The Royal Melbourne Hospital

DIABETES RESEARCH CENTRE

FIAT LUX
Walter+Eliza Hall Institute of Medical Research
DISCOVERIES FOR HUMANITY

Diabetes Research Update

ADEA Conference Melbourne, March 2019

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The DRC Team

Who are we?

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Institute of Medical Research

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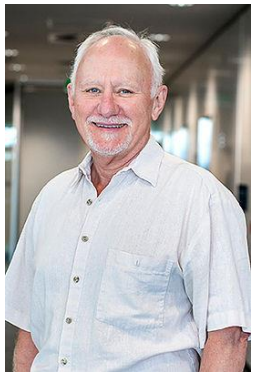

Endocrinologists
Immunologists
Nurses & Midwives
Diabetes Educators
Scientists &
Laboratory Technicians

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Our Focus

- Pre-clinical diagnosis, prediction and prevention of type 1 diabetes
- The role of the environment in promoting both type 1 and 2 diabetes
- The mechanisms of insulin resistance and new treatments for type 2 diabetes

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What have we been up to?

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The EXSCEL Study

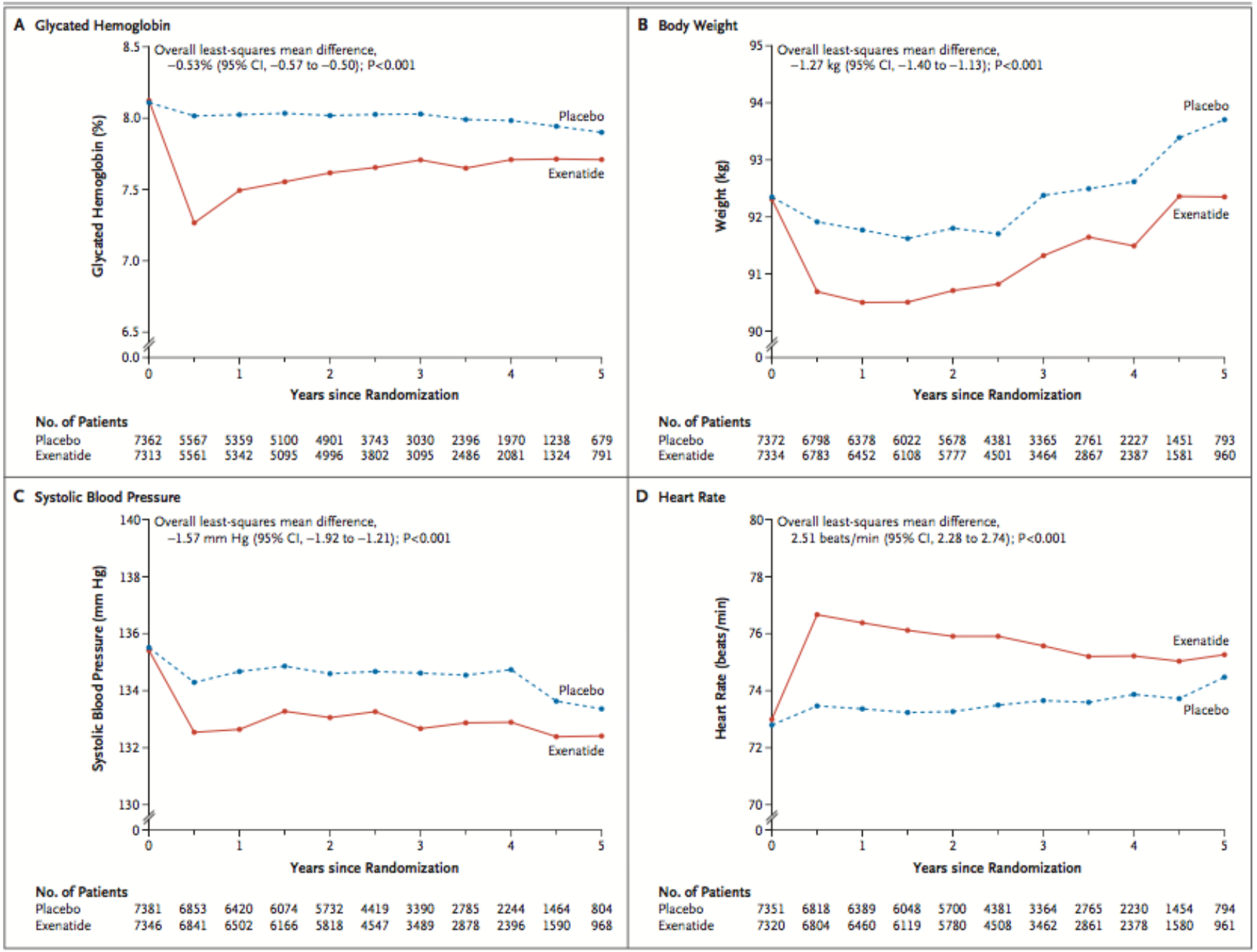
Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Nayyar Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.S., for the EXSCEL Study Group*

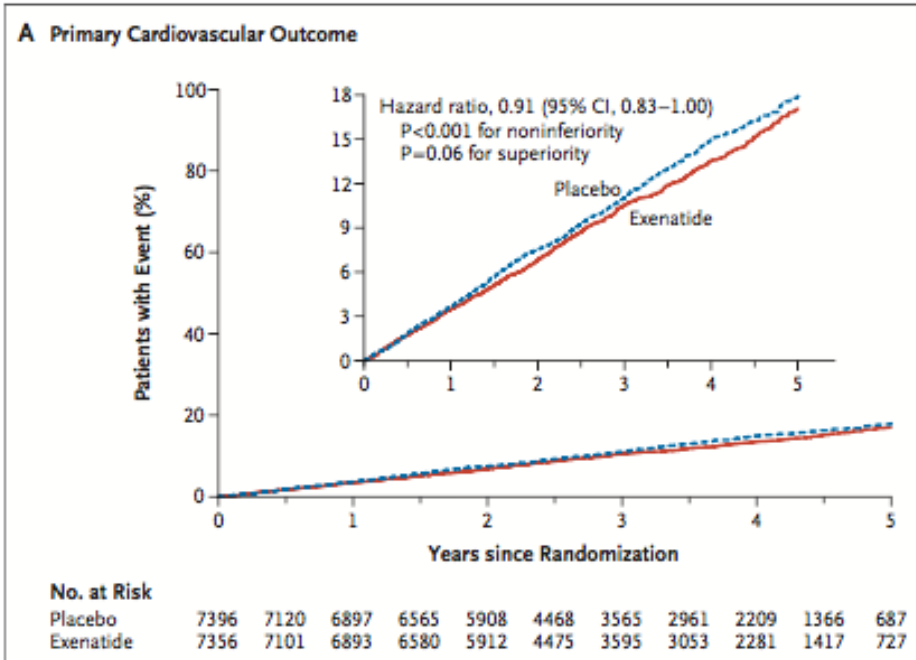
ABSTRACT

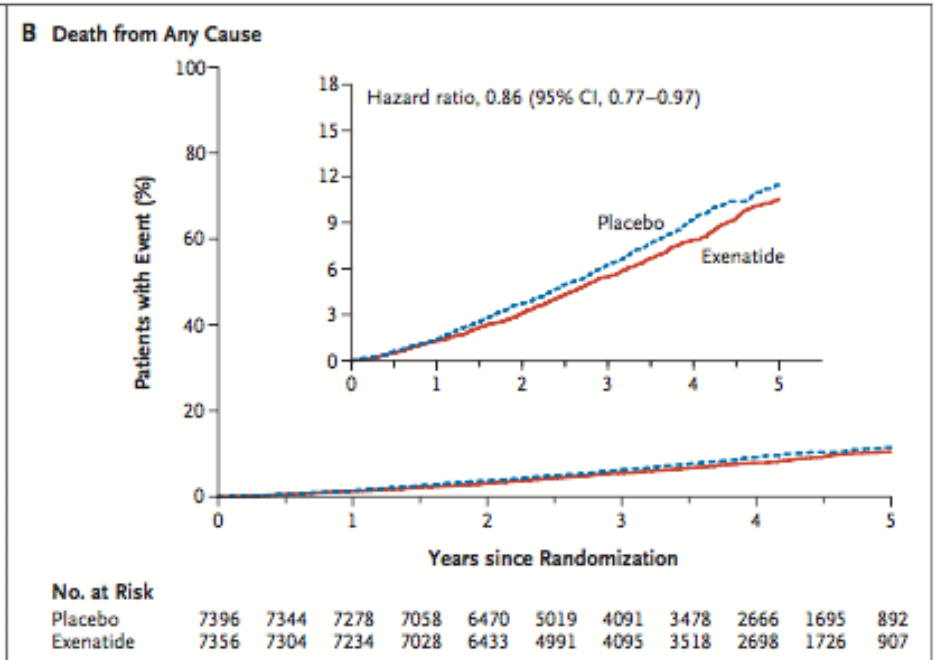
BACKGROUND

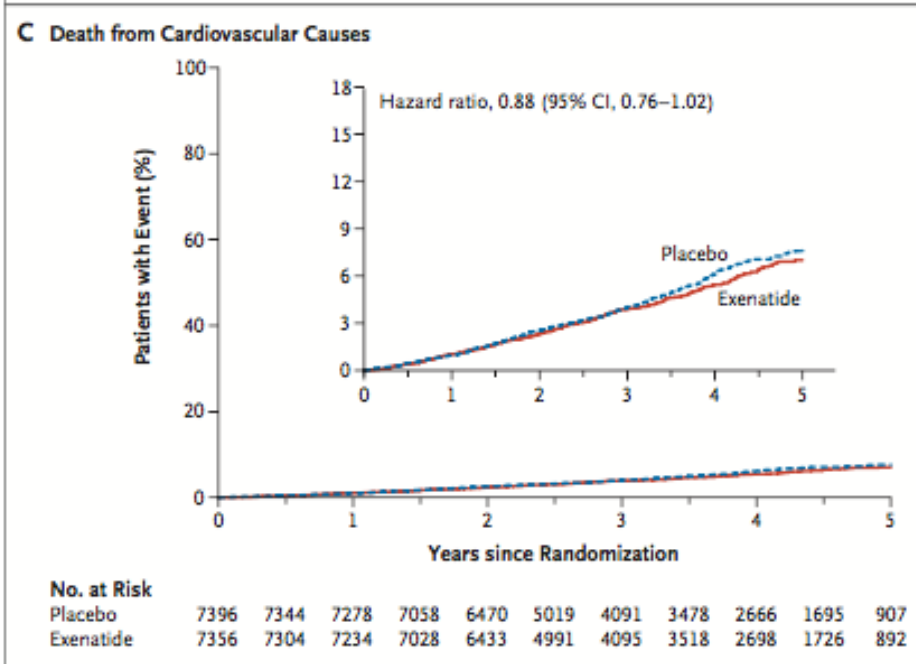
The cardiovascular effects of adding once-weekly treatment with exenatide to usual care in patients with type 2 diabetes are unknown.

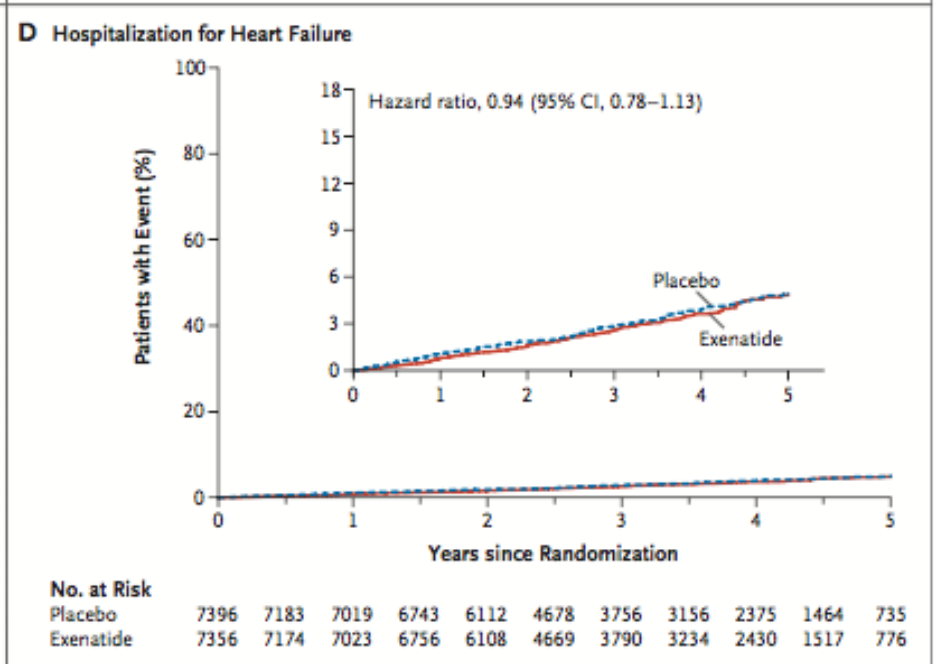


Holman R. et al (2017)









Holman R. et al (2017)

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The Tandem3 Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

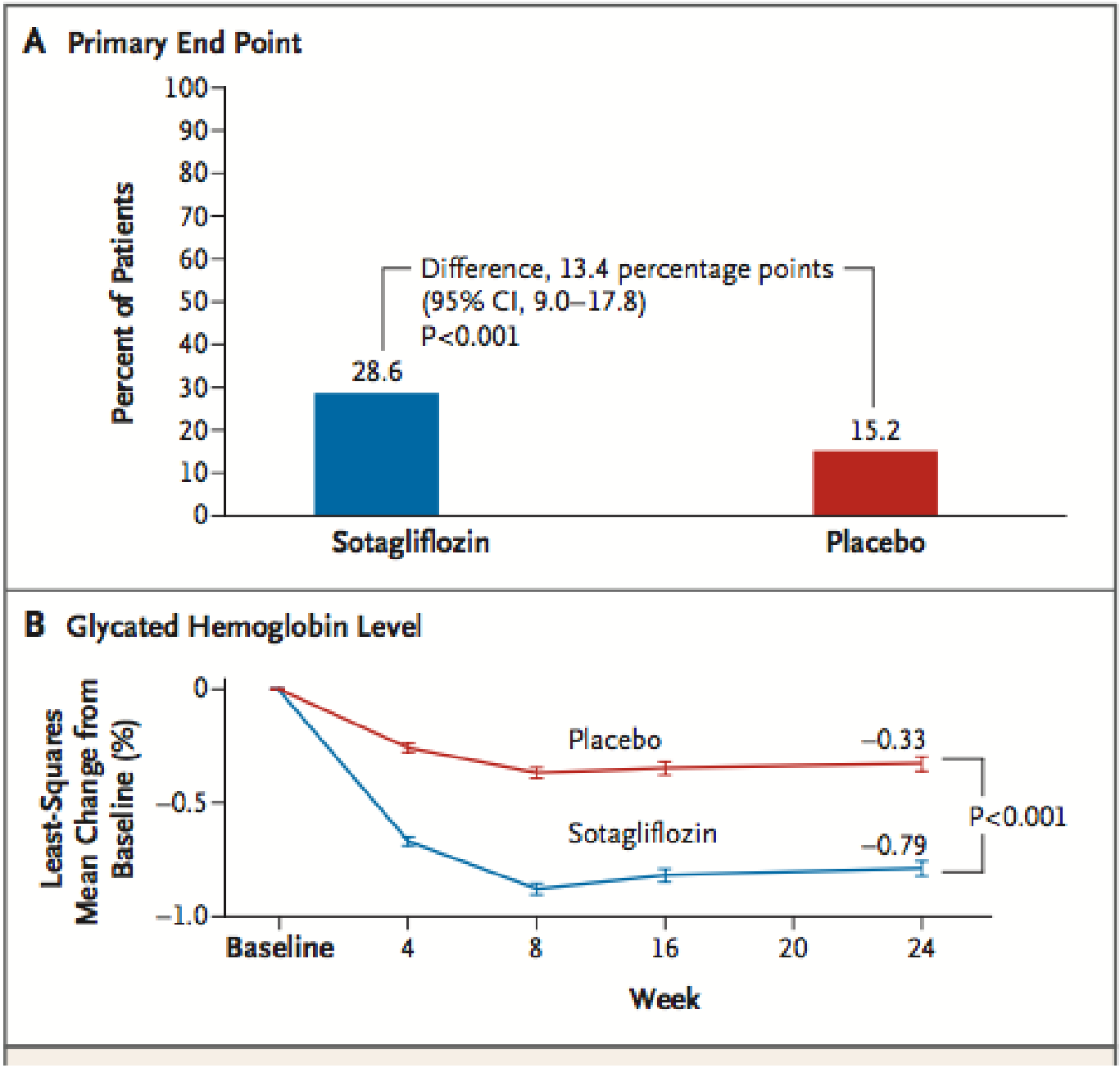
Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

ABSTRACT

BACKGROUND

In most patients with type 1 diabetes, adequate glycemic control is not achieved with insulin therapy alone. We evaluated the safety and efficacy of sotagliflozin, an oral inhibitor of sodium–glucose cotransporters 1 and 2, in combination with insulin treatment in patients with type 1 diabetes.



Garg S.. et al (2017)

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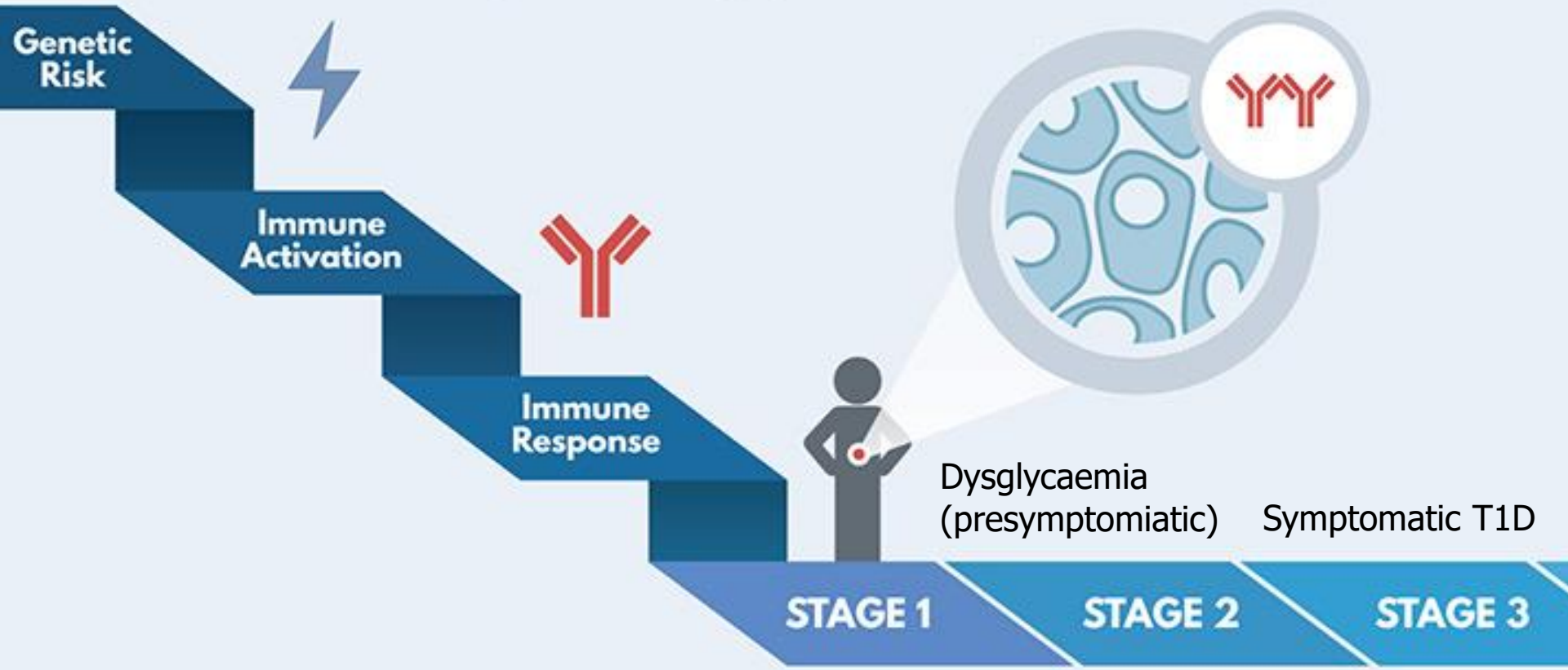
What are we working on now?

Stages of Type 1 Diabetes



Stage 1: Start of T1D
Beta cell autoimmunity

STAGE 1
- TN Pathway to Prevention
- ENDIA

STAGE 2
- TN Abatacept

- TN Immune Effects of OI
- TN Anti-CD3
- INIT II
- TN Oral Insulin

STAGE 3
- TN LIFT
- Closed-Loop
- Nox 1/4 Inhibitor Study

- Tandem3 (Sotagliflozin)
- Gleevec

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Trial Net

Type 1 Diabetes TrialNet

- Type 1 Diabetes TrialNet is a global network of 18 clinical centres dedicated to conducting diabetes prevention research and studying intervention therapies for children and adults with newly diagnosed diabetes.

- TrialNet in Australia is screening relatives of people with type 1 diabetes to find out if these family members are at risk for developing diabetes.

- Screening involves a simple blood test for the presence of diabetes-related autoantibodies that may appear years before type 1 develops.

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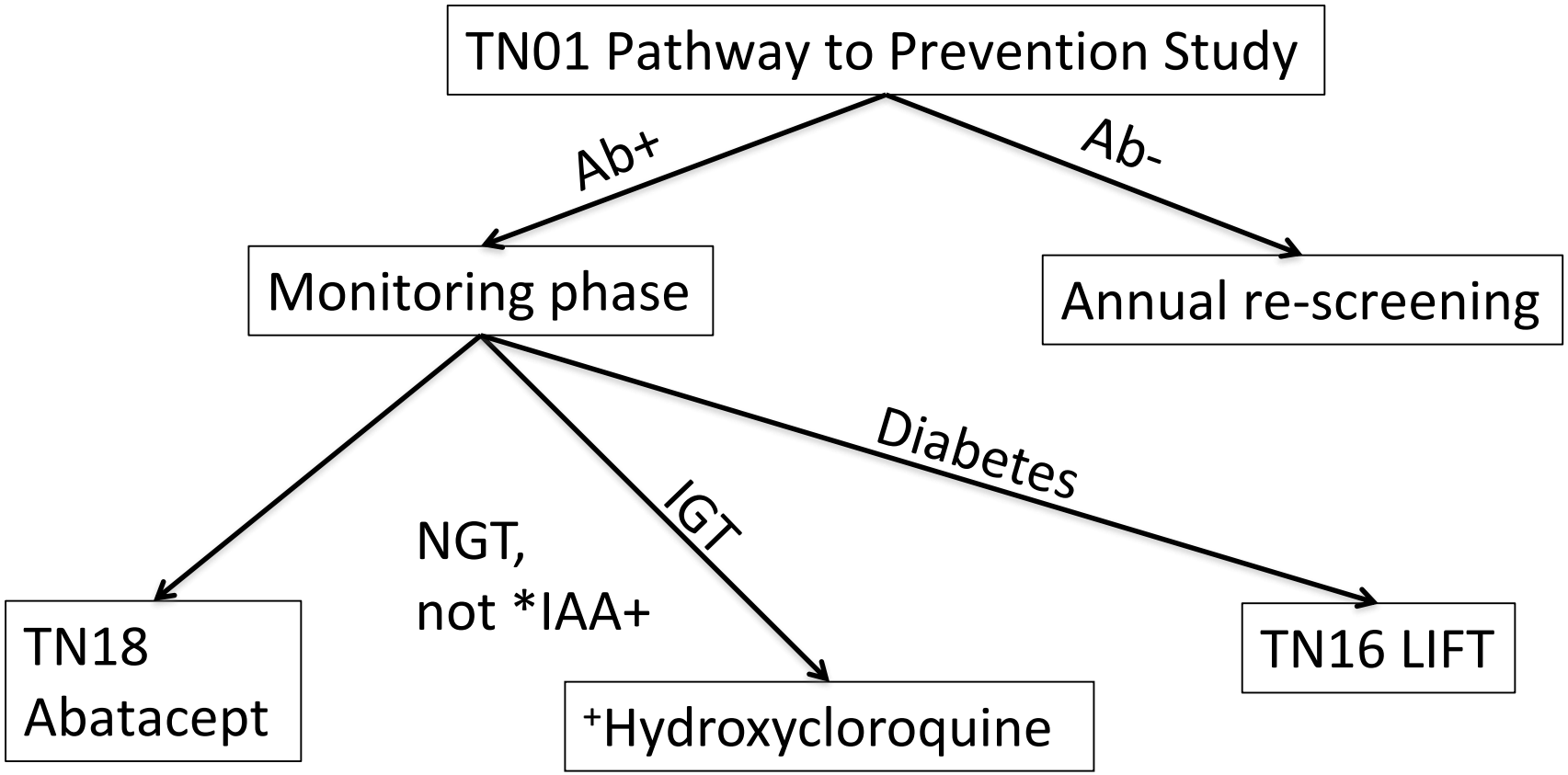
Study Population

Participants eligible for screening;

- Are aged between 1 and 45 years and have a first degree blood relative (brother, sister, child, parent) with type 1 diabetes, OR
- Are aged between 1 and 20 years and have a second degree blood relative (grandparent, half-brother, or half-sister with type 1 diabetes) with type 1 diabetes.

Go to https://trialnet.org/ for more information

TrialNet studies at RMH



*IAA: insulin autoantibody

+Coming soon

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ENDIA

Environmental Determinants of Islet Autoimmunity

Primary Objective

•To determine how genotype, microbiome and environmental factors, such as vitamin d, infection, diet and weight, relate to the development of type 1 diabetes

If we can understand what environmental factors are harmful or protective, and how they interact with our genes, then we can modify the environment to prevent type 1 diabetes

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Study Population

- Pregnant women with type 1 diabetes
- Pregnant women whose partner has type 1 diabetes
- Pregnant women with an older child with type 1 diabetes
- Babies less than six months of age whose parent or sibling has type 1 diabetes

An observational study from pregnancy through the first 10 years of life, with the aim to recruit 1400 participants across the country, 300 at the RMH.

Go to http://www.endia.org.au/ for more information

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Study Visits

How often are the visits?

- Each trimester, then at birth
- Hospital visit within 1-2 days post birth
- Home visit within 5-7 days.
- Every 3mths until 2yrs of age
- Every 6mths from 2-3yrs of age
- Every 6mths from 4-10yrs of age

What do we collect?

- Bloods-coeliac screen, vitamin D, Glucose, various antibodies, T-Cells, HLA, virology
- Swabs-throat, tongue, cheek (buccal), nose, skin and saliva
- Urine, stool, breast milk
- Questionnaires: diet, physical activity and lifestyle
- Tests are done at RMH, WEHI and Adelaide

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Nox-1/4 inhibitor (GKT137831) in adults with type 1 diabetes

A physician-initiated double-blind, randomised, placebo- controlled , phase 2 study evaluating the efficacy and safety of inhibition of NADPH Oxidase with the first-in- class Nox-1/4 inhibitor, GKT137831, in adults with type 1 diabetes and persistently elevated urinary albumin excretion.

Primary Objective

•To test whether participants assigned to treatment with GKT137831, when compared to those on placebo, will achieve a lower urinary albumin excretion at end of treatment

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Study Population

- People with T1D aged 18-65yrs
- HbA1c <10%
- BMI 18.5-40.0
- Taking antihypertensive medication – either an Angiotensin-converting-enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB) and with an eGFR >40
- Diagnosed T1D >12mths (before the age of 40yrs)

Aiming to recruit 10x participants at the RMH site.

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SCORED Study

Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED)

Primary Objectives:

- To demonstrate that, when compared to placebo in patients with type 2 diabetes (T2D), cardiovascular (CV) risk factors, and moderately impaired renal function, sotagliflozin:
- Does not increase the risk of cardiovascular events including death from cardiovascular disease, non-fatal heart attack and non-fatal stroke;
- Reduces the risk of death from CV disease or hospitalization for heart failure.

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Study Population

- Suitable for people with T2DM >18yrs, with an eGFR ≥25 and ≤60 and a combination of major/minor cardiovascular risk factors.
- Looking for 10,500 participants worldwide, and 10x at the RMH

The study will consist of 3 phases: a Screening period of 1 to 4 weeks, a randomized, Double-blind Treatment period, and a Post-treatment period.

The dose of sotagliflozin or matched placebo will be increased from 200 mg to 400 mg in the first 6 months of the randomized Double-blind Treatment period, if tolerated.

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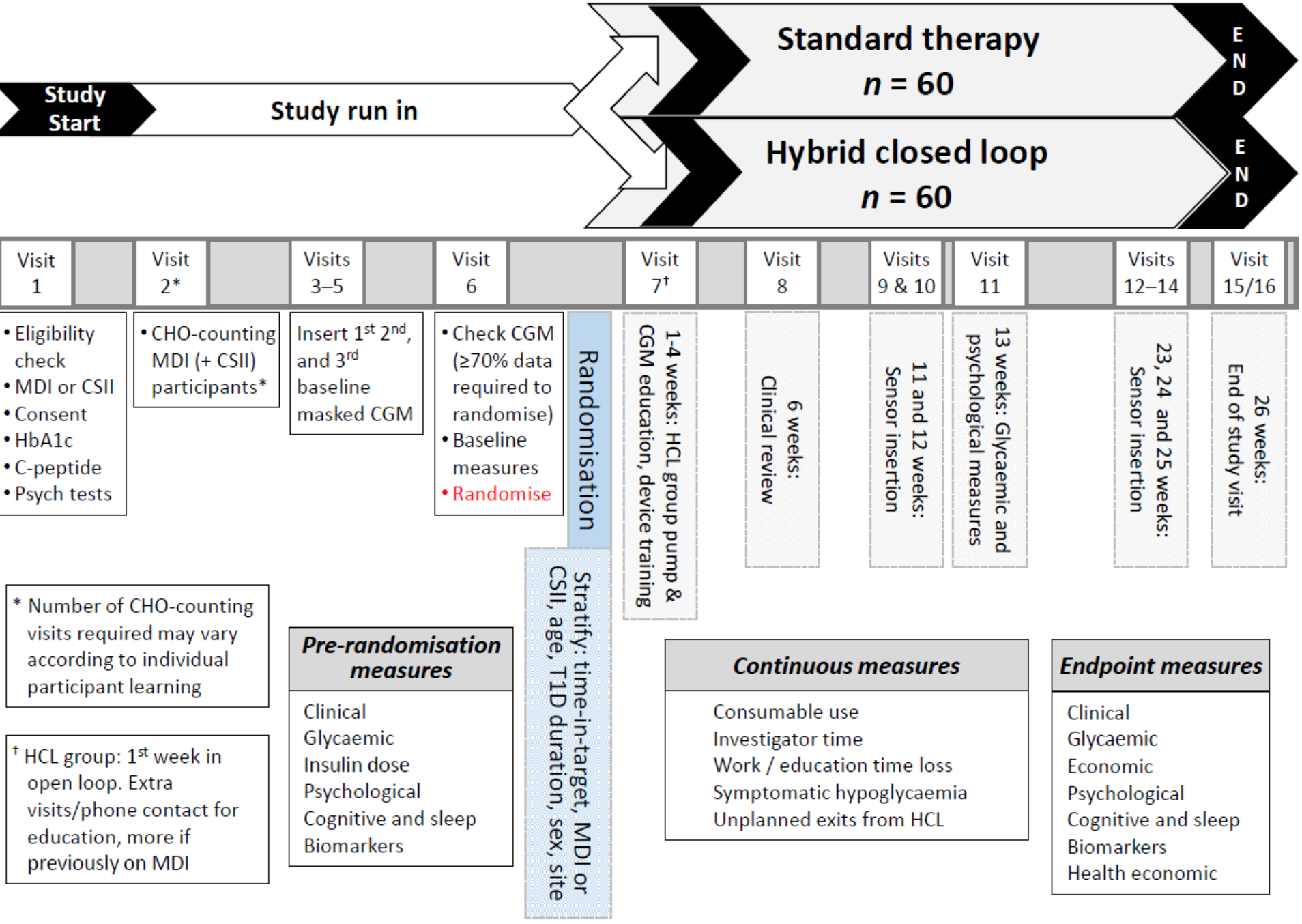
Closed Loop Insulin Pump

Evaluation of the efficacy and cost-effectiveness of long-term hybrid closed loop insulin delivery in improving glycaemia, psychosocial wellbeing, sleep quality, cognition, and biochemical markers of vascular risk in adults with type 1 diabetes

- Two groups: Closed loop system / standard therapy
- Mix of those on pumps and MDI
- 17x participants per site with staged recruitment based on HbA1c and pump/MDI status at screening

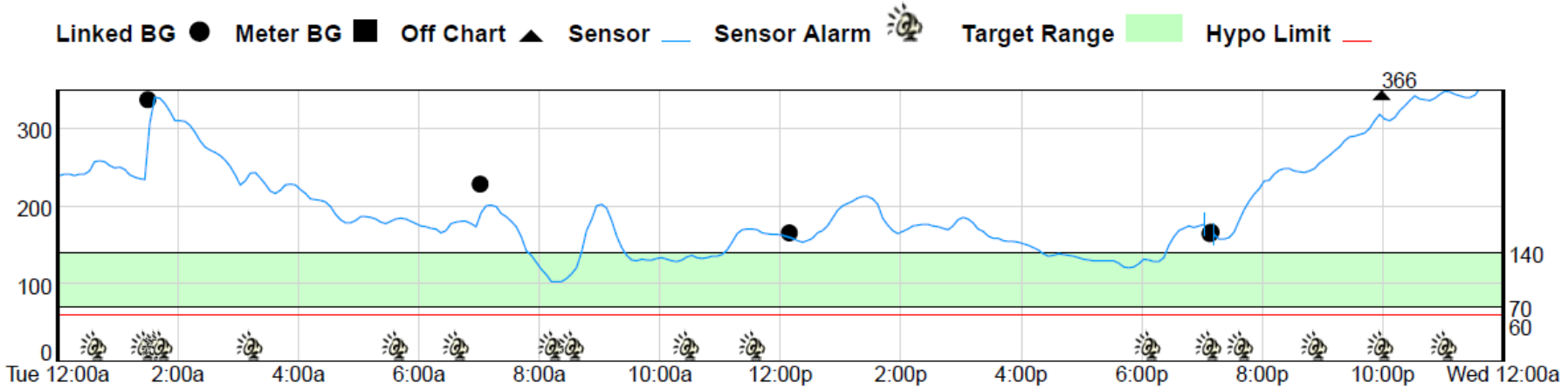

Study Start
Study run in
Standard therapy
n = 60
END
Hybrid closed loop
n = 60
END
Visit 1
Visit 2*
Visits 3–5
Visit 6
Visit 7†
Visit 8
Visits 9 & 10
Visit 11
Visits 12–14
Visit 15/16
• Eligibility check
• MDI or CSII
• Consent
• HbA1c
• C-peptide
• Psych tests
• CHO-counting MDI (+ CSII) participants*
Insert 1st 2nd, and 3rd baseline masked CGM
• Check CGM (≥70% data required to randomise)
• Baseline measures
• Randomise
Randomisation
Stratify: time-in-target, MDI or CSII, age, T1D duration, sex, site
1-4 weeks: HCL group pump & CGM education, device training
6 weeks: Clinical review
11 and 12 weeks: Sensor insertion
13 weeks: Glycaemic and psychological measures
23, 24 and 25 weeks: Sensor insertion
26 weeks: End of study visit
* Number of CHO-counting visits required may vary according to individual participant learning
† HCL group: 1st week in open loop. Extra visits/phone contact for education, more if previously on MDI
Pre-randomisation measures
Clinical
Glycaemic
Insulin dose
Psychological
Cognitive and sleep
Biomarkers
Continuous measures
Consumable use
Investigator time
Work / education time loss
Symptomatic hypoglycaemia
Unplanned exits from HCL
Endpoint measures
Clinical
Glycaemic
Economic
Psychological
Cognitive and sleep
Biomarkers
Health economic

Daily Summary for Subject ID: 0186130101
Jul 18, 2017

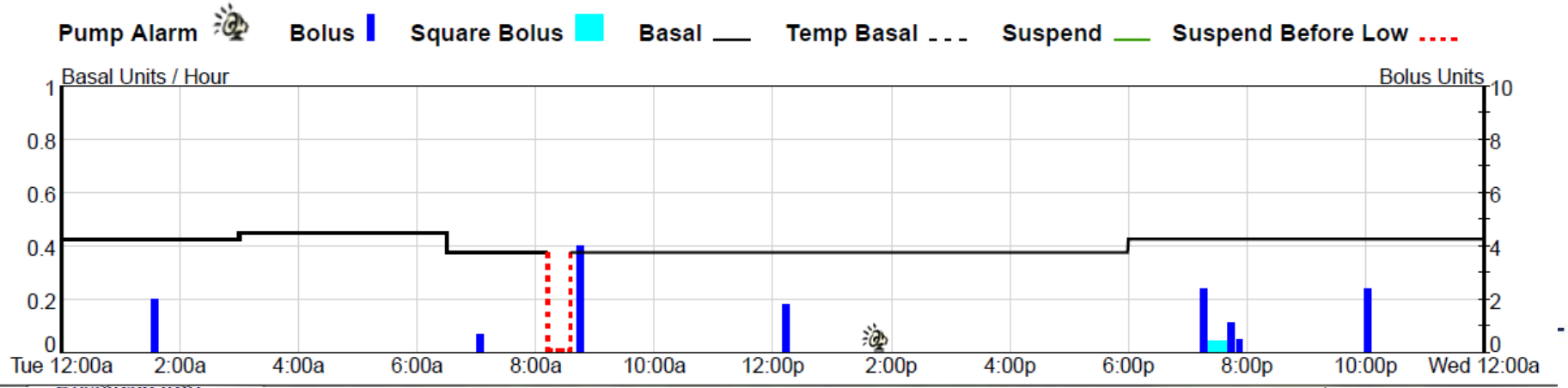
Meter: Linked Meter #BG1123154B
Pump: MiniMed Hybrid Closed Loop - 1582/1782 #NG1229966H
Sensor: In use

HbA1c: No Data

Glucose (mg/dL)



Insulin Delivery

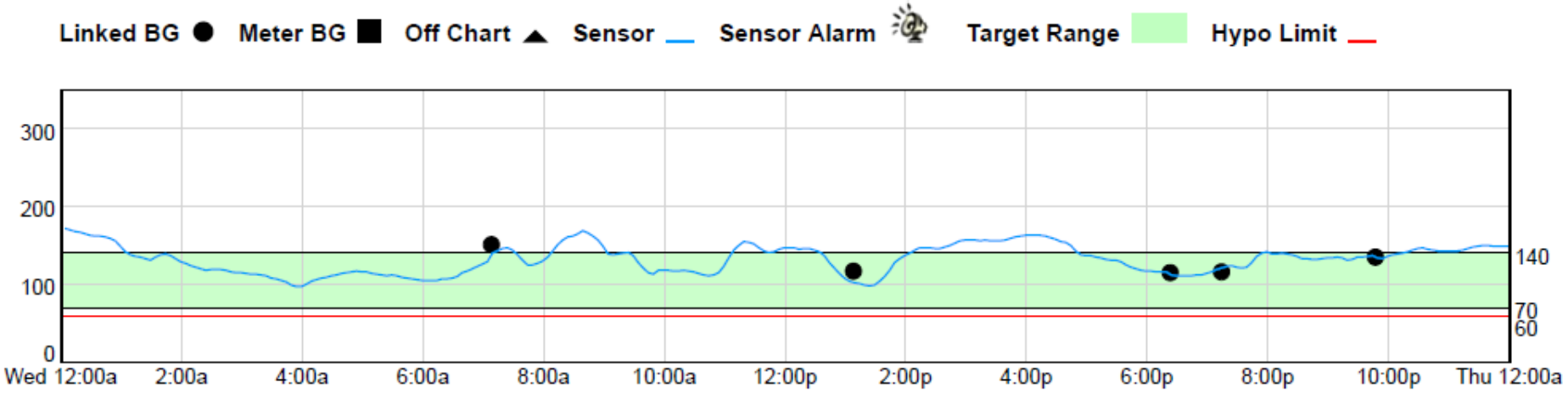


Daily Summary for Subject ID: 0186130101
Jul 26, 2017

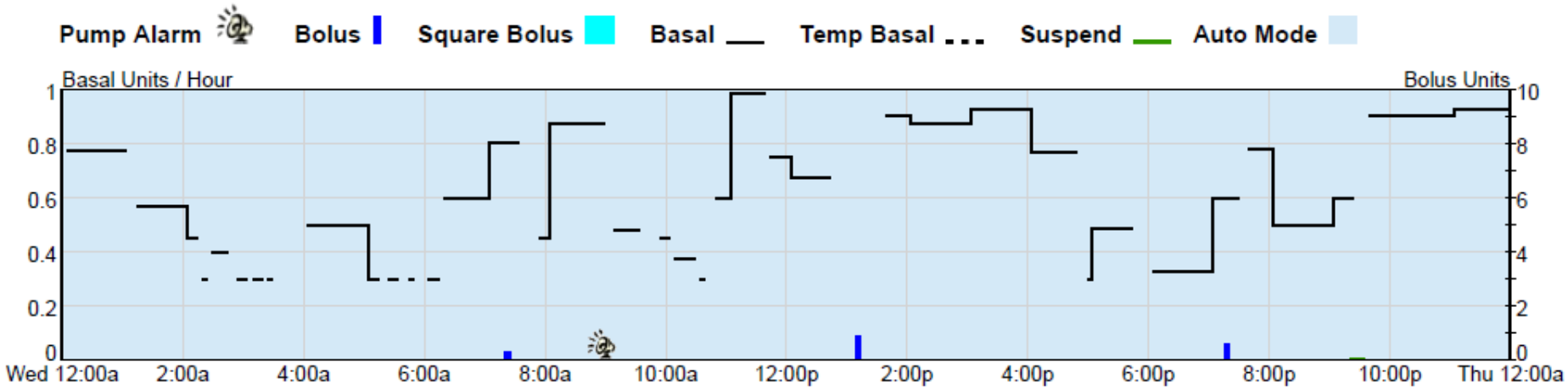
Meter: Linked Meter #BG1123154B
Pump: MiniMed Hybrid Closed Loop - 1582/1782 #NG1229966H
Sensor: In use

HbA1c: No Data

Glucose (mg/dL)



Insulin Delivery



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What's coming in 2019?

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- GIP/GLP-1 in type 2 diabetes
- Closed Loop in Older Adults (>60yrs)
- Fenofibrate in type 1 diabetes & retinopathy

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Contact Details

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Facebook

- https://www.facebook.com/diabetesresearchcentre/

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Questions?

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References

- Garg S, et al (2017) *Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes*. New England Journal of Medicine, DOI: 10.1056/NEJMoa1708337
- Mathieu C, et al (2016) *Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial*. Diabetes Care. DOI: 10.2337/dc16-0691
- Petrie J et al (2016) Card*iovascular and metabolic e ects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial*. Lancet Diabetes and Endocrinology, published online at http://dx.doi.org/10.1016/ S2213-8587(17)30194-8
- Holman R, et al (2017) *Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes*. New England Journal of Medicine, DOI: 10.1056/NEJMoa1612917
- https://www.trialnet.org
- http://www.endia.org.au
- Reutens, A. (2018) *A physician-initiated double-blind, randomised, placebo-controlled , phase 2 study evaluating the efficacy and safety of inhibition of NADPH Oxidase with the first-in-class Nox-1/4 inhibitor, GKT137831, in adults with type 1 diabetes and persistently elevated urinary albumin excretion*. Protocol Version: 1.6 dated 11 Oct 2018
- Sanofi (2017) Clinical Trial Protocol: The SCORED Trial. *A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function*. Version 2 7thSep2017