HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 November 2014

INVOKANA 100 mg, film-coated tablet

B/30 tablets (CIP: 34009 276 728 9 7)
B/90 tablets (CIP: 34009 585 986 2 3)

INVOKANA 300 mg, film-coated tablet

B/30 tablets (CIP: 34009 276 729 5 8)
B/90 tablets (CIP: 34009 585 987 9 1)

Applicant: JANSSEN

INN	Canagliflozin
ATC code (year)	A10BX11 (blood glucose lowering drugs)
Reason for the request	**Inclusion**
List(s) concerned	**B/30 tablets:** **National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)** **B/90 tablets:** **Hospital use (French Public Health Code L.5123-2)**
Indications concerned	**"INVOKANA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:** **Monotherapy** **When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.** **Add-on therapy** **Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control."**

Actual Benefit	- **Insufficient as monotherapy** - **Substantial as dual therapy in combination with metformin** - **Insufficient as dual therapy in combination with sulfonylureas or insulin** - **Substantial as triple therapy in combination with metformin and a sulfonylurea** - **Moderate as triple therapy in combination with metformin and insulin**
Improvement in Actual Benefit	**<u>In the indications as dual therapy with metformin, and as triple therapy with metformin and a sulfonylurea or with metformin and insulin:</u>** **Taking into account the evidence that canagliflozin is non-inferior to its active comparators, the lack of evidence of its superiority to sitagliptin for the 100 mg dosage, and the lack of long-term safety data, the Committee considers that the INVOKANA proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of patients with poorly controlled type 2 diabetes, as dual oral therapy in combination with metformin and as triple therapy in combination with metformin and a sulfonylurea or in combination with metformin and insulin.** **<u>In the indications as monotherapy, and as dual therapy in combination with sulfonylureas or insulin:</u>** Not applicable.
Therapeutic use	**Canagliflozin is an additional medicine for poorly controlled type 2 diabetes:** - **as dual therapy in combination with metformin, as one of the oral antidiabetic drugs available, if sulfonylureas are not tolerated or are contraindicated;** - **as triple therapy in combination with metformin and sulfonylureas, as one of the recommended oral antidiabetic drugs available;** - **as triple therapy in combination with metformin and insulin.** **As monotherapy, canagliflozin has no role in the treatment of type 2 diabetes that is inadequately controlled by lifestyle and dietary measures, since there are no data versus active comparators in the Marketing Authorisation population (patients with an intolerance or contraindications to metformin).** **Canagliflozin cannot be recommended as dual therapy with sulfonylureas or insulin, due to methodological weaknesses in the studies supplied and problems with applicability.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated: 15 November 2013 (centralised procedure, rapporteur: Germany)
Prescribing and dispensing conditions / special status	List I Initial annual prescription restricted to specialists in endocrinology, diabetes and metabolic disorders or specialists in internal medicine.

ATC Classification	2014	
	A	Alimentary tract and metabolism
	A10	Drugs used in diabetes
	A10B	Blood glucose lowering drugs, excluding insulins
	A10BX	Other blood glucose lowering drugs, excl. insulins
	A10BX11	canagliflozin

02 BACKGROUND

Request for inclusion of the INVOKANA proprietary medicinal products, which are oral antidiabetic drugs, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use, in the indication: treatment of adult patients with type 2 diabetes, as dual therapy with metformin, as triple therapy with metformin and a sulfonylurea, and in combination with insulin.
The company is not seeking to have this medicinal product included as monotherapy or as dual therapy in combination with a sulfonylurea. However, in accordance with Article R.163-18 of the French Social Security Code, the Transparency Committee has to assess the actual benefit of INVOKANA in all its possible indications.
The active substance in INVOKANA is canagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), which partially blocks the reabsorption of glucose by the kidneys and causes it to be eliminated in urine.

03 THERAPEUTIC INDICATIONS

"INVOKANA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

<u>Monotherapy</u>

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

<u>Add-on therapy</u>

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations)."

04 DOSAGE

"Posology

The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m² or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily orally (see below and section 4.4).

Care should be taken when increasing the dose in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom initial canagliflozin-induced diuresis poses a risk (see section 4.4). In patients with evidence of volume depletion, correcting this condition prior to initiation of canagliflozin is recommended (see section 4.4).

When canagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g. sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

Elderly (≥ 65 years old)
Renal function and risk of volume depletion should be taken into account (see section 4.4).

Patients with renal impairment
For patients with an eGFR 60 mL/min/1.73 m² to < 90 mL/min/1.73 m² or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m² or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).

Canagliflozin should also not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in such populations (see sections 4.4 and 5.2).

Patients with hepatic impairment
For patients with mild or moderate hepatic impairment, no dose adjustment is required.

Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see section 5.2).

Paediatric population
The safety and efficacy of canagliflozin in children under 18 years of age have not yet been established. No data are available.

Method of administration

INVOKANA should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole.

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day."

05 THERAPEUTIC NEED[1,2,3,4]

The aim of treatment in type 2 diabetes is to reduce morbidity and mortality, particularly through good glycaemic control. The short-term objective is to improve symptoms (thirst, polyuria, asthenia, emaciation and blurred vision) and prevent acute complications (infections and hyperosmolar coma). The longer-term objective is to prevent chronic microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (myocardial infarction, strokes and obliterative arteriopathy of the legs) and to reduce mortality.

According to the 2013 HAS guidelines,[4] the glycaemic target for type 2 diabetes patients should be set individually based on comorbidities and life expectancy; the target HbA1c ranges from 6.5% to 8%. An HbA1c target ≤ 7% is recommended for most patients. Drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%. Diabetes is progressive and all aspects of treatment should be re-assessed regularly: lifestyle and dietary measures, health education and drug treatment.

Special cases: for patients newly diagnosed with diabetes, who have a life expectancy of more than 15 years and no history of cardiovascular events, a target of ≤ 6.5% is recommended, but this should be achieved by implementing or strengthening lifestyle and dietary measures then, if these fail, through oral monotherapy.
In a certain number of special cases, the glycaemic target will be less demanding: age > 75 years; history of a macrovascular complication; chronic renal disease; proven serious comorbidity; limited life expectancy (< 5 years); long duration of diabetes (> 10 years); and patients in whom a target of 7% proves difficult to achieve because increased medication causes severe hypoglycaemia.
Implementing effective lifestyle and dietary measures is a prerequisite to drug treatment for glycaemic control.

Drug strategy:
According to HAS guidelines, if the glycaemic target is not met despite lifestyle and dietary measures, monotherapy should be started with metformin as the first-line treatment or, if there are contraindications, with sulfonylureas (if both of these substances are contraindicated, repaglinide or alpha-glucosidase inhibitors are recommended).
If there are symptoms or very poorly controlled diabetes with recurrent blood glucose levels above 3 g/L or with an HbA1c greater than 10%, dual therapy or insulin therapy may be initiated from the start.

Combinations recommended as dual therapy:
If the glycaemic target is not achieved with monotherapy, dual therapy is recommended, combining metformin and sulfonylureas as first-line treatment, and monitoring weight and episodes of hypoglycaemia.

If sulfonylureas are not tolerated or are contraindicated, and if the patient is within 1% of the HbA1c target, the following treatment regimens may be offered:
- combined metformin + repaglinide (if food intake is irregular);

[1] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[2] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.
[3] ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.
[4] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes]. Recommandations de bonne pratique de la HAS [HAS good practice guidelines]. January 2013.

- combined metformin + alpha-glucosidase inhibitors (if episodes of hypoglycaemia give cause for concern);
- combined metformin + DPP-4 inhibitors/gliptins (if episodes of hypoglycaemia or weight gain give cause for concern).

If metformin is not tolerated or is contraindicated, and if the patient is within 1% of the HbA1c target, the following treatment regimens may be offered:

- combined sulfonylurea + alpha-glucosidase inhibitors;
- combined sulfonylurea + DPP-4 inhibitors.

GLP-1 analogues may be considered at the dual therapy stage if BMI is ≥ 30 kg/m² or if weight gain on insulin or episodes of hypoglycaemia give cause for concern.

Combinations recommended as triple therapy:

If the glycaemic target is not achieved despite metformin + sulfonylurea dual therapy and if the patient is within 1% of the HbA1c target, the following treatment regimens may be offered:

- combined metformin + sulfonylurea + alpha-glucosidase inhibitors;
- combined metformin + sulfonylurea + DPP-4 inhibitors/gliptins.

Recommended combinations with insulin therapy:

Clinicians should assess whether to continue non-insulin antidiabetic drugs based on the expected benefits from each substance:

- metformin should be continued;
- the dosage of sulfonylureas or repaglinide should be adjusted, if necessary, to the insulin regimen;
- DPP-4 inhibitors and alpha-glucosidase inhibitors should be stopped;
- the insulin + GLP-1 analogue combination requires specialist advice.

In its guidelines, HAS states that combining a GLP-1 analogue with insulin requires specialist advice.

Sodium-glucose co-transporter 2 inhibitors

To date, this new therapeutic category contains three substances: dapagliflozin, canagliflozin, and empagliflozin. Canagliflozin is the subject of this assessment. According to the Transparency Committee opinion,[5] dapagliflozin cannot be recommended as monotherapy or as dual therapy with insulin. However, it is an additional treatment resource for type 2 diabetes as dual therapy with metformin or sulfonylureas, or as triple therapy after the insulin/metformin combination has failed. The American Association of Clinical Endocrinologists recently added SGLT2 inhibitors to each of its therapeutic strategy lines, stating that they should be used with caution.[6]

[5] Transparency Committee Opinion of 23 April 2014 for FORXIGA.

[6] American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. https://www.aace.com/files/aace_algorithm.pdf [Accessed 5/11/2014]

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

These are the proprietary medicinal products indicated **in combination** in the treatment of type 2 diabetes, in patients with inadequate glycaemic control on the maximum tolerated doses of the following medicines (together with lifestyle and dietary measures):

- metformin in combination with sulfonylureas, then if this fails, glinides, alpha-glucosidase inhibitors, gliptins (administered orally), GLP-1 analogues (injected) or dapagliflozin (only as dual therapy);
- sulfonylureas in combination with metformin or, if metformin is contraindicated or not tolerated, with dapagliflozin, alpha-glucosidase inhibitors, gliptins or GLP-1 analogues;
- insulin in combination with an oral antidiabetic drug: metformin, sulfonylureas, GLP-1 analogues or dapagliflozin (as triple therapy with metformin).

It should be noted that dapagliflozin (FORXIGA) is in the same therapeutic category (sodium-glucose co-transporter 2 inhibitors) and has already been assessed by the Transparency Committee but not yet included on the lists for National Health Insurance reimbursement and hospital use.

The comparators are presented in an appendix to this document.

06.2 Other health technologies

Not applicable.

◗ Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The INVOKANA proprietary medicinal products were granted Marketing Authorisation in Europe and the United States in 2013.

COUNTRY	MARKETING AUTHORISATION		REIMBURSEMENT	
	Date	Indications	Yes/No	Population
Europe	15/11/2013	**INVOKANA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:** **<u>Monotherapy</u>** **When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.** **<u>Add-on therapy</u>** **Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.**	UK, Switzerland, Belgium, Netherlands, Denmark, Sweden, Austria and Norway (under assessment)	Marketing Authorisation
United States	29/03/2013	**Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes.**	Yes	Marketing Authorisation

08 ANALYSIS OF AVAILABLE DATA

The request for reimbursement of the INVOKANA proprietary medicinal products is supported by data from phase III clinical studies conducted in patients with type 2 diabetes who did not have adequate glycaemic control and were treated with canagliflozin:

- as monotherapy versus placebo: study DIA3005;[7]
- as dual therapy with metformin in two studies, versus combinations of:
  - metformin/placebo in study DIA3006;[8]
  - metformin/glimepiride (a sulfonylurea) in study DIA3009;[9]
- as triple therapy with the metformin/sulfonylurea combination in two studies, versus:
  - metformin/sulfonylurea/placebo triple therapy in study DIA3002;[10]
  - metformin/sulfonylurea/sitagliptin triple therapy in study DIA3015;[11]
- as triple therapy with the metformin/pioglitazone combination in study DIA3012, versus metformin/pioglitazone/placebo triple therapy; as pioglitazone was withdrawn from use in France in 2011, study DIA3012 was not accepted by the Committee.

These clinical data are supplemented by three phase III studies conducted in special populations, comparing canagliflozin combinations to placebo, as monotherapy or in combination with another oral antidiabetic drug:

- Study DIA3010[12] in patients aged 55 to 80 years;
- Study DIA3008 in patients with a cardiovascular risk factor. This is a safety study including two substudies: one conducted in patients treated with a sulfonylurea, and the other in patients treated with insulin;
- Study DIA3004[13] in patients with moderate renal impairment; as this criterion is a contraindication to starting canagliflozin (see Dosage), this study was not accepted.

The results of seven clinical trials, including two conducted in special populations, will therefore be presented.
In addition, an indirect comparison meta-analysis evaluating the relative efficacy of canagliflozin versus GLP-1 analogues was submitted and will be described.

[7] Stenlöf K, Cefalu WT, Kim KA et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15:372-82.
[8] Lavalle-González F. J. et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013 56:2582–2592.
[9] Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase III non-inferiority trial. Lancet 2013;382:941-50.
[10] Wilding JP et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulfonylurea: a randomised trial. Int J Clin Pract. 2013;67:1267-82.
[11] Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin Compared with Sitagliptin for Patients with Type 2 Diabetes Who Do Not Have Adequate Glycemic Control with Metformin plus Sulfonylurea: A 52-week randomized trial. Diabetes Care 2013.36:2508-15.
[12] Bode B, Stenlöf K, Sullivan D, et al. Efficacy and Safety of Canagliflozin Treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hospital Practice 2013;41:72-84.
[13] Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463-73

08.1 Efficacy

8.1.1 Monotherapy study (DIA3005)

Study DIA3005 is a randomised, controlled, double-blind, multi-centre[14] study which took place between February 2010 and August 2011. The primary objective was to evaluate the efficacy of canagliflozin versus placebo, over a duration of 26 weeks, in patients with type 2 diabetes inadequately controlled by lifestyle and dietary measures.

Methods

Inclusion criteria:

- aged between 18 and 80 years with poorly controlled type 2 diabetes;
- naive to oral antidiabetic drugs (OADs) with HbA1c ≥ 7.0% and ≤ 10.0%
- or treated with an OAD as monotherapy (excluding alpha-glucosidase inhibitors and thiazolidinediones), or with low-dose metformin/sulfonylurea dual therapy, with HbA1c ≥ 6.5% and ≤ 9.5% on inclusion then HbA1c ≥ 7.0% and ≤ 10.0% and blood glucose > 15 mmol/L after an eight-week washout period.

Non-inclusion criteria included:

- a history of diabetic ketoacidosis, type 1 diabetes, pancreas transplant or islet transplantation, diabetes secondary to pancreatitis or pancreatectomy;
- treatment with a thiazolidinedione, insulin, another sodium-glucose co-transporter inhibitor, or another OAD in the previous 12 weeks;
- myocardial infarction, unstable angina, revascularisation surgery, CVA in the previous three months, NYHA class III heart disease;
- uncontrolled hypertension;
- glomerular filtration rate (GFR) < 55 mL/min/1.73 m² or serum creatinine ≥ 1.4 mg/dL in men and ≥ 1.3 in women.

The study's primary efficacy endpoint was change in HbA1c value at 26 weeks.
Patients were randomised to three groups: canagliflozin 100 mg, canagliflozin 300 mg and placebo. They received treatment for 26 weeks.
Assuming a difference in change in HbA1c of 0.5% (standard deviation: 1.0) between placebo and canagliflozin, the number of subjects required was estimated at 85 per group to demonstrate the superiority of canagliflozin with a power of 90% (α risk = 0.05). The difference between the groups was evaluated using an analysis of covariance (ANCOVA), adjusted for whether patients had already received OADs and for the HbA1c value on inclusion. Differences were estimated using the method of least squares.[15]

The results of this study are presented. However, it should be noted that the company has not requested the inclusion of canagliflozin 100 mg/day and 300 mg/day as monotherapy.

Results

A total of 584 patients were randomised to three groups and were treated: placebo (n=192), canagliflozin 100 mg (n=195) and canagliflozin 300 mg (n=197). The mean duration of treatment was 24.1 weeks (±6).
Patient characteristics were similar between the groups, with a mean age of 55.4 years (±10.6) and 55.8% women. The mean weight was 86.8 kg (±20.4). More than half the patients (54.5%) had a BMI greater than or equal to 30 (obesity). Patients had had diabetes for a mean duration of 4.3 years (±4.4) and 48% of patients were pre-treated with an oral antidiabetic drug. The average HbA1c level on inclusion was 8.0% (±1.0).

[14] 90 centres in 17 countries, with the majority in North America and Eastern Europe.
[15] This method will be used in each of the following studies.

Efficacy on the primary efficacy endpoint

This study showed that canagliflozin was superior to placebo at 26 weeks in terms of change in HbA1c levels, with an intergroup difference of -1.2 for canagliflozin 300 mg and -0.9 for canagliflozin 100 mg (Table 1).

It should be noted that the response rate (patients with HbA1c < 7%) was 44.5% and 62.4% in the canagliflozin 100 mg and 300 mg groups respectively, and 20.6% in the placebo group (p<0.001).

Table 1. Results of analysis for secondary endpoints in the mITT population at 26 weeks

	Canagliflozin 100 mg N=196	**Canagliflozin 300 mg N=197**	**Placebo N=194**	**Intergroup difference**	
				placebo-cana. 100 mg	**placebo-cana. 300 mg**
Primary efficacy endpoint					
HbA1c on inclusion (%), *mean (SD*)*	8.06 (0.96)	8.01 (0.99)	7.97 (0.96)	-	-
Change in HbA1c at 26 weeks, *mean (SD*)*	-0.77 (0.07)	-1.03 (0.06)	0.14 (0.07)	-0.91 (0.09) [-1.09; -0.73]** p<0.001	-1.16 (0.09) [-1.34; -0.99] p<0.001

* SD: standard deviation

** 95% confidence interval

8.1.2 Studies of dual therapy with metformin (DIA3006 and DIA3009)

Studies DIA3006 and DIA3009 are two phase III, randomised, comparative, double-blind, parallel-group and multicentre[16] studies.

The primary objective of these studies was to evaluate the efficacy of canagliflozin/metformin dual therapy, in patients with type 2 diabetes inadequately controlled by the maximum dose of metformin monotherapy, versus:

- combined placebo/metformin, after 26 weeks of treatment, in superiority study DIA3006;
- glimepiride/metformin dual therapy, after 52 weeks of treatment, in non-inferiority study DIA3009 which was converted to a superiority study.

The methods of these two studies are described in Table 2.

[16] 169 centres in study DIA3006 and 157 centres in study DIA3009, mostly in North, Central and South America and in Europe.

1 Table 2. Methods of studies DIA3006 and DIA3009, evaluating canagliflozin as dual therapy with metformin

	Study DIA3006: versus placebo/metformin	**Study DIA3009: versus glimepiride/metformin**
Dates and sites	April 2010 – August 2012	August 2009 – December 2011
Inclusion criteria	- Aged between 18 and 80 years - HbA1c [7.0; 10.5] on immediate-release metformin as monotherapy at a stable dose ≥ 2 g/day for at least 8 weeks, or after 8-week dose adjustment for patients on IR metformin < 2 g/day, or metformin XR, or metformin/sulfonylurea with HbA1c [6.5; 9.5] - Fasting blood glucose < 270 mg/dL on inclusion and [110; 270] on the day of randomisation	- Aged between 18 and 80 years - HbA1c [7.0; 9.5] on metformin monotherapy at a stable dose ≥ 2 g/day for at least 12 weeks, or after 10-week dose adjustment for patients on IR metformin < 2 g/day with HbA1c [7.5; 10] or metformin/OAD with HbA1c [6.5; 9]
Main non-inclusion criteria*	*Same as non-inclusion criteria in study DIA3005*	- History of severe hypoglycaemic episode in the previous six months - History of weight gain/loss of 5% in the previous three months - Treatment with a thiazolidinedione in the previous 16 weeks
Treatments administered	After a two-week period on metformin 2 g/day and placebo, patients were randomised** to four groups (2:2:2:1 design): - Canagliflozin 100 mg - Canagliflozin 300 mg - Sitagliptin 100 mg - Placebo Patients received treatment for 26 weeks. Rescue therapy with glimepiride or metformin was authorised. 2nd treatment phase: 26 weeks of additional treatment, with patients on placebo changed to sitagliptin 100 mg.	After a two-week period on metformin 2 g/day and placebo, patients were randomised** to three groups (1:1:1 design): - Canagliflozin 100 mg: once daily - Canagliflozin 300 mg: once daily - Glimepiride 1 mg to 8 mg Patients received treatment for 52 weeks. Rescue therapy was authorised for patients with doses of 300 mg canagliflozin or ≥ 6 mg glimepiride. Treatment extension phase for 52 additional weeks
Primary efficacy endpoint	Change in HbA1c at 26 weeks	Change in HbA1c at 52 weeks
Secondary endpoints included	Change at 26 weeks and 52 weeks in: - Percentage of patients with HbA1c < 7.0% - Weight - Fasting blood glucose	Change at 52 weeks in: - Incidence of hypoglycaemia (confirmed by laboratory or severe) - Weight - Fasting blood glucose
Statistical analysis	Difference between the canagliflozin and placebo groups evaluated using an analysis of covariance (ANCOVA), adjusted for whether patients were treated with metformin or metformin/sulfonylurea on inclusion and for the HbA1c value on inclusion. Method of handling missing data: replaced by last observed value (LOCF analysis). *Non-inferiority analysis versus sitagliptin performed subsequently from inclusion to week 52 (margin of 0.30% and α risk of 0.05), converted to superiority analysis if upper limit of 95% CI < 0.*	Difference between the canagliflozin and glimepiride groups evaluated using an ANCOVA, adjusted for whether patients were treated with metformin or metformin/OAD on inclusion, for whether they had a washout period, for country and for the HbA1c value on inclusion. The non-inferiority analysis with a margin of 0.30% was converted to a superiority analysis if the upper limit of the 95% CI for the difference was below 0. Method of handling missing data: LOCF analysis.
Calculation of the number of subjects required (NSR)	Assuming a difference in change in HbA1c of 0.5% between placebo and canagliflozin with a standard deviation of 1.0%, the NSR was estimated at 86 per group to demonstrate the superiority of canagliflozin 300 mg with a power of 90% and an α risk of 0.05. *Calculation of NSR for the non-inferiority analysis versus sitagliptin set at 360 patients in total.*	Assuming a difference in change in HbA1c of 0.0% with a standard deviation of 1.0% between one of the canagliflozin groups and the glimepiride group, the NSR was estimated at 277 per group to demonstrate the non-inferiority of canagliflozin (margin 0.3%; α risk = 0.0125) with a power of 90%.

* The non-inclusion criteria from study DIA3005 were repeated in each of these studies (except for uncontrolled hypertension in study DIA3009).
** Randomisation stratified by whether patients were treated with metformin or metformin/sulfonylurea on inclusion.

Results of studies DIA3006 and DIA3009

In study DIA3006, 1,284 patients treated with metformin were randomised to four groups: canagliflozin 100 mg (n=368), canagliflozin 300 mg (n=367), sitagliptin 100 mg (n=366) and placebo (n=183). The study withdrawal rate was similar between the groups (n=165, 12.9%). The mean duration of treatment was about 24 weeks.

In study DIA3009, 1,452 patients treated with metformin were randomised to three groups: canagliflozin 100 mg (n=483), canagliflozin 300 mg (n=485) and glimepiride (n=482). The study withdrawal rate was similar between the groups (n=289, 19.9%) and the mean duration of treatment was about 46 weeks. In this study, the mean daily dose of the comparator, glimepiride, was 5.5 mg.

Patient characteristics

Patient characteristics were similar between treatment groups in each study. Overall characteristics are presented in Table 3. About two thirds of patients had hypertension.

Table 3. Patient characteristics in studies DIA3006 and DIA3009

	Study DIA3006 N=1284	Study DIA3009 N=1452
Age (years), *mean (standard deviation)*	55.4 (9.4)	56.2 (9.2)
Female, *n (%)*	679 (52.9)	694 (47.9)
Average weight (kg), *mean (standard deviation)*	87.2 (21.7)	86.6 (19.8)
BMI ≥ 30 (obesity), *n (%)*	718 (55.9)	777 (53.6)
Hypertension, *n (%)*	776 (60.4)	976 (67.3)
Duration of diabetes (years), *mean (SD)*	6.9 (5.4)	6.6 (5.3)
HbA1c on inclusion (%), *mean (SD)*	7.9 (0.9)	7.8 (0.8)
Fasting blood glucose on inclusion (mmol/L), *mean (SD)*	9.4 (2.3)	9.2 (2.1)
Average metformin dose (mg/day), *mean (SD)*	2151 (351)	2180 (369)

Efficacy on endpoints: study DIA3006 (versus metformin/placebo)

This study showed that canagliflozin, in combination with metformin, is superior to placebo at 26 weeks in terms of change in HbA1c levels, with an intergroup difference of -0.7 between canagliflozin 300 mg and placebo and -0.6 between canagliflozin 100 mg and placebo (p<0.001). The per-protocol analysis confirmed these results with intergroup differences of -0.5 (±0.1) and -0.4 (±0.1) respectively (p<0.001).
In terms of the secondary endpoints, this study showed that canagliflozin is superior to placebo at 26 weeks (Table 4).

It should be noted that the percentage of patients receiving rescue therapy was 14.8% in the placebo group, and 1.6% and 0.3% in the canagliflozin 100 mg and 300 mg groups respectively.

Table 4. Results of analysis for primary efficacy and secondary endpoints in the mITT population at 26 weeks in study DIA3006

	Canagliflozin 100 mg N=368	Canagliflozin 300 mg N=367	Sitagliptin 100 mg N=366	Placebo N=183	Intergroup difference	
					Cana. 100 mg - placebo	Cana. 300 mg - placebo
Primary efficacy endpoint						
HbA1c on inclusion (%), *mean (SD*)*	7.94 (0.88)	7.95 (0.93)	7.92 (0.88)	7.96 (0.90)	-	-
Change in HbA1c at 26 weeks, *mean (SD*)*	-0.79 (0.04)	-0.94 (0.04)	-0.82 (0.04)	-0.17 (0.06)	-0.62 (0.07) [-0.76; -0.48] p<0.001	-0.77 (0.07) [-0.91; -0.64] p<0.001
Secondary endpoints						
Patients with HbA1c < 7.0%, n (%)	166 (45.5)	208 (57.8)	193 (54.5)	54 (29.8)	p<0.0001	p<0.0001
Change in fasting	-1.5 (0.1)	-2.1 (0.1)	-1.1 (0.1)	0.1 (0.1)	-1.7 (0.2)	-2.2 (0.2)

	Canagliflozin 100 mg N=368	Canagliflozin 300 mg N=367	Sitagliptin 100 mg N=366	Placebo N=183	Intergroup difference	
					Cana. 100 mg - placebo	Cana. 300 mg - placebo
blood glucose (mmol/L), mean (SD)					[-2.0; -1.3] p<0.001	[-2.6; -1.9] p<0.001
Change in weight (kg), mean (SD)	-3.7 (0.2)	-4.2 (0.2)	-1.2 (0.2)	-1.2 (0.3)	-2.5 (0.3) [-3.1; -1.9] p<0.001	-2.9 (0.3) [-3.5; -2.3] p<0.001

Efficacy at 52 weeks

At 52 weeks, the analysis showed that canagliflozin was non-inferior to sitagliptin 100 mg in the per-protocol population (canagliflozin 100 mg (n=244), canagliflozin 300 mg (n=265) and sitagliptin (n=237)), with an intergroup difference versus sitagliptin of +0.12% (±0.06; 95% CI [0.01; 0.24]) for canagliflozin 100 mg and -0.03 (±0.06; 95% CI [-0.15; 0.09]) for the 300 mg dose. These results were confirmed in the mITT analysis. In the superiority analysis following the demonstration of non-inferiority, for the 300 mg dose only, the upper limit of the confidence interval was below 0, meeting the definition of superiority (-0.15; 95% CI [-0.27; -0.03]). It should be noted that at 52 weeks, 28% of patients in the canagliflozin 300 mg group and 35% in the sitagliptin 100 mg group were excluded from the per-protocol analysis.

Efficacy on endpoints: study DIA3009 (versus metformin/glimepiride)

This study showed that canagliflozin, in combination with metformin, was non-inferior to glimepiride at 52 weeks in terms of change in HbA1c levels, in the per-protocol population with an intergroup difference of 0.05 (95% CI [-0.05; 0.14]) for canagliflozin 100 mg and -0.06 (95% CI [-0.15; -0.03]) for the 300 mg dose. These results were confirmed in the mITT analysis (Table 5). In the superiority analysis following the demonstration of non-inferiority, for the 300 mg dose only, the upper limit of the confidence interval was below 0, meeting the definition of superiority (-0.12; 95% CI [-0.22; -0.02]). It should be noted that 26% of patients in the canagliflozin groups and 30% in the glimepiride comparator group were excluded from the per-protocol analysis.

In terms of the secondary endpoints, this study showed that canagliflozin is superior to glimepiride at 52 weeks, except for change in fasting blood glucose with the 100 mg dose of canagliflozin (Table 5).

It should be noted that the percentage of patients with HbA1c < 7.0% was 55.8% in the glimepiride group, and 53.6% and 60.1% in the canagliflozin 100 mg and 300 mg groups respectively.

Table 5. Results of analysis for primary efficacy and secondary endpoints in the mITT population at 52 weeks in study DIA3009

	Canagliflozin 100 mg N=483	Canagliflozin 300 mg N=485	Glimepiride N=482	Intergroup difference	
				Cana. 100 mg - glimepiride	Cana. 300 mg - glimepiride
Primary efficacy endpoint					
HbA1c on inclusion (%), *mean (SD*)*	7.78 (0.79)	7.79 (0.78)	7.83 (0.80)	-	-
Change in HbA1c at 52 weeks, *mean (SD*)*	-0.82 (0.04)	-0.93 (0.04)	-0.81 (0.04)	-0.01 (0.05) [-0.11; 0.09]	-0.12 (0.05) [-0.22; -0.02]
Secondary endpoints					
Change in fasting blood glucose (mmol/L), *mean (SD*)*	-1.35 (0.09)	-1.52 (0.09)	-1.02 (0.09)	-0.33 (0.11) [-0.56; 0.11]	-0.51 (0.11) [-0.73; -0.28]
Change in weight (kg), *mean (SD*)*	-4.2 (0.2)	-4.7 (0.2)	1.0 (0.2)	-5.2 (0.3) [-5.7; -4.7] p<0.001	-5.7 (0.3) [-6.2; -5.1] p<0.001
Incidence of hypoglycaemia, *n (%)*	27 (5.6)	24 (4.9)	165 (34.2)	OR = 0.10 [0.06; 0.16]	OR = 0.09 [0.05; 0.14]

Efficacy on the primary efficacy endpoint at 104 weeks
At 104 weeks, the change in HbA1c was -0.65 (±0.04) in the canagliflozin 100 mg group, -0.74 (±0.04) in the canagliflozin 300 mg group and -0.55 (±0.04) in the glimepiride group.

8.1.3 Studies of triple therapy with metformin and sulfonylureas (DIA3002 and DIA3015)

Studies DIA3002 and DIA3015 are two phase III, randomised, comparative, double-blind, parallel-group and multicentre studies.
The primary objective of these studies was to evaluate the efficacy of canagliflozin/metformin/sulfonylurea triple therapy, in patients with type 2 diabetes inadequately controlled by metformin/sulfonylurea dual therapy, versus:

- combined placebo/metformin/sulfonylurea, after 26 weeks of treatment, in superiority study DIA3002;
- sitagliptin/metformin/sulfonylurea triple therapy, after 52 weeks of treatment, in non-inferiority study DIA3015 which was converted to a superiority study.

Table 6. Methods of studies DIA3002 and DIA3015, evaluating canagliflozin as triple therapy with metformin/sulfonylurea

	Study DIA3002 ***Versus placebo/metformin/sulfonylurea***	**Study DIA3015** ***Versus sitagliptin/metformin/sulfonylurea***
Dates and sites	April 2010 – September 2011. 85 centres in 11 countries, mainly in North America and Europe.	June 2010 – March 2012. 140 centres in 17 countries, mainly in North America and Europe.
Inclusion criteria	- age between 18 and 80 years with type 2 diabetes treated with metformin/sulfonylurea - HbA1c [7.0; 10.5] on metformin/sulfonylurea* dual therapy for at least 8 weeks, or after 8-week dose adjustment for patients on dual therapy at lower doses and with HbA1c ≥ 7.5%	- age ≥ 18 years with type 2 diabetes treated with metformin/sulfonylurea - HbA1c [7.0; 10.5] on metformin/sulfonylurea* dual therapy for at least 8 weeks, or after 8-week dose adjustment for patients on dual therapy at lower doses and with HbA1c ≥ 7.5%
Main non-inclusion criteria**	- Fasting blood glucose ≥ 270 mg/dL before randomisation	- Fasting blood glucose ≥ 300 mg/dL before randomisation
Treatments administered	After a 2-week period on metformin/sulfonylurea and placebo, patients were randomised to three groups (1:1:1 design): - Canagliflozin 100 mg - Canagliflozin 300 mg - Placebo Patients received treatment for 26 weeks. Rescue therapy with insulin was authorised.	After a 2-week period on metformin/sulfonylurea and placebo, patients were randomised to two groups: - Canagliflozin 300 mg: once daily - Sitagliptin 100 mg Patients received treatment for 52 weeks as long as they did not meet any of the following criteria: - From D1 to week 6: fasting blood glucose (FBG) > 270 mg/dL - From week 7 to week 12: FBG > 240 mg/dL - From week 13 to week 26: FBG > 200 mg/dL - After 26 weeks: HbA1c > 8.0%
Extension phase	26 additional weeks of treatment.	-
Primary efficacy endpoint	Change in HbA1c at 26 weeks	Change in HbA1c at 52 weeks
Secondary endpoints included	Change at 26 weeks in: - Weight - Fasting blood glucose - Percentage of patients with HbA1c < 7.0%	Change at 52 weeks in: - Weight - Fasting blood glucose
Statistical analysis	Difference between the canagliflozin and placebo groups evaluated using an analysis of covariance (ANCOVA), adjusted for whether patients had a dose adaptation period and for the HbA1c value on inclusion. The difference was estimated using the method of least squares. Method of handling missing data: LOCF analysis.	Difference between the canagliflozin and sitagliptin groups evaluated using an ANCOVA, adjusted for whether patients had HbA1c ≥ 9% before randomisation and for the HbA1c value on inclusion. The non-inferiority analysis with a margin of 0.30% was converted to a superiority analysis if the upper limit of the 95% CI for the difference was below 0. Method of handling missing data: LOCF analysis.
Calculation of the number of subjects required (NSR)	Assuming a difference in change in HbA1c of 0.5% between placebo and canagliflozin with a standard deviation of 1.0%, the NSR was estimated at 85 per group to demonstrate the superiority of canagliflozin 300 mg with a power of 90% and an α risk of 0.05.	Assuming a difference in change in HbA1c of 0.0% with a standard deviation of 1.0 between one of the canagliflozin groups and the glimepiride group, the NSR was estimated at 234 per group to demonstrate the non-inferiority of canagliflozin (margin 0.3%; α risk = 0.025) with a power of 90%.

* Metformin dose ≥ 2000 mg / Sulfonylurea: glipizide, glibenclamide, glimepiride, gliclazide.

** The non-inclusion criteria from study DIA3005 also applied to each of these studies.

Results from studies DIA3002 and DIA3015

In study DIA3002, 469 patients treated with metformin/sulfonylurea were randomised to three groups: canagliflozin 100 mg (n=157), canagliflozin 300 mg (n=156), and placebo (n=156). The study withdrawal rate was similar between the groups (n=88, 18.8%). The mean duration of treatment was about 23.2 weeks (±6.3) and the mean daily dose of metformin was 2,146 mg.

In study DIA3015, 755 patients treated with metformin/sulfonylurea were randomised to two groups: canagliflozin 300 mg (n=377) and sitagliptin 100 mg (n=378). The study withdrawal rate was 32.6% (n=123) in the canagliflozin group and 44.4% in the sitagliptin group (n=168); the most common reason was failure to reach the glycaemic target (10.6% and 22.5% respectively), and the mean duration of treatment was about 42 weeks.

In both these studies, the most common sulfonylureas were glibenclamide (35%) and glimepiride (30%).

Patient characteristics
Patient characteristics were similar between treatment groups for each study; overall characteristics are presented in Table 7. About two thirds of patients had hypertension.

Table 7. Patient characteristics in studies DIA3002 and DIA3015

	Study DIA3002 N=469	Study DIA3015 N=755
Age, *mean (standard deviation)*	56.7 (9.3)	56.7 (9.5)
Female, *n (%)*	230 (49.0)	333 (44.1)
Average weight (kg), *mean (standard deviation)*	92.8 (22.4)	88.3 (23.2)
BMI ≥ 30 (obesity), *n (%)*	310 (66.1)	400 (53.0)
Hypertension, *n (%)*	296 (63.1)	522 (69.1)
Duration of diabetes (years), *mean (SD)*	9.6 (6.3)	6.6 (6.2)
HbA1c on inclusion (%), *mean (SD)*	8.1 (0.9)	8.1 (0.9)
Fasting blood glucose (mmol/L), *mean (SD)*	9.5 (2.2)	9.3 (2.6)
Average metformin dose (mg/day), *mean (SD)*	2146 (355)	2175 (340)
Mean sulfonylurea dose*		
Glibenclamide (mg/day)	13.6 (4.4)	15.2 (6.4)
Glimepiride (mg/day)	5.1 (2.0)	5.2 (5.9)

* for the most common sulfonylureas

Efficacy on endpoints: study DIA3002 (versus metformin/sulfonylurea/placebo)
This study showed that canagliflozin was superior to placebo at 26 weeks as triple therapy (in combination with metformin/sulfonylurea), in terms of change in HbA1c level, with an intergroup difference of -0.9 between canagliflozin 300 mg and placebo and -0.7 between canagliflozin 100 mg and placebo ($p<0.001$). The per-protocol analysis confirmed these results with intergroup differences of -0.7 (±0.1) and -0.5 (±0.1) respectively ($p<0.001$).
In terms of secondary endpoints, this study showed that canagliflozin was superior to placebo at 26 weeks (Table 8).

Table 8. Results of primary efficacy and secondary endpoint analysis in the mITT population at 26 weeks in study DIA3002

	Canagliflozin 100 mg N=157	Canagliflozin 300 mg N=156	Placebo N=156	Intergroup difference	
				Cana. 100 mg - placebo	Cana. 300 mg - placebo
Primary efficacy endpoint					
HbA1c on inclusion, *mean (SD*)*	8.13 (0.93)	8.13 (0.94)	8.12 (0.90)	-	-
Change in HbA1c at 26 weeks, *mean (SD*)*	-0.85 (0.08)	-1.06 (0.08)	-0.13 (0.08)	-0.71 (0.10) [-0.90; -0.52] p<0.001	-0.92 (0.10) [-1.11; -0.73] p<0.001
Secondary endpoints					
Patients with HbA1c < 7.0%, *n (%)*	67 (43.2)	86 (56.6)	27 (18.0)	p<0.001	p<0.001
Change in fasting blood glucose (mmol/L), *mean (SD*)*	-1.01 (0.20)	-1.69 (0.20)	0.23 (0.20)	-1.24 (0.26) [-1.75; -0.73] p<0.001	-1.92 (0.26) [-2.43; -1.41] p<0.001
Change in weight (kg), *mean (SD*)*	-2.1 (0.3)	-2.6 (0.3)	-0.7 (0.3)	-1.4 (0.4) [-2.1; -0.7] p<0.001	-2.0 (0.4) [-2.7; -1.3] p<0.001

Efficacy on the primary efficacy endpoint at 52 weeks
At 52 weeks, the change in HbA1c was -0.74 (±0.08) in the canagliflozin 100 mg group, -0.96 (±0.08) in the canagliflozin 300 mg group, and +0.01 (±0.08) in the placebo group.

Efficacy on endpoints: study DIA3015 (versus metformin/sulfonylurea/sitagliptin)
This study showed that canagliflozin 300 mg was non-inferior to sitagliptin 100 mg at 52 weeks in terms of change in HbA1c levels, in the per-protocol population with an intergroup difference of -0.21 (95% CI [-0.34; -0.08]) for the 300 mg dose. These results were confirmed in the mITT analysis (Table 9). In the superiority analysis following the demonstration of non-inferiority, the upper limit of the confidence interval was below 0, meeting the definition of superiority (-0.37; 95% CI [-0.50; -0.25]). It should be noted that 34% of patients in the canagliflozin 300 mg group and 45% in the sitagliptin 100 mg comparator group were excluded from the per-protocol analysis.
In terms of the secondary endpoints, this study showed that canagliflozin was superior to sitagliptin 100 mg at 52 weeks (Table 9).
The proportion of patients who achieved HbA1c < 7.0%, an exploratory endpoint, was 45.6% in the canagliflozin group and 35.3% in the sitagliptin group.

Table 9. Results of primary efficacy and secondary endpoint analysis in the mITT population at 52 weeks in study DIA3015

	Canagliflozin 300 mg N=377	Sitagliptin 100 mg N=378	Intergroup difference Canagli.-sitagliptin
Primary efficacy endpoint			
HbA1c on inclusion (%), *mean (SD*)*	8.12 (0.91)	8.13 (0.92)	
Change in HbA1c at 52 weeks, *mean (SD*)*	-1.03 (0.05)	-0.66 (0.05)	-0.37 (0.06) [-0.50; -0.25]
Secondary endpoints			
Change in fasting blood glucose (mmol/L), *mean (SD*)*	-1.66 (0.12)	-0.32 (0.12)	-1.34 (0.16) [-1.66; -1.01] p<0.01
Change in weight (kg), *mean (SD*)*	-2.5 (0.2)	-0.3 (0.2)	-2.8 (0.3) [-3.3; -2.2] p<0.001

8.1.4 Studies in special populations

8.1.4.1 Patients aged 55 to 80 years (DIA3010)

Study DIA3010 is a randomised, double-blind, multicentre, placebo-controlled study.
The primary objective was to evaluate the efficacy and safety of canagliflozin 100 and 300 mg, at 26 weeks versus placebo, in patients aged 55 to 80 years with poorly controlled type 2 diabetes (HbA1c [7.0; 10.0]) who were not treated with OADs or had been treated at a stable dose[17] for at least 8 weeks.
The non-inclusion criteria included:

- fasting blood glucose > 270 mg/dL
- use of bisphosphonates, parathyroid hormones or denosumab in the previous 12 months or non-stable osteoporosis treatment
- osteoporosis (T-score < -2.5), severe vitamin D deficiency, hypercalcaemia, bone fractures in the previous 12 months or unhealed fractures

After a 2-week period on placebo, patients were randomised to three groups (canagliflozin 100 mg, canagliflozin 300 mg and placebo) and then treated for 26 weeks.

The primary efficacy endpoint was change in HbA1c at 26 weeks.
The number of subjects required was estimated at 86 per group to demonstrate the superiority of canagliflozin with a power of 90%, based on the hypothesis that the intergroup difference in change in HbA1c at 26 weeks would be 0.5% (standard deviation: 1.0) and with an α risk of 0.05.[18]
The difference between the canagliflozin and placebo groups was evaluated using an ANCOVA adjusted for T-score, whether treatment was combined with pioglitazone or not, and HbA1c value on inclusion.

Results
A total of 716 patients were randomised to three groups, and 714 of them were treated (mITT population): placebo (n=237), canagliflozin 100 mg (n=241) and canagliflozin 300 mg (n=236). The study withdrawal rate was 16.9% in the placebo group, 6.2% in the canagliflozin 100 mg group and 11.4% in the canagliflozin 100 mg group. The mean duration of treatment was about 24 weeks.

About 76% of patients were treated with two or more classes of antidiabetic drugs and 44% were on triple therapy. The treatments most commonly combined with canagliflozin during the study were metformin in 85.3% of patients (n=609), sulfonylureas (48.7%, n=348) and insulin (32.7%, n=234); metformin was combined with sulfonylureas in 43.6% of patients (n=311) and with insulin in 25.2% (n=180).
It should be noted that the rescue therapy rate was 11.0% in the placebo group (n=26), 2.1% on canagliflozin 100 mg (n=5) and 0.4% on the 300 mg dose (n=1).

Patient characteristics were similar between the groups, with a mean age of 63.6 years (±6.2), distributed as follows: 61% between 55 and 64 years, 32% between 65 and 74 years and 7% between 75 and 80 years. About 44.5% of patients were female. The mean weight was 89.5 kg (±16.8). More than two thirds of patients (62.2%) had a BMI greater than or equal to 30.
The diagnosis of diabetes had been made an average of 11.7 years ago. The mean HbA1c level on inclusion was 7.7% (±0.8). Fasting blood glucose was 8.7 mg/dL (±2.1).

[17] Approved treatments: metformin, sulfonylurea, gliptin, alpha-glucosidase inhibitors, GLP-1 analogues and insulin for at least 12 weeks, or pioglitazone for at least 6 months.
[18] The NSR was increased to 156 per group to ensure that the half-width of the 95% CI was less than 0.9%.

Efficacy on endpoints

This study showed that canagliflozin, alone or in combination with other antidiabetic drugs, was superior to placebo at 26 weeks in terms of change in HbA1c levels, with an intergroup difference of -0.7 between canagliflozin 300 mg and placebo and -0.6 between canagliflozin 100 mg and placebo (Table 10). The per-protocol analysis confirmed superiority with intergroup differences of -0.6 (±0.1) and -0.5 (±0.1) respectively (p<0.001).

The response rate was 47.7% and 58.5% in the canagliflozin 100 mg and 300 mg groups respectively, and 28% in the placebo group.

Table 10. Results of primary efficacy and secondary endpoint analysis in the mITT population at 26 weeks in study DIA3010

	Canagliflozin 100 mg N=90	**Canagliflozin 300 mg N=89**	**Placebo N=90**	**Intergroup difference**	
				Cana. 100 mg - placebo	**Cana. 300 mg - placebo**
Primary efficacy endpoint					
HbA1c on inclusion (%), *mean (SD*)*	7.77 (0.77)	7.69 (0.78)	7.76 (0.79)	-	-
Change in HbA1c at 26 weeks, *mean (SD*)*	-0.60 (0.06)	-0.73 (0.06)	-0.03 (0.06)	-0.57 (0.07) [-0.71; -0.44] p<0.001	-0.70 (0.07) [-0.84; -0.57] p<0.001

8.1.4.2 Patients with cardiovascular risk factors (DIA3008)

The CANVAS study (DIA3008) is a randomised, double-blind, placebo-controlled, multicentre study which started in 2009 and is ongoing (4-year follow-up). The primary objective is to evaluate safety and cardiovascular risk in patients:

- with poorly controlled type 2 diabetes (HbA1c [7.0; 10.5]) not treated with OADs or treated at a stable dose[19] for at least 8 weeks;
- at cardiovascular risk, defined as:
  - age ≥ 30 years with documented, symptomatic atherosclerotic disease: CVA, myocardial infarction, admission for unstable angina, coronary bypass, percutaneous coronary intervention, peripheral revascularisation, carotid or peripheral artery atheromatous disease, amputation secondary to a cardiovascular disease
  - or age ≥ 50 years with at least two cardiovascular risk factors: type 2 diabetes for 10 years, current use of tobacco, hypertension on antihypertensive treatment, micro/macroalbuminurea, HDL cholesterol < 1 mmol/L.

Of note, patients were not included if their fasting blood glucose was < 270 mg/dL or < 110 mg/dL in case of treatment with sulfonylureas or insulin.

After a 2-week period on placebo, 4,330 patients were randomised (1:1:1 design) to three groups and treated: canagliflozin 100 mg (n=1,445), canagliflozin 300 mg (n=1,441) and placebo (n=1,441).

Two substudies had the primary objective of evaluating the efficacy of canagliflozin versus placebo in these patients, in combination with insulin in one substudy and sulfonylureas in the other (these treatments could themselves be combined) for 18 weeks.

In both these substudies, the primary efficacy endpoint was change in HbA1c at 18 weeks. The secondary efficacy endpoints were change in fasting blood glucose and weight at 18 weeks as well as the percentage of patients with HbA1c < 7.0%.

[19] Approved treatments: metformin, sulfonylurea, gliptin, alpha-glucosidase inhibitor, GLP-1 analogue, insulin, or pioglitazone.

Substudy of canagliflozin in combination with sulfonylureas

The results of this substudy are presented. However, it should be noted that the company has not requested the inclusion of canagliflozin 100 mg and 300 mg as dual therapy with sulfonylureas.

This substudy included patients from the CANVAS study who had been treated with sulfonylureas as monotherapy at a stable dose for at least 10 weeks. The number of subjects required was estimated at 50 per group to demonstrate the superiority of canagliflozin to placebo, with a power of 90%, but the calculation of this number is imprecise. The difference between the canagliflozin and placebo groups was evaluated using an ANCOVA adjusted for concomitant antidiabetic treatment and the HbA1c value on inclusion.

A total of 127 patients treated with sulfonylureas were randomised to three groups: canagliflozin 100 mg (n=42), canagliflozin 300 mg (n=40), and placebo (n=45). The number of subjects required was not reached. The results for the primary efficacy endpoint are presented for information only in Table 11, and will not be taken into account in the assessment.

Table 11. Results of primary efficacy and secondary endpoint analysis in the mITT population at 18 weeks in the substudy of combination with sulfonylureas

	Canagliflozin 100 mg N=42	Canagliflozin 300 mg N=40	Placebo N=45	Intergroup difference	
				Cana. 100 mg – placebo	Cana. 300 mg - placebo
Primary efficacy endpoint					
HbA1c on inclusion (%), *mean (SD*)*	8.29 (0.83)	8.28 (1.01)	8.49 (1.13)	-	-
Change in HbA1c at 26 weeks, *mean (SD*)*	-0.70 (0.15)	-0.79 (0.15)	0.04 (0.15)	-0.74 (0.21) [-1.15; -0.33]	-0.83 (0.21) [-1.24; -0.42]

Substudy of canagliflozin in combination with insulin

Patients from the CANVAS study treated with insulin (dose ≥ 20 IU/day) were included in the substudy and analysed in each of the following three populations: dose ≥ 20 IU/day, dose ≥ 30 IU/day, dose ≥ 30 IU/day + metformin ≥ 2,000 mg/day.[20]

The number of subjects required was estimated at 86 per group to demonstrate the superiority of canagliflozin with a power of 90%, based on the hypothesis that the intergroup difference in change in HbA1c at 26 weeks would be 0.5% (standard deviation: 1.0) and with an α risk of 0.05. The difference between the canagliflozin and placebo groups was evaluated using an ANCOVA adjusted for whether an OAD was taken and for the HbA1c value on inclusion.

Patient characteristics

A total of 2,072 patients on an insulin dose ≥ 20 IU/day (including 1,718 in the ≥ 30 IU/day population) were randomised to three groups and treated: placebo (n=690), canagliflozin 100 mg (n=692) and canagliflozin 300 mg (n=690). The patient characteristics were similar between the treatment groups and between the two populations. Patients had a mean age of 62.8 years (±7.7) and 33.9% were female. The mean weight was 94.7 kg (±21.7) and more than two thirds of patients (68.8%) had a BMI ≥ 30. On inclusion, fasting blood glucose was 9.2 mmol/L (±2.7) and HbA1c was 8.3% (±0.9). Patients had had type 2 diabetes for an average of 16.2 years (±7.5).

The majority of patients were treated with a basal/bolus insulin regimen (63%) or with basal insulin alone (26%). The mean daily dose of insulin was 73 IU/day (median dose: 60 IU/day). About 70% of patients were treated with at least one oral antidiabetic drug in combination with insulin, including biguanides (metformin) in 62.9% of patients, sulfonylureas in 23.7% and thiazolidinediones in 5.6% (the other OADs were taken by 3% of patients).

The rescue therapy rate was 8.1% on placebo (n=56), 4.0% on canagliflozin 100 mg (n=28) and 2.9% on the 300 mg dose (n=20).

Efficacy on endpoints

[20] According to the EMA, the dose of 20 IU chosen was too low (Procedure No. EMEA/H/SA/1252/1/FU/2009/II).

This substudy showed that canagliflozin, in combination with insulin alone or with OADs, was superior to placebo at 18 weeks in terms of change in HbA1c levels, with an intergroup difference of -0.7 between canagliflozin 300 mg and placebo and -0.6 between canagliflozin 100 mg and placebo. The per-protocol analysis confirmed superiority with intergroup differences of -0.7 (±0.04) and -0.6 (±0.04) respectively (p<0.001).
In terms of the secondary endpoints, this study showed that canagliflozin 100 mg and 300 mg was superior to placebo at 18 weeks (Table 12).
Similar results were found in the population on an insulin dose ≥ 30 IU/day (n=1,718). Efficacy was also evaluated in the subpopulation taking insulin ≥ 30 IU/day and metformin ≥ 2,000 mg/day as dual therapy (n=432). These patients had a mean HbA1c level of 8.2% on inclusion. The intergroup differences versus placebo were -0.7 (±0.1) and -0.8 (±0.1) for the 100 mg and 300 mg doses of canagliflozin respectively (p<0.001).

Table 12. Results of primary efficacy and secondary endpoint analysis in the mITT population at 26 weeks in study DIA3008 (insulin substudy)

	Canagliflozin 100 mg N=692	**Canagliflozin 300 mg N=690**	**Placebo N=690**	**Intergroup difference**	
				Cana. 100 mg – placebo	**Cana. 300 mg - placebo**
Primary efficacy endpoint					
HbA1c on inclusion (%), *mean (SD*)*	8.31 (0.91)	8.27 (0.90)	8.21 (0.85)	-	-
Change in HbA1c at 18 weeks, *mean (SD*)*	-0.62 (0.03)	-0.74 (0.03)	-0.01 (0.03)	-0.62 (0.04) [-0.69; -0.54] p<0.001	-0.73 (0.04) [-0.81; -0.65] p<0.001
Percentage of patients with HbA1c < 7.0%, *n (%)*	131 (19.8)	170 (25.8)	53 (8.3)	p<0.001	p<0.001
Change in fasting blood glucose (mmol/L), *mean (SD*)*	-0.97 (0.09)	-1.38 (0.10)	0.20 (0.10)	-1.16 [-1.43; -0.90]	-1.58 [-1.84; -1.32]
Change in weight (kg), *mean (SD*)*	-1.74 (0.10)	-2.26 (0.10)	0.04 (0.10)	-1.78 (0.14) [-2.06; -1.49]	-2.30 (0.14) [-2.59; -2.02]

8.1.5 Indirect comparison meta-analysis

The objective of this meta-analysis was to evaluate, via an indirect comparison, the relative efficacy of canagliflozin versus GLP-1 analogues in patients with type 2 diabetes inadequately controlled by oral antidiabetic drugs or insulin.

This network meta-analysis was performed as an ancillary analysis to a comprehensive network meta-analysis initially performed for all type 2 diabetes treatments.
A literature search was carried out on MEDLINE, MEDLINE In-Process, Embase and the Cochrane Central Register up to February 2013, as well as a manual search of conferences and the NICE, Scottish Medicines Consortium and Wales Medicines Strategy Group websites. The selection of trials seemed to conform to the guidelines. Among other criteria, the trials included in this meta-analysis had to run for longer than or equal to 12 weeks and include patients initially treated with metformin, a sulfonylurea, insulin, combined metformin/sulfonylurea or combined metformin/pioglitazone. In the indirect comparisons performed as part of this network meta-analysis, the treatment of interest was canagliflozin as dual or triple therapy or combined with insulin.

A total of 15 trials were included, consisting of eight where patients were treated with metformin and seven where they were treated with metformin and a sulfonylurea. Patients' general characteristics seemed to be similar across the trials, except that:

- one trial in patients treated with metformin, which compared sitagliptin to glimepiride, had a lower baseline HbA1c than the other trials (7.5% instead of 8%);
- one trial in patients treated with metformin and a sulfonylurea, which compared exenatide with insulin, had a higher baseline HbA1c (10% instead of 8%).

The results of the indirect comparisons, in terms of change in HbA1c level (the primary efficacy endpoint in the trials), are presented in Table 13. The indirect comparisons suggest that canagliflozin 100 mg and 300 mg may be inferior to liraglutide 1.2 mg and 1.8 mg at 26 and 52 weeks. No difference versus liraglutide was found at 104 weeks.

Table 13. Results of indirect comparisons for HbA1c obtained at 26 and 52 weeks in the trials of combination with metformin

	Mean HbA1c (%) – *Change from baseline [95% CrI]**	
Comparator	**26 weeks**	**52 weeks**
canagliflozin 100 mg		
vs. Liraglutide 1.2 mg	0.31 [0.15; 0.47]	0.39 [0.16; 0.62]
vs. Liraglutide 1.8 mg	0.50 [0.34; 0.66]	0.61 [0.38; 0.84]
vs. Exenatide 5 mg	-0.17 [-0.47; 0.14]	
vs. Exenatide 10 mg	0.22 [-0.07; 0.50]	0.03 [-0.25; 0.31]
canagliflozin 300 mg		
vs. Liraglutide 1.2 mg	0.20 [0.03; 0.36]	0.26 [0.03; 0.50]
vs. Liraglutide 1.8 mg	0.39 [0.22; 0.55]	0.49 [0.25; 0.71]
vs. Exenatide 5 mg	-0.28 [-0.58; 0.03]	
vs. Exenatide 10 mg	0.10 [-0.18; 0.39]	-0.09 [-0.37; 0.18]

* 95% credible interval (Bayesian method)

As regards combination with metformin and a sulfonylurea, no significant difference was found between canagliflozin and GLP-1 analogues.

08.2 Safety/Adverse effects

8.2.1 Clinical study data

Safety data from the main clinical studies

The adverse events from the clinical studies submitted that were not conducted in special populations are presented in Table 14 for the maximum study durations (including extension phases).

In total, 2,785 patients received at least one dose of canagliflozin (including 1,582 at the maximum dose of 300 mg).
The percentage of patients with adverse events in the canagliflozin groups varied depending on the study: about 60% at 26 weeks, 63% to 77% at 52 weeks and 64% to 69% at 104 weeks. Most of these events were of mild to moderate intensity.
The same applies to the percentage of patients with canagliflozin-related adverse events, which varied depending on the study and the dosage (fewer adverse events with the 100 mg dose than the 300 mg dose). These events were mainly urinary tract and vulvovaginal infections, balanitis, pollakiuria and vulvovaginal pruritus.

It should be noted that an increase in LDL cholesterol level was found in most studies, with a difference versus placebo of +0.5% to +7.9% for the 100 mg dose and +4.6% to +12.2% for the 300 mg dose, and differences versus active comparators of +4.5% and +6% to +9% for each dose respectively. A parallel increase in HDL cholesterol level was found; the LDL/HDL ratios were similar between inclusion and the end of the studies.

Serious adverse events were observed in 1% to 6% of patients, primarily infections. Between 2% and 8% of patients stopped their treatment due to adverse events.
Six deaths occurred in the canagliflozin groups (versus two in the comparator groups): septic shock, stroke, fall, myocardial infarction and cardiac arrest. These deaths were not attributed to the treatment.

Table 14. Most common adverse events in clinical studies (≥ 2.0%)

Study	Monotherapy			Dual therapy with metformin							Triple therapy with metformin/sitagliptin				
	DIA3005 (26 weeks)			DIA3006 (52 weeks)				DIA3009 (104 weeks)			DIA3002 (52 weeks)			DIA3015 (52 weeks)	
	Plac* N=192	Cana* 100 mg N=195	Cana 300 mg N=197	Plac/ Sita* N=183	Sita N=366	Cana 100 mg N=368	Cana 300 mg N=367	Glim* N=482	Cana 100 mg N=483	Cana 300 mg N=485	Plac N=156	Cana 100 mg N=157	Cana 300 mg N=156	Sita N=378	Cana 300 mg N=377
AEs, *n (%)*	**94 (49.0)**	**118 (60.5)**	**118 (59.9)**	**122 (66.7)**	**236 (64.5)**	**266 (72.3)**	**230 (62.7)**	**326 (67.6)**	**310 (64.2)**	**332 (68.5)**	**111 (71.2)**	**106 (67.5)**	**114 (73.1)**	**293 (77.5)**	**289 (76.7)**
Treatment-related AEs, *n (%)*	**18 (9.4)**	**33 (5.9)**	**50 (25.4)**	**23 (12.6)**	**72 (19.7)**	**97 (26.4)**	**73 (19.9)**	**109 (22.6)**	**118 (24.4)**	**145 (29.9)**	**24 (15.4)**	**41 (26.1)**	**57 (36.5)**	**105 (27.8)**	**128 (34.0)**
Hypoglycaemia	0	1 (0.5)	1 (0.5)	1 (0.5)	6 (1.6)	4 (1.1)	3 (0.8)	45 (9.3)	8 (1.7)	7 (1.4)	4 (2.6)	6 (3.8)	10 (6.4)	53 (14.0)	40 (10.6)
Abdominal discomfort	-	-	-	4 (2.2)	1 (0.3)	0	1 (0.3)	0	2 (0.4)	1 (0.2)	-	-	-	-	-
Diarrhoea	3 (1.6)	0	2 (1.0)	3 (1.6)	5 (1.4)	3 (0.8)	5 (1.4)	6 (1.2)	8 (1.7)	13 (2.7)	1 (0.6)	2 (1.3)	4 (2.6)	6 (1.6)	4 (1.1)
Nausea	0	1 (0.5)	3 (1.5)	2 (1.1)	2 (0.5)	5 (1.4)	3 (0.8)	5 (1.0)	6 (1.2)	14 (2.9)	1 (0.6)	1 (0.6)	2 (1.3)	3 (0.8)	5 (1.3)
Thirst	1 (0.5)	2 (1.0)	4 (2.0)	0	0	0	4 (1.1)	0	7 (1.4)	12 (2.5)	0	1 (0.6)	2 (1.3)	-	-
Urinary tract infection	2 (1.0)	4 (2.1)	5 (2.5)	2 (1.1)	11 (3.0)	20 (5.4)	9 (2.5)	8 (1.7)	15 (3.1)	12 (2.5)	3 (1.9)	6 (3.8)	9 (5.8)	7 (1.9)	8 (2.1)
Vulvovaginal infection	3 (1.5)	2 (1.0)	4 (2.0)	0	0	9 (2.4)	5 (1.4)	1 (0.2)	1 (0.2)	9 (1.9)	2 (1.3)	8 (5.1)	8 (5.1)	1 (0.3)	9 (2.4)
Vulvovaginal pruritus	0	1 (0.5)	4 (2.0)	0	1 (0.3)	3 (0.8)	5 (1.4)	1 (0.2)	4 (0.8)	15 (3.1)	0	2 (1.3)	2 (1.3)	0	11 (2.9)
Balanoposthitis/ balanitis	0	0	1 (0.5)	1 (0.5)	1 (0.3)	7 (1.9)	4 (1.1)	2 (0.4)	4 (0.8)	13 (2.7)	2 (1.3)	2 (1.3)	4 (2.6)	1 (0.3)	10 (2.6)
Pollakiuria	1 (0.5)	3 (1.5)	5 (2.5)	1 (0.5)	1 (0.3)	16 (4.3)	9 (2.5)	1 (0.2)	10 (2.1)	11 (2.3)	1 (0.6)	3 (1.9)	4 (2.6)	3 (0.8)	6 (1.6)
Polyuria	0	0	5 (2.5)	0	1 (03)	3 (0.8)	3 (0.8)	2 (0.4)	4 (0.8)	4 (0.8)	1 (0.6)	1 (0.6)	3 (1.9)	-	-
Decreased GFR	-	-	-	0	3 (0.8)	0	4 (1.1)	0	2 (0.4)	4 (0.8)	2 (1.3)	2 (1.3)	4 (2.6)	2 (0.5)	7 (1.9)
Headache	1 (0.5)	3 (1.5)	4 (2.0)	3 (1.6)	0	3 (0.8)	0	4 (0.8)	6 (1.2)	5 (1.0)	0	5 (3.1)	5 (3.2)	3 (0.8)	4 (1.1)
Severe AEs, *n (%)*	**4 (2.1)**	**8 (4.1)**	**2 (1.0)**	**7 (3.8)**	**18 (4.9)**	**15 (4.1)**	**12 (3.3)**	**38 (7.9)**	**24 (5.0)**	**25 (5.2)**	**13 (8.3)**	**7 (4.5)**	**8 (5.1)**	**21 (5.6)**	**24 (6.4)**
Infections	1 (0.5)	4 (2.1)	0	1 (0.5)	4 (1.1)	4 (1.1)	1 (0.3)	7 (1.5)	5 (1.0)	4 (0.8)	3 (1.9)	1 (0.6)	2 (1.3)	5 (1.3)	1 (0.3)
Heart disease	0	1 (0.5)	0	1 (0.5)	5 (1.4)	4 (1.1)	1 (0.3)	10 (2.1)	3 (0.6)	5 (1.0)	2 (1.3)	2 (1.3)	0	4 (1.1)	4 (1.1)
Nervous system disorders	1 (0.5)	0	0	1 (0.7)	1 (0.3)	0	0	1 (0.2)	3 (0.6)	4 (0.8)	0	1 (0.6)	0	3 (0.8)	1 (0.3)
Neoplasms	0	0	0	1 (0.5)	2 (0.5)	0	4 (1.1)	2 (0.4)	0	3 (0.6)	1 (0.6)	0	0	1 (0.3)	3 (0.8)
Severe treatment-related AEs, *n (%)*	**0**	**3 (1.5)**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**	**2 (0.4)**	**2 (0.4)**	**0**	**0**	**0**	**1 (0.6)**	**1 (0.3)**	**0**
Discontinuation related to AEs, *n (%)*	**2 (1.0)**	**6 (3.1)**	**4 (2.0)**	**8 (4.4)**	**16 (4.4)**	**19 (5.2)**	**12 (3.3)**	**28 (5.8)**	**25 (5.2)**	**32 (6.6)**	**7 (4.5)**	**11 (7.0)**	**12 (7.7)**	**11 (2.9)**	**20 (5.3)**
Deaths, *n*	**1**	**1**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**2**	**0**	**0**	**0**	**0**	**2**

* plac, cana, glim, sita = placebo, canagliflozin, glimepiride, sitagliptin

Safety data from studies in special populations

Study DIA3008 (CANVAS)

The primary objective of study DIA3008 was to evaluate the safety and cardiovascular risk of canagliflozin in patients with type 2 diabetes and cardiovascular risk factors (see 8.1.4.3. Patients with cardiovascular risk factors).

These safety data results come from an interim analysis performed at 18 weeks, as the study started in November 2009 with a four-year follow-up period.

In total, 2,888 patients have received at least one dose of canagliflozin.

The percentage of patients with adverse events was 71% (n=1,445) and 73.4% (n=1,441) in the canagliflozin 100 mg and 300 mg groups, and 69.6% (n=1,441) in the placebo group.

These adverse events were treatment-related in 26.9% and 32.5% of patients in the canagliflozin 100 mg and 300 mg groups, and in 17.5% of patients in the placebo group. In the canagliflozin 100 mg and 300 mg groups, they were mainly:

- hypoglycaemia (4.8% and 6.9% respectively versus 4.6% on placebo)
- pollakiuria (3.1% and 4.1% versus 0.7%)
- urinary tract infections (3% and 3.3% versus 1.9%)
- balanitis (2.8% and 2.5% versus 0.6%)
- vulvovaginal infections (2.6% and 2.1% versus 0.3%)

Serious adverse events resulted in treatment being stopped in 4.1% and 6.4% of patients in the canagliflozin 100 mg and 300 mg groups respectively, and in 3.5% of patients on placebo.

The serious adverse event rate was 11.5% and 12.7% in the canagliflozin 100 mg and 300 mg groups, with primarily infections (2.6% and 1.7%) and gastrointestinal disorders (1.5% and 1.0%). These were treatment-related in 1.0% (n=14) and 1.2% (n=17) of patients on canagliflozin 100 mg and 300 mg (including 5 patients with urinary tract infections and 4 patients with renal failure).

Ten deaths occurred in each of the canagliflozin groups, versus 13 in the placebo group. These were not treatment-related and were mainly due to cardiovascular or cerebral events (n=15 patients on canagliflozin).

Study DIA3010 (patients aged 55 to 80 years)

In total, 477 patients aged 55 to 80 years received at least one dose of canagliflozin. These patients were followed up for 26 weeks.

One of the secondary objectives was to evaluate the effect of canagliflozin on bone density. No difference versus placebo was found; however, the exclusion criteria restricted patients with bone disease.

The percentage of patients with adverse events was 71.8% (n=173) and 78.0% (n=184) in the canagliflozin 100 mg and 300 mg groups, and 73.4% (n=174) in the placebo group.

These adverse events were treatment-related in 26.6% and 33.5% of patients in the canagliflozin 100 mg and 300 mg groups, and in 27.4% of patients in the placebo group. In the canagliflozin 100 mg and 300 mg groups, they were mainly:

- hypoglycaemia (7.1% and 4.2% respectively versus 10.5% on placebo)
- pollakiuria (4.2% and 2.1% versus 2.1%)
- urinary tract infections (4.6% and 5.1% versus 1.7%)
- vulvovaginal infections (2.1% and 2.1% versus 0.4%)

Adverse events resulted in treatment being stopped in 2.1% and 7.2% of patients in the canagliflozin 100 mg and 300 mg groups respectively, and in 4.2% of patients in the placebo group.

The serious adverse event rate was 4.1% and 3.4% in the canagliflozin 100 mg and 300 mg groups. These were treatment-related in 1 patient on canagliflozin 300 mg only.

No deaths occurred in this study.

8.2.2 SPC data

"Summary of the safety profile

The safety of canagliflozin was evaluated in 10,285 patients with type 2 diabetes, including 3139 patients treated with canagliflozin 100 mg and 3,506 patients treated with canagliflozin 300 mg, who received medicinal product in nine double-blind, controlled phase 3 clinical studies.

The primary assessment of safety and tolerability was conducted in a pooled analysis (n=2,313) of four 26-week placebo-controlled clinical studies (monotherapy and add-on therapy with metformin, metformin and a sulfonylurea, and metformin and pioglitazone). The most commonly reported adverse reactions during treatment were hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (i.e. urinary volume and frequency). Adverse reactions leading to discontinuation of ≥ 0.5% of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of female patients) and balanitis or balanoposthitis (0.5% of male patients). Additional safety analyses (including long-term data) from data across the entire canagliflozin programme (placebo- and active-controlled studies) were conducted to assess reported adverse reactions in order to identify adverse reactions (see table 1) (see sections 4.2 and 4.4)."

It should be noted that in this pooled analysis, the common adverse effects observed were gastrointestinal disorders (constipation, thirst, nausea), dyslipidaemia and increased haematocrit. The uncommon adverse effects were nervous system disorders (postural dizziness, syncope), vascular disorders (hypotension and orthostatic hypotension), metabolic disorders (dehydration), skin disorders (rash and urticaria), and increased blood creatinine, urea, potassium and phosphate.

"*Adverse reactions related to volume depletion*
In the pooled analysis of the four 26-week, placebo-controlled studies, the incidence of all adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) was 1.2% for canagliflozin 100 mg, 1.3% for canagliflozin 300 mg, and 1.1% for placebo. The incidence with canagliflozin treatment in the two active-controlled studies was similar to comparators.

Hypoglycaemia in add-on therapy with insulin or insulin secretagogues
The frequency of hypoglycaemia was low (approximately 4%) among treatment groups, including placebo, when used as monotherapy or as an add-on to metformin. When canagliflozin was added to insulin therapy, hypoglycaemia was observed in 49.3%, 48.2%, and 36.8% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, and severe hypoglycaemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. When canagliflozin was added to a sulfonylurea therapy, hypoglycaemia was observed in 4.1%, 12.5%, and 5.8% of patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively (see sections 4.2 and 4.5)."

"Special populations"
Patients with renal impairment (eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min)
Patients with a baseline eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min had a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) with incidences of 4.7%, 8.1%, and 1.5% on canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively (see sections 4.2 and 4.4).
Increases in serum creatinine of 10-11% and BUN of approximately 12% were observed with both doses of canagliflozin. The proportion of patients with larger decreases in eGFR (> 30%) at any time during treatment was 9.3%, 12.2%, and 4.9% with canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively."

08.3 Summary & discussion

The request for inclusion of INVOKANA in combination with other antidiabetic drugs is supported by data from seven phase III, randomised, controlled, multicentre, double-blind studies, conducted in patients with type 2 diabetes inadequately controlled by lifestyle and dietary measures with or without an antidiabetic treatment. Two of these seven studies were conducted in special populations (elderly patients or patients with cardiovascular risk factors).
The primary efficacy endpoint used in all these studies was change in HbA1c over predefined periods.

Monotherapy study
Study DIA3005 included 584 patients with a mean age of 55 years, who had had type 2 diabetes for about 4 years, and were randomised to three groups: canagliflozin 100 mg, 300 mg and placebo. Canagliflozin 100 mg and 300 mg was shown to be superior to placebo in terms of change in HbA1c at 26 weeks in treatment-naive patients or patients on OAD monotherapy (48%). The intergroup difference versus placebo was -0.9 (±0.1) for canagliflozin 100 mg (±0.1; 95% CI: [-1.1; -1.3]) and -1.2 for canagliflozin 300 mg (±0.1; 95% CI: [-1.3; -0.99]).
As there is no comparison of canagliflozin with another oral antidiabetic drug, and no knowledge of the oral antidiabetic drug administered before the study, INVOKANA as monotherapy cannot be positioned and evaluated in relation to sulfonylureas; INVOKANA is indicated in patients with an intolerance or contraindication to metformin.

Studies of dual therapy with metformin
Two studies had the primary objective of evaluating canagliflozin in combination with metformin, one versus placebo (study DIA3006) and one versus a sulfonylurea, glimepiride (DIA3009).

Study DIA3006 included 1,284 patients with a mean age of 55 years, who had had type 2 diabetes for almost 7 years, and with a mean HbA1c level of 7.9% on inclusion. These patients were randomised to four groups with a 2:2:2:1 ratio (canagliflozin 100 mg, canagliflozin 300 mg, placebo and sitagliptin 100 mg) for a duration of 26 weeks. The sitagliptin group served as an active comparator for a secondary non-inferiority analysis, which was converted to a superiority study, over a period of 52 weeks.
At 26 weeks, this study showed that canagliflozin 100 mg and 300 mg was superior to placebo in terms of change in HbA1c, with an intergroup difference versus placebo of -0.6 (±0.1; 95% CI:[-0.8; -0.5]) for canagliflozin 100 mg and -0.8 (±0.1; 95% CI: [-0.9; -0.6]) for canagliflozin 300 mg.
The change in secondary endpoints at 26 weeks also favoured canagliflozin 100 mg and 300 mg over placebo, with a response rate (HbA1c < 7.0%) of 45.5% and 57.8% respectively versus 29.8%, and an intergroup difference in weight versus placebo of -2.5 kg (±0.3) and -2.9 kg (±0.3) respectively.
It should be noted that canagliflozin was non-inferior to sitagliptin 100 mg at 52 weeks with a per-protocol intergroup difference of 0.12% (±0.06; 95% CI: [0.01; 0.24]) for canagliflozin 100 mg and -0.03% (±0.06; 95% CI: [-0.15; 0.09]) for canagliflozin 300 mg, using a non-inferiority margin of 0.30%. These results were confirmed in the mITT analysis. In the superiority analysis following the demonstration of non-inferiority, for the 300 mg dose only, the upper limit of the confidence interval was just below 0, meeting the definition of superiority (-0.15; 95% CI [-0.27; -0.03]). This result should be interpreted with caution due to the high percentage of patients (28% in the canagliflozin 300 mg group and 35% in the sitagliptin 100 mg group) who were excluded from the per-protocol analysis.

Study DIA3009 included 1,452 patients with a mean age of 56 years, who had had type 2 diabetes for almost 7 years, and with a mean HbA1c level of 7.8% on inclusion. These patients were randomised to three groups: canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride.
This study showed that canagliflozin 100 mg and 300 mg was non-inferior to glimepiride at 52 weeks, in terms of change in HbA1c, with an intergroup difference versus glimepiride of -0.01 (±0.05; 95% CI: [-0.11; -0.09]) for canagliflozin 100 mg and -0.12 (±0.05; 95% CI: [-0.22; -0.02]) for canagliflozin 300 mg, which was within the non-inferiority upper limit of the 95% confidence interval, set at 0.30.

The change in secondary endpoints at 52 weeks also favoured canagliflozin 100 mg and 300 mg over glimepiride, with 5.6% and 4.9% of patients having hypoglycaemia versus 34.2%, and with an intergroup difference in weight versus glimepiride of -5.2 kg (±0.3) and -5.7 kg (±0.3) respectively. The response rate, an exploratory endpoint, was 53.6% and 60.1% in the canagliflozin 100 mg and 300 mg groups and 55.8% in the glimepiride group.

In summary, these studies showed that canagliflozin 100 mg and 300 mg, in combination with adequate doses of metformin, was superior to placebo, and that both doses were non-inferior to glimepiride (a sulfonylurea) using a non-inferiority margin of 0.30% as per the guidelines. Non-inferiority to sitagliptin 100 mg was demonstrated in a second analysis. In both studies, the reduction in HbA1c between inclusion and 26 or 52 weeks was 0.8% to 0.9% on canagliflozin, starting from a mean baseline HbA1c value that was moderately high (7.8%).
The difference versus placebo in the response rate was 15.7% and 28% for the 100 mg and 300 mg doses respectively at 26 weeks; in the second study, the response rate did not differ much from glimepiride. The change in weight should be interpreted in light of canagliflozin's mechanism of action, as change in weight is accompanied by water loss.[21]

Studies of triple therapy with metformin/sulfonylureas
Two studies had the primary objective of evaluating canagliflozin in combination with metformin/sulfonylureas, one versus placebo (study DIA3002) and one versus a gliptin, sitagliptin (DIA3015).

Study DIA3002 included 469 patients with a mean age of 56 years, who had had type 2 diabetes for almost 10 years, and with a mean HbA1c level of 8.1% on inclusion. These patients were randomised to three groups: canagliflozin 100 mg, canagliflozin 300 mg, and placebo.
At 26 weeks, this study showed that canagliflozin 100 mg and 300 mg was superior to placebo, in terms of change in HbA1c, with an intergroup difference versus placebo of -0.7 (±0.1; 95% CI: [-0.9; -0.5]) for canagliflozin 100 mg and -0.9 (±0.1; 95% CI: [-1.1; -0.7]) for canagliflozin 300 mg.
The change in secondary endpoints at 26 weeks also favoured canagliflozin 100 mg and 300 mg over placebo, with a response rate of 43.2% and 56.6% respectively versus 18%, and an intergroup difference in weight versus placebo of -1.4 kg (±0.4) and -2.0 kg (±0.4) respectively.

Study DIA3015 included 756 patients with a mean age of 57 years, who had had type 2 diabetes for almost 7 years, and with a mean HbA1c level of 8.1% on inclusion. About 33% of patients withdrew from the study, mainly because of failure to reach glycaemic targets during the study. These patients were randomised to two groups: canagliflozin 300 mg and sitagliptin 100 mg.
This study showed that canagliflozin 300 mg was non-inferior to sitagliptin 100 mg at 52 weeks in terms of change in HbA1c levels, with an intergroup difference versus sitagliptin of -0.21 (95% CI [-0.34; -0.08]) in the per-protocol population (95% CI [-0.34; -0.08]). These results were confirmed in the modified ITT analysis. In the superiority analysis following the demonstration of non-inferiority, the upper limit of the confidence interval in the modified ITT population was below 0, meeting the definition of superiority (-0.37; 95% CI [-0.50; -0.25]). This result should be interpreted with caution due to the high percentage of patients (34% in the canagliflozin 300 mg group and 45% in the sitagliptin 100 mg group) who were excluded from the per-protocol analysis.
The change in secondary endpoints at 52 weeks also favoured canagliflozin 300 mg over sitagliptin, with an intergroup difference in weight versus sitagliptin of -2.8 kg (±0.3). The response rate, an exploratory endpoint, was 45.6% in the canagliflozin 300 mg group and 35.3% in the sitagliptin group.

In summary, these studies showed that canagliflozin, in combination with metformin and a sulfonylurea (glimepiride), is superior to placebo; for the 300 mg dose only, they also demonstrated non-inferiority, using a non-inferiority margin of 0.30% as per the guidelines, and then superiority to

[21] Bouhanick B. Nouveautés dans le traitement du diabète de type 2. Les recommandations HAS 2013 et ses points généraux. Une nouvelle classe thérapeutique : les gliflozines [New developments in the treatment of type 2 diabetes. The HAS 2013 guidelines and general points. A new therapeutic category: gliflozins].

sitagliptin 100 mg. It should be noted that a third of patients were excluded from the non-inferiority study, mainly due to failure to reach the glycaemic targets set. It is regrettable that the 100 mg dosage was not evaluated. The change from baseline HbA1c with canagliflozin triple therapy was 0.8% for the 100 mg dose and 1% for the 300 mg dose (at 26 and 52 weeks), starting from an HbA1c value of 8.1%.
The difference in the response rate versus placebo was 25.2% and 38.6% for the 100 mg and 300 mg dosages respectively at 26 weeks; in study DIA3015, this difference was +10% versus sitagliptin.

Studies in special populations (including study of combination with insulin)

Study DIA3010 in patients aged 55 to 80 years
Study DIA3010 included 714 patients with a mean age of 64 years, who had had type 2 diabetes for almost 12 years. These patients were randomised to three groups (canagliflozin 100 mg, canagliflozin 300 mg, and placebo).
This study showed that at 26 weeks, canagliflozin 100 mg and 300 mg alone or in combination with other OADs (primarily metformin and combined metformin/sulfonylurea in 50% of patients) was superior to placebo in terms of change in HbA1c, with an intergroup difference versus placebo of -0.6 (±0.1; 95% CI: [-0.7; -0.4]) for canagliflozin 100 mg and -0.7 (±0.1; 95% CI: [-0.8; -0.6]) for canagliflozin 300 mg.

Study DIA3008 in patients with cardiovascular risk factors
Two substudies of the DIA3008 safety study, conducted in patients at high cardiovascular risk, evaluated the efficacy of canagliflozin versus placebo in combination with sulfonylureas in one substudy and with insulin in the other; these drugs could themselves be combined with other OADs.
In the substudy of combination with sulfonylureas, the number of subjects required was not achieved.

The substudy conducted in combination with insulin (at a dose ≥ 20 IU/day) included 2,072 patients who were randomised to three groups (canagliflozin 100 mg, canagliflozin 300 mg, and placebo). These patients had a mean age of 63 years and had had type 2 diabetes for just over 16 years; the mean HbA1c level on inclusion was 8.3%. Almost two thirds of the patients were obese.
At 18 weeks, this study showed that canagliflozin 100 mg and 300 mg, in combination with insulin, was superior to placebo in terms of change in HbA1c, with an intergroup difference versus placebo of -0.6 (±0.1; 95% CI: [-0.7; -0.5]) for canagliflozin 100 mg and -0.7 (±0.1; 95% CI: [-0.8; -0.7]) for canagliflozin 300 mg.
The change in secondary endpoints at 18 weeks also favoured canagliflozin 100 mg and 300 mg over placebo, with a response rate of 19.8% and 25.8% respectively versus 8.3%, and an intergroup difference in weight versus placebo of -1.7 kg (±0.1) and -2.3 kg (±0.1) respectively.
Efficacy was evaluated in a subpopulation on insulin ≥ 30 IU/day and metformin ≥ 2,000 mg/day (n=432): intergroup difference versus placebo -0.7 (±0.1) and -0.8 (±0.1) for the 100 mg and 300 mg doses respectively ($p<0.001$).

In summary, these studies showed that canagliflozin is superior to placebo in elderly patients, as well as in patients with cardiovascular risk factors in combination with insulin, including in the insulin/metformin subpopulation. Study DIA3008 is the only study evaluating canagliflozin in combination with sulfonylureas or insulin. However, the evaluation of combination with sulfonylureas did not achieve the number of subjects required and cannot be taken into account.
The superiority of canagliflozin in combination with insulin has been evaluated over a shorter period (18 weeks) with a moderate effect size. The percentage of patients who responded seems low and the difference versus placebo is 11.5% for the 100 mg dosage and 17.5% for the 300 mg dosage.
In addition, these evaluations were performed in populations with heterogeneous concomitant OAD treatments.

Adverse effects

An adverse event rate of between 60% and 77% was observed in the clinical studies submitted.
Most events were of mild to moderate intensity. The most frequently reported treatment-related adverse events were hypoglycaemia, vulvovaginal fungal infections, urinary tract infections and pollakiuria/polyuria.
Adverse events related to volume depletion were observed (1.2% for canagliflozin 100 mg and 1.3% for the 300 mg dose): hypotension and orthostatic hypotension, dizziness, dehydration and syncope. These events were more common in the special populations (patients aged 55 to 80 years, moderate renal impairment).
An increase in LDL cholesterol level was found in the clinical studies.

08.4 Planned studies

A risk management plan (RMP) aims to monitor certain safety-related aspects. The risks monitored are:
Important risks: vulvovaginal candidiasis, balanitis/balanoposthitis, urinary tract infections, hypoglycaemia (when combined with insulin or an OAD), volume depletion, bone fractures
Potential risks: renal failure, increased haematocrit, photosensitivity, hypoglycaemia (as monotherapy), misuse
Important missing information: long-term cardiovascular efficacy, use in patients with severe heart failure or severe hepatic impairment, use in pregnant or breast-feeding women, patients aged 10 to 18 years, and patients aged over 85 years

Study DIA3008, evaluating the safety of canagliflozin on major cardiac events in patients with poorly controlled type 2 diabetes who have a high cardiac risk, started in 2009 and should be complete in 2018.
Study DIA4003 aims to evaluate the safety of canagliflozin on renal endpoints in adult patients with poorly controlled type 2 diabetes who also have a high cardiac risk. The results of this study should be available in 2018.
A meta-analysis will be performed from the two studies above.

Finally, the clinical development of a paediatric form is envisaged, with a pharmacokinetic study (DIA1055) that started in 2013 (expected to end in 2015) and a phase III study of the safety of canagliflozin in children and adolescents; the latter should start in 2015 and finish in 2018.

09 THERAPEUTIC USE

The aim of treatment in type 2 diabetes is to reduce morbidity and mortality, particularly through good glycaemic control. According to the 2013 HAS guidelines,[4] the glycaemic target for patients with type 2 diabetes should be set individually based on comorbidities and life expectancy; the target HbA1c ranges from 6.5% to 8%. An HbA1c target ≤ 7% is recommended for most patients. Drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

Monotherapy

According to the HAS guidelines, in general, if the glycaemic target is not met despite lifestyle and dietary measures, monotherapy should be started with metformin as the first-line treatment or, if there are contraindications, with sulfonylureas (if both of these substances are contraindicated, repaglinide or alpha-glucosidase inhibitors are recommended).
As there are no data in patients with contraindications or intolerance to metformin and no data versus the recommended active comparators cited above, canagliflozin monotherapy has no role in the treatment of type 2 diabetes inadequately controlled by lifestyle and dietary measures in this population.

Dual therapy with oral antidiabetic drugs

If the glycaemic target is not achieved with monotherapy, dual therapy is recommended, combining metformin and sulfonylureas as first-line treatment, and monitoring weight and episodes of hypoglycaemia. If sulfonylureas are not tolerated or are contraindicated,[22] metformin may be combined with alpha-glucosidase inhibitors, with DPP-4 inhibitors/gliptins, and with repaglinide. In the clinical studies submitted, in combination with metformin, canagliflozin 100 mg or 300 mg was superior to placebo at 26 weeks and non-inferior to glimepiride at 52 weeks in terms of reduction in HbA1c. In view of these data, canagliflozin is an additional treatment resource, as dual therapy in combination with metformin, from among the oral antidiabetic drugs available when sulfonylureas are not tolerated or are contraindicated.

If metformin is not tolerated or is contraindicated, sulfonylureas may be used in combination with alpha-glucosidase inhibitors and with gliptins. Given the methodological weaknesses of the study submitted for this indication, canagliflozin cannot be recommended as dual therapy with sulfonylureas.

The use of GLP-1 analogues may be considered at the dual therapy stage if BMI is ≥ 30 kg/m² or if weight gain on insulin or episodes of hypoglycaemia give cause for concern.

Triple therapy with oral antidiabetic drugs

If the glycaemic target is not reached despite dual therapy with metformin + sulfonylurea, an alpha-glucosidase inhibitor or a gliptin may be added.
In the clinical studies submitted, in combination with metformin, canagliflozin 100 mg or 300 mg was superior to placebo at 26 weeks. Canagliflozin 300 mg (the maximum dose) was non-inferior to sitagliptin at 52 weeks in terms of reduction in HbA1c. In view of these data, canagliflozin as triple therapy in combination with metformin and a sulfonylurea is an additional treatment resource from among the recommended oral antidiabetic drugs available.

Combined with insulin therapy

Clinicians should assess whether to continue oral antidiabetic drugs based on the expected benefits from each substance. Thus, where applicable, metformin or sulfonylureas may be continued (after adjusting the dose).[23,24,25]
In the clinical studies submitted, canagliflozin was evaluated in combination with insulin as well as with other oral antidiabetic drugs, and the proportion of patients on insulin alone was small (30%). In a subpopulation of this study consisting of patients treated with metformin ≥ 2,000 mg/day and insulin ≥ 30 IU/day, a greater reduction in HbA1c was observed with canagliflozin than with placebo.
Taking into account the difficulties in applying these results to patients on dual therapy with insulin, and the fact that the validated dual therapy combinations are insulin/metformin and insulin/sulfonylurea, the INVOKANA proprietary medicinal products cannot be recommended as dual therapy with insulin.
However, the INVOKANA proprietary medicinal products are an additional resource as triple therapy with insulin and metformin.

It should be reiterated that because of canagliflozin's diuretic action, caution is recommended in patients who could be at risk of a drop in blood pressure: patients with cardiovascular disease, with

[22] if the patient is within 1% of the HbA1c target
[23] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012 Apr 19;344:e1771. doi: 10.1136/bmj.e1771.
[24] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R*, et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia 2009;52(1):17-30.*
[25] Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. http://www.sign.ac.uk/pdf/sign116.pdf

mild or moderate renal impairment, on antihypertensive treatment with a history of hypotension, on diuretics, or aged 65 years and over.

Diabetes is progressive and all aspects of treatment should be re-assessed regularly: lifestyle and dietary measures, health education and drug treatment.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ These proprietary medicinal products are intended as symptomatic treatment of hyperglycaemia in type 2 diabetes.
◗ The efficacy/adverse effects ratio is:

- High as dual therapy with metformin and as triple therapy with metformin/sulfonylurea, in view of the effect size for HbA1c in the clinical studies, which is similar to other recommended oral antidiabetic drugs;
- Modest as triple therapy with metformin and insulin, in view of the methodological weaknesses;
- Unquantifiable:
    - as monotherapy, given the lack of data in the Marketing Authorisation indication;
    - as dual therapy with a sulfonylurea, given the methodological weaknesses in the study;
    - as dual therapy with insulin, given the applicability issues with the results of the study that had a low proportion of patients treated with dual therapy, and the lack of guidelines other than for metformin and sulfonylureas.

◗ Canagliflozin is an additional treatment resource in poorly controlled type 2 diabetes:

- as dual therapy in combination with metformin, as one of the oral antidiabetic drugs available, if sulfonylureas are not tolerated or are contraindicated;
- as triple therapy in combination with metformin and sulfonylureas, as one of the recommended oral antidiabetic drugs available;
- as triple therapy in combination with metformin and insulin.

As monotherapy, canagliflozin has no role in the treatment of type 2 diabetes that is inadequately controlled by lifestyle and dietary measures, since there are no data versus active comparators in the Marketing Authorisation population (patients with an intolerance or contraindications to metformin).
Canagliflozin cannot be recommended as dual therapy with sulfonylureas or insulin, due to methodological weaknesses in the studies supplied and problems with applicability.
◗ There are treatment alternatives to this proprietary medicinal product.

◗ Public health benefit:

The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications. The public health burden in the subpopulation of patients with each of the indications for INVOKANA is considered to be moderate.
Improving the therapeutic management of type 2 diabetes patients is a public health need which is an established priority (objective 55 of the Public Health Policy Law of 9 August 2004, National Plan for Improving the Quality of Life of Patients with Chronic Diseases 2007-2011). Access to effective treatments which are well tolerated in type 2 diabetes patients is a public health need.
In view of the results of the clinical studies performed across all indications, no additional impact on glycaemic control is expected from the proprietary medicinal product INVOKANA. Moreover, the impact of INVOKANA on morbidity/mortality and quality of life in patients with type 2 diabetes, compared with currently available treatments, cannot be assessed from the

data available; and due to frequent safety issues particularly in the form of genitourinary infections, a negative impact from INVOKANA cannot be ruled out.
INVOKANA is not expected to have any impact on the organisation of care.
In addition, it is unclear whether the experimental data are applicable to clinical practice because of uncertainties about the long-term effect of this treatment including its effect on glycaemic control.
In the current state of knowledge, the proprietary medicinal product INVOKANA offers a partial response to the identified public health need.
It is therefore not expected that the proprietary medicinal product INVOKANA will impact public health in all its Marketing Authorisation indications.

Taking account of these points, the Committee considers that the actual benefit of INVOKANA is:

- **Insufficient as monotherapy**
- **Substantial as dual therapy in combination with metformin**
- **Insufficient as dual therapy in combination with sulfonylureas or insulin**
- **Substantial as triple therapy in combination with metformin and a sulfonylurea**
- **Moderate as triple therapy in combination with metformin and insulin**

In the indications as dual therapy with metformin, and as triple therapy with metformin and a sulfonylurea or insulin:
The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use at the dosages in the Marketing Authorisation.

◗Proposed reimbursement rate: 65%

In the indications as monotherapy, and as dual therapy with sulfonylureas or insulin:
The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

010.2 Improvement in actual benefit (IAB)

In the indications as dual therapy with metformin, and as triple therapy with metformin and a sulfonylurea or with metformin and insulin:
Taking into account the evidence that canagliflozin is non-inferior to its active comparators, the lack of evidence of its superiority to sitagliptin for the 100 mg dosage, and the lack of long-term safety data, the Committee considers that the INVOKANA proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of patients with poorly controlled type 2 diabetes, as dual oral therapy in combination with metformin and as triple therapy in combination with metformin and a sulfonylurea or in combination with metformin and insulin.

In the indications as monotherapy, and as dual therapy in combination with sulfonylureas or insulin:
Not applicable.

010.3 Target population

The target population corresponds to patients with type 2 diabetes poorly controlled on metformin, if sulfonylureas are contraindicated, or poorly controlled on metformin/sulfonylurea or metformin/insulin dual therapy.
The target population for INVOKANA was calculated from data from the Echantillon Généraliste des Bénéficiaires (EGB) (a representative sample of individuals covered by National Health Insurance) and from the Cegedim Longitudinal Patient Data (LPD) panel.
In 2012, 26,308 diabetic patients were identified from the EGB, i.e. 2,943,147 after extrapolation to the whole of France. According to the ENTRED 2007-2010 study, 91.9% of diabetic patients have type 2 diabetes. The number of patients with type 2 diabetes in France is therefore 2,714,292. The number of patients treated with:

- metformin monotherapy is 702,905, of whom 8%, namely 56,232 patients, have hypoglycaemic episodes, i.e. an intolerance, on sulfonylureas (HAS 2006 study);
- metformin/sulfonylurea dual therapy is 274,733;
- triple oral therapy (likely to be the source population for patients treated with insulin therapy) is 261,741.

The Cegedim LPD panel consists of longitudinal data collected from a representative sample of private doctors in France. 4,208 patients in this database were on oral metformin monotherapy, and 19.4% of these had an HbA1c > 7%.
Similarly, 1,486 patients were on metformin/sulfonylurea dual therapy with 45.4% having an HbA1c < 7.0%. This percentage rises to 56.2% for patients on triple oral therapy.
Therefore, on the basis of these data, the number of patients in France inadequately controlled on metformin monotherapy with an intolerance to sulfonylureas is 10,185, with 124,795 inadequately controlled on metformin/sulfonylurea dual therapy and 147,098 on metformin/insulin.

The target population is estimated as 282,078 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

1 APPENDIX

INN	Name (Company)	Date of opinion	AB	IAB	Reimbursed
Biguanide					
Metformin and its generics	GLUCOPHAGE (Merck Santé)	21 July 2010 (RI)	Substantial		Yes
Insulin secretagogues					
Sulfonylureas and their generics			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (RI)	Substantial		Yes
Repaglinide	NOVONORM (Novo Nordisk)	21 July 2010 (RI)	Substantial		Yes
Injectable incretin mimetic or GLP-1 analogues (not indicated as monotherapy)					
Exenatide	BYETTA (Bristol-Myers Squibb)	28 February 2007	Substantial as dual therapy in combination with metformin or a sulfonylurea	-	Yes
			Under assessment as dual therapy with insulin and as triple therapy with insulin + metformin		
Liraglutide	VICTOZA (Novo Nordisk)	2 December 2009	Substantial as dual therapy in combination with metformin or a sulfonylurea	IV	Yes
Lixisenatide	LYXUMIA (Sanofi Aventis)	*Under assessment by the TC*			
Gliptins					
Sitagliptin and its fixed-dose combinations with metformin	JANUVIA 100 mg/ XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012	Insufficient as monotherapy	-	
		6 June 2007	Substantial as dual therapy in combination with metformin	IV	Yes
		24 June 2009	Low as dual therapy in combination with a sulfonylurea	V	Yes
		18 July 2012	Insufficient as dual therapy in combination with insulin	-	No
		18 July 2012	Substantial as triple therapy in combination with insulin and metformin	V	Yes
Vildagliptin and its fixed-dose combinations with metformin	GALVUS/JALRA (Novartis Pharma)[26]	21 Nov. 2012	Insufficient as monotherapy	-	
		10 December 2008	Substantial as dual therapy in combination with metformin or a sulfonylurea	V	Yes

[26] On 20 September 2012, vildagliptin-based proprietary medicinal products received a favourable opinion from the CHMP in the following extension of indication: “in combination with insulin, with or without metformin, when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.”

INN	Name (Company)	Date of opinion	AB	IAB	Reimbursed
Saxagliptin and its fixed-dose combination with metformin	ONGLYZA (Bristol-Myers Squibb)[27]	2 December 2009	Substantial as dual therapy in combination with metformin or a sulfonylurea	V	Yes
		15 May 2013	Insufficient as dual therapy in combination with insulin	-	No
			Low as triple therapy in combination with insulin and metformin	V	Yes
Linagliptin and its fixed-dose combination	TRAJENTA (Boehringer Ingelheim)[28]	20 June 2012	Insufficient as monotherapy	-	No
			Substantial as dual therapy in combination with metformin	V	
		20 March 2013	Insufficient as dual therapy in combination with insulin	-	
			Substantial as triple therapy in combination with insulin and metformin	V	
Sodium-glucose co-transporter 2 inhibitors					
Dapagliflozin	FORXIGA	23 April 2014	Insufficient as monotherapy		No
			Moderate as dual therapy in combination with metformin	V	
			Insufficient as dual therapy in combination with insulin		
			Moderate as triple therapy in combination with insulin and metformin	V	

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[27] Not indicated as monotherapy
[28] Not indicated as dual therapy in combination with a sulfonylurea