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▼ **Invokana® (canagliflozin)** *This medicinal product is subject to additional monitoring and it is therefore important to report any suspect adverse reactions related to this medicinal product.*

The role of SGLT2 inhibitors and where to use them

Jill Hill

Diabetes Specialist Nurse, Shropshire

Co-chair TREND-UK

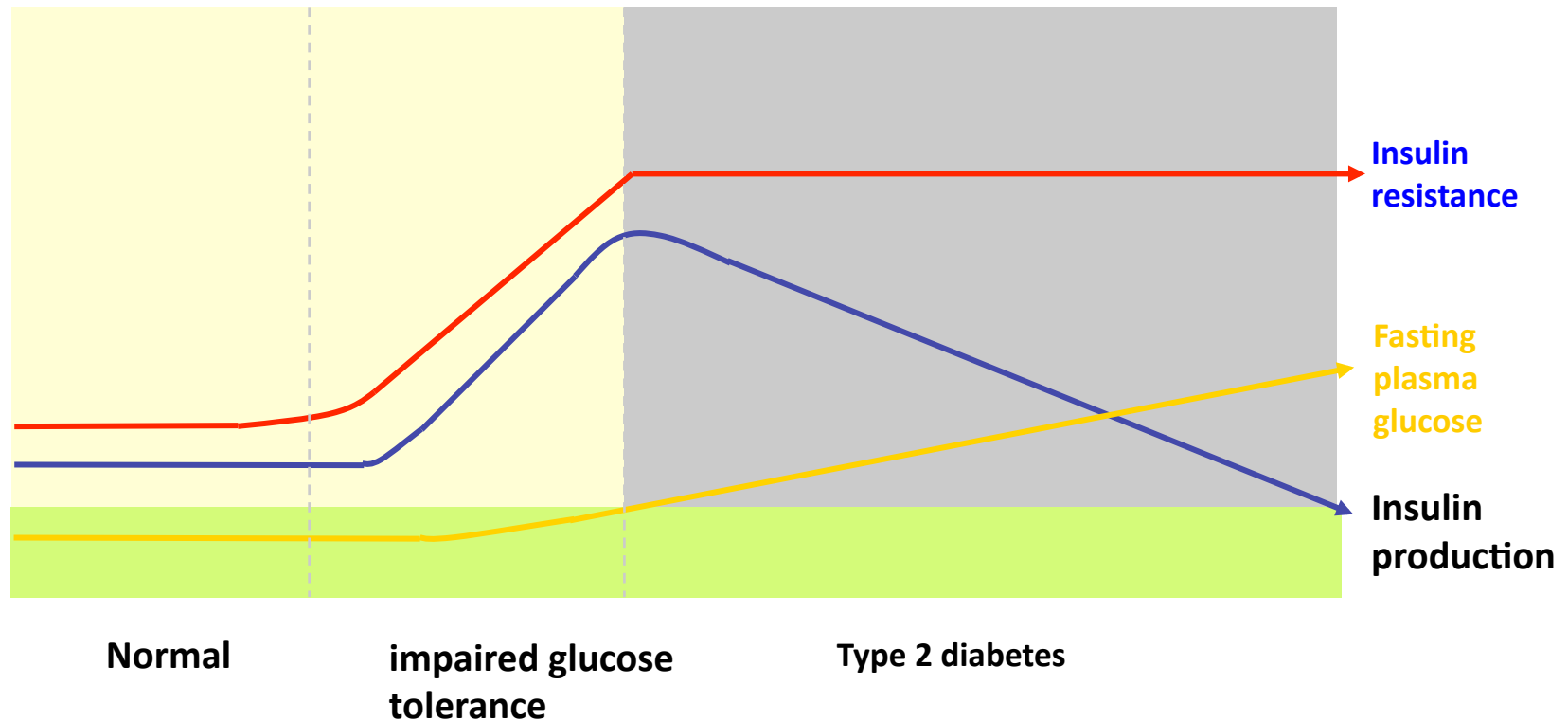
Disclosures

- I have received funding from the following companies for providing educational sessions and documents, and for attending advisory boards:
- Astra Zeneca, Janssen, MSD, Boeringer Ingelheim, Takeda, Eli Lilly, Sanofi, Novo Nordisk

What am I going to talk about?

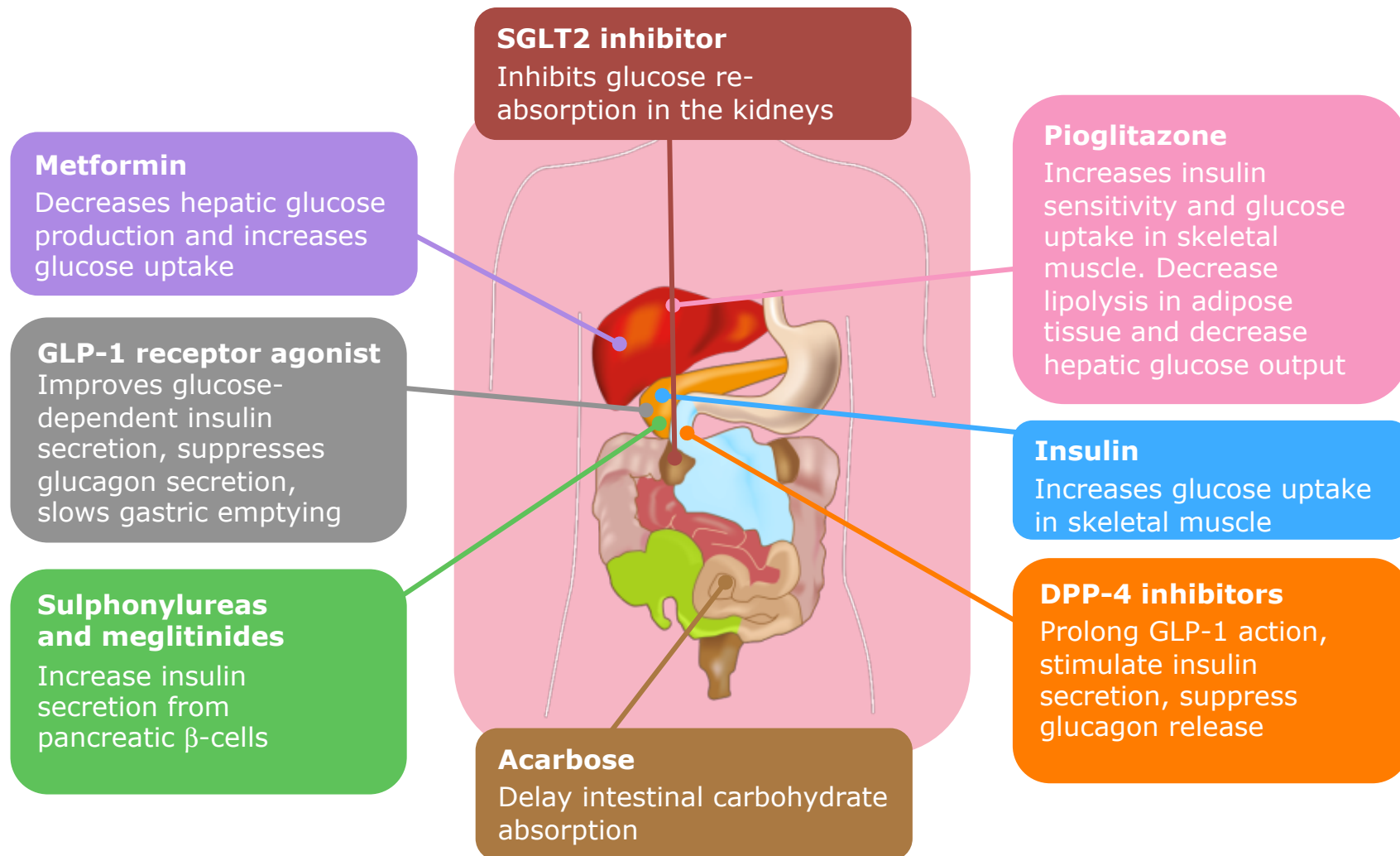
- Type 2 diabetes-what goes wrong?
- Current treatments for Type 2 diabetes
- What are SGLT2 inhibitors and how do they work?
- Are they effective?
- How to use SGLT2 inhibitors
- Safety and side effects
- Summary

Type 2 diabetes is progressive: so insulin therapy will need to change over time



Adapted from Bailey C. British Journal of Cardiology 2000;7(6):350-360
DeFronzo RA, Ferrannini E. Diabetes Care 1991;14(3):173-194

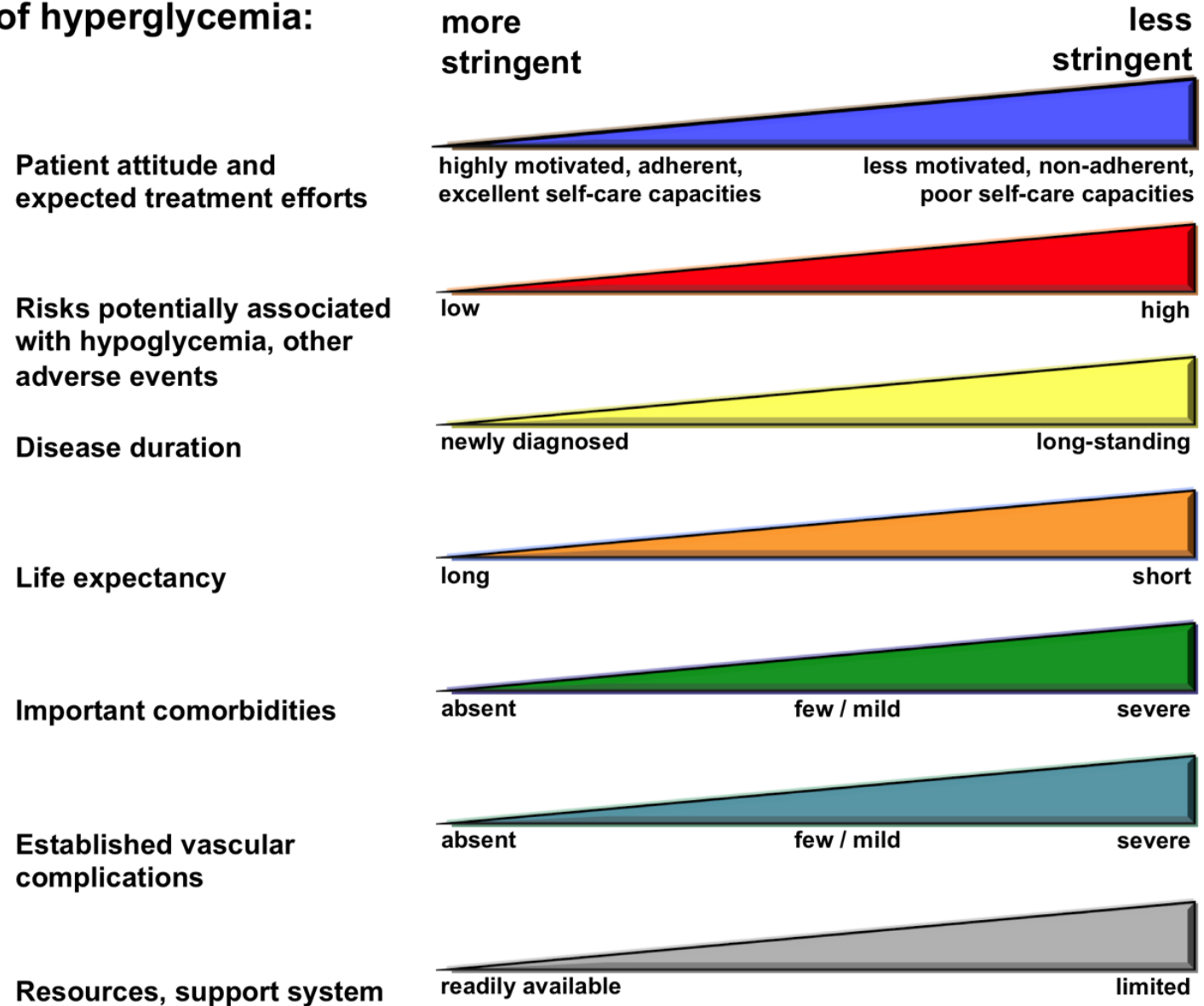
What treatments do we have?



Which treatment to use?

- Insulin deficiency or resistance?
- Renal function
- Concerns about hypoglycaemia
- Weight
- Licence
- NICE/SIGN/local guidelines
- The individual's age, circumstances, ability to self-care etc

Approach to management of hyperglycemia:



. Adapted with permission from Ismail-Beigi et al

**“HOW CAN WE
IMPROVE AND SUSTAIN
GLYCAEMIC CONTROL?”**

**34% OF TYPE 2 DIABETES PATIENTS IN ENGLAND HAVE NOT
ACHIEVED HbA1c LEVELS ≤ 58 mmol/mol ($\leq 7.5\%$)¹**

Reference:

1. National Diabetes Audit 2011-2012 Report 1: Care Processes and Treatment Targets. Available at: <http://www.hscic.gov.uk/catalogue/PUB12421/nati-diab-audi-11-12-care-proc-rep.pdf>. Accessed: October 2013.

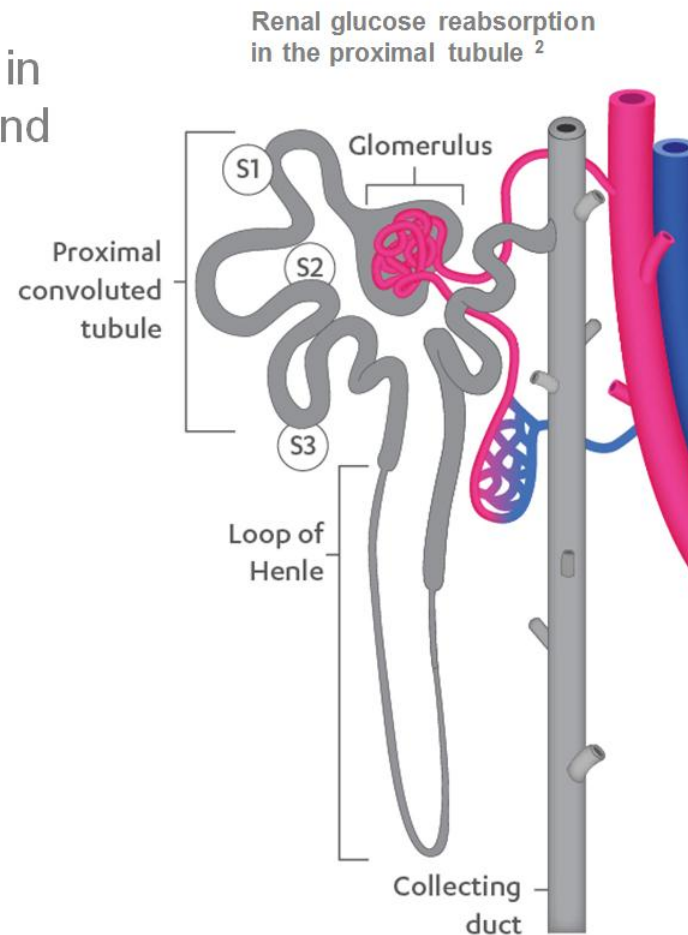
SGLT2 inhibitors



- Glycosuria has been seen as a marker of hyperglycaemia
- These agents actively promote the excretion of glucose (and therefore calories) in the urine

SGLT2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) is found almost exclusively in the proximal tubule of the nephron and accounts for about 90% of glucose reabsorption into the blood.¹



References: 1. [DEFRONZO 2012] DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes Metab.* 2012 Jan;14(1):5-14. 2 [TOMISATO W 2013] Tomisato W et al, Record for jimbee. MUTAGENETIX (TM), B. Beutler and colleagues, Department of Genetics, The Scripps Research Institute, La Jolla, CA. Last updated Mar 07, 2013. Accessed Jul 02, 2013. http://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cfm?pk=598

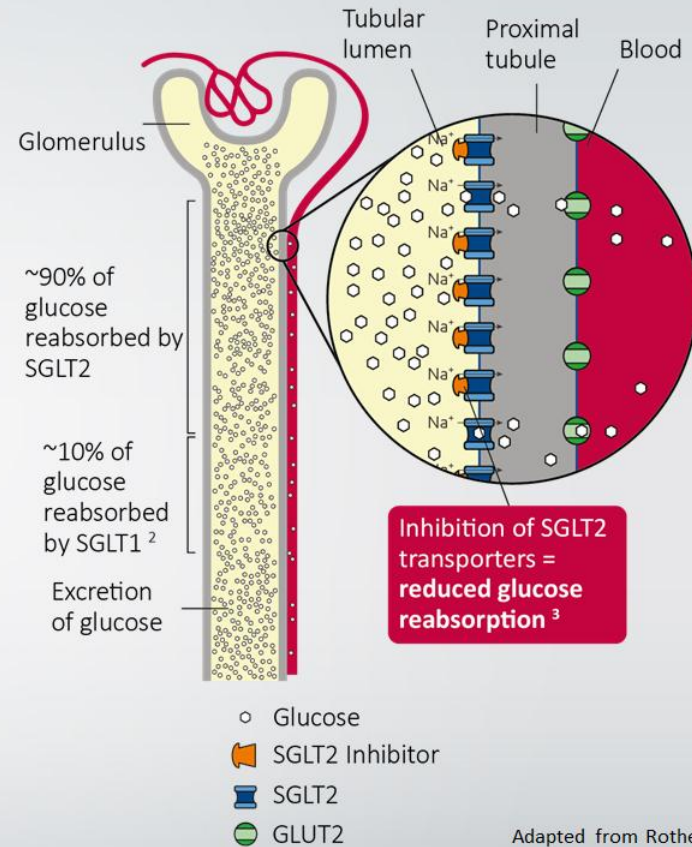
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WHAT CAN BE DONE WHEN METFORMIN FAILS?

INVOKANA® SELECTIVELY INHIBITS SGLT2* IN THE KIDNEYS, RESULTING IN URINARY GLUCOSE EXCRETION 1-2

- » This reduction in glucose reabsorption helps to:
 - Lower HbA1c 2
- with the additional benefits of:
 - Weight loss**2
 - Blood pressure reduction**2

INVOKANA® IS AN INSULIN-INDEPENDENT THERAPY TO TREAT TYPE 2 DIABETES



Adapted from Rothenberg P et al.

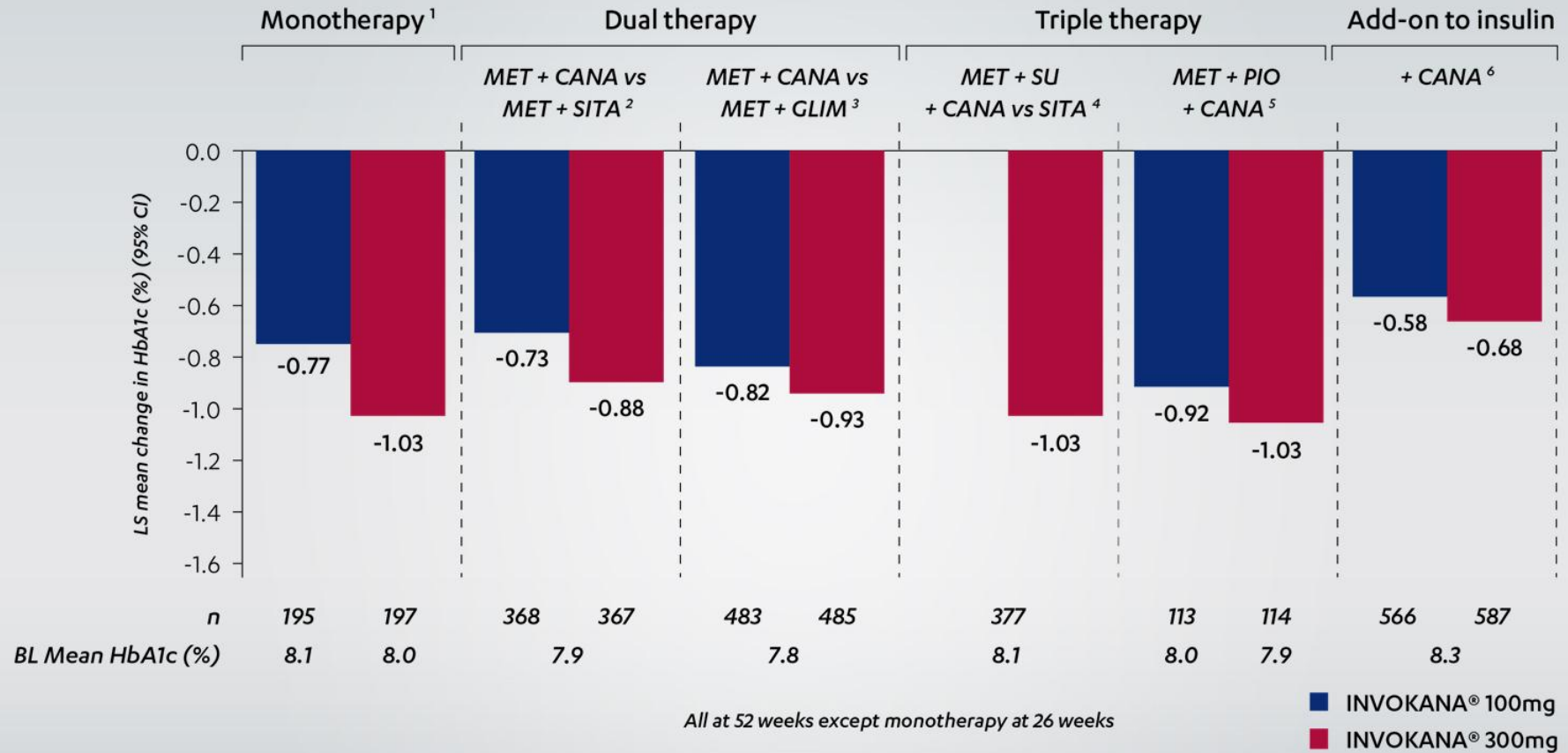
*Sodium glucose co-transporter 2.

**INVOKANA® is not indicated for weight loss or the treatment of hypertension.

References:

1. Bailey CJ. Trends Pharmacol Sci. 2011; 32(2): 63-71.
2. INVOKANA® 100mg and 300mg Summary of Product Characteristics. Available from www.medicines.org.uk last accessed 1st June 2014
3. Nair S, Wilding JP. J Clin Endocrinol Metab. 2010 Jan;95(1):34-42.
4. Rothenberg P et al. EASD poster 2010.

SUMMARY HbA1c CHANGE FROM BASELINE (LOCF) ¹⁻⁶

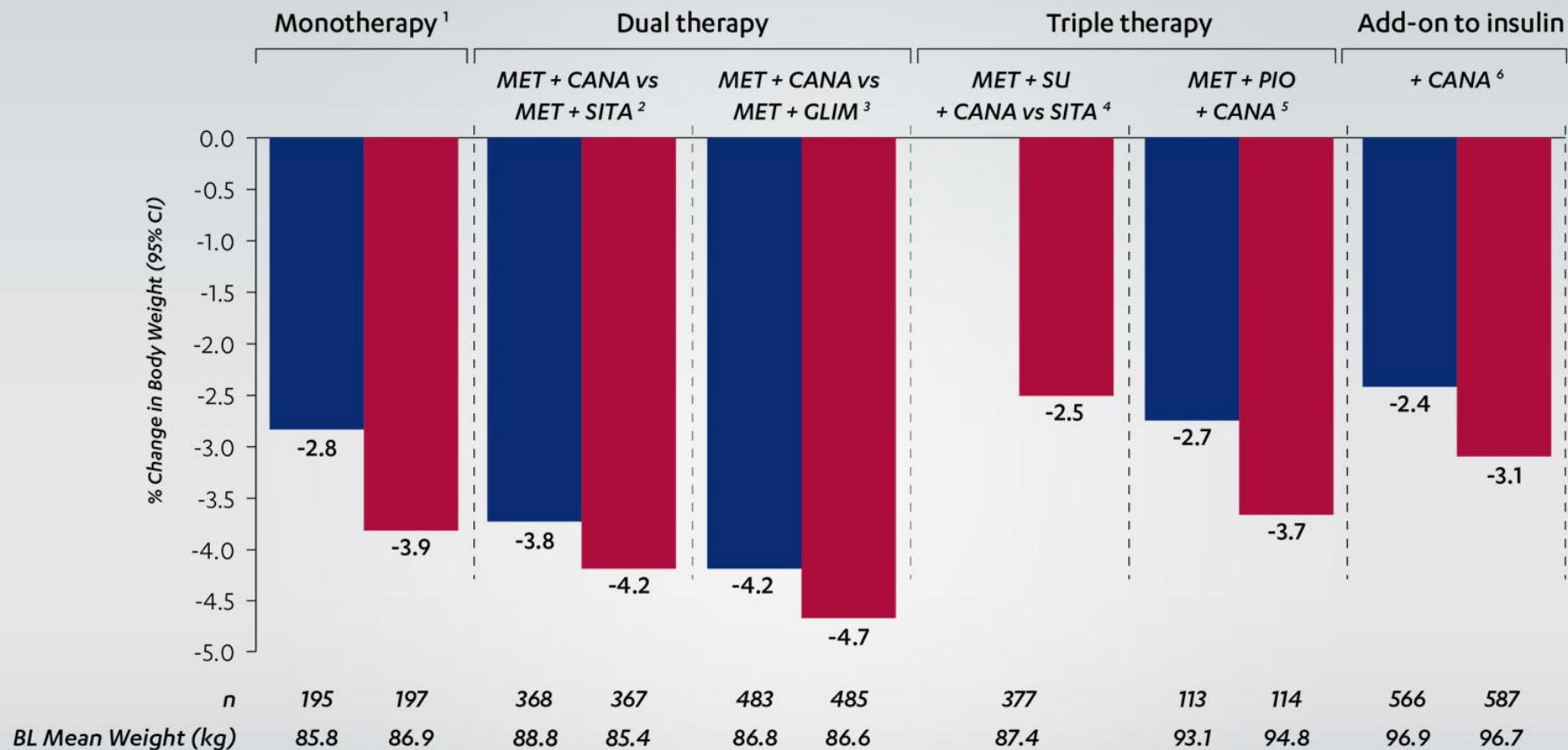


Based on ANCOVA models, data prior to rescue (LOCF)

References:

1. Stenlof K et al. Diabetes Obes Metab 2013; 15(4): 372-382.
2. Lavallo-González FJ et al. Diabetologia 2013; 56:2582-2592.
3. Cefalu WT et al. The Lancet 2013, 382 (9896); 941-950.
4. Schernthaner G et al. Diabetes Care 2013; 36(9); 2508-2515.
5. Forst T, et al. Diabetes Obes Metab. 2014; 16: 467-477.
6. Neal B, et al. Poster presented at the World Diabetes Congress of the International Diabetes Federation (IDF), 2-6 December 2013, Melbourne, Australia.

SUMMARY BODY WEIGHT PERCENT CHANGE FROM BASELINE (LOCF) ¹⁻⁶



All at 52 weeks except monotherapy at 26 weeks

■ INVOKANA® 100mg
■ INVOKANA® 300mg

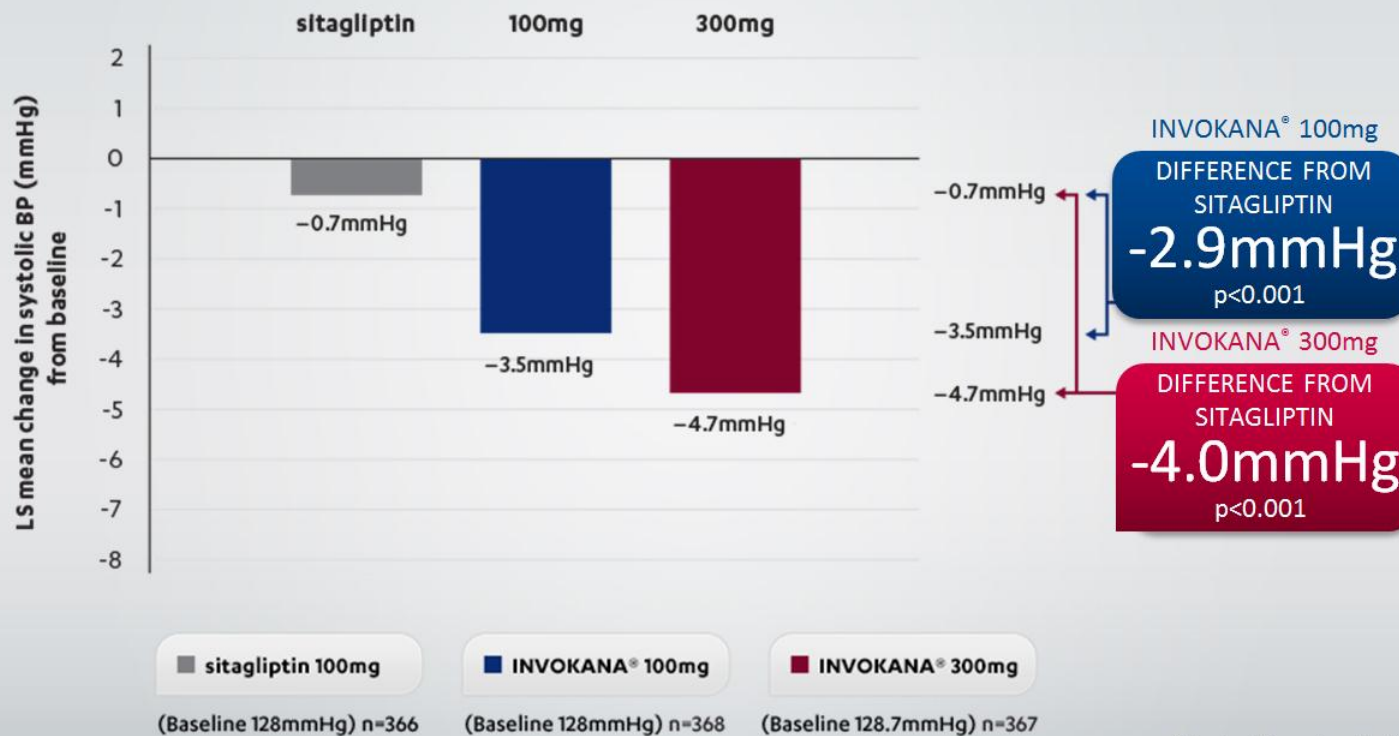
Based on ANCOVA models, data prior to rescue (LOCF).
INVOKANA® is not indicated for weight loss.

References:

1. Stenlof K et al. Diabetes Obes Metab 2013; 15(4): 372-382.
2. Lavallo-González FJ et al. Diabetologia 2013; 56:2582-2592.
3. Cefalu WT et al. The Lancet 2013, 382 (9896); 941-950.
4. Schernthaner G et al. Diabetes Care 2013; 36(9); 2508-2515.
5. Forst T, et al. Diabetes Obes Metab. 2014; 16: 467-477.
6. Neal B, et al. Poster presented at the World Diabetes Congress of the International Diabetes Federation (IDF), 2-6 December 2013, Melbourne, Australia.

DUAL THERAPY – LS MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE COMPARED WITH SITAGLIPTIN (LOCF) ¹

IN A 52-WEEK STUDY AS ADD-ON TO METFORMIN (LOCF)



Adapted from Lavelle-Gonzalez FJ et al. 2013.

INVOKANA® is not indicated for the treatment of hypertension.

LS: Least-squares. LOCF: Last observation carried forward.

Reference:

1. Lavelle-González FJ et al. Diabetologia 2013; 56:2582-2592.

Sarah

- Age 53
- Type 2 diabetes diagnosed 5 years ago
- Currently treated with metformin 1g BD and gliclazide 160mg BD
- BMI 29
- HbA1c 64 mmol/mol (8.0%)
- BP 143/86
- eGFR > 90
- Referred by GP for injection therapy

Sarah

- Works as a sales representative
- Job involves a lot of driving
- “Grazes” throughout the day
- Concerned about weight
- Does not want injections

- What are her options?

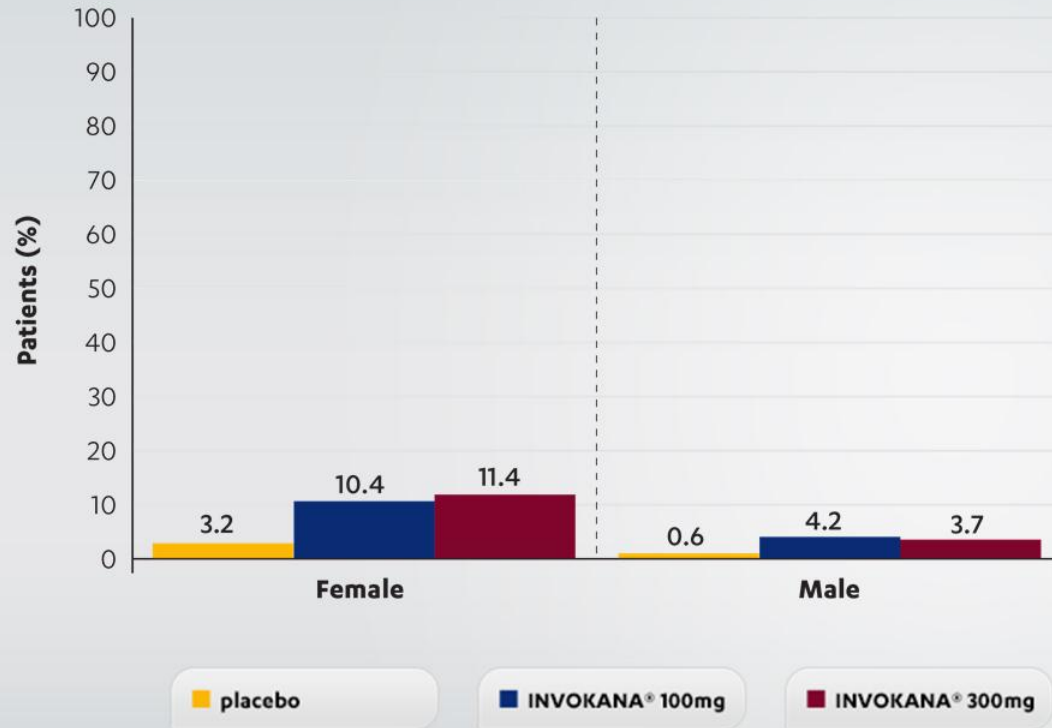
Sarah's options: pros and cons

- Reduce carbohydrate intake/stop “grazing”
- Increase physical activity
- Add a gliptin
- Add pioglitazone
- Add SGLT2 inhibitor
- Persuade her to start GLP-1 receptor agonist
- Start insulin

Add in SGLT2 inhibitor

- Warned about genital thrush
- Gliclazide: reduced glycaemic load so may have increased risk of hypoglycaemia:
 - Reduce dose of gliclazide
 - Revise hypo identification/management
 - Increase BGM initially especially related to driving
- Which SGLT2 inhibitor can we use?
- What benefits can we expect for Sarah?

GENITAL MYCOTIC INFECTIONS ARE COMMON WITH INVOKANA® TREATMENT ¹



IN A POOLED ANALYSIS OF FOUR, 26-WEEK PLACEBO-CONTROLLED TRIALS:* ^{1,2}

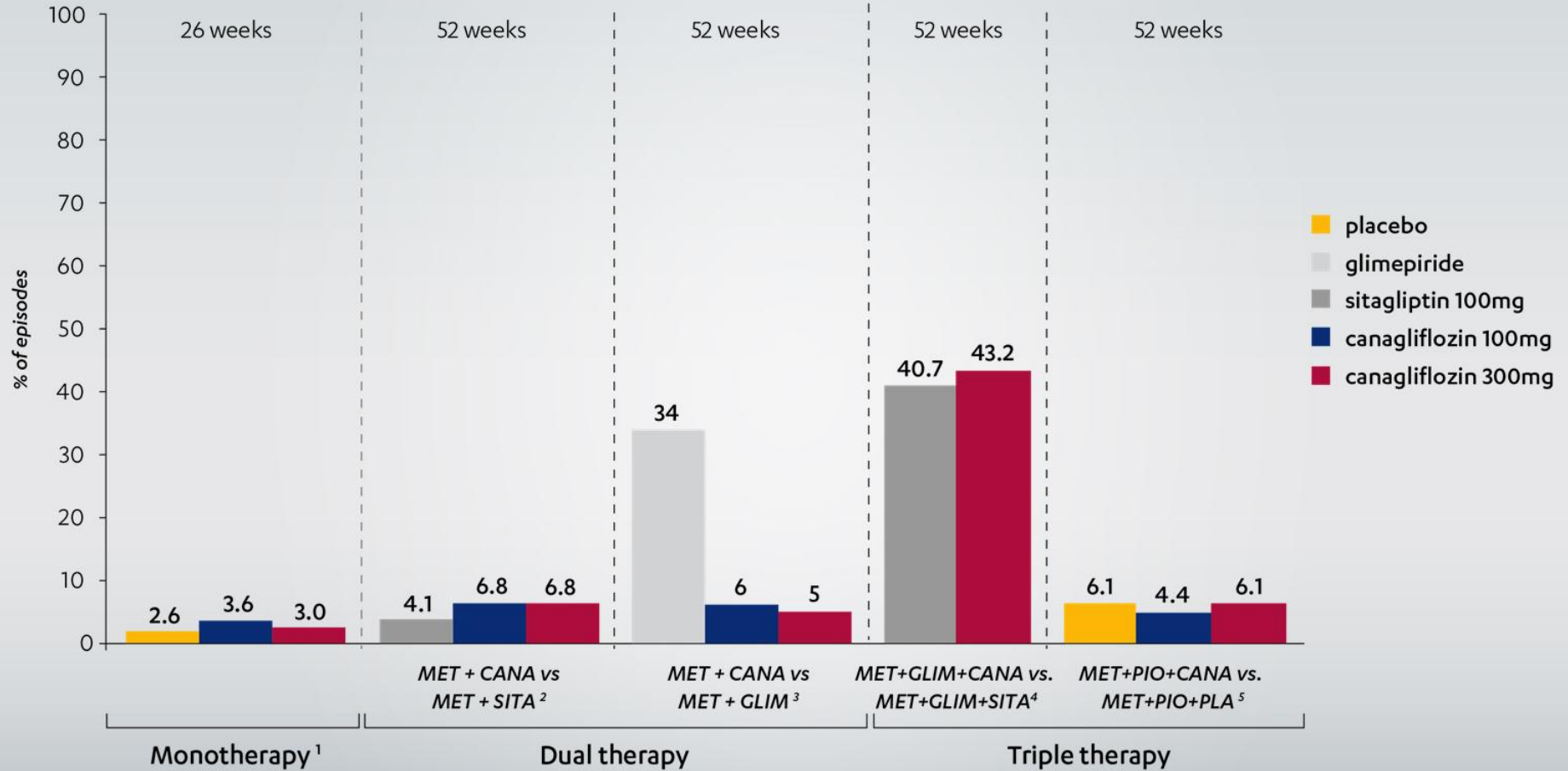
- >> 2.3% of females taking INVOKANA® experienced more than one infection
- >> 0.9% of males had more than one infection
- >> Balanitis and balanoposthitis occurred more frequently in uncircumcised male patients

*The four placebo-controlled trials included one monotherapy and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

References:

1. INVOKANA® 100mg and 300mg Summary of Product Characteristics. Available from www.medicines.org.uk last accessed 1st June 2014
2. Nyrjesy P et al. Poster presented at the 73rd Scientific Sessions of the American Diabetes Association (ADA) 2013 21-23 June. Chicago, Illinois, USA.

HYPOGLYCAEMIA INCIDENCES WITH INVOKANA® IN PHASE 3 TRIALS



References:

1. Stenlof K et al. Diabetes Obes Metab 2013; 15(4): 372-382.
2. Lavallo-González FJ et al. Diabetologia 2013; 56:2582-2592.
3. Cefalu WT et al. The Lancet 2013, 382 (9896); 941-950.
4. Schernthaner G et al. Diabetes Care 2013; 36(9); 2508-2515.
5. Forst T, et al. Diabetes Obes Metab. 2014; 16: 467-477.

CARDIOVASCULAR SAFETY INTERIM ANALYSIS ¹

- » There is currently no evidence of an increase in cardiovascular risk with INVOKANA[®] from an ongoing cardiovascular outcome study
- » A pre-specified interim meta-analysis was conducted of adjudicated cardiovascular events in the Phase II and III clinical studies (n=9,632):
 - 4,327 patients (44.9%) with cardiovascular disease, or at high risk of cardiovascular disease, who are participating in an on-going cardiovascular study
- » Similar hazard ratios for the primary endpoint (MACE-Plus*):
 - INVOKANA[®] 100mg and 300mg doses had similar HRs versus combined active and placebo comparators (both doses pooled): 0.91 (95% CI: 0.68; 1.22)
- » Dyslipidemia has been reported as a common adverse event associated with INVOKANA[®] therapy
 - INVOKANA[®] increased HDL-C and LDL-C and tended to decrease triglycerides. LDL:HDL ratio remained relatively unchanged

*MACE-Plus = major adverse cardiac events (time to event in composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction and unstable angina requiring hospitalisation).

Reference:

1. INVOKANA[®] 100mg and 300mg Summary of Product Characteristics. Available from www.medicines.org.uk last accessed 1st June 2014

INVOKANA®: WARNINGS AND PRECAUTIONS ¹

PATIENTS WITH RENAL IMPAIRMENT

INITIATION

- » INVOKANA® should not be initiated in patients with an eGFR <60mL/min/1.73m².
- » In patients with an eGFR <60mL/min/1.73m², a dose-dependant higher incidence of adverse reactions associated with volume depletion was reported.

MAINTENANCE

- » INVOKANA® should be adjusted to or maintained at 100mg for patients developing moderate renal impairment eGFR 45-60mL/min/1.73m².

DISCONTINUATION

- » If eGFR falls persistently below 45mL/min/1.73m², INVOKANA® treatment should be discontinued.

Reference:

1. INVOKANA® 100mg and 300mg Summary of Product Characteristics. Available from www.medicines.org.uk last accessed 1st June 2014

SGLT2[†] INHIBITORS CURRENTLY AVAILABLE FOR THE TREATMENT OF TYPE 2 DIABETES

| | INVOKANA® ¹ | dapagliflozin ² | empagliflozin ³ |
|---|---------------------------------------|-----------------------------|---------------------------------------|
| Statistically superior HbA1c reductions vs a DPP-4 inhibitor in dual and triple therapy | ✓ ^{4,5} (300mg) | ✗ | ✗ |
| Statistically superior HbA1c reductions vs a sulphonylurea | ✓ ⁶ (300mg at 52 weeks) | ✗ | ✓ ⁷ (25mg at 104 weeks) |
| Ability to increase dose for tighter control? | ✓ | ✗ | ✓ |
| Consistent dose dependant HbA1c reductions | ✓ | N/A | ✗ |
| Can continue at eGFR <60mL/min/1.73m ² down to 45mL/min/1.73m ² | ✓ (100mg only) | ✗ | ✓ (10mg only) |
| Can be used with pioglitazone | ✓ | ✗ | ✓ |
| Urinary Glucose Excretion (UGE)* | 77 - 119g/day ¹ | Approx 70g/day ² | Average of 78g/day ³ |

The recommended starting dose of INVOKANA® is 100mg once daily. In patients tolerating INVOKANA® 100mg once daily, who have an eGFR ≥60mL/min/1.73m² and need tighter glycaemic control, the dose can be increased to 300mg once daily.¹

[†]SGLT2: Sodium glucose co-transporter 2.

*Figures quoted from respective summaries of product characteristics.

References:

1. INVOKANA® 100mg and 300mg Summary of Product Characteristics. Available at www.medicines.org.uk last accessed 1st June 2014.
2. Forxiga 5mg and 10mg Summary of Product Characteristics. Available at www.medicines.org.uk last accessed 23rd June 2014.
3. Jardiance 10mg and 25mg Summary of Product Characteristics. Available at www.medicines.org.uk last accessed 7th August 2014.
4. Schernthaner G et al. Diabetes Care 2013; 36(9):2508-2515.
5. Lavalley-González FJ et al. Diabetologia 2013; 56:2582-2592.
6. Cefalu WT et al. The Lancet 2013; 382(9896): 941-950.
7. Ridderstale M et al. Lancet Diabetes Endocrinol 2014. Published online June 16, 2014.

INVOKANA® (CANAGLIFLOZIN) IN COMBINATION THERAPY FOR TREATING TYPE 2 DIABETES

NICE TECHNOLOGY APPRAISAL GUIDANCE (TA315) JUNE 2014 ¹

INVOKANA® IN DUAL THERAPY



INVOKANA® in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- >> a sulphonylurea is contraindicated or not tolerated
- >> **or**, the person is at significant risk of hypoglycaemia or its consequences

INVOKANA® IN TRIPLE THERAPY



INVOKANA® in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- >> metformin and a sulphonylurea
- >> **or**, metformin and a thiazolidinedione

INVOKANA® COMBINATION WITH INSULIN



INVOKANA® in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes

References:

1. National Institute for Health and Care Excellence 2014. Canagliflozin in combination therapy for treating type 2 diabetes (TA315). Available at: www.nice.org.uk. Last accessed 25th June 2014.

Summary

- Type 2 diabetes is complex and progressive
- Hypoglycaemia and weight gain are significant concerns
- SGLT2 inhibitors promote the excretion of glucose in the urine
- This reduces glycaemic load and can reduce HbA1c
- The loss of calories can result in weight loss