol compliance and the completeness, consistency and accuracy of the data being entered. The Monitor should have access to the laboratory test reports and other subject records to verify the entries on the eCRFs. The Investigator (or designee) agrees to cooperate with the Monitor to ensure that any problems detected in the course of these Monitoring Visits are reviewed and resolved.

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Details about requirements for Source Data Verification (SDV) and other aspects of Monitoring will be described in the Study Handbook.

13.4.2 Clinical Site Visit Schedule

A Pre-Study Qualification Visit will be conducted prior to the start of the study to ensure that:

- Study sites and their facilities meet the requirements of the study.

A Site Initiation Visit will be conducted prior to the start of the study to ensure:

- Investigator understands and accepts his/her obligations in conducting the clinical study according to the protocol.
- Investigator and study staff have reviewed and understood the study protocol.
- Training regarding study devices and study procedures.

Regular Monitoring Visits will take place during the course of the study to ensure:

- Continued acceptability of facilities and oversight of the study by the EC.
- Adherence to protocol and applicable regulation.
- Maintenance of adequate subject records.
- All SAEs/AEs are reported to Sponsor and to responsible authority, as required.
- Verification of source data to eCRFs.

At the study termination, study staff will collect all applicable materials and supplies and return them to the Sponsor. After all study data has been collected and verified and the study database has been locked, a **Close-Out Visit** will occur to:

- Ensure all supplies have been accounted for and documented according to the study protocol and the remaining materials either returned to the Sponsor or distributed to the subjects as outlined in the study protocol.

- Complete all monitoring at the study site and close-out any open data discrepancies.
- Ensure all regulatory documents are on file at the clinical site.
- Review the Investigator's responsibilities after the termination activities have been completed.

13.5 Training of Investigators and Study Site Staff

All Investigators and study staff, authorized to perform study procedures, will receive training on the following aspects of the study:

- Clinical study protocol including:
  - Principles of GCP and ISO 14155
  - Protocol and study procedures
  - SAE Reporting procedures including completion of SAE Report Form (eCRF) and/or Malfunction /Incident Reporting procedures
  - Monitoring and Audits
  - As necessary for compliant study conduct
- Investigational devices
- Completion of eCRF:
  - Passwords, Data Entry, Corrections, Query process, and Sign-off
  - Completion of SAE Report Form and sending to the Sponsor
- Completion of Subject Questionnaire
- Documentation of protocol deviations
- Procedures for Central Lab (Handbook etc.)

14 Reporting of Protocol Deviations

Deviation is any instance of failure to follow, intentionally or unintentionally, the requirements of the study protocol.

In order to match all of possible regulations and fulfill all of the responsibilities regarding recording and reporting as well as to allow correct handling of different deviations there are three categories of deviations defined:

Non Relevant Deviation - Deviation which does not affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.

Relevant Deviation – Deviation which may affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.

Serious Deviation - Deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Deviation must be reported to the Sponsor, who is responsible to report according to national regulations.

Protocol Deviations will be recorded in the eCRF throughout the study, and documented further via a specific form or the query-system, as applicable.

The Investigator must notify the Sponsor and ,if required by local regulations, the respective IRB/EC of any **serious deviation** to protect the life or physical well-being of a subject in an emergency as soon as possible/promptly after the emergency occurred.

In this study, visit time windows deviations are considered as protocol deviations, but will not be documented separately. There will be review of these during each data analysis

15 References

1. Jeitler, K., et al., Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia, 2008. 51(6): p. 941-51.
2. Pickup, J.C. and A.J. Sutton, Severe hypoglycemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med, 2008. 25(7): p. 765-74.
3. Misso, M.L., et al., Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus (Review). Cochrane.Database.Syst.Rev., 2010(1): p. 1-140.
4. Cummins, E., et al., Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess, 2010. 14(11): p. iii-iv, xi-xvi, 1-181.