THE DENTAL AND
PHARMACEUTICAL BENEFITS AGENCY

Health technology assessment report in support of county council decision-making

FreeStyle Libre

Method for self-monitoring of glucose level in people with type 1 and 2 diabetes treated with basal insulin in combination with mealtime insulin or who are using an insulin pump

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TLV's medical device commission

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) conducts health technology assessment of selected medical devices. TLV does not make any decision regarding the assessed device, but prepares health technology assessment reports to provide a basis for decisions made by the county councils.

TLV's health technology assessments are conducted at the request of the NT Council (The New Therapies Council), which provides recommendations to county councils based on the health technology assessment reports provided by TLV.

The health technology assessment report provided by the Swedish Dental and Pharmaceutical Benefits Agency has been developed in accordance with TLV's general guidelines and other established economic methods.

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TLV's assessment and summary

- Diabetes is a condition that leads to high blood glucose levels (hyperglycemia) due to a malfunction in the body's ability to produce or handle the hormone insulin. The most common forms of diabetes are type 1 and type 2 diabetes.
- A person with type 1 diabetes is normally treated with basal insulin in combination with fast-acting mealtime insulin. There are approximately 48,000 people with type 1 diabetes in Sweden, of which roughly 7,000 are children.
- Approximately 40,000 people with type 2 diabetes are like those with type 1 diabetes treated with a combination of basal and mealtime insulin.
- TLV assesses the severity of type 1 and type 2 diabetes that is treated with a combination of basal and mealtime insulin as moderately high.
- In order to adjust the insulin according to current glucose level, those with type 1 diabetes or insulin treated type 2 diabetes are recommended to monitor their glucose level on a regular basis. A person who often needs to monitor the glucose level can use a continuous glucose monitor instead of a blood glucose test strip.
- TLV assesses that people with diabetes who are treated with basal and mealtime insulin and who have a clinical picture where it is recommended that they screen their glucose levels at least ten times per day can benefit just as much from glucose monitoring regardless what type of diabetes they suffer from. Therefore, TLV assesses that the cost-effectiveness analysis can apply to those with type 1 or type 2 diabetes treated with a combination of basal and mealtime insulin.
- *FreeStyle Libre* is a sensor-powered system for continuous glucose monitoring which is CE certified for adults with diabetes and for children with diabetes aged 4 to 17 under adult supervision.
- The company's health economic model is based on two clinical studies and a quality of life measurement in the form of a so called time-trade-off-study (TTO-study).
- TLV assesses that the company's clinical studies indicate that glucose monitoring with *FreeStyle Libre* leads to shorter times in hypoglycemia, fewer hypoglycemic episodes and reduced glucose variability for people with type 1 and type 2 diabetes.
- The company's cost-effectiveness analysis is primarily driven by the quality of life gain of 0.03, obtained from the TTO-study performed by the company. The aim of the study is to quantify the quality of life gain as a result of glucose monitoring with *FreeStyle Libre* compared to test strips.
- TLV assesses that the comparison alternative used by the company, self-monitoring with glucose test strips, is a relevant comparator. In the company's base-case scenario it is assumed that a person with diabetes monitors blood glucose with test strips 5.4 times per day.
- In the company's base-case scenario the cost per quality-adjusted life years (QALYs) is SEK 291,000 for people with type 1 diabetes.
- TLV assesses that those who benefit the most from glucose monitoring with *FreeStyle Libre* are those who are recommended to monitor their glucose levels often. Hence, TLV has based its base-case scenario on the assumption of ten blood glucose measurements per day.
- TLV assesses that the results from the company's TTO-study are uncertain. However, clinical adherence to glucose monitoring with *FreeStyle Libre* and results from other

TTO studies that have quantified quality of life parameters that are not directly health related motivate a quality of life gain of 0.01.

- TLV also assesses that there is evidence to suggest that people with type 1 diabetes who monitor blood glucose with *FreeStyle* Libre gain a small but clinically relevant decrease in HbA1c. Thus, TLV's base-case scenario makes the assumption that such a glucose monitoring results in a HbA1c decrease of 0.3 percent points. TLV assesses that one can assume that the analysis can also apply to people with type 2 diabetes who are treated with basal and mealtime insulin.
- In TLV's base-case scenario the cost per QALY is SEK 389,000. TLV bases its estimates on a product cost of SEK 13,000 per year for *FreeStyle Libre* and a product cost of SEK 7,300 per year for blood glucose monitoring with test strips (SEK 2 per test strip).
- The cost per QALY in TLV's cost-effectiveness analysis is primarily based on estimated number of used test strips per day and on what level the quality of life gain is presumed to be.
- The uncertainties regarding the results mainly stem from how many test strips are actually used per day and how large the quality of life gain is presumed to be.

The conclusions in this health technology assessment may change if the preconditions underlying the assessment change in any substantial manner.

Table of content

1 Medical background

1.1 Diabetes mellitus

Diabetes mellitus (diabetes) is the common name of conditions that lead to high blood glucose levels (hyperglycemia) due to a malfunction in the body's ability to produce or handle the hormone insulin. Insulin is produced in the pancreas and is necessary for the body's cells to absorb energy in the form of glucose from food or glucose that has been stored in the liver. The most common forms of diabetes are type 1 and type 2 diabetes [1].

Type 1 diabetes is an autoimmune condition that causes the insulin producing cells in the pancreas to be destroyed by the own immune system thus preventing the body from producing insulin. The onset of type 1 diabetes often takes place in childhood or adolescence and treatment with insulin is lifelong. A person with type 1 diabetes is generally on an insulin regimen with a long-acting insulin as a base and a rapid-acting mealtime insulin in order to cut the blood sugar elevation in connection to food intake. Insulin supply can also take place with the use of an insulin pump where the dosage is controlled by the user based on glucose monitoring and experience. There are roughly 48,000 people with type 1 diabetes in Sweden, of which approximately 7,000 are children [2, 3].

Type 2 diabetes is a condition where the cells have become less sensitive to insulin (*insulin resistance*) at the same time as the insulin production in the pancreas has decreased. There are roughly 400,000 people with type 2 diabetes in Sweden, of which the majority are over 60 years old [2]. At the onset of the condition, hyperglycemia can in many cases be kept under control with life style changes and tablet treatment. However, approximately half of those with type 2 diabetes need treatment with insulin after ten years [1]. There are roughly 40,000 insulin treated people with type 2 diabetes who are treated with both mealtime insulin and basal insulin in a regimen that is similar to that for people with type 1 diabetes[2-4].

In order to, among other things, assess the risk of complications as a result of the diabetes condition, the patients monitor the level of HbA1c, a glucose sensitive protein in the blood;. The level of HbA1c is correlated to the average glucose level during the past six to eight weeks. HbA1c is also a *surrogate measurement* (an indicator) for primarily the risk of developing small-vessel disease but also to some extent for large-vessel disease, both of which are long-term complications of hyperglycemia in diabetes conditions [5]. The unit used for HbA1c in Sweden is mmol/mol (IFCC unit). For instance, in the USA and in many scientific publications the unit percent (DCCT-unit) is used instead.

The goal of diabetes treatment is to achieve as low HbA1c level as possible without obtaining adverse effects from blood glucose decreasing drugs. *The treatment goal* (the aimed HbA1c level) is adjusted according to individual conditions. With type 1 diabetes a value of <52 mmol/mol is considered indicative [1].

1.2 Self-monitoring of glucose level

Insulin treatment entails a risk of acute episodes of low blood glucose (hypoglycemia). Mild hypoglycemia can manifest itself as only a feeling of discomfort or concentration difficulties and can be rectified with an intake of carbohydrates. Serious hypoglycemia, on the other

hand, leads to decreased awareness and requires assistance in order to treat it. If left untreated, serious hypoglycemia can lead to death.
According to systematic overviews, roughly a third of those with type 1 diabetes suffer at least one serious hypoglycemia per year [6, 7]. Furthermore, according to a British prospective study the risk of serious hypoglycemia with type 1 diabetes increases with the duration of the disorder. Of the people who have had diabetes for less than five years 22 percent experienced one or several serious hyperglycemias per year compared to the 46 percent of those who had been suffering from diabetes for fifteen years or longer [8].

With the help of self-monitoring of glucose, insulin doses, physical activity and carbohydrate intake can be adjusted so that the risk of hypoglycemia decreases [9]. The marker for median glucose level, HbA1c, usually improves with regular and frequent glucose monitoring in insulin treated people with diabetes [10, 11].

The recommended number of measuring times per day varies depending on, among other things, metabolic monitoring and age. The recommendation in for example Stockholm county council is at least four and up to ten or more measuring times per day for adults with insulin treated diabetes [12]. However, since glucose monitoring can be inconvenient and time consuming it is common that people with diabetes are not able to measure their glucose level to the recommended extent. For example, less than half of the participants in a Swedish survey said that they self-monitore their glucose level at least four times per day [13].

Self-monitoring can be done using different methods, as presented below.

Finger-stick - self-monitoring of blood glucose (SMBG)
Self-monitoring of blood glucose can be done through the transfer of a drop of blood to a test strip after pricking the finger with a lancet. After that the test strip is analysed in a blood glucose meter. Hereinafter this method is referred to as SMBG.

Continuous glucose monitoring (CGM system)
The glucose level can also be monitored continuously with a CGM system where the sensor is attached to the subcutaneous tissue. Most manufacturers' CGM systems consist of a replaceable sensor that is usually attached to the abdomen together with a transmitter and a receiver that shows the glucose value on a display. A CGM system is primarily used by people with type 1 diabetes who are in need of more frequent glucose level monitoring. Many systems have an alarm function if the glucose level should become too low or high [14]. Most CGM systems also require daily calibration with blood glucose monitoring with SMBG. One exception is *FreeStyle Libre*.

The accuracy of the CGM systems is assessed based on how much an analysed test differs from the same test analysed with SMBG, so called *mean absolute relative difference* (MARD) and is expressed in percent. The test results that are obtained with the CGM systems are less precise than those that are obtained with SMBG [15]. One reason for this is that the CGM systems measure the glucose levels in the tissue between the cells (interstitium) while SMBG measures the glucose levels inside the cells. The glucose level in the interstitium is affected more slowly than the intracellular glucose level. This means that the CGM systems show the values with a few minutes delay when there are rapid changes. However, even with stable values the CGM systems' measurements are less precise than measurements with SMBG [14, 16].

FreeStyle Libre

FreeStyle Libre is a sensor-based system for glucose monitoring. *FreeStyle Libre* is CE certified for two age groups of people with diabetes; adults and children aged 4-17 under adult supervision. *FreeStyle Libre's* sensor is worn on the arm [14]. The glucose level is read with the help of a hand unit. On the hand unit there is a screen that shows the current glucose level. A mobile phone can function as a hand unit. *FreeStyle Libre* lacks an alarm function.

FreeStyle Libre's sensor can store measurement values for up to eight hours and the measurement values are transferred over the to the hand unit when read (flash) and the hand unit can store data for up to three months. From the hand unit data can be transferred to wireless software or cable and be saved. When more than eight hours pass between readings, data corresponding to the time that exceeds eight hours is lost.

According to *FreeStyle Libre* manufacturer, approximately 36,000 people with diabetes in Sweden are currently monitoring glucose with this method, of which the majority have type 1 diabetes and roughly 2,000 people have type 2 diabetes and are treated with basal insulin and mealtime insulin in a regimen that is similar to what is usually prescribed for people with type 1 diabetes.

1.3 Treatment and degree of severity

Current treatment recommendations

1.3.1 According to the National Board of Health and Welfare's national guidelines for diabetes care (2015) *all* people with type 1 or type 2 diabetes who are treated with insulin are offered self-monitoring of glucose levels with SMBG (priority 1)[1] [17]. Glucose monitoring with a CGM system *may* be offered to people with type 1 diabetes who have recurring hypo- or hyperglycemia (priority 5). There are according to the treatment recommendations no evidence that people who achieve the treatment goal benefit from continuous glucose monitoring (priority 9). The National Board of Health and Welfare's guidelines do not include glucose monitoring with CGM system for people with type 2 diabetes [17].

1.3.2 The national program council for diabetes in Sweden's municipalities and county councils (SKL) recommends in its care program that the use of CGM systems should be considered for, among other things, recurring problems with hyper- and hypoglycemia, hypoglycemic unawareness, difficulty achieving the treatment goal, recommendation about frequent blood glucose monitoring and pronounced anxiety and fear of hypoglycemia.

Degree of severity for the condition

In previous decisions TLV has assessed that the degree of severity for type 1 diabetes and insulin treated type 2 diabetes is moderately high[2]. TLV makes the same assessment in this material.

In the light of the current investigation involving a method for glucose monitoring, TLV has also identified subgroups in the total diabetes population whose clinical picture may motivate a higher priority according to the need and solidarity principle when distributing resources for glucose monitoring. The subgroups that are believed to be suitable for prioritisation are

[1]The National Board of Health and Welfare's national guidelines serve as support for prioritisation and provides guidance about what treatments and methods different operations in care and welfare should invest resources into.
[2] See e.g. TLV's decision with registration number 4075/2017.

those that have further need of frequent glucose monitoring compared to the total diabetes population and they are presented below.

Children with type 1 diabetes have in addition to the long expected lifetime of a treatment-demanding condition also a therapeutic interval for insulin that is hard to predict during growth, which requires more frequent glucose level monitoring.

Among those with type 1 diabetes and mealtime insulin treated type 2 diabetes there are people who have developed so called *hypoglycemic unawareness* (20-40 percent of the people)[6]. That means that the body no longer has the ability to recognize the symptoms of an approaching hypoglycemia, which in combination with insulin treatment may be a life threatening condition. People who have developed hypoglycemic unawareness must rely on frequent glucose monitoring in order to avoid serious hypoglycemias.

Beyond that, people with type 1 or type 2 diabetes who *despite optimal insulin treatment with basal and mealtime insulin cannot achieve the treatment goal* risk both long term complications due to vascular damaging effects caused by the hyperglycemia and acute complications due to intensified insulin treatment. For this subgroup, more frequent monitoring of the glucose level may help the person achieve the treatment goal through an intensified insulin regimen without being affected by more hypoglycemias.

TLV's assessment: TLV assesses that the degree of severity for insulin treated diabetes is moderately high, but that the need for frequent glucose monitoring - not to be confused with the number of actual glucose measurements per day - is relevant when prioritising resources for glucose monitoring.

TLV assesses that children and people with insulin treated diabetes who have developed hypoglycemic unawareness or who despite adhering to their insulin regime have not achieved the treatment goal have a greater need and would most likely benefit more from regular and frequent glucose monitoring than other people with diabetes.

1.4.1

1.4 Clinical effect

TLV has evaluated scientific studies that involve structured blood glucose monitoring with SMBG, CGM systems in general and *FreeStyle Libre* in particular as well as real world data (RWD) for *FreeStyle Libre* on a local and global level. One should take into consideration the fact that the majority of the scientific studies that are available, like local available RWD, have been conducted mainly on people with type 1 diabetes.

Clinical studies

The company that manufactures *FreeStyle Libre* has performed two clinical studies, IMPACT and REPLACE, where the effect on metabolic and hypoglycemic parameters has been evaluated. Both studies have been published in scientific journals during 2016 and 2017 [20, 21]. The studies were performed at several (>20) diabetes centres in Europe but with one common laboratory for HbA1c analysis. Karolinska University Hospital participated in the IMPACT study.

The control groups measured blood glucose with SMBG. Thus, blinding and placebo control were not possible. In order to obtain baseline values for glucose parameters measured with

FreeStyle Libre and comparable values at the end of the study from the control group, the control group also wore a *FreeStyle Libre sensor*, whose measurements were concealed to the test subject, during the study's first two weeks and last two weeks. Table 1 presents an overview of the studies.

Table 1. Overview randomised clinical studies, FreeStyle Libre

Study	Study design	Study population	Study period	Intervention/ control group (N)	Comparison alternatives	Primary outcome
IMPACT	Randomised non-masked prospective	Adult patients with well controlled type 1 diabetes	six months	119/120	SMBG	Time in hypoglycemia
REPLACE	Randomised open prospective	Adult patients with poorly controlled type 2 diabetes (insulin treated) and long diabetes duration	six months	149/75	SMBG	HbA1c

IMPACT study

The study's primary outcome was time in hypoglycemia. Secondary outcomes were among other things HbA1c and the number of hypoglycemic episodes. The main results are presented in table 2.

Table 2. Main results after six months

	FreeStyle Libre (n=119)	SMBG (n=120)	p-value
Time in hypoglycemia/day	-1.39 hours	-0.14 hours	P=<0.0001
Number of hypoglycemias/day (≤3.9 mmol/l)	1.32 (SD 0.81)	1.69 (SD 0.83)	P=<0.0001
Number of nightly hypoglycemias/day (≤3.1 mmol/l)	0.19	0.3	P=0.005
HbA1c	7.2 mmol/l	7.2 mmol/l	0.9543
Number of serious hypoglycemias during the study period (number of patients)	2 (2)	4 (3)	

Both the intervention group and the control group consisted of persons with well controlled type 1 diabetes (HbA1c ≤ 58 mmol/l) and had a comparable composition at the baseline. Glucose variability, measured as the coefficient for variation (CV) decreased by 4.4±1.3 percent (p=0.0001) in the intervention group. There were no statistically significant differences in self-reported quality of life between the groups (*Diabetes quality of life* (DQoL), *hypoglycemia fear behaviour* and *diabetes distress*) but the group that measured glucose with *FreeStyle Libre* were more satisfied with their treatment ("treatment satisfaction", p=<0.0001).

TLV's assessment of the IMPACT study

The intervention group had a significantly shorter time in hypoglycemia (primary outcome) compared to the control group after the treatment period. What value can be attributed to this difference is hard to asses. There is currently a lack of consensus regarding what, if any, effects that decreased time in asymptomatic hypoglycemia entail [22], even though certain assumptions can be made. One such assumption is that decreased time in hypoglycemia without concurrently increased concentration of HbA1c (such as in the current study) reflects a decreased glucose variability. The decreased coefficient for variation, as the study has shown, provides further support for the method having contributed to decreased variability. There are studies that hint at a connection between glucose variability and the risk of

atherosclerosis in people with type 1 diabetes as well, whose HbA1c is kept at the target value [1] [23-26], which is why TLV assesses that the results are noteworthy.

The monitoring with *FreeStyle Libre* at the baseline showed an average of 1.81 hypoglycemic episodes per day while the participants themselves said that they only experienced 1.18 such episodes per week. Since self-reporting of symptomatic hypoglycemia was not documented at the end of the study period this complicated the assessment of the decrease in the secondary outcome of the number of hypoglycemic episodes. Just as for time in hypoglycemia there is no consensus surrounding the significance of mild symptomatic hypoglycemia. Such hypoglycemias were not for example believed to be connected to cardiovascular disease in a study from 2013 [27].

The REPLACE study

The study's primary outcome was HbA1c. Secondary outcomes were among other things effects on hypoglycemia. The main results are presented in table 3.

Table 3. Main results after six months

	FreeStyle Libre (n=149)	SMBG (n=75)	p-value
HbA1c	−0.27 % (± 1,01)	−0.41 % (± 0,99)	p=0.08222
Time in hypoglycemia (≤3.9 mmol/l) hours/day (SD)	−0.61 (± 0,081)	−0.14 (± 0,112)	p=<0.001
Number of hypoglycemias/day (≤3.9 mmol/l)(SD)	-0.24 (± 0,039)	−0.08 (± 0,054)	p=0.0164
Number of nightly hypoglycemias/day (≤3.9 mmol/l) (SD)	−0.35 (± 0,07)	0.06 (± 0,09)	p=0.0003
Number of serious hypoglycemias during the study period (number of patients)	3 (3)	1(1)	

Both the intervention group and the control group consisted of persons with insulin treated type 2 diabetes with unsatisfactory metabolic control (HbA1c ≥ 7.5 percent (58 mmol/mol) but ≤ 12 percent (108 mmol/mol), high Body Mass Index (BMI) and long term disorder). The glucose variability, measured as the coefficient for variation (CV) also decreased with 2.26 percent ±0.71 percent (p=0.0017). There were no statistically significant differences in the self-reported questionnaires between the groups (*Diabetes quality of life* (DQoL), *hypoglycemia fear behaviour* and *diabetes distress*) but the group that measured glucose with *FreeStyle Libre* was more satisfied with the treatment ("total treatment satisfaction" p=<0.0001).

TLV's assessment of the REPLACE study

The primary outcome, HbA1c, decreased in both the intervention and the control group but no significant difference was noted. One possible interpretation is that the study population's problem to achieve the target value is improved by increased regularity in glucose monitoring, regardless of monitoring technique, and that participation in the study has lead to a higher frequency of glucose monitoring, even with SMBG.

The population that was studied, which had been selected to represent those with insufficient metabolic control for type 2 diabetes, does not appear to correspond to any representative part of the insulin treated type 2 population in Sweden. The average age (59 years) in relation to the duration of the disorder (17 years) in the study population can be compared to Swedish data from the National Diabetes Register (NDR) from 2015 where the average age among

insulin treated type 2 diabetics was 73. In the subgroup of type 2 diabetics in NDR who despite insulin treatment had high HbA1c levels (>70 mmol/mol) the average age was 70.5 years [2]. In Sweden, half of those who suffer from type 2 diabetes are estimated to need insulin treatment after ten years [1].

TLV's assessment of the clinical studies

IMPACT and REPLACE have shown that measured time in hypoglycemia and the number of measured hypoglycemic episodes decreased significantly with glucose measurement with *FreeStyle Libre*. HbA1c did not significantly decrease in any of the studied total populations.

The value of the statistically significant findings in both studies is hard to interpret since there is a lack of scientific consensus for the clinical importance of elapsed time in measured hypoglycemia and the number of measured hypoglycemic episodes that are not correlated to the number of symptomatic hypoglycemic episodes in persons with a preserved ability for hypoglycemic awareness. Thus, TLV assesses that the degree of uncertainty of the results is moderately high to high.

TLV assesses that the studies show that the people prefer to do glucose monitoring with *FreeStyle Libre* compared to SMBG (total treatment satisfaction).

Non-randomised studies

1.4.2 The investigation has identified eight published or conference presented interventional or observational studies that have evaluated the efficacy of *FreeStyle Libre* (four studies [28-31]) or monitoring accuracy (four studies [14, 32, 33]). The studies are presented in table 4.

Table 4. Interventional and observational studies

Study Publication **Authors**	**Control group**	**Population**	**Number of patients**	**Length**	**Outcomes**	**Result**
Flash Glucose Monitoring Improves Outcomes in a Type 1 Diabetes Clinic [Letter] *J Diabetes Sci Technol July 26, 2016* **Dover et al.**	The patient serves as his or her own control	Adults with type 1 diabetes. Eight had pump, the remaining had injection	25	16 weeks	HbA1c and quality of life parameters (Diabetes Distress Scale).	The average value for HbA1c dropped from 8.0 ± 0:14% to 7.5 ± 0.14% (-0.48%, P = .001) There was also a decrease in the average value in the Diabetes Distress Scale (P= .006), emotional burden (P=.035) and regimen-related distress subscores (P= .005).
Improvement in Glucose Control in Difficult-to-Control Patients with Diabetes Using a Novel Flash Glucose Monitoring Device [Letter] *Journal of Diabetes Science and Technology 1–2 © 2016* **Maya Ish-Shalom et al.**	The patient serves as his or her own control	Adults with type 1 or type 2 diabetes with a disorder that is difficult to control (HbA1c over 58 mmol/mol)	31	8 weeks respectively 24 weeks	HbA1c	HbA1c decreased with -1.33 ± 0.29% after 8 weeks (mean ± SE, P <.0001). The change still remained after 24 weeks, -1.21 ± 0.42% (P=.009)
Flash glucose monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre [Letter] *Diabet Med 2017;34:732* **McKnight JA and Gibb FW.**	Patients who measures blood glucose with SMBG	Adults with type 1 diabetes; HbA1c median 7.7% FSL. 8.0% SMBG, 29-51 years old	169/177	Not known	HbA1c	Patients who measured glucose with FreeStyle Libre achieved a decrease in HbA1c of 0.2% while those who measured with SMBG had an increase if HbA1c of 0.1% after the study period.
Flash Glucose monitoring in non-compliant children and adolescents with type 1 diabetes [Abstract] *Diabetes Technol Ther 2017; A-83* **Tirelli E, Frontino G, Favalli V et al.**	The patient serves as his or her own control	Pediatric patients with type 1 diabetes, age (SD): 14 (4.1) years old	13	12 weeks	HbA1c and number of measurements per day	The median value of HbA1c dropped an average of 15 mmol/mol (p<0.001). Average number of SMBG per day before the study: 1.7 (± 1.3), average number of readings per day with *FreeStyle Libre* during the study: 10.7 (± 6.6).

Clinical accuracy evaluation of *FreeStyle Libre* flash glucose monitoring system when used by children and young people with diabetes [Abstract] *Abstracts from ATTD 2016 9th International Conference* **F. Campbell et al.**	The patient serves as his or her own control	Paediatric patients with type 1 diabetes, 4-19 years old	87	One month	Measuring accuracy and safety	83.8% of the measurements within error grid zone A, >99% of the results in zone A&B (clinically acceptable measurement values)
A clinical trial of the accuracy and treatment experience of the flash glucose monitor *FreeStyle Libre* in persons with type 1 diabetes [Abstract]. *EASD Abstract #856, 2016* **Olafsdottir et al.**	The patient serves as his or her own control	Adults with type 1 diabetes	56	10-14 days	Measuring accuracy and user experience	FSL had a similar MARD** as CGM systems in previous studies during outpatient conditions.
Head-to-head comparison between flash and continuous glucose monitoring systems in outpatients with type 1 diabetes. *J Endocrinol Invest. 2016 Jun 10* **Bonora et al.**	The patient serves as his or her own control	Adults with type 1 diabetes	8	14 days	Concordance between FSL and Dexcom G4 Platinum	Good correlation between FSL and DG4 (r 2 = 0.76; MARD = 18.1 ± 14.8%), large variability between patients. MARD significantly higher day 11-14 compared to day 1-10 and during hypoglycaemia (19%), than during hyperglycaemia (13%)
The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System *Diabetes technology & therapeutics Volume 17, Number 11, 2015* **Bailey et al.**	The patient serves as his or her own control	Adults with type 1 or type 2 diabetes	75	14 days	Measuring accuracy and usability	MARD 11.4% 86.7% of sensor measurements in consensus Error Grid Zone A.

TLV's assessment of the non-randomised studies

The clinical observational studies that have examined the effect on HbA1c during glucose measurements with *FreeStyle Libre* are associated with many uncertainties but imply a correlation between glucose monitoring with *FreeStyle Libre* and improved metabolic control (lower HbA1c) as well as more testing occasions compared to glucose monitoring with SMBG.

1.4.3 TLV assesses that the clinical studies that have examined the reliability of *FreeStyle Libre*'s measurements *in vivo* have shown that the measuring accuracy is acceptable according to established standard (MARD).

Local clinical efficacy evaluations

FreeStyle Libre has, to a varying degree, been used since 2014 in Swedish healthcare. A national systematic review of user data from the user's records or through NDR (where the variable "CGM/FGM" became available in June 2016) has not been performed but local efficacy evaluations have been made. The efficacy has then been evaluated by the comparison of the patient's HbA1c level during glucose measuring with SMBG to the value after some time of measuring with *FreeStyle Libre*. The company that markets *FreeStyle Libre* has not participated in the implementation of the local evaluations.

TLV has obtained results from four such evaluations, from the University Hospital in Örebro (USÖ), Skåne University Hospital (SUS), Södra Älvsborg Hospital (SÄS) and Uppsala University Hospital in Uppsala. In total, the evaluations involve 1,553 individuals. Table 5 shows the results from the local evaluations [34].

Table 5 Summarising table of local evaluations of change in HbA1c after use of Freestyle Libre

Region/hospital	Indication	Number of patients with Freestyle Libre	Use in months	Average HbA1c in mmol/mol with introduction to *FreeStyle Libre* (min-max)	Average change in HbA1c
Uppsala University Hospital	HbA1c over 70; Finger pricking more than 10 times/day; special difficulties pricking in fingers - job associated such as professions healthcare, cooking, hairdressers, mechanics; Indication for CGM but where this cannot be used	326	3–6	72	-9 mmol/mol
Örebro University Hospital	Difficulty achieving treatment goal, fluctuating blood glucose, recurring hypoglycemia	164	12	68.9	-5.4 mmol/mol
Skåne University Hospital	Difficulty achieving the treatment goal, recurring hypo- or hyperglycemias	803	3-21	66.5 (±14,5)*	-7.3 mmol/mol
Södra Älvsborg Hospital	Fluctuating blood sugar, HbA1c over 70 mmol/mol, nightly hypoglycemia, hypoglycemic unawareness but where CGM has functioned poorly, or work environment reasons (e.g. sterile or very dirty work), age <25 years old.	260	18	65,6	-3.3 mmol/mol
Total/mean		1553		68.25	

**After first three months - 7 mmol/mol*

TLV's assessment of local efficacy evaluations

The company has in its randomised clinical studies not examined the efficacy of *FreeStyle Libre* in people with type 1 diabetes who have difficulty achieving the treatment goal so the retrospective local efficacy evaluations therefore contribute, judging from the indications for the method, with supplementary information about this population. The significance of *FreeStyle Libre* for the consistent decrease in HbA1c in people who measure their glucose with this method is the hardest to asses however, since additional factors that may have affected the result have not been examined.

1.4.4

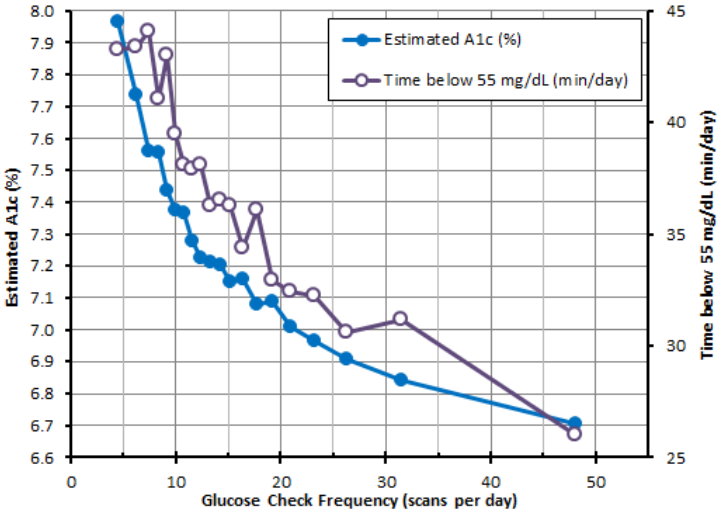
User data

Users of *FreeStyle Libre* have the option of storing measurement data in cloud service through software with internet connection. The company presented an abstract at the conference Advanced Technology and Treatment for Diabetes 2017 where this data has been re-identified and analysed on a group level. For inclusion in the analyses the patient needed to have used *FreeStyle Libre* for at least 120 hours. Based on the grouped measurement data one then estimated the expected HbA1c level. The results from the analysed units are presented in table 6 and figure 1.

Table 6 Results from the company's analysis of user data

Number of included units	50,831
Number of sensors that have been used by the units	279,446
Number of readings per unit and day	16.3 (median 14)

Figure 1. Estimated HbA1c as function of reading frequency.



According to the company the analysis indicates a significant connection between the number of daily readings with *FreeStyle Libre* and the assumed HbA1c level, in other words more daily readings were associated with lower glucose levels in readings, which one assumed was the reflection of a lower estimated HbA1c level. The company also felt that the analysis showed similar connections between the number of measurements and time within the normal interval for the glucose level.

TLV's assessment of the company's analysis of user data

Users of *FreeStyle Libre* who use the company's cloud service appear to measure their glucose levels to a higher extent (median 14 times/day) than what was reported in studies that have examined the SMBG frequency in people with type 1 diabetes (less than four times/day) [13, 36]. According to TLV no causality can be assumed and the risk of selection
1.4.5 bias is great but the results indicate an increased testing frequency per day compared to SMBG.

Systematic overviews, meta-analyses and indirect comparisons

FreeStyle Libre has not yet become subject to a systematic overview or meta-study since too few RCT:s (randomised controlled trials) have been performed. However, material for assessment of the system's efficacy can in all likelihood be collected from systematic overviews and meta-studies, and to some extent also from RCT:s, that involve blood glucose monitoring with SMBG or glucose monitoring with other CGM systems (where the first system became available in 2000) [15]. A summary of the knowledge situation for glucose monitoring with SMBG and other CGM systems are therefore presented below.

Glucose monitoring for type 1 diabetes

Metabolic control

The scientific support for the importance of self-monitoring, regardless of the method, as an aid in reaching the treatment goal for type 1 diabetes is good. That the number of daily glucose measurements, regardless of the method, increases the likelihood of reaching the treatment goal also appears to be well substantiated [11, 37-41]. There is also scientific support to suggest that self-monitoring with CGM systems compared to SMBG systems lead to further improved metabolic control for those with type 1 diabetes, since systematic overview with homogeneity have indicated clinically significant, if modest, improvements in

metabolic control for glucose monitoring with CGM compared to SMBG (~0.3 percent, which equals approximately 3 mmol/mol) [42-46].

The most current meta-study was published in 2017 [47]. In it, results from eleven RCT:s were analysed regarding HbA1c in people with type 1 diabetes with CGM systems in comparison with SMBG users. One discovered that the CGM systems produced a statistically significant decrease of HbA1c (-0.276 percent; 95 percent CI -0,465 to -0.087) in people with type 1 diabetes over the age of 15. It is worth pointing out however that the changes in HbA1c apply to the population of people with type 1 diabetes as a whole. Subgroup analyses and targeted studies have shown that the HbA1c reducing effects have been larger in subgroups that have been characterised by unsatisfactory metabolic control [19, 44, 48, 49].

A corresponding comparison for children with type 1 diabetes has shown similar minor improvements in metabolic control in children who are at the age where the treatment is mainly the parent's responsibility [50, 51] while teenagers and young adults (<25 years) appear to obtain fewer health gains than other groups [43, 52]. The suggested mechanism behind a lack of effect on metabolic control is linked to a lower adherence to usage in teenagers and young adults [52, 53].

There is evidence in systematic overviews or meta-studies to suggest that the documented improvement in metabolic control leads to an increased risk of hypoglycemia during glucose monitoring with CGM systems [46, 47, 54] even though such a risk is theoretically feasible.

Hypoglycemia
There is scientific support for the importance of self-monitoring when it comes to preventing or treating hypoglycemia [6, 55, 56]. The scientific support for CGM systems having an additional positive effect on the occurrence of hypoglycemia is doubtful. Granted, the German HTA authority IQWIQ did discover in one evaluation that was published in March that there is evidence to suggest that the CGM systems contribute to a combination of reduced HbA1c and a reduced number of severe hypoglycemias in adults with type 1 diabetes [57]. For time in hypoglycemia or the number of hypoglycemic episodes as individual outcomes, published systematic overviews or meta-studies have not shown a definite decrease with CGM systems for the entire patient population [47, 54]. However, for people who have developed hypoglycemic unawareness there are RCT:s that have shown that glucose monitoring with CGM systems decrease the number of serious hypoglycemic episodes [57, 58].

Glucose variability
Glucose variability is a measurement of how much the glucose level fluctuates during the day. The variability has among other things been associated with the excess mortality in large vessel disease that people with type 1 diabetes are at risk for and with retinopathy [26, 59, 60]. Several RCT:s have evaluated the effect on glucose variability with the use of CGM systems. Statistically significant decreases in parameters connected to glucose variability have been found, both for a general diabetes population [61] as well as for people who find it difficult to achieve the treatment goal [62].

Adherence to glucose monitoring improves the results
The results from both the randomised clinical studies and systematic overviews show that the user's adherence to the CGM systems is crucial to the effect on the metabolic control for both children and adults with type 1 diabetes. Factors that have shown to decrease adherence is a

lack of personal maturity in children and young people, a feeling that the CGM systems interfere with daily activities or that the alarms are uncomfortable, the high cost of the sensors and that the calibration with SMGB is complicated.

TLV's assessment of the knowledge situation of glucose monitoring for people with type 1 diabetes

TLV assesses that systematic overviews and meta-studies have consistently shown a small but clinically relevant decrease of HbA1c in children and adults with type 1 diabetes who monitor glucose with a CGM system compared to SMBG. The studies have mainly pertained to people with good or only slightly worsened metabolic control. For hypoglycemic parameters, performed studies have so far homogeneously not managed to capture a definite gain compared to SMBG. TLV also assesses that the effect on HbA1c for glucose monitoring with CGM systems is correlated to the degree of use. TLV therefore assesses that the likelihood of health gains is greater if the monitoring method is user friendly.

In all overall, TLV assesses that the scientific findings concerning glucose monitoring with CGM systems can be assumed to apply to glucose monitoring with *FreeStyle Libre* as well.

Glucose monitoring for type 2 diabetes

Metabolic control

Self-monitoring of blood glucose for insulin treated diabetes, regardless of type, with SMBG has been given priority 1 in the National Board of Health and Welfare's guidelines for diabetes care. The recommendation has been made based on established practice [17]. Support for the prioritisation can also be found in randomised clinical trials and observational studies of insulin treated people with type 2 diabetes and difficulty to reach the treatment goal [38, 69-71]. Additional health gains with glucose monitoring with CGM systems have been evaluated in randomised clinical trials in people with type 2 diabetes but the studied population has mainly been people with type 2 diabetes who do not medicate with insulin or who take insulin as an addition to oral administration of blood glucose reducing drugs. These studies have rendered contradictory results regarding additional metabolic control, hypoglycemic parameters and life quality with glucose monitoring with CGM systems [54, 72-75].

TLV's assessment of the level of knowledge on glucose monitoring for people with type 2 diabetes

In the literature there is no structured documentation of the effect on the metabolic control with glucose monitoring with CGM systems in people with mealtime insulin treated type 2 diabetes. However, TLV assesses that since blood glucose monitoring with SMGB has demonstrated effect on insulin treated type 2 diabetes (but not for diet or tablet treatment) one may assume that the results from systematic overviews in the type 1 population is also transferrable to people with type 2 diabetes, whose insulin regime is built on the basal and bolus insulin.

2 Cost-effectiveness analysis

The cost-effectiveness analysis of *FreeStyle Libre* is based on data that pertains to people with type 1 diabetes since there is a lack of relevant information on continuous glucose monitoring in those with type 2 diabetes. However, TLV finds that the evaluation can serve as guidance for people with type 2 diabetes who are treated with insulin pump or insulin regime consisting of basal insulin in combination with mealtime insulin, since their need for glucose monitoring corresponds to the need in people with type 1 diabetes.

In its cost-effectiveness analysis the company uses the CORE model owned by QuintilesIMS (previously IMS Health). In the area of diabetes the CORE model is one of several models that is frequently used and TLV has previously assessed that it produces credible results [76]. The CORE model is published, has been validated and has reproduced results from many clinical trials [77]. The time horizon in the analysis is 50 years.

The company uses data from the clinical trial IMPACT and a time trade-off-study (TTO-study) in its health economic analysis regarding people with type 1 diabetes. In the IMPACT study among other things, the number of hypoglycemias during six months (see chapter 1.4.1) was measured. Fewer experienced hypoglycemias results in an improved quality of life in the health economic model. However, it is the quality of life gain estimated from the company's TTO-study that is the main driving force behind the cost-effectiveness analysis (see chapter 2.2.2).

The company has in connection with a previous subsidy application done a cost-effectiveness analysis regarding people with type 2 diabetes where data from the clinical trial REPLACE is used. Since the REPLACE study in TLV's opinion has not been performed on a population that is relevant to the reality of Swedish clinical practice, this analysis will not be discussed any further (see chapter 1.4.1 for an assessment of REPLACE).

As a supplement to the company's cost-effectiveness analysis the Swedish Institute for Health Economics (IHE) has, on behalf of TLV, carried out supplementary analyses of the use of *FreeStyle Libre* in comparison to SMBG. This has been done in the standardised health economic model (ECHO T1DM) that IHE has developed for diabetes analysis. The population has been collected from NDR [78-80].

2.1.1

2.1 Efficacy measurement

In order to estimate future risks due to diabetes related complications, a decrease of the glucose level in the blood is normally used as a clinical efficacy measurement. The established measurement of blood glucose levels that is used is HbA1c (see chapter 1.1). Additional measures such as number and degree of severity of hypoglycemias can be used to measure efficacy of interventions regarding diabetes.

Hypoglycemia

The primary clinical outcome used in the company's analysis is the number of symptomatic hypoglycemias. These occur with insulin treatment when the blood sugar level decreases to such a low level that it causes physical discomfort.

It is primarily the difference in the number of non-serious symptomatic hypoglycemias that affects the results. These are based on the results from IMPACT (see also chapter 1.4.1). Table

7 shows the clinical effects that the modelling is based on. In its analyses, the company has only included the risk of non-serious symptomatic hypoglycemias.

Table 7 Clinical effects in modelling, symptomatic hypoglycemias per year

	FreeStyle Libre	SMBG
Non-serious hypoglycemia, daytime	36.90	49.55
Non-serious hypoglycemia, nighttime	12.07	18.07
Serious hypoglycemia, daytime	0.28	0.28
Serious hypoglycemia, nighttime	0.09	0.10
Moderately serious hypoglycemia	2.82	2.82

Decrease of HbA1c

In the IMPACT study glucose monitoring with *FreeStyle Libre* has not demonstrated an additional effect on HbA1c in comparison with SMBG. Nor has the company claimed such an effect in its cost-effectiveness alalysis for people with type 1 diabetes.

2.1.2 In the supplementary analysis done by TLV it is assumed that people with diabetes and who use *FreeStyle Libre* can lower their blood sugar level without increasing the risk of obtaining hypoglycemias. This assumption is based on systematic overviews that have examined sensor-driven continuous glucose monitoring in people with type 1 diabetes and that indicate a decrease in HbA1c by 0.3 percent points (see chapter 1.4.5) and Swedish clinical efficacy evaluations of glucose monitoring with *FreeStyle Libre* (see chapter 1.4.3). Based on these sources, TLV has assumed that the use of *FreeStyle Libre* leads to a decrease in HbA1c by 0.3 percent, which is the limit of what is characterised as clinically relevant.

A clinically relevant decrease in HbA1c leads to a decrease in the risk of diabetes related complications. The risk of diabetes related complications is estimated in the health economic model with the help of risk equations based on data from NDR.

TLV's assessment of efficacy data

TLV assesses that there is a moderately high degree of uncertainty regarding how large the decrease in the number of non-serious hypoglycemias is. The hypoglycemias that are presented in the IMPACT study are those that are measured by the glucose value being under 3.9 mmol/mol regardless of whether they cause the person to experience symptoms or not. In order for a non-serious hypoglycemia to be relevant enough to be included it should be symptomatic and entail inconvenience to the person. The results in the company's analysis are marginally affected if the decrease is adjusted down in the sensitivity analyses (see chapter 3.1.3).

TLV assesses that the assumption of a small but clinically relevant decrease in HbA1c for glucose monitoring with *FreeStyle Libre* compared to SMBG is relevant based on existing documentation.

2.2 Health related quality of life

In the company's analysis, two components that affect quality of life are taken into consideration; the number of symptomatic non-serious hypoglycemias (see chapter 3.1.1) and what method is used to measure glucose, in this case *FreeStyle Libre* in comparison with SMBG. The results in the company's analysis are mainly affected by the quality of life significance that comes from a TTO-study that has intended to quantify the quality of life gain from monitoring glucose level with *FreeStyle Libre* instead of with SMBG.

For the supplementary analysis that TLV has done and where a clinically relevant decrease of HbA1c has been assumed, the quality of life loss for diabetes related complications has also been taken into account.

Life quality loss due to hypoglycemia

That symptomatic hypoglycemias affect a person's life quality has been demonstrated and evaluated in several studies [81-83]. Published studies also show that people who are affected by many hypoglycemias have a smaller quality of life decrease per hypoglycemia than people who are affected by few hypoglycemias [82, 84]. The company's analysis has taken into account the fact that people experience a diminishing quality of life loss in relation to the number of hypoglycemias.

2.2.1 The company bases its analysis on the results from a study that estimates patient benefits from fewer hypoglycemias with over 8,000 respondents [82]. This analysis takes into account the quality of life loss that occurs due to non-serious hypoglycemias as a (diminishing) function of the number of non-serious hypoglycemias.

Table 8 shows the quality of life loss that is used in the company's modelling. The result show that people with *FreeStyle Libre* have an annual quality of life gain as a result of fewer non-serious hypoglycemias of 0.0064 if it is assumed that all hypoglycemias occur during the day respectively 0.0121 if the hypoglycemias occur both during day and during the night according to the results in the IMPACT study.

Table 8. Quality of life reduction due to hypoglycemia, per year

Non-serious hypoglycemia, all daytime, *FreeStyle Libre*	0.0528
Non-serious hypoglycemia, all daytime, SMBG	0.0592
Non-serious hypoglycemia, adjusted according to time of day, *FreeStyle Libre*	0.0979
Non-serious hypoglycemia, adjusted according to time of day, SMBG	0.1100

2.2.2 In TLV's supplementary analysis a quality of life gain due to a decreased number of hypoglycemias has not been assumed since TLV assesses that the company has overestimated the degree of seriousness and frequency of symptomatic hypoglycemias in its analysis (see chapter 3.1.1).

Quality of life gain from use of *FreeStyle Libre*

In order to evaluate the quality of life gain that results from monitoring blood glucose levels with *FreeStyle Libre* instead of SMBG the company that markets *FreeStyle Libre* has performed a TTO-study [85] where a general British population (n=209) has expressed its preference for monitoring glucose with *FreeStyle Libre* or SMBG.

In the TTO-study the disorder and treatment with insulin injection was described to the participants. The participants were thereafter introduced to two methods by which they could monitor their blood glucose levels, either with SMBG three times per day or with *FreeStyle Libre*. The study also included an explanation of how the products work, an instruction film and information about the accessories that a person with diabetes needs for glucose monitoring during a period of two weeks.

According to the TTO-study, glucose monitoring with *FreeStyle Libre* resulted in a quality of life gain that is 0.03 higher than for those who measure glucose with SMBG. The difference was statistically significant.

Quality of life effects due to diabetes related complications

In the supplementary analysis performed by TLV where the assumption is that the use of *FreeStyle Libre* decreases HbA1c, there is also the assumption that the risk of diabetes related complications decreases. Such complications are associated with loss of quality of life. The loss of quality of life that is assumed in this analysis is mainly collected from the European CODE-2 study, which studied costs and quality of life related to diabetes [86]. The quality of life gains that were used in the analysis are presented in appendix 2.

TLV's assessment of the health related quality of life

2.2.3 The source that has been used for quality of life reductions from non-serious hypoglycemias is relevant and takes into account the important aspect that the person tends to suffer less per additional hypoglycemia when the number of hypoglycemias increases.

The TTO-study that is the basis of the quality of life gain values qualities in an aid used for glucose monitoring decoupled from the clinical effect. TLV assesses that TTO studies have certain methodological problems, for example how respondents have been selected and how health conditions are described to and perceived by people who have no experience with them. It is also unclear as to what extent such studies capture different dimensions of quality of life, such as comfort, flexibility, concern about hypoglycemias and disorder complications - dimensions that are very important to people with insulin treated diabetes - and it is likely that the measured quality of life gain also includes non-health related aspects.

TLV therefor assesses that the company's cost-effectiveness analysis is primarily driven by a quality of life measurement that in an imponderable way has attempted to quantify the quality of life gain with using *FreeStyle Libre* to monitor glucose. Thus, the company's cost-effectiveness analysis is associated with a number of uncertainties.

3.1.1

3 Result

3.1 The company's base-case scenario

Assumptions in the company's base-case scenario

The company's analysis in the base-case scenario is based on the following assumptions:

- Annual quality of life gain as a result of a decreased number of non-serious symptomatic hypoglycemias: 0.0064.
- Annual quality of life gain from the use of *FreeStyle Libre* itself: 0.030.
- Use of *FreeStyle Libre;*
  - Number of sensors per person and year: 26
  - Number of test strips: 0.5 per day (equals 182.5 per year).
  - Number of lancets: 0.7 per day.
  - The hand unit has a presumed durability of two years.[3]

[3]Corresponding to the company's warranty time of two years.

- Use of SMBG (comparator)
  - Number of test strips: 5.4 per day (equals 1,971 per year).
  - Number of lancets: 1.8 per day.

Result in the company's base-case scenario

The company's base-case scenario is based on a time horizon of 50 years and the cost per gained quality-adjusted life year (QALY) is estimated to SEK 291,000.

Table 9. Result of the company's base-case scenario

	FreeStyle Libre	SMBG (5.4 per day)	Difference
Total costs (SEK)	1,222,333	989,051	233,283
-Of which direct treatment costs (SEK)	445,188	211,906	233,283
Total costs (incl. indirect costs in SEK)	1,943,889	1,710,606	233,283
Life years	21.10	21.10	0.00
QALY:s	13.26	12.46	0.80
Cost per gained QALY			**SEK 291,130**

3.1.2

The result of the company's sensitivity analyses

3.1.3 Table 10 presents the results from the company's sensitivity analyses. The results show that the cost per gained QALY is not significantly affected by adjustments to variables connected to time. This is due to the fact that costs and quality of life gains in essence increase linearly over time. The sensitivity analyses that mainly deviate are those that speculate about an improved clinical effect from using *FreeStyle Libre* instead of SMBG. For example, an improvement of HbA1c of 0.3 percent points for glucose monitoring with *FreeStyle Libre* would lower the cost per gained QALY with approximately 50 percent. The company has not presented a sensitivity analysis where the patient-evaluated benefit from using *FreeStyle Libre* was not taken into account.

Uncertainties regarding the results are discussed in chapter 3.2.4.

Table 10 The company's sensitivity analyses

Sensitivity analyses		Cost difference (SEK)	Difference in gained quality adjusted life years (number)	Cost per gained quality adjusted life year (SEK)
Discounting of costs and effect	0 percent			290,439
	five percent			291,644
Time horizon	five years			297,460
	ten years			293,770
Lower number of non-serious hypoglycemia at baseline[4]	29 per year	233,283	0.76	305,784
Alternative physiological parameters[5]		246,539	0.77	319,061
Alternative resource use year 1[6]		232,648	0.80	290,338
Alternative resource use all years[7]		219,272	0.80	273,664
Alternative modelling of serious hypoglycemias[8]		232,648	0.80	290,338
Decrease of serious hypoglycemias by 55 percent in people who use *FreeStyle Libre*		206,786	1.66	124,705
Decrease of HbA1c by 0.3 percent points in people who use *FreeStyle Libre*		151,399	1.01	150,436
Patient evaluated benefit with *FreeStyle Libre* 0.023		233,283		292,290

3.2 TLV's base-case scenario

3.2.1

Assumptions in TLV's base-case scenario

TLV has in its base-case scenario chosen to modify the company's base-case scenario in such way that the cost-effectiveness analysis reflects the clinical reality. In TLV's base-case scenario the population comes from NDR, indirect costs and quality of life gain due to fewer hypoglycemias have not been included and a quality of life gain that has been set to 0.01 (see below). Also, the assumption is that glucose monitoring with *FreeStyle Libre* contributes to a decrease of HbA1c by 0.3 percent points. This base-case scenario makes it possible to value specific qualities, and how they affect assumptions and estimates associated with uncertainties and how these affect the cost in relation to the effect.

TLV assesses that glucose monitoring with *FreeStyle Libre* is most likely associated with gains in quality of life, but that the result that is based on the company's TTO-study has not managed to quantify these gains in a credible way. Based on the gain in quality of life obtained from TTO studies regarding flexibility and comfort [87-89] as well as adherence to *FreeStyle Libre*, TLV makes the assumption that the benefit from using *FreeStyle Libre* is probably not lower than 0.01. For this reason, TLV's base-case scenario includes a quality of life gain of 0.01.

[4]Instead of basing its analysis on the number of symptomatic hypoglycemias at baseline in IMPACT, the company uses the UK Hypo study (2007) where 29 non-serious hypoglycemias per year with SMBG is stated.
[5]Outcome from IMPACT on SBP, T-chol, LDL, HDL, TRIG and BMI included.
[6] More visits to emergency room, ambulance transportation and hospitalisation for people who use SMBG measured in IMPACT.
[7]Resource use according to above extrapolated into all years.
[8]Recreates the results for how serious hypoglycemias were modelled in the CORE model v8.5

Table 11. Differences between the company's model and TLV's model

	The company's model	TLV's model
Quality of life connected to fewer hypoglycemias	Yes	No
Quality of life gain	0.03	0.01
HbA1c decrease	No	Yes (0.3%)
Number of test occasions	5.4	10
Indirect costs	Yes	No
Model (data)	Core (IMPACT)	ECHO T1DM (NDR)

Result from TLV's base-case scenario

TLV's base-case scenario is based on the costs and treatment length presented in table 12 and 13. The greatest impact on the result is the price of the sensors for *FreeStyle Libre* followed by the price of the test strips. In TLV's base-case scenario a price of two SEK for one test strip is assumed, which equals the pharmacy purchase price within the pharmaceutical benefits.

3.2.2 This number is then varied in the sensitivity analyses in order to show how a change in the price changes the cost per QALY.

Table 12. Annual cost in TLV's base-case scenario

	FreeStyle Libre after year 1*			SMBG (10 per day)		
	Price (SEK)	Amount	Cost (SEK)	Price (SEK)	Amount	Cost (SEK)
Reader	599.00	0.50	299.50	-	-	-
Sensors	490.00	26.00	1,2740	-	-	-
Test strips	2.75	182.00	500.50	2.00	3,650.00	7,300.00
Lancets	0.16	182.00	29.03	0.16	3,650.00	584.00
Doctor visit	1 427.00	1.00	1,427.00	1,427.00	1.00	1,427.00
Insulin (Units)	0.20	14,600.00	2,920,00	0.20	14,600.00	2,920.00
Total cost			**17,916.03**			**12,231.00**

**The first year there is an additional cost of SEK 1,427 for an extra doctor visit.*

Table 14 shows the cost per QALY for people with type 1 diabetes. The costs are obtained from the results in IHE's ECHO TD1DM model, where input comes from NDR.

3.2.3

Table 13. TLV's base-case scenario

	FreeStyle Libre	SMBG (ten per day)	Difference
Total costs (SEK)	414,935	282,531	132,404
Life years	23.16	23.10	0.06
QALY:s	22.59	21.78	0.34
Cost per gained QALY			**SEK 389,424**

TLV's sensitivity analyses

TLV's different sensitivity analyses aim at capturing the uncertainties that TLV assesses to be the most relevant based on the decision situation, but also to highlight the factors that have the greatest impact on the cost per quality adjusted life year. The effects that have the

greatest impact on the model are level of quality of life gain assumed for *FreeStyle Libre*, followed by the number of test strips that are used per day as well as the price of the test strips. The purpose of the sensitivity analysis on the price of test strips aim to highlight that there are different types of test strips used and that there are also test strips that are procured at a different price than what is assumed in TLV's base-case scenario. The cost per QALY also changes a lot when the change in HbA1c varies. Different levels are still presented in TLV's sensitivity analyses in order to show how a change like this could affect the results.

TLV has also included a sensitivity analysis for people with type 1 diabetes with a HbA1c > 70 mmol/mol. This group should be viewed as a representation for people who have a greater need of frequent and regular glucose monitoring, since a higher HbA1c implies a need for a more intense insulin treatment, than the general diabetes population and not as a limitation of what people may be assumed to benefit from *FreeStyle Libre*.

Table 14. TLV's sensitivity analyses

	Cost difference (SEK)	Difference in gained quality adjusted life years (number)	Cost per gained quality adjusted life year (SEK)
HbA1c decrease: 1.0%	134,273	0.58	231,506
HbA1c decrease: 0.5%	132,858	0.41	324,045
HbA1c decrease: 0.0%	131,477	0.23	571,640
Number of test strips SMBG: 3	259,886	0.34	764,371
Number of test strips SMBG: 7	187,039	0.34	550,115
Number of test strips SMBG: 15	41,345	0.34	121,604
Quality of life gain 0.00	132,404	0.11	1,203,675
Quality of life gain 0.02	132,404	0.56	236,436
Quality of life gain 0.03	132,404	0.81	163,462
Price of test strips: SEK 2.5	90,242	0.34	265,417
Price of test strips: SEK 1.5	174,557	0.34	513,402
Persons with type 1 diabetes and a HbA1c >70 mmol/mol	126,465	0.34	371,957

3.2.4

Uncertainty of the results

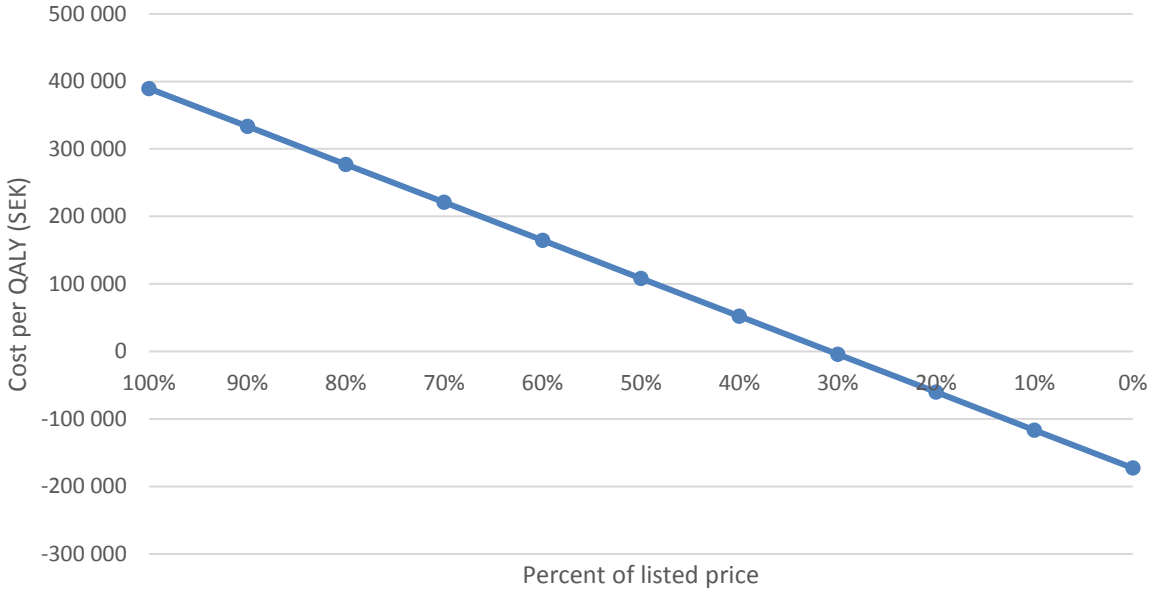
Both the company's and TLV's analyses contain uncertainties where the most tangible one is what weight should be placed on the results from the company's TTO-study. The quality of life gain that has been estimated from the TTO-study is crucial to the results and there is uncertainty regarding both the method used and specificity. In an attempt to limit the uncertainty, TLV has done sensitivity analyses that show the cost for different levels of the quality of life gain (table 14).

Cost for different levels of price, test strips and quality of life gains

Figure 2 shows the difference in cost per QALY when the price is varied, figure 3 for test strips and figure 4 for quality of life gain.

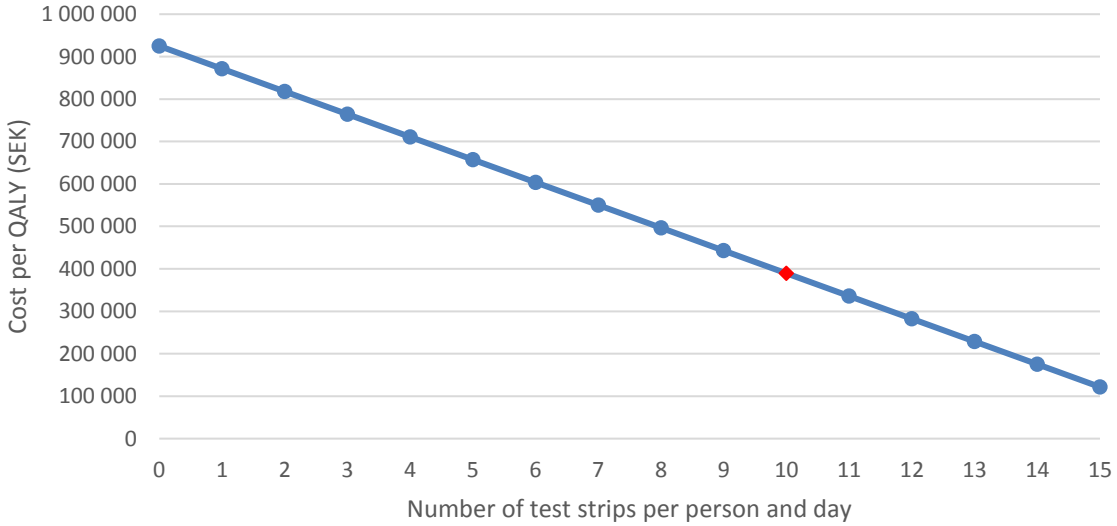
3.2.5

Figure 2. Cost for different levels of the price for FreeStyle Libre



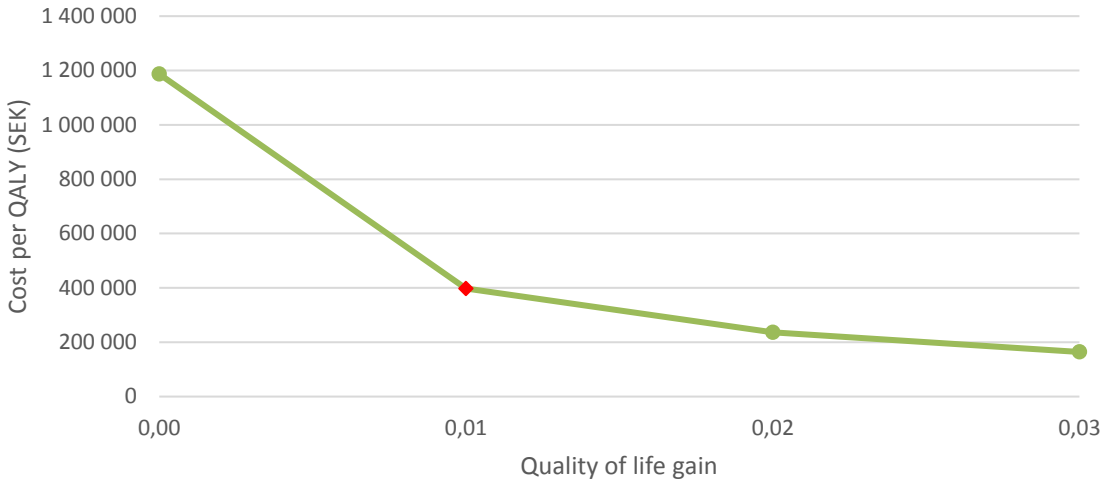
NB: At roughly 30% FreeStyle Libre becomes cost saving since the cost for FreeStyle Libre then becomes lower than the cost of the comparator. The estimates are made on a price reduction of reader and sensor, as well as a reduction of the price difference between FreeStyle Libre's test strips and the test strips that are used with the comparator.

Figure 3. Cost per QALY for different numbers of test strips that the person uses per day.



NB: The red square indicates TLV's base-case scenario.

Figure 4. Cost per QALY for different levels of the quality of life gain



NB: *The red square indicates TLV's base-case scenario.*

3.3 Budget impact

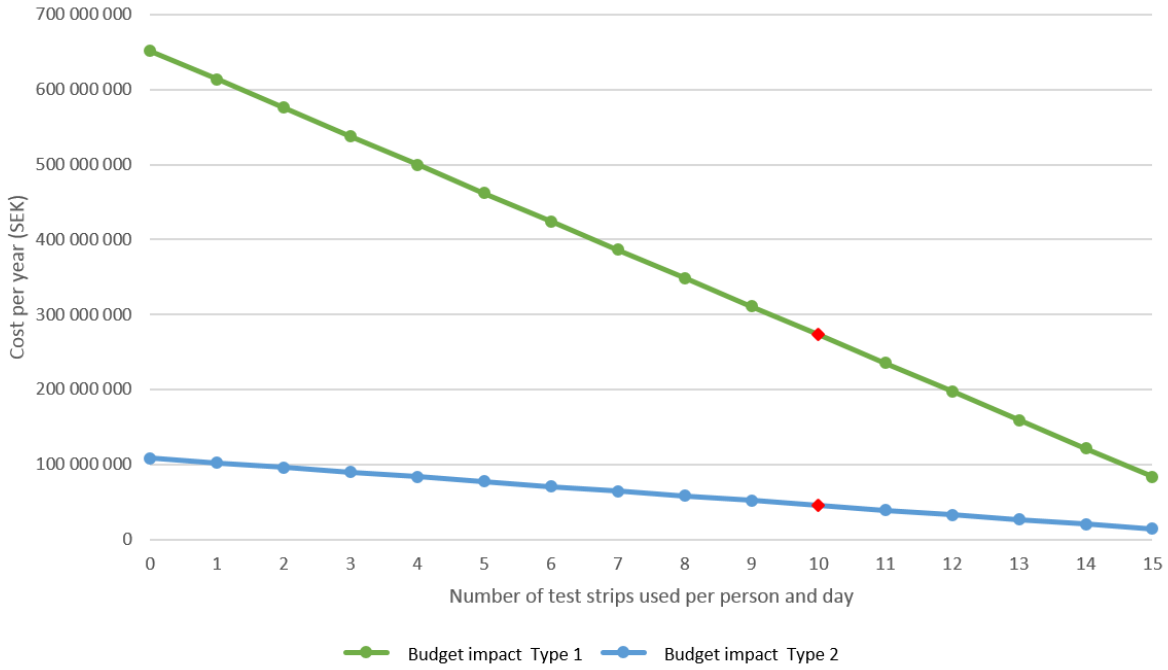
In Sweden, there are currently 48,000 people with type 1 diabetes and roughly 40,000 people with type 2 diabetes who are treated with basal insulin in combination with mealtime insulin. Information from NDR shows that approximately 8,000 people with type 2 diabetes, who are treated with basal insulin in combination with mealtime insulin, have a HbA1c over 70 mmol/mol. In the light of this, TLV assesses that 8,000 people is a fair estimate of how many people with type 2 diabetes have the need to monitor their glucose levels at least 10 times per day. The total cost for treatment with *FreeStyle Libre* is estimated to SEK one billion each year and the increased cost that is added to that compared to the existing treatment is estimated to be potentially SEK 318 million per year. One should take into consideration that this is under the assumption that people use ten test strips per day, which is a recommendation and not the actual use. Hence, TLV has made a graph (see figure 5) which shows the increased cost for different numbers of test strips used per day in order to demonstrate how the budget impact changes when the amount of test strips a person is assumed to use per day varies.

Table 15. Budget impact divided among people with type 1 and type 2 diabetes.

Diabetes type	Number of persons	Total cost *FreeStyle Libre* (SEK)	Total cost SMBG (ten strips per day)	Difference (SEK)
Type 1	48,000	859,969,000	587,088,000	272,881,000
Type 2	8,000	143,328,000	99,071,100	45,480,000
Total	**56,000**	**1,003,298,000**	**684,936**	**318,362,000**

NB: This pertains to people with basal insulin in combination with mealtime insulin or who use an insulin pump

Figure 5. Budget impact



NB: The red squares indicate TLV's base-case scenario.

3.4 Overall assessment of the results

In the company's base-case scenario the cost per QALY is SEK 291,000. The company's cost-effectiveness analysis is primarily driven by a quality of life gain of 0.03, which has been obtained from a TTO-study. The aim of the TTO-study is to quantify the value of monitoring blood glucose with *FreeStyle Libre* instead of with SMBG. TLV assesses that the results in the company's base-case scenario are uncertain due to the ambiguity surrounding the TTO-study that is presented in the material.

In TLV's base-case scenario the cost per QALY is SEK 389,000. In TLV's cost-effeciveness analysis a quality of life gain of 0.01 is used since previous studies and adherence to glucose monitoring with *FreeStyle Libre* indicates that the quality of life gain is larger than zero. In TLV's cost-effectiveness analysis there is also the assumption of a small but clinically relevant decrease in HbA1c of 0.3 percent points based on RWD and systematic overviews of the CGM systems. In TLV's base-case scenario it is also assumed that glucose monitoring needs to be performed ten times per day (5.4 times per day in the company's base-case scenario) since that is one of the recommendations that the programme council for diabetes makes for continuous glucose monitoring.

TLV's sensitivity analyses show how the cost per QALY changes at different levels on the factors that have the most impact on the model. To summarise, it is the level of the quality of life gain and the number of test strips that people use per day that determines the cost per QALY. Above all, the difference is the greatest when the quality of life gain goes from 0.00 to 0.01. However, TLV finds that a quality of life gain of 0.00 is not feasible and has therefore in its base-case scenario used a quality of life gain of 0.01. If the quality of life gain is adjusted up even further to the level that the company provides in its base-case scenario the cost per QALY becomes SEK 142,000.

In the sensitivity analysis for the group with HbA1c >70 mmol/mol the cost per QALY is SEK 372,000, which is somewhat lower than in TLV's base-case scenario. This indicates that glucose monitoring with *FreeStyle Libre* would provide a larger health gain for those who have a difficulty in achieving the treatment goal.

TLV's sensitivity analyses also show that the number of glucose measurements that a person with diabetes is recommended to do per day has a large impact on the cost. The need for frequent and regular glucose monitoring in order to achieve the treatment goal or to avoid hypoglycemia should therefore carry more weight than what type of diabetes the person has during prioritisation of resources for glucose monitoring.

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Appendix – quality of life utilities

Complication	Use in Modeling		Comment/Source
	Mean	SE	
Baseline Utility	1,027	0,027	CODE 2
Patient Characteristics			
Age (per 10 Years)	-0,0235	0,001	CODE 2
Female	-0,093	0,009	CODE 2
Duration of DM (per 10 Years)	-0,016	0,001	CODE 2
Macrovascular Complications			
CHF	-0,028	0,010	Assumed from CHD in CODE 2
CVD	-0,057	0,012	CVD
PVD	-0,061	0,015	CODE 2
Microvascular Complications			
Retinopathy: BDR or PDR	0,000	0,000	CODE 2
Blindness (one or both eyes, incl. combinations)	-0,057	0,022	CODE 2
BDR Only	0,000		Included above
PDR (not blind)	0,000		Included above
ME (not blind)	0,000		Included above
PDR And ME (not blind)	0,000		Included above
Blind in One Eye, But Not Both	0,000		Included above
Blind in Both Eyes	0,000		Included above
Microalbuminuria	0,000	0,000	Excl from CODE 2
Gross Proteinuria	-0,048	0,022	CODE 2
ESRD	0,000	0,000	Included in eGFR<15
GFR 30-59	0,000	0,000	Antar symptomfrihet
GFR 15-29	0,000	0,000	Antar symptomfrihet
GFR <15	-0,175	0,028	CODE 2
Symptomatic Neuropathy	-0,084	0,014	CODE 2
Symptomatic Neuropathy & PVD	-0,085	0,018	CODE 2
Diabetic Foot Ulcer	-0,170	0,019	CODE 2
One Lower Extremity Amputation	-0,272	0,029	CODE 2
Two Lower Extremity Amputations	-0,272	0,029	CODE 2
Hypertensive (>140mmHg) or treated hypertension	0,000	0,000	Assumption
Hypoglycemic Events			
NSHE	-0,014		Lauridsen et al. (2014)
SHE 1	-0,018	0,000	Marret 2011
SHE 2	-0,055	0,000	Evans 2013
Other Adverse Events (per episode)			
Ketoacidosis			
Excess Weight			
Per 1 BMI > 25kg/m²	-0,006	0,001	CODE 2