InnovaStar® analyzer

A system for measurement of HbA1c
manufactured by
DiaSys Diagnostic Systems GmbH

Report from the evaluation SKUP/2014/101

organised by SKUP at the request of

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The report was written by SKUP, 2014. For more details about SKUP, see attachment 1.
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Attachments 6, 8 and 10 are included only in the copy to Med-Kjemi AS.

1. Summary

Background
Med-Kjemi, Norway turned to SKUP for an evaluation of InnovaStar HbA1c. The evaluation was performed in the Department of Clinical Biochemistry, Nordsjællands Hospital, Denmark and in two primary health care centres, December 2013 to January 2014.

The aim of the evaluation
The aim of the evaluation was to examine the repeatability and accuracy of InnovaStar HbA1c achieved with capillary and venous samples in a hospital laboratory and to examine the repeatability and accuracy achieved with capillary samples by the intended end-users in two primary health care centres. The aim was also to evaluate the use of the control materials TruLab HbA1c liquid from DiaSys and to evaluate the user-friendliness of InnovaStar HbA1c.

Materials and methods
102 venous whole blood EDTA samples and 40 capillary samples were examined in a hospital laboratory. Capillary samples from 88 patients were analysed in the primary health care centres. Repeatability and bias were calculated from duplicate results for three or two levels of HbA1c. Three lots of reagent cartridges were used. Quality goals for repeatability was ≤3% CV and for accuracy ≥95% of results deviating ≤±10% from the results of the comparison method (based on calculations in IFCC units (mmol/mol)..

Results
At the hospital laboratory the repeatability was 1,9% for capillary samples and 1,6% for venous samples. In one primary health care centre the CV was 0,9% and 1,2% in two concentration levels, and in the other the CV was 1,8% and 3,2% at HbA1c mean 36,9 and 53,6 mmol/mol, respectively.
In one primary health care centre the bias was +3,6 and -0,5%, while the other centre and the hospital laboratory had positive bias between +3,3 and +7,5%. In the hospital laboratory 68% of the capillary and 84% of the venous results were within the limits ±10% from the comparison method. For results >37 mmol/mol, 94% were within the limits. For the two primary health care centres, the percentages within the limits ±10% were 88% and 67%, respectively. The percentage of technical errors was 0,6%. The reproducibility was less than 3% for the control material TruLab HbA1c liquid level 1 and 2 in hospital and one of the primary health care centres. The other centre had CV% 4,5 and 3,5 for level 1 and 2, respectively. The users were satisfied with the user manual. The operation facilities were assessed as satisfactory. All evaluators agreed that the instrument required laboratory experience. The time factors and the quality control possibilities related to the InnovaStar HbA1c instrument were assessed as satisfactory.

Conclusion
The goal for repeatability (<3%) was fulfilled with venous, capillary and control results in the hospital laboratory. In one primary health care centre the quality goal for repeatability was fulfilled. In the other centre the goal was also fulfilled for low results, but most likely not fulfilled for high results and with the control materials.
The quality goal for accuracy (≥95% of results deviating ≤±10% from the results of the comparison method) was neither fulfilled by the hospital laboratory (84 and 68%), nor by the two primary health care centres (73 and 88%). For results >37 mmol/mol, 94% of the venous results had a deviation less than ±10% in hospital. The internal quality control material from the manufacturer was assessed as satisfactory.
The percentage of technical errors fulfilled the goal ≤2%. The user-friendliness of the manual and the operation facilities was satisfactory. The InnovaStar HbA1c instrument requires users with laboratory experience.

Comments from the manufacturer DiaSys Diagnostic Systems GmbH
A letter with comments from DiaSys Diagnostic Systems GmbH is attached to the report.

2. Abbreviations

CI	Confidence Interval
C-NPU	Committee of Nomenclature, Properties and Units
CV	Coefficient of Variation
DAK-E	Danish Quality Unit of General Practice
DCCT	Diabetes Control and Complications Trial
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
DSKB	Dansk Selskab for Klinisk Biokemi (Danish Society for Clinical Biochemistry)
EDTA	Ethylenediaminetetraacetic acid
ERL	European Reference Laboratory
EQA	External Quality Assessment
Equalis	External quality assurance in laboratory medicine in Sweden
GP	General Practitioner
HPLC	high-performance liquid chromatography
HbA1c	B-Haemoglobin A1c
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
NGSP	National Glycohaemoglobin Standardization Program
Noklus	Norwegian Quality Improvement of Primary Care Laboratories
SD	Standard Deviation
SKUP	Scandinavian evaluation of laboratory equipment for primary health care
VUK	Videnskabelige udvalg for kvalitetssikring (Scientific committee for quality assurance)

3. Quality goals

3.1. Analytical quality

There are no generally recognised analytical quality goals for B-Haemoglobin A1c (HbA1c) determinations. Various ways of setting analytical quality goals are presented below.

3.1.1. *Comparing different quality goals*

The quality goals set in this evaluation assume that the HbA1c results are presented in IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) units (mmol/mol). Several other quality goals are set for HbA1c results in NGSP (National Glycohaemoglobin Standardization Program) units. In this report the NGSP unit (%) is referred to as DCCT%, named after the Diabetes Control and Complications Trial. Quality goals specified for HbA1c results in DCCT% have to be recalculated to quality goals for results in IFCC units mmol/mol. Weykamp *et al.*[1] have explained why the analytical goals for HbA1c measurement in mmol/mol and DCCT% are different.

The Danish Society of Clinical Chemistry has a Scientific committee for quality assurance (videnskabelige udvalg for kvalitetssikring = VUK). In 2012 the committee specified the following quality goals for HbA1c mmol/mol when used for diagnosis and monitoring of diabetes in Denmark [2]:

Maximum allowable imprecision: 2,8% CV (coefficient of variation)
Maximum allowable bias: ±2,8%

The Danish specifications for analytical quality requirements in general practice for monitoring HbA1c are presently re-evaluated by the National Danish Committee for General Practice Laboratory Testing. The analytical imprecision expressed as CV should be less than 3,0% and the bias should not exceed 5,0% at the level 48 mmol/mol [personal communication, 3,4].

In Sweden, the national analytical quality goals are set up by External quality assurance in laboratory medicine in Sweden (Equalis) Expert Group for Protein Analysis and were approved by the Swedish Association for Clinical Chemistry in 2010 [5]:

Maximum bias: ±1,5 mmol/mol
Between-laboratories-variation: 2,5% CV
Allowable deviation: bias + z × $CV_{\text{Between-laboratories-variation}}$ ~ bias + 1,65 × 2,5 %

The quality goal used by the Finnish external quality assessment (EQA) organisation Labquality is a maximum allowable deviation of 9,0% [6].

3.2. User-friendliness

The evaluation of user-friendliness was carried out by asking the evaluating persons (end-users) to fill in a questionnaire divided into four sub-areas, see section 5.5.

3.3. Technical errors

SKUP recommends that the percentage of "tests wasted" caused by technical errors should not exceed 2%.

3.4. Principles for the assessments

To qualify for an overall good assessment in a SKUP evaluation, the measuring system must show satisfactory analytical quality as well as satisfactory user-friendliness.

3.4.1. *Assessment of the analytical quality*

The analytical results are assessed according to the quality goals set for the evaluation.

Precision

The decision whether the achieved CV fulfils the quality goal or not is made on a 5% significance level. The distinction between the ratings, and the assessment of precision according to the quality goal, are shown in table 1.

Table 1. The rating of precision

Distinction between the ratings	**Assessment according to the quality goal**
The CV is lower than the quality goal (statistically significant)	The quality goal is fulfilled
The CV is lower than the quality goal (not statistically significant)	Most likely the quality goal is fulfilled
The CV is higher than the quality goal (not statistically significant)	Most likely the quality goal is not fulfilled
The CV is higher than the quality goal (statistically significant)	The quality goal is not fulfilled

Trueness

The measured bias is given with a 95% confidence interval (CI). The CI is used for deciding if a difference between the two methods is statistically significant (two-tailed test, 5% significance level).

Accuracy

The accuracy is illustrated in a difference-plot with limits for the allowable deviation according to the quality goal. The fraction of results within the limits is counted. The accuracy is assessed as either fulfilling the quality goal or not fulfilling the quality goal.

3.4.2. *Assessment of three lots*

Separate lot calculations are not performed. The results achieved with the three lots are included in the assessment of accuracy in the difference plots. If distinct differences between the lots appear, this will be pointed out and discussed.

3.4.3. *Assessment of the user-friendliness*

The user-friendliness is assessed according to the answers and comments given in the questionnaire (see section 5.5.). For each question, the user must choose between three given ratings, as for instance satisfactory, intermediate or unsatisfactory. The response from the users is reviewed and summed up. To achieve the overall rating ”satisfactory”, the tested equipment

must reach the total rating of "satisfactory" in all four sub-areas of characteristics mentioned in section 5.5.

3.4.4. *Assessment of the technical errors*

The evaluating persons register the number of error codes and technical errors during the evaluation.

3.5. SKUP´s quality goals in this evaluation

In this evaluation SKUP has tightened the quality goals compared to previous SKUP evaluations. In the latest published SKUP evaluation of HbA1c (SKUP/2012/91), all results were presented in DCCT%. The quality goal for repeatability was ≤4,0 CV% and the limit for allowable deviation was ≤±10%.

Based on the discussion about alternative quality goals above, SKUP will assess the results from the evaluation of InnovaStar HbA1c instrument against the following quality goals using results reported in IFCC unit mmol/mol:

Repeatability (CV) ..... ≤3%

Allowable deviation
in the individual result from the comparison method result..... ≤±10%

Required percentage of individual results
within the allowable deviation ..... ≥95%

Fraction of technical errors ..... ≤2%

User-friendliness ..... Satisfactory

If using results reported in DCCT% at HbA1c 6,5% (48 mmol/mol) these quality goals correspond to repeatability (CV) ≤2% and the goal for allowable deviation limit for the individual results from the comparison method result ≤±6,7%.

4. Materials and methods

4.1. Definition of the measurand

The Committee on Nomenclature, Properties and Units (C-NPU) describes clinical laboratory tests in a database [7]. In the NPU-database the specifications for the measurand in this evaluation are as shown in table 2.

Table 2. NPU-specifications

NPU code	Name of test according to NPU	Unit
NPU27300	Hb beta chain(B)—N-(1-deoxyfructos-1-yl)Hb beta chain; substance fraction,	mmol/mol
NPU03835	Hb(Fe; B)—Hemoglobin A1c(Fe); substance fraction, = ?	no unit, often given in %

HbA1c mmol/mol (NPU27300) was expected to be used worldwide. However; some still accept the NPU03835 specification because the DCCT% was used in Diabetes Control and Complications Trial [8] and the UK Prospective Diabetes Study [9] that documented complications to diabetes type 1 and 2.

Results can be recalculated between the two units with the following equations:

HbA1c (IFCC, mmol/mol) = 10,93 × HbA1c (DCCT, %) – 23,54

HbA1c (DCCT, %) = 0,0915 × HbA1c (IFCC, mmol/mol) + 2,153

In this report the term “HbA1c”, in the unit mmol/mol, will be used for the measurand. The conclusions in the report are based on calculations in HbA1c, mmol/mol. Some results in the tables and figures are also shown in the unit DCCT%.

4.2. InnovaStar HbA1c instrument

InnovaStar® analyzer is an analyser for biochemical in-vitro diagnostics of various components i.e., HbA1c and glucose. The system should only be used and operated by trained personnel. It consists of an instrument, a slider with reagent and wash solution and a ParamCard, in this evaluation an oneHbA1c IS card, see Figure 1a. Figure 1b depicts the slider with a sample cup containing a capillary, the reagent cartridge for the HbA1c measurement and the cleaner. The application, calibration and lot data are stored on the ParamCard. According to the producer, the system enables the determination of diagnostic HbA1c as well as HbA1c as a marker for blood glucose control. The method is particle enhanced immunoturbidimetric and the measurement principle is spectrophotometric using the wavelength range from 450 nm to 700 nm. This evaluation deals with the HbA1c test on InnovaStar.

InnovaStar uses the following equations for calculating results in mmol/mol and DCCT%:
HbA1c (mmol/mol) = (HbA1c (DCCT% – 2,15) / 0,0915
HbA1c (DCCT%) = 0,0915 x HbA1c (mmol/mol) + 2,15

Figure 1a. The instrument InnovaStar including one HbA1c IS ParamCard (top).

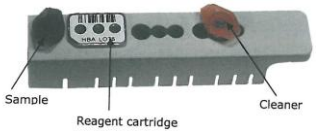

Figure 1b.The slider with the sample cup in which a capillary is located (not seen), the reagent cartridge and the cleaner.

For more technical data about the InnovaStar system, see table 3 and attachment 2. For information about the manufacturer DiaSys Diagnostic Systems GmbH and the suppliers in the Scandinavian countries, see attachment 3. For product information, see attachment 4.

Table 3. Technical data from the manufacturer

Technical data for the InnovaStar system	
Sample material	Capillary blood/ whole blood
Sample volume	10 µL
Measuring time	6 minutes to result, additional 1 minute for cleaning procedures
Measuring range	9 – 130 mmol/mol 3%-14% DCCT
Storage capacity	50 results
Electrical power supply	Power supply adapter, 12 W

4.3. The selected comparison method

A selected comparison method is a fully specified method which, in the absence of a Reference method, serves as a common basis for the comparison of an evaluated method.

4.3.1. *The selected comparison method in this evaluation*

The selected comparison method in this evaluation is the Tosoh G8 high-performance liquid chromatography (HPLC) ion exchange method in the Department of Clinical Biochemistry, Nordsjællands Hospital, Hillerød, hereafter called "the comparison method".
Tosoh is the most used instrument for HbA1c measurements in Denmark. The method is calibrated with frozen whole blood calibrators from MCA Laboratory, Queen Beatrix Hospital, the Netherlands. The values are assigned with IFCC Reference Measurement Procedure.
The comparison method is accredited after DS/EN ISO 15189:2008.Two Tosoh G8 instruments were used in the evaluation. The deviation between the two instruments should be ≤1,4%.

4.3.2. *Verification of the analytical quality of the comparison method*

4.3.2.1. Precision

The repeatability of the comparison method was estimated from duplicate measurements of venous ethylenediaminetetraacetic acid (EDTA) samples from patients with and without diabetes. The goal for the maximum allowable imprecision is ≤2,8%.

4.3.2.2. Trueness

The trueness of the comparison method was documented with the EQA results before, during and after the evaluation. The goal for the bias when compared to other Tosoh instruments was ≤±2,8%.

4.3.2.3. Internal quality control

Internal quality control samples from DEKS and Bio-Rad were analysed daily on the comparison method instruments.The repeatability of the comparison method was calculated from internal quality control results.

4.3.2.4. External quality control

The Department of Clinical Biochemistry participates in the Labquality survey number 3044 sent out five times every year. About 237 laboratories from 14 countries participate, were 155 of the laboratories are from the Nordic countries.
The EQA control materials are unmodified fresh whole blood. The materials get assigned values from the European Reference Laboratory (ERL) in the Netherlands. The laboratory uses two IFCC secondary reference methods; Menarini HA 8160 HPLC (ion exchange) and Primus HPLC (affinity).

4.4. The evaluation

The aim of the evaluation
In the hospital laboratory:

- examine the analytical quality of HbA1c results achieved with InnovaStar under standardised and optimal conditions with about 100 venous and 40 capillary patient samples
- compare capillary and venous results achieved with InnovaStar with an established hospital laboratory method for HbA1c
- evaluate the control materials for InnovaStar
- evaluate the user-friendliness of InnovaStar

In each of the primary health care centres:

- examine the analytical quality of HbA1c results achieved with InnovaStar under intended conditions with at least 40 capillary patient samples
- compare capillary results achieved with InnovaStar in two primary health care centres with an established hospital laboratory method for HbA1c
- evaluate the control materials for InnovaStar
- evaluate the user-friendliness of InnovaStar

According to the protocol, the HbA1c results in this evaluation should be calculated in the unit mmol/mol; the results should also be presented in DCCT% units.

4.4.1. *Planning of the evaluation*

Background for the evaluation
InnovaStar manufactured by DiaSys Diagnostic Systems GmbH in Germany has been launched in many countries but not in Scandinavia.

Inquiry about an evaluation
Med-Kjemi AS, Norway, applied for a SKUP evaluation of InnovaStar HbA1c prior to launch in Scandinavia. SKUP in Denmark accepted to carry out this evaluation.

Protocol and contract
The protocol for the evaluation was approved in November 2013. Med-Kjemi AS, Norway and SKUP in Denmark signed the contract the 19th of November 2013.

Preparations and training program
Diasys Diagnostics tested the agreement of the four instruments before the instruments were sent to Denmark. In December 2013 Esther Jensen, SKUP, the nurses Bibi Gotlieb and Majbrit Due, Birkevej, Skibby and the biomedical laboratory scientists Sofie Bagge and Helle Bojesen-Koefoed, Hørsholm, were trained by Lisbeth Andrén, Med-Kjemi AS for approximately one hour at their respective location.
Esther Jensen, SKUP and the local biomedical laboratory scientists that were consultants for the General Practitioner (GP) were present in Skibby and Hørsholm and taught the participants the logistic procedures for the evaluation.

During the training Lisbeth Andrén contacted the manufacturer because the instrument in Hørsholm was set up with a wrong date, and the printer in the hospital printed the whole print

setup after calibrations. DiaSys immediately offered a new instrument and a new printer for the evaluation. It was decided to use the instrument with the wrong date in the evaluation and to use the printer as a back-up for the three other printers in order to avoid time delay.

The practical work with the evaluation was carried out in December 2013 and January 2014.

4.4.2. *Evaluation sites and persons involved*

The hospital evaluation took place at the Department of Clinical Biochemistry, Nordsjællands Hospital.
The primary health care evaluation took place in medical centres in Skibby and Hørsholm. They normally do not use capillary samples to analyse HbA1c.
All participants in the evaluation are presented in table 4.

Table 4. Persons responsible for various parts of the evaluation

Name	Title	Organisation	Responsibility
Lisbeth Andrén	Product Manager	Med-Kjemi AS, Norway	Ordered the evaluation
Esther Jensen	Physician	SKUP Department of Clinical Biochemistry, Nordsjællands Hospital	Practical work with the evaluation Author of the report Responsible for the comparison method
Emmelie Svane	Biomedical laboratory scientist	Department of Clinical Biochemistry, Nordsjællands Hospital	Contact person for Lægerne Birkevej, Skibby
Karin Eirheim	Biomedical laboratory scientist	Department of Clinical Biochemistry, Nordsjællands Hospital	Contact person for Lægerne Hovedgaden, Hørsholm
Bibi Gotlieb Majbrit Due	Nurses	Lægerne Birkevej, Skibby	Practical work with the evaluation
Sofie Bagge Helle Bojesen-Koefoed	Biomedical laboratory scientists	Lægerne hovedgaden 43 Hørsholm	Practical work with the evaluation
Steen Ingemann Hansen	Civil engineer	Department of Clinical Biochemistry, Nordsjællands Hospital	Responsible for the comparison method
Doris Nellemann	Biomedical laboratory scientist	Department of Clinical Biochemistry, Nordsjællands Hospital	Responsible for the comparison method

4.4.3. *The evaluation model*

The evaluation consists of two parallel parts. One part of the evaluation was carried out under standardised and optimal conditions by laboratory educated personnel in a hospital laboratory using at least40 capillary and 100 venous samples from as many individuals. The evaluation in the hospital laboratory lasted more than 20 days, and 3 lots of test cartridges were used. This part of the evaluation documents the quality of the system under conditions optimal for achieving good analytical quality.
The second part of the evaluation was performed in two primary health care centres by the intended end-users. The centres each included at least 40 patients. From each patient, two capillary samples for InnovaStar and a venous sample for the comparison method were taken. At least one of the centres should not have a biomedical laboratory scientist employed.

4.4.4. *The evaluation procedure in the hospital laboratory, standardised and optimal conditions*

Internal analytical quality control

Two levels of the internal quality control samples for the InnovaStar (TruLab HbA1c liquid, DiaSys level 1 and level 2) were measured in duplicate each evaluation day.
Internal quality control samples are used daily to assure that the method and the instrument works satisfactory. It will be evaluated, whether the control material can be used for this purpose.

Recruitment of patients and sample collection

40 outpatients coming to the hospital laboratory to have their HbA1c measured were invited to participate in the hospital laboratory evaluation. Participation was voluntary and verbal consent was considered sufficient. Each patient was included only once. The 40 capillary samples were analysed with lot 65, n=5, lot 66, n=19 and lot 67, n=16.
Additionally 62 venous EDTA samples from the routine production were included in the evaluation. There were no request for distribution of concentration levels; however, the aim was that the sample results covered the full measurement range. Samples that were included due to their concentration were often analysed with the comparison method the day before. Thus, the two results with the comparison method can be achieved with up to 48 hours apart.
34 venous samples were measured using lot 65, 37 using lot 66 and 31 using lot 67.

Devices for collection of samples for InnovaStar

Haemolance plus, depth 1,4 mm from HaeMedic was used for skin puncturing.
Capillaries (10 µL, Na-heparin) were used for sampling and then added to a sample cup with buffer.

Handling of samples and measurements for InnovaStar

40 outpatients had two capillary samples and a venous EDTA sample drawn.
The two capillary samples were collected from one finger prick. The first drop of blood was removed; the two capillaries were filled from the second drop if possible. The capillaries were immediately placed in a sample cup with buffer. The cups were shaken until the blood was washed out of the capillary, as described in the manual [10]. The sample cup with the capillary, reagent cartridge and cleaner was placed on the slider and the sample was measured on InnovaStar within one hour.

The venous sample for InnovaStar and the comparison method was collected using a 4 mL K_2-EDTA tube from Greiner. The tube was inverted 8-10 times to ensure thorough mixing. The sample was stored at room temperature before analysed in duplicate.

Four measurements (two capillary and two venous) per patient were performed using one lot number of test cartridges and one InnovaStar instrument. Three lot numbers of InnovaStar test cartridges of various production dates were used in this evaluation. The results were printed from the InnovaStar Thermal printer in the unit mmol/mol and in DCCT%.

Analysing on the comparison method
Two instruments were used for the comparison method. Most of the 102 venous samples were analysed once on both Tosoh G8 instruments, the rest of the duplicate results were obtained from one Tosoh instrument. The time from blood sampling to analysis of the last measurement was less than eight hours for the outpatient samples and less than 48 hours for all samples. The duplicate patient chromatograms from Tosoh G8 were printed and stored. The results were given in the unit mmol/mol and in DCCT%.

Recording of results
All results were registered consecutively on a registration form prepared by SKUP. All errors were reported. All results were signed by the person performing the practical work.

Data processing
The data was checked for outliers. A possible bias of the comparison method results was ruled out using the external quality survey Labquality HbA1c EQA program 3044. Bias and repeatability of the comparison method and InnovaStar were calculated. The CV is calculated with a 90% confidence interval.

Evaluation of user-friendliness
The evaluator of InnovaStar evaluated the user-friendliness after the practical work by means of the user-friendliness questionnaire worked out by SKUP.

4.4.5. *Evaluation procedure in primary health care*
Internal analytical quality control
Two InnovaStar quality control samples (TruLab HbA1c liquid, DiaSys level 1 and/or level 2) were measured each evaluation day.

Recruitment of patients and sample collection
Two primary health care centres were enrolling patients. At least 40 patients per centre, coming to have their HbA1c measured, were invited to participate in the evaluation. Participation was voluntary and verbal consent was considered to be sufficient. Each patient was included only once. There were no demands to the HbA1c concentrations of the results. The distribution of the three lots was: lot 65; 27 patients; lot 66, six patients and lot 67; 55 patients.

Handling of samples and measurements for InnovaStar and the comparison method
From each patient two capillary samples were collected from one finger prick and measured on InnovaStar. The first drop of blood was removed; the two capillaries were filled from the second drop if possible. The capillaries were immediately placed in a sample cup with buffer. The cups were shaken until the blood had left the capillary, as described in the manual [10]. The sample cup with the capillary, reagent cartridge and cleaner were placed on the slider and the sample was measured on InnovaStar within one hour. Two lots of reagent cartridges were used in each primary care centre.

A venous sample for the comparison method was collected from each patient using a K_2-EDTA tube from Greiner. The samples were stored at room temperature until being sent to Nordsjællands Hospital and analysed in duplicate with the comparison method the same day.

Recording of results
All results were registered consecutively on a registration form prepared by SKUP. All errors were reported. All results were signed by the person performing the practical work.

The precision of InnovaStar
Repeatability was calculated from the results of approximately 80 duplicate capillary samples measured on InnovaStar. Formula 2 in attachment 5 was used for the calculation. The results are divided into two HbA1c levels, and the CV is given with a 90% confidence interval.

Comparison between InnovaStar and Tosoh G8
The comparison of InnovaStar versus Tosoh G8 was carried out with the first result from 88 duplicate capillary samples measured on InnovaStar and the mean result from 88 duplicate measurements of EDTA whole blood samples on Tosoh G8 instrument 1 or 2.

Evaluation of user-friendliness
After the practical work was completed, the evaluators evaluated the user-friendliness of InnovaStar by means of the user-friendliness questionnaire worked out by SKUP.

5. Results and discussion

Statistical expressions and calculations used by SKUP are shown in attachment 5.
Formula 2 is used for the calculations of repeatability in this evaluation.

5.1. Number of samples

Hospital

In the hospital laboratory evaluation, 40 individuals participated with capillary and venous samples for measurements on InnovaStar. All measurements were made in duplicates, in total four results for each patient. In addition 62 venous samples were collected from the laboratory's routine measurements. The 62 samples were measured on InnovaStar and the comparison method in duplicates.

Primary health care centres

In the primary health care evaluation, one centre recruited 40 patients and the other 48 patients for duplicate capillary measurements on InnovaStar and duplicate venous measurements on the comparison method.

5.1.1. *Excluded and missing results*

In the hospital laboratory

Three sample results were excluded as outliers according to the rules of Burnett [11] from bias calculations because of large differences between InnovaStar and the comparison method:

- No. 8: InnovaStar capillary sample results: 59,1 and 59,7 mmol/mol. The two venous sample InnovaStar results were 51,1 and 52,7 mmol/mol and the two Tosoh results were 34,2 and 35,9 mmol/mol.
- No. 17: InnovaStar venous sample results were 54,8 and 54,9 mmol/mol and the two Tosoh results were 38,6 and 38,3 mmol/mol.
- No. 75: InnovaStar capillary sample results: 86,0 and 88,5 mmol/mol. The two venous sample InnovaStar results were 89,7 and 91,9 mmol/mol and the two Tosoh results were 38,8 and 39,1 mmol/mol.

The segregation of outliers is made with repeated truncations, and all results are checked. The results are classified according to low, medium and high HbA1c concentration levels, and the outlier-testing is carried out at each level separately.

One sample was higher than the upper measuring limit (130 mmol/mol) twice with InnovaStar. The duplicate results with the comparison method was 143,4 and 142,3. The result is excluded from the calculations; however it is counted as correct.

- No. 27: The display showed LimH.

In primary health care centre 1

Two capillary sample results were excluded as outliers according to Burnett's model [11] in the calculation of repeatability of InnovaStar. These results were also removed before calculation of trueness. The data is specially marked in figure 4.

- No. 112: InnovaStar capillary sample results: 65,3 and 68,2 mmol/mol. The two Tosoh results were 67,5 and 68,1 mmol/mol.

- No. 132: InnovaStar capillary sample results: 48,1 and 41,4 mmol/mol. The two Tosoh results were 42,3 and 42,6 mmol/mol.

Sample no. 116 was excluded as outlier according to the rules of Burnett [11] from bias calculations because of large differences between InnovaStar and the comparison method:

- No. 116: InnovaStar capillary sample results: 50,3 and 48,9 mmol/mol. The two Tosoh results were 41,3 and 41,8 mmol/mol.

In primary health care centre 2
Five capillary sample results were excluded as outliers according to Burnett's model [11] in the calculation of repeatability of InnovaStar. These results were also removed before calculation of trueness. The data is specially marked in figure 4.

- No. 209: InnovaStar capillary sample results: 30,1 and 14,3 mmol/mol. The two Tosoh results were 27,4 and 28,7 mmol/mol.
- No. 223: InnovaStar capillary sample results: 48,1 and 58,6 mmol/mol. The two Tosoh results were 55,3 and 55,4 mmol/mol.
- No. 230: InnovaStar capillary sample results: 45,0 and 37,0 mmol/mol. The two Tosoh results were 42,4 and 42,0 mmol/mol.
- No. 234: InnovaStar capillary sample results: 29,5 and 37,8 mmol/mol. The two Tosoh results were 36,6 and 36,3 mmol/mol.
- No. 236: InnovaStar capillary sample results: 11,5 and 36,8 mmol/mol. The two Tosoh results were 33,7 mmol/mol twice.

Sample no. 248 was excluded as an outlier according to the rules of Burnett [11] from bias calculations because of large differences between InnovaStar and the comparison method:

- No. 248: InnovaStar capillary sample results: 41,1 and 39,1 mmol/mol. The two Tosoh results were 29,8 and 29,4 mmol/mol.

No. 245 and 246 were only measured once with the comparison method in the hospital. The single results are used in the calculations for accuracy and bias.

5.1.2. *Failed measurements*

In the hospital laboratory

- No. 42. "Failure Reagent". The reason was that 'System solution' was empty.
- No. 73: 1st result: error LimL, which means that the result is lower than the lower limit of the measuring range. When repeated, the sample was run without comments.
- Before sample no. 97 the following message was displayed: "Failure Cassette Switch off!". After calibration, the sample was run without comments.

The total number of technical errors in the hospital laboratory and the primary health care centres was three of 380 patient results and 130 control measurements ~ 0,6%.

Conclusion
InnovaStar had three technical errors and did fulfil the quality goal of a maximum of 2% waste due to technical errors.

5.2. Analytical quality of the selected comparison method

5.2.1. *Internal quality control*

Three internal quality control samples, one from DEKS and two from Bio-Rad were analysed daily on the comparison method instruments.

For the DEKS control material, 2045 NL, no 9153, analysed twice a day in 'diluent' mode, the CV for the two Tosoh instruments was 0,6% and 0,7% at the concentration 59,17 mmol/mol. The deviation from 59,17 mmol/mol was less than ±1% in 2013.

The Bio-Rad control materials were analysed once daily at two levels. The imprecision for the low level (33,08 mmol/mol) was 1,2% and 0,8% for Tosoh 1 and 2, respectively. Both Tosoh instruments had a CV of 0,6% with the high concentration (80,49 mmol/mol).

The goal for the Tosoh instruments is that the difference between the results of the instruments do not exceed 1,4%. This goal had been met during a six month period before the evaluation as well as during the evaluation.

5.2.2. *The precision of the comparison method*

The double determinations were performed within two days from sampling with a time span of up to 48 hours between the duplicates, and the duplicate results originate from two different Tosoh G8 instruments.

Table 5a. Repeatability of HbA1c, Tosoh G8 with venous whole blood EDTA samples

Level	HbA1c interval		Excluded results	HbA1c mean	*CV (90% CI)
	mmol/mol	n	n	mmol/mol	% (%)
Low	26,3 — 46,4	34	0	37,4	1,2 (1,0 — 1,4)
Medium	47,1 — 72,8	34	0	59,1	0,7 (0,6 — 0,9)
High	77,2 — 143	34	0	93,1	0,9 (0,7 — 1,1)
All	26,3 — 143	102	0	63,2	

*The calculated CV values are measures of imprecision under intermediate conditions: The duplicate measurements were often analysed with a time span of two days, and the duplicate results originate from two instruments.

As seen in table 5a, the imprecision under intermediate conditions of the Tosoh G8 instruments fulfils the quality goal for the comparison method of CV ≤ 2,8% even when calculations are made with results from two instruments. The CV 1,2% for the low concentration group is higher than the CV 0,7% for the medium HbA1c concentration. Therefore CV all is not calculated.

All duplicate chromatograms were analysed for abnormalities. No abnormalities were found, and none of the patients had a haemoglobin variant.

Calculations for the same samples in the unit DCCT% can be seen in table 5b. Raw data is presented in attachment 6.

Table 5b. Repeatability of HbA1c, Tosoh G8. Results achieved by venous whole blood EDTA samples

Level	HbA1c interval DCCT%	n	Excluded results n	HbA1c mean DCCT%	*CV (90% CI) % (%)
Low	4,56 — 6,34	34	0	5,55	0,7 (0,6 — 0,9)
Medium	6,40 — 8,82	34	0	7,55	0,5 (0,4 — 0,6)
High	9,22 — 15,22	34	0	10,67	0,7 (0,6 — 0,9)
All	4,56 — 15,22	102	0	7,93	0,6 (0,6 — 0,7)

*The calculated CV values are measures of imprecision under intermediate conditions: The duplicate measurements were often analysed with a time span of two days, and the duplicate results originate from two instruments.

5.2.3. *The trueness of the comparison method*

The Labquality Scheme number 3044 demonstrated November 2013 (2013-5) and February 2014 (2014-1) that the two comparison instruments (Tosoh-1 and Tosoh-2) had no deviation at the concentrations 53,3 mmol/mol and 60,4 mmol/mol. At the concentration 74,3 and 74,9 mmol/mol the deviation was +2,6 and +5,0%, see table 6. Both the Tosoh group and 'all' instruments in the survey had a positive deviation when compared with the assigned value 74,9 mmol/mol. The European Reference Laboratory (ERL) in the Netherlands in 2014 have assigned the values using Menarini HA 8160 HPLC (ion exchange) and Primus HPLC (affinity),

Table 6. Deviation when compared with Labquality HbA1c EQA program

	HbA1c mmol/mol	**deviation** %	**HbA1c** mmol/mol	**deviation** %	**HbA1c** DCCT %	**deviation** %	**HbA1c** DCCT %	**deviation** %
2013-5 target	***53,3***		***74,3***		***7,03***		***8,95***	
Tosoh-G8-1	54,0	+1,3	76,3	+2,7	7,09	+0,9	9,13	+2,0
Tosoh-G8-2	53,3	0,0	76,2	+2,6	7,07	+0,6	9,12	+1,9
2014-1 target	***60,4***		***74,9***		***7,68***		***9,00***	
Tosoh-G8-1	60,5	+0,2	78,7	+5,0	7,7	+0,3	9,4	+4,4
Tosoh-G8-2	60,3	−0,2	78,7	+5,0	7,7	+0,3	9,4	+4,4

In Sweden the maximum allowable bias for measurements in mmol/mol is ±1,5 mmol/mol from target. In Denmark, where almost all laboratories use Tosoh instruments, the maximum allowable bias for measurements in mmol/mol is ±2,8% compared to the Tosoh-group results.
Results from the comparison method in this evaluation are not adjusted for a possible deviation to the ERL target. All instruments and methods in the Labquality EQA program had a high positive deviation with the sample 2014-1 (target 74,9 mmol/mol). It is believed, that this target value should be lower. With the same calibrator the comparison instruments have both positive and negative deviations within ±2,8% from the ERL target values in other periods. There has been no change in the three internal control levels from Bio-Rad and DEKS during the period.

5.3. Analytical quality of InnovaStar in a hospital laboratory

5.3.1. *External quality assessment*

No EQA samples from Labquality were received during the evaluation period.

5.3.2. *Internal quality control*

In daily operation of the InnovaStar, the analytical quality of HbA1c is monitored with the internal quality control TruLab HbA1c liquid, DiaSys level 1 and level 2. The target and accept limits for the materials were 38,9 mmol/mol (31,1 – 46,6 mmol/mol) and 106 mmol/mol (85,2 – 128 mmol/mol), respectively.
During the 20 days of evaluation the InnovaStar quality control samples were measured twice each day. The samples for double determinations originated from two different sample cups.

The reproducibility was assessed using three lot numbers of reagent cartridges and one lot of low and high control materials (individually packed bottles). Control material may have other matrix effects than whole blood, and may therefore give other results than results achieved with blood.
The reproducibility of TruLab HbA1c liquid, DiaSys level 1 and level 2 with InnovaStar is shown in table 7a and 7b and raw data is shown in attachment 7.
One bottle of TruLab HbA1c liquid, DiaSys level 2 contained an HbA1c concentration that gave the result "LimH" which indicates a result higher than 130 mmol/mol. The results were confirmed with new samples in new sample cup preparations and measurements on the back-up instrument with other reagent lot numbers. All other results were within the accept limits.

Table 7a. Reproducibility of InnovaStar with control materials in the hospital laboratory

Material	n	Mean HbA1c (± 1,96 sd) mmol/mol	Reproducibility CV %
TruLab HbA1c liquid, DiaSys level 1	44	39,8 (37,9—41,7)	2,4
TruLab HbA1c liquid, DiaSys level 2	42	110,2 (104,5—116,0)	2,6

Table 7b. Reproducibility of InnovaStar with control materials (DCCT%) in the hospital laboratory

Material	n	Mean HbA1c, DCCT%	Reproducibility CV %
TruLab HbA1c liquid, DiaSys level 1	44	5,79	1,7
TruLab HbA1c liquid, DiaSys level 2	42	12,23	2,3

Discussion

The InnovaStar display and the printer were set so the results of the samples were given in both mmol/mol and DCCT%. The results in table 7a and 7b originates from the same measurements. For mathematical reasons the CV% are not the same in the same measurements given in mmol/mol and DCCT%.
The CV achieved with the control materials was 2,4%and 2,6% for level 1 and level 2 control material, respectively. The quality goal for imprecision for genuine samples, a CV less than 3,0%

was achieved with both control materials analysed during 20 days with three lot of reagents. These results show that the TruLab HbA1c liquid, DiaSys might be useful to check whether the InnovaStar instrument works satisfactory.

5.3.3. *Comparison of the 1st and 2nd measurements*

Two capillary and two venous whole blood measurements were performed on samples drawn from 40 and 102 individuals, respectively for measurements on InnovaStar. The results were checked to meet the imposed condition for using formula 2 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).

5.3.4. *The precision of InnovaStar*

Repeatability under standardised and optimal measuring conditions in a hospital laboratory was obtained with capillary (table 8a and 8b) and venous whole blood samples (table 9a and 9b). For the capillary samples the repeatability was calculated for two subgroups, the 20 lowest and the 20 highest results with the comparison method. For the venous samples the repeatability was calculated for three subgroups: the lowest (n=34), the middle (n=34) and the highest level of HbA1c-values (n=34). The three groups were chosen according to their concentration with the comparison method. The InnovaStar raw data in attachment 8 is only available for Med-Kjemi.

Table 8a. Repeatability of HbA1c (mmol/mol) InnovaStar with capillary samples in the hospital laboratory

Level	**HbA1c interval Tosoh G8**	**Excluded results**		**HbA1c mean InnovaStar**	**CV (90% CI)**
	mmol/mol	**n**	**n**	**mmol/mol**	**% (%)**
Low	28,6 — 40,0	20	0	40,6	1,8 (1,5 — 2,3)
High	40,6 — 84,0	20	0	58,7	2,0 (1,7 — 2,5)
All	28,6 — 84,0	40	0	49,7	1,9 (1,7 — 2,2)

Table 8b. Repeatability of HbA1c (DCCT%) InnovaStar with capillary patient samples in the hospital laboratory

Level	**HbA1c interval Tosoh G8**	**Excluded results**		**HbA1c mean InnovaStar**	**CV (90% CI)**
	DCCT%	**n**	**n**	**DCCT%**	**% (%)**
Low	4,76 — 5,81	20	0	5,87	1,1 (1,0 — 1,5)
High	5,86 — 9,84	20	0	7,53	1,4 (1,1 — 1,7)
All	4,76 — 9,84	40	0	6,70	1,2 (1,1 — 1,5)

Table 9a. Repeatability of HbA1c (mmol/mol) InnovaStar with venous whole blood EDTA patient samples in the hospital laboratory

Level	HbA1c interval Tosoh G8	Excluded results		HbA1c mean InnovaStar	CV (90% CI)
	mmol/mol	n	n	mmol/mol	% (%)
Low	26,3 — 46,4	34	0	41,9	1,5 (1,3 — 1,8)
Medium	47,1 — 72,8	34	0	48,8	1,8 (1,6 — 2,1)
High	77,2 — 143	34	1*	95,5	1,6 (1,4 — 1,9)
All	26,3 — 143	102	1*	63,2	1,6 (1,5 — 1,8)

The given numbers of results (n) are counted before the exclusion of results. Mean are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.1.
*one duplicate result was higher than 130 HbA1c mmol/mol which is the upper range of the measurement range.

Table 9b. Repeatability of HbA1c (DCCT%) InnovaStar with venous whole blood EDTA samples in the hospital laboratory

Level	HbA1c interval Tosoh G8	Excluded results		HbA1c mean InnovaStar	CV (90% CI)
	DCCT%	n	n	DCCT%	% (%)
Low	4,56 — 6,38	34	0	6,01	1,0 (0,9 — 1,2)
Medium	6,40 — 8,82	34	0	7,69	1,3 (1,2 — 1,6)
High	9,22 — 15,7	34	1*	10,88	1,3 (1,2 — 1,6)
All	4,56 — 15,7	102	1*	8,17	1,2 (1,1 — 1,4)

See table 9a, *one duplicate result was higher than 14,0 HbA1c DCCT%, see 5.1.1.

Discussion
The InnovaStar results were given in both mmol/mol and DCCT%. The CV% result is not the same for measurements given in mmol/mol and DCCT%.
Table 8b and 9b are calculations of the same measurements as used in table 8a and 9a.

The calculated CV values are measures of repeatability. The CV for the results in IFCC units is significantly lower than the quality goal 3,0% (corresponding to ≤2,0 CV% using DCCT%-units) for both the capillary and the venous subgroups and samples.

Conclusion
The analytical precision fulfils the goals for diagnostic HbA1c measurements.

5.3.5. *The trueness of InnovaStar*
Bias was calculated for the 40 patients with capillary sample results (two subgroups of HbA1c values), see table 10, and for the 102 patients with venous sample results divided into three subgroups of HbA1c values, see table 11. The subgroups were chosen according to their concentrations as measured by the comparison method.

The 40 capillary samples were analysed with lot 65, n=5, lot 66, n=19 and lot 67, n=16. The 34 venous samples were measured using lot 65, 37 using lot 66 and 31 using lot 67.

Table 10. Bias of InnovaStar HbA1c with capillary patient samples in the hospital laboratory

Level	HbA1c interval Tosoh G8		Excluded results	Bias (95% CI)	Bias (95% CI)
	mmol/mol	n	n	mmol/mol(mmol/mol)	% (%)
Low	28,6 — 40,0	20	2*	+2,4 ((+1,3) — (+3,6))	+7,5 ((+3,9)—(+11,1))
High	40,6 — 84,0	20	0	+1,6 ((+0,5) — (+2,7))	+3,3 ((+1,3) — (+5,4))
All	28,6 — 84,0	40	2*	+2,0 ((+1,3) — (+2,7))	+5,4 ((+3,3) — (+7,4))

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.1. *exclusion according to Burnett's model.

Table 11. Bias of InnovaStar HbA1c with venous patient samples in the hospital laboratory

Level	HbA1c interval Tosoh G8		Excluded results	Bias (95% CI)	Bias (95% CI)
	mmol/mol	n	n	mmol/mol (mmol/mol)	% (%)
Low	26,3 — 46,4	34	3*	+2,3 ((+1,5) — (+3,0))	+6,6 ((+4,3) — (+9,0))
Medium	47,1 — 72,8	34	0	+1,8 ((+1,0) — (+2,6))	+3,0 ((+1,7) — (+4,4))
High	77,2 — 143	34	1**	+3,9 ((+2,7) — (+5,1))	+4,4 ((+3,1) — (+5,6))
All	26,3 — 143	102	4	+2,7 ((+2,1) — (+3,2))	+4,6 ((+3,6) — (+5,6))

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.1. *exclusion according to Burnett's model. ** one duplicate result was higher than 130 HbA1c mmol/mol which is the upper range of the measurement range.

Discussion

There is no difference in bias for capillary and venous results; however both capillary and venous sample results have a positive bias compared to Tosoh instruments. The comparison method Tosoh might have a positive bias in the high concentrations during the evaluation (table 6). The bias of the InnovaStar might therefore be even a little higher than given in table 10 and 11 for the high concentration.

In this evaluation there was no quality goal for bias. In case of a high bias the quality goals for accuracy are more difficult to achieve.

5.3.6. *The accuracy of InnovaStar in the hospital laboratory*

To evaluate the accuracy of HbA1c results on InnovaStar in the hospital laboratory, the agreement between InnovaStar and the comparison method on Tosoh G8 is illustrated in an accuracy plot. The plot shows the deviation of single measurement results on InnovaStar from the comparison method, and gives a picture of both random and systematic deviation, reflecting the

total measuring error on InnovaStar. The accuracy is demonstrated for the first measurement of the paired results, only.

The accuracy of the HbA1cresults on InnovaStar is shown in figure 3a. The limits for the tolerated deviation according to the quality goal (±10%), are shown with dotted lines.

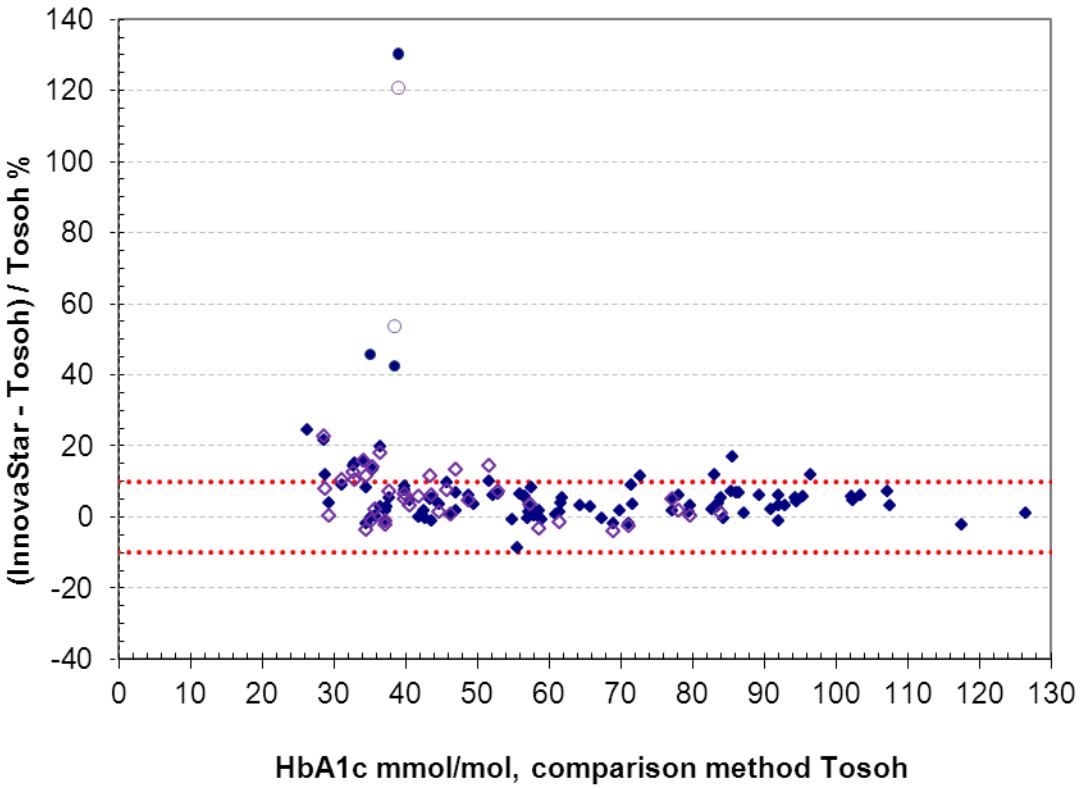

Figure 3a. Difference plot showing the accuracy of the InnovaStar HbA1c results measured in 40 capillary whole blood samples (open symbols) and 102 venous whole blood EDTA samples (closed symbols)in the hospital laboratory. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the first measurement of InnovaStar and the mean value of the duplicate results with the comparison method, n= 102. The five round symbols represent outliers originating from three individuals, see 5.1.1. Stippled lines represent allowable deviation ±10%.

Discussion

95% of the results should be within ≤±10% to fulfil the quality goal for allowable deviation. 27 of 38 capillary sample results (71,0%) and 86 of 99 venous sample results (86,9%) were within the maximal allowable deviation.

When including the outliers in the calculations, 27 of 40 capillary results ~ 67,5% and 86 of 102 ~ 84,3% venous results were within the maximal allowable deviation. The majority of the deviating results were found among the results below 37 mmol/mol. For results above 37 mmol/mol 94,3% of the venous samples had a deviation less than ±10% . The capillary and the venous sample results with InnovaStar are very alike, the duplicate measurements for the capillary and the venous samples for the outliers were similar. Probably the outlier deviation is

caused due to the differences in measurement systems: Tosoh is a HPLC method, while InnovaStar is an immunological method.
Three patients who would not have been diagnosed as "diabetic" with the comparison method would, according to the capillary and the venous InnovaStar results receive the diagnosis.
The deviating results did not have any connection to a particular lot.

Conclusion
94,3% of the venous sample results above 37 mmol/mol had a deviation less than ±10%. When including the low results between 19 and 37 mmol/mol, the quality goal was not fulfilled with a total of 84,3% of the venous samples and 68% of the capillary results being within a ±10% deviation. Results <37 mmol/mol are not relevant for diagnosing diabetes.

Calculations in the unit DCCT%
Figure 3a and 3b shows the same data in the unit mmol/mol and DCCT%.

As mentioned in chapter 3, the quality goal for HbA1c DCCT% previous was ±10%, this goal is shown with red dotted lines, and the present tolerated deviation for HbA1c DCCT% ±6,7% is shown in blue stippled line.

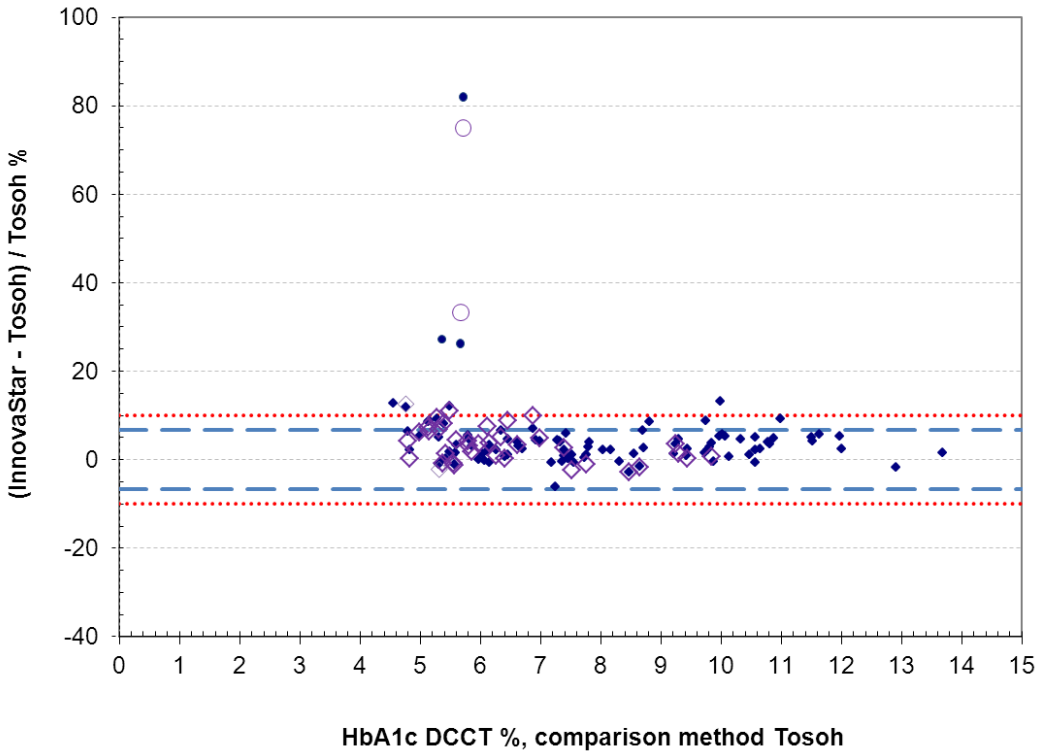

Figure 3b. Difference plot showing the accuracy of the InnovaStar HbA1c results measured with 40 capillary whole blood samples (open symbols) and 102 venous whole blood EDTA samples (closed symbols) in the hospital laboratory. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the first measurements of InnovaStar and the mean value of the duplicate results with the comparison method, n= 102. The five round symbols represent outliers originating from three individuals, see 5.1.1. Dotted red lines represent the previous allowable deviation ±10%. Stippled blue lines

represent the present quality goal of ±6,7%.The sample results are the same as in Figure 3a, the only difference is the unit.

Discussion
29 of 40 capillary sample results (73%) were within the maximal allowed deviation of ±6,7%.
87 of 102 of the venous sample results (85%) were within ±6,7%.
The InnovaStar display and the printer were set so the results of the samples were given in both mmol/mol and DCCT%. For mathematical reasons the CV% are not the same in the same measurements given in mmol/mol and DCCT%. Figure 3b illustrates the previous quality goals for HbA1c in DCCT% that were used in the first eleven SKUP reports (attachment no 13).
The sample results are the same as in Figure 3a, the only difference is the unit. 94 of 102 (92%) of the venous results and 35 of 40 (87,5%) of the capillary results were within <±10% from the comparison method (DCCT%). The numbers within <±10% (for measurements given in mmol/mol) and <±6,7% (for measurements given in DCCT%) are not quit the same despite the measurements are "identical".

Conclusion
InnovaStar did not fulfil the quality goals ±10% used in the previous reports nor the present diagnostic quality goal ±6,7%.

5.4. Analytical quality of InnovaStar in primary health care

5.4.1. *Internal quality control*
In daily operation of InnovaStar, the analytical quality of HbA1c is monitored with the internal quality control TruLab HbA1c liquid, DiaSys level 1 and level 2. The target and accept limits for the materials were 38,9 mmol/mol (31,1 – 46,6 mmol/mol) and 106 mmol/mol (85,2 – 128 mmol/mol), respectively.
The control material was measured daily in both primary health care centres. All results were within the accept limits. The reproducibility of TruLab HbA1c liquid, DiaSys level 1 and level 2 with InnovaStar is shown in table 12 and raw data is shown in attachment 9.

Table 12. Reproducibility of InnovaStar achieved with control materials at the primary health care centres

Primary health care centre	TruLab HbA1c liquid, DiaSys	N	mean HbA1c (± 1,96 sd) mmol/mol (mmol/mol)	Reproducibility CV%
1	Level 1	11	39,5 (38,2 — 40,8)	1,6
	Level 2	11	108,0 (104,3 — 111,7)	1,8
2	Level 1	12	40,7 (39,5 — 41,9)	4,5
	Level 2	10	117,3 (114,4 — 120,2)	3,5

Discussion
The reproducibility achieved with the control materials in primary health care centre 1 was <3,0 CV% for both levels.

The reproducibility achieved with the control materials in primary health care centre 2 was >3,0 CV% for both levels. The mean values for the high control were significantly different in the two centres.
The results originate from one bottle of each level in each centre. One reason for the differences could be that the haemoglobin concentration of the bottles might be different. This hypothesis is supported by the fact that the results from one of the bottles of TruLab HbA1c liquid, DiaSys level 2 in the hospital laboratory were above the upper end of the measuring range (attachment 7).
The higher reproducibility percentages in primary health care centre 2 are discussed in 5.4.5.

5.4.2. *The precision of InnovaStar*

The repeatability achieved in the two primary health care centres is shown in table 13. The raw data in attachment 10 is only available for Med-Kjemi.

Table 13. Repeatability InnovaStar, capillary samples. HbA1c results achieved by the primary health care centres

Level	HbA1c interval Tosoh G8		Excluded results	HbA1c mean InnovaStar	CV (90% CI)
	mmol/mol	n	n	mmol/mol	% (%)
Centre 1					
Low	33,0 — 39,1	20	0	36,9	0,9 (0,8 — 1,2)
High	39,3 — 67,8	20	2*	43,0	1,2 (1,0 — 1,5)
All	33,0 — 67,8	40	2*	39,8	1,0 (0,9 — 1,3)
Centre 2					
Low	29,6 — 41,9	24	3*	39,1	1,8 (1,6 — 2,3)
High	42,3 — 65,5	24	2*	53,6	3,2 (2,7 — 4,0)
All	29,6 — 65,5	48	5	46,3	2,6 (2,3 — 3,1)

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.1. *exclusion according to Burnett's model.

Discussion

The calculated CV values are measures of repeatability. The CV is significantly lower than the quality goal 3,0% for the capillary samples in primary health care centre 1 and for the low results (HbA1c < 42,0 mmol/mol) in centre 2. For the concentrations above 42,0 mmol/mol the CV 3,2% was higher than the quality goal 3,0 % (not statistically significant). Most likely the quality goal is not fulfilled in this subgroup.
The imprecision is significantly higher in centre 2 than in centre 1. The explanation for the outliers and the higher CV could, as discussed in 5.4.5, be caused by various ways to make sure that the 10µL of blood was shook out of the capillaries.
In 5.1.1 it is seen that primary health care centre 1 have outliers excluded because of small differences of 2,9 and 6,7 mmol/mol, respectively. The outliers of centre 2 deviated between 8,0 and 25,3 mmol/mol from each other. In centre 2, it is always the highest results that correspond to the comparison result.

5.4.3. *The trueness of InnovaStar in primary health care*

Bias was calculated for the 88 patient results from the two primary health care centres. The results were divided in two subgroups of HbA1c values. The groups were chosen according to their HbA1c-values on the comparison method.

Table 14. Bias of InnovaStar HbA1c with capillary patient samples in the primary health care centres

Level	**HbA1c interval Tosoh G8**		**Excluded results**	**Bias (95% CI)**	**Bias (95% CI)**
	mmol/mol	**n**	**n**	**mmol/mol (mmol/mol)**	**% (%)**
Centre 1					
Low	33,0 — 39,1	20	0	+1,3 ((+0,4) — (+2,1))	+3,6 ((+1,2) — (+5,9))
High	39,3 — 67,8	20	3*	−0,2 ((−1,1) — (+0,7))	−0,5 ((−2,4) — (+1,5))
All	33,0 — 67,8	40	3*	+0,7((+0,1) — (+1,3))	+2,1((+0,5) — (+3,6))
Centre 2					
Low	29,9 — 41,9	24	4*	+2,3 ((+1,5) — (+3,1))	+6,4 ((+4,1) — (+8,6))
High	42,3 — 65,5	24	2*	+2,6 ((+1,3) — (+3,9))	+5,0 ((+2,4) — (+7,7))
All	29,9 — 65,5	48	6*	+2,4 ((+1,6) — (+3,2))	+5,7 ((+4,0) — (+7,4))

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.1. *exclusion according to Burnett's model, see 5.1.1.

The primary health care centre 2 had no explanation for the outliers. Therefore some additional experiments were made in the hospital laboratory, see 5.4.5.

5.4.4. *The accuracy of InnovaStar in the primary health care centres*

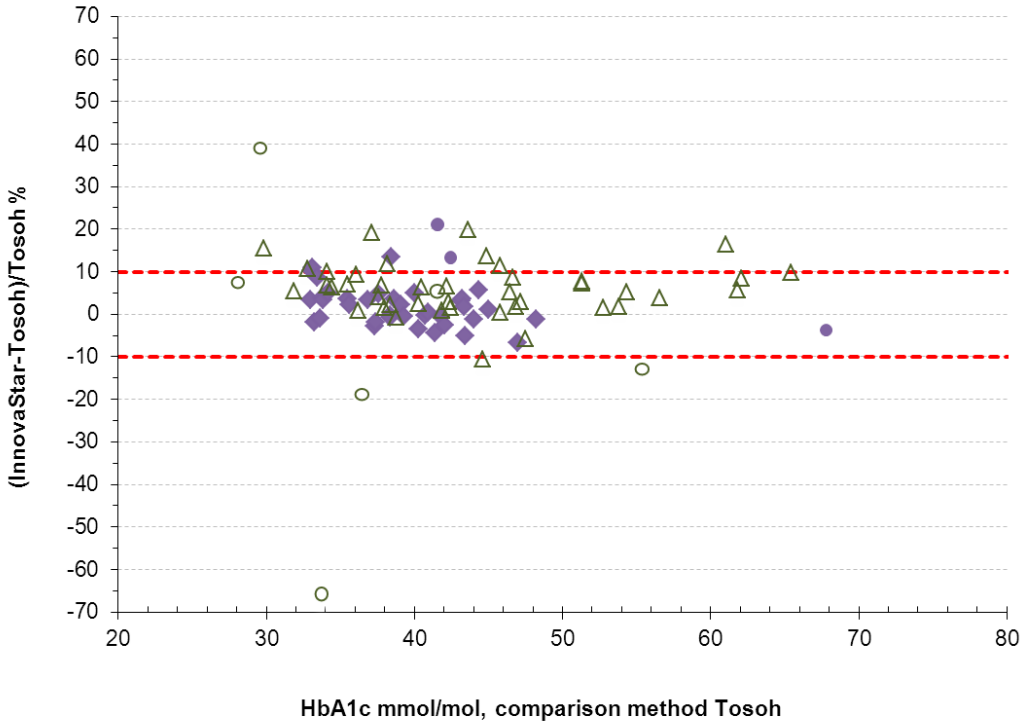

Figure 4. Difference plot showing the accuracy of the InnovaStar HbA1c results measured with 40 capillary whole blood samples (closed symbols) from primary health care centre 1 and 48 capillary whole blood samples (open symbols) from primary health care centre 2. The x-axis represents the mean value of the duplicate results with the comparison method. The y-axis shows the deviation in percent between the first measurements of InnovaStar and the mean value of the duplicate results with the comparison method. The round symbols represent outliers originating from nine individuals, see 5.1.1. Stippled lines represent allowable deviation ±10%.

Discussion

95% of the results should be within <±10% to fulfil the quality goals for allowable deviation. 35 of 40 capillary sample results (87,5%) at primary health care centre 1 and 35 of 48 sample results (73%) at primary health care centre 2 were within ±10%.
The deviating results did not have any connection to a particular lot.

Conclusion

The quality goal for accuracy (a deviation less than ±10% for ≥95% of the samples) was not fulfilled with capillary samples in the primary health care centres.

5.4.5. *Additional experiments*

Attempt was made to examine what might have caused the high imprecision in primary health care centre 2. According to the manufacturer, temperature deviation, drafts, direct sunlight and vibrations can result in faulty measuring values. The locations of the instruments in the primary health care centres were approved by Med-Kjemi. Diasys had examined the instruments just before the evaluation to assure they measured correctly.

Volume: It was investigated whether a sample of 10 µL was crucial: one sample (No. 18) was analysed using 10, 5, 20 and 30 µL (~100%, 50%, 200% and 300% volume) venous EDTA whole blood. The results were 41,9 – 41,2 – 41,7 and 41,3 mmol/mol.

Sedimentation of blood in blood drop: A EDTA whole blood drop was placed on parafilm 0, 2 and 15 minutes before added to the buffer. The results were not affected: 110, 112 and 112 mmol/mol.

Every morning the 'supposed' number of reagent cartridges to be used were taken from the refrigerator and placed randomly on the table, where the testing was performed in the primary health care centres. The conditions chosen (table 15) is regarded as the most extreme, that possibly can happen according to temperature and reagents. The same four cups with TruLab HbA1c liquid, Diasys level 1 and 2 were analysed with instrument 597 and reagent cartridge at 'normal', 'low' and 'high' temperature and with too little reagent in the bottom of the cartridge.

Temperature: Control material was analysed with reagent cartridges at room temperature, reagent cartridges taken directly from refrigerator or reagent cartridges placed close to a heat source (table 15).

Reagent volume: The reagent cartridges were also placed 'up-side-down' and analysed without ensuring the reagent was at the bottom of the reagent cartridges (table 15).

Table 15 Influence of temperature and reagent cartridge position

Lot	Blood volume	Temperature of reagent cartridge	TruLab HbA1c liquid, DiaSys level 1		TruLab HbA1c liquid, DiaSys level 2		Position of reagent cartridge
	µL	ºC	mmol/mol		mmol/mol		
66	10	22	38,1	39,6	109	108	
66	10	4,4	37,7	36,6	103	101	
66	10	30	42,6	44,3	124	124	
66	10	22	43,5	39,5	113	111	'up-side-down'

It is demonstrated in table 15 that InnovaStar results are sensitive to the temperature of the reagent cartridge (using one lot and one instrument). The results in the first row are assumed to be correct. In the following rows it is shown that a low temperature (4ºC) lowers the results 4 to 6% for the low and high control, respectively and a high temperature (30ºC) elevates the results 12 to 14%. Lack of reagent in the bottom of the reagent cartridge container also gave elevated results of 3 to 7%.

Effect of shaking

After the evaluation, an old sample with a haemoglobin variant was run in duplicates with InnovaStar in the hospital laboratory. The results of the two cups were deviating, 34,0 and 49,9 mmol/mol. When repeated, the results were 37,7 and 50,0 mmol/mol and it was observed, that the colour of the capillary in the cup with the low result was dark red compared to the other. After shaking and reanalysing both cups again, the duplicate results became similar, 51,4 and 50,5 mmol/mol.

Discussion

Three patients had significantly different results with InnovaStar and the comparative method. The difference was verified by using two comparison instruments, two reagent cartridge lot, two InnovaStar instruments and in two cases both capillary samples and two different venous EDTA tubes from patients.

In the hospital laboratory and a medical centre very alike measurements were obtained in duplicate while the second medical centre had some duplicate measurements with high imprecision. During the evaluation a small trial was conducted to possibly explain the cause for this. Sample volume is not important for the InnovaStar HbA1c result. Sedimentation of a blood drop during 15 minutes before analysing did not change the results. Temperature of the reagent cartridge can cause differences in the duplicate results. If the cartridge was used too quick after removal from refrigerator it would be expected that the first result should deviate, which is not the case in the evaluation.

Lack of reagent at the bottom of the reagent cartridge container can cause higher results. However, in this evaluation it was always the highest result in centre 2 that correlated with the comparison method. Low or high temperature of the reagent can influence the result. However, all reagent cartridges were treated after the recommendations and the outliers did not fit with 'new cups' from refrigerator that have not received room temperature. In the hospital laboratory the cups were shaken 15 times each. In centre 1 the cups were shaken 15 times and they were visually inspected for whole blood in the capillary. In centre 2, the cups were shaken less than 15 times and then visually assessed.

The difference in CV% might originate from these differences in procedure. If the capillary in the cup is not completely emptied, the result becomes falsely low. If so, this means that the partial emptying of the capillary is not homogeneous, as it is demonstrated that 5 µl venous whole blood ~ 50% volume does not affect the result.

A deviating duplicate result was changed after shaking: the duplicate results became similar.

Conclusion

The hypothesis that the cause for the higher repeatability in primary health care centre 2, may be due to partial emptying of the capillary is supported by the small additional experiments and the fact that it is the highest duplicate result that corresponds to the comparison result.

5.5. Evaluation of user-friendliness

5.5.1. *Questionnaire to the evaluators*

The most important response regarding user-friendliness comes from the users themselves. The end-users often emphasize other aspects than those pointed out by more extensively trained laboratory personnel.

At the end of the evaluation period, each user fills in a questionnaire about the user-friendliness of the instrument. The questionnaire is divided into four sub-areas:

Table A) Rating of the information in the manual / insert / quick guide
Table B) Rating of operation facilities. Is the system easy to handle?
Table C) Rating of time factors for the preparation and the measurement
Table D) Rating of performing internal and external quality control

The end-users fill in table A and B. SKUP fills in table C and D, and in addition topics marked with grey colour in table A and B.

In the tables the first column shows what is up for consideration. The second column in table A and B shows the rating by the individual users at the evaluation sites. The last three columns show the rating options. The overall ratings from all the evaluating sites are marked in coloured and bold text. The last row in each table summarises the total rating in the table. The total rating is an overall assessment by SKUP of the described property, and not necessarily the arithmetic mean of the rating in the rows. Consequently, a single poor rating can justify an overall poor rating, if this property seriously influences on the user-friendliness of the system.

Unsatisfactory and intermediate ratings will be marked with an asterisk and explained below the tables.

Comment

In this evaluation, the user-friendliness was assessed by five persons at three evaluation sites; two primary health care centres and one hospital laboratory in the rating order centre 1 (two persons), centre 2(two persons) and hospital laboratory (one person).

Table A. Rating of the information in the manual / insert / quick guide

Topic	Rating	Assessment	Assessment	Assessment
General impression	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Table of contents	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Preparations / Pre-analytic procedure	**I, I, I, I, I**	Satisfactory	**Intermediate**[1]	Unsatisfactory
Specimen collection	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Measurement procedure	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Reading of result	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Description of the sources of error	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Help for troubleshooting	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Readability / Clarity of presentation	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Keyword index	**S, S, S, S, S**[2]	**Satisfactory**	Intermediate	Unsatisfactory
Measurement principle	**S, S, S, S, S**[2]	**Satisfactory**	Intermediate	Unsatisfactory
Available insert in Danish, Norwegian, Swedish	**S, S, S, S, S**[2]	**Satisfactory**[3]	Intermediate	Unsatisfactory
Total rating by SKUP		**Satisfactory**		

[1]There is an error in the manual, since the manual says that the capillary must be broken. It should not.
[2]The evaluators in primary health care should not answer the 'grey area questions'. However, they did anyway.
[3]The manual is in Norwegian and English. Of the Scandinavian countries, the test is only meant for Norway at the moment.

Table B. Rating of operation facilities

Topic	Rating	Assessment	Assessment	Assessment
To prepare the test / instrument	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
To prepare the sample	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Application of specimen	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Specimen volume	**S, S, S, I, I**	**Satisfactory**	**Intermediate**[1]	Unsatisfactory
Number of procedure step	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Instrument / test design	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Reading of the test result	**E, E, E, E, E**	**Easy**	Intermediate	Difficult
Sources of errors	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Cleaning / Maintenance	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Hygiene, when using the test	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Size and weight of package	**S, S, S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Storage conditions for tests, unopened package	**S, S, S, S, S**[2]	**+15 to +30°C**	**+2 to +8°C**	–20°C
Storage conditions for tests, opened package	**S, S, S, S, S**[2]	**+15 to +30°C**	**+2 to +8°C**	–20°C
Environmental aspects: waste handling	**S, S, S, S, S**[2]	**No precautions**	Sorted waste	Special precautions
Intended users	**L, L, L, L, L**[2]	Health care personnel or patients	**Laboratory experience**[3]	Biomedical laboratory scientists
Total rating by SKUP		**Satisfactory**		

[1a]The capillaries are very small and difficult to handle in large hands - but easy to use.
[1b]The capillaries sometimes difficult to pick from holder.
[2]The evaluators in primary health care should not answer the 'grey area questions'. However, they did anyway.
[3]All evaluators agreed the instrument demanded laboratory experience.

Table C. Rating of time factors (filled in by SKUP)

Topic	Assessment	Assessment	Assessment
Required training time	**<2 hours**	2 to 8 hours	>8 hours
Durations of preparations / Pre-analytical time	**<6 min.**	6 to 10 min.	>10 min
Duration of analysis	**<10 min.**	10 to 20 min.	>20 min
Stability of test, unopened package	**>5 months**	3 to 5 months	<3 months
Stability of test, opened package	**>30 days**	14 to30 days	<14 days
Stability of quality control material, unopened	**>5 months**	3 to 5 months	<3 months
Stability of quality control material, opened	**>6 days or disposable**	2 to 6 days	≤1 day
Total rating by SKUP	**Satisfactory**		

Table D. Rating of quality control (filled in by SKUP)

Topic	Assessment	Assessment	Assessment
Reading of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
Usefulness of the internal quality control	**Satisfactory**	Intermediate	Unsatisfactory
External quality control	**Satisfactory**	Intermediate	Unsatisfactory
Total rating by SKUP	**Satisfactory**		

The control material should be stored at 2-8ºC.

5.5.2. *Assessment of the user-friendliness*

Assessment of the information in the manual (table A)

The information in the manual was assessed as satisfactory. The manual was not fully updated with the procedure for the capillaries. The procedure was explained during training.

Assessment of the operation facilities (table B)

The operation facilities were assessed as satisfactory. The capillaries were sometimes difficult to shake out of a narrow hole in the cap of the container. It was, however, possible to remove the cap from the container and pick the capillaries.

Both nurses and biomedical laboratory scientists noted in the evaluation that the instrument required laboratory experience.

Assessment of time factors (table C)
The time factors were assessed as satisfactory. It is an advantage that the test cup with sample can be stored at room temperature and analysed up to 10 hours later.

Assessment of quality control possibilities (table D)
The quality control possibilities were assessed as satisfactory. The material can be used for revealing failing analytical quality. The system can also use external liquid control material.

6. References

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Attachment 1 The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of Noklus[1] in Norway, DAK-E[2] in Denmark, and Equalis[3] in Sweden. SKUP was established in 1997 at the initiative of laboratory medicine professionals in the three countries. SKUP is led by a Scandinavian *steering committee* and the secretariat is located at Noklus in Bergen, Norway.

The purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information on analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

SKUP offers manufacturers and suppliers evaluations of equipment for primary health care and also of devices for self-monitoring. Provided the equipment is not launched onto the Scandinavian market, it is possible to have a confidential pre-marketing evaluation. The company requesting the evaluation pays the actual testing costs and receives in return an impartial evaluation.

There are *general guidelines* for all SKUP evaluations and for each evaluation a specific *SKUP protocol* is worked out in co-operation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. A *complete evaluation* requires one part performed by experienced laboratory personnel as well as one part performed by the intended users.

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned.The code is composed of the acronym SKUP, the year and a serial number. A report code, followed by an asterisk (*), indicates a special evaluation, not complete according to the guidelines, e.g. the part performed by the intended users was not included in the protocol. If suppliers use the SKUP name in marketing, they have to refer to www.skup.nuand to the report code in question. For this purpose the company can use a logotype available from SKUP containing the report code.

SKUP reports are published atwww.skup.nu.

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[1] Noklus (Norwegian Quality Improvement of Primary Care Laboratories)is an organisation founded by Kvalitetsforbedringsfond III (Quality Improvement Fund III), which is established by The Norwegian Medical Association and the Norwegian Government. Noklus is professionally linked to “Seksjon for Allmennmedisin” (Section for General Practice) at the University of Bergen, Norway.

[2] SKUP in Denmark is placed in Nordsjællands Hospital. SKUP in Denmark reports to DAK-E (Danish Quality Unit of General Practice), an organisation that is supported by KIF (Foundation for Quality and Informatics) and Faglig udvalg (Professional Committee), which both are supported by DR (The Danish Regions) and PLO (The Organisation of General Practitioners in Denmark).

[3] Equalis AB (External quality assurance in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by “Sveriges Kommuner och Landsting” (Swedish Association of Local Authorities and Regions), “Svenska Läkaresällskapet” (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

Attachment 2 Facts about the measurement system

These forms are is filled in by SKUP and DiaSys Diagnostic Systems GmbH on behalf of Med-Kjemi AS

Table 1. Basic facts

Name of the measurement system:	InnovaStar instrument
Dimensions and weight:	Width: 200 mm Depth: 170 mm Height: 150 mm Weight: 4 kg
Components of the measurement system:	Photometrical measurement: Tungsten lamp → flow cell → microspectrometer
Measurand:	HbA1c (other components are not part of evaluation)
Sample material:	Capillary blood, EDTA whole blood
Sample volume:	10 µL
Measuring principle:	Latex enhanced immunoturbidimetric test
Traceability:	IFCC and NGSP traceable
Calibration:	Factory 5 point pre-calibrated, no calibration at customer site
Measuring range:	3-14 % HbA1c (DCCT)
Linearity:	3-14 % HbA1c (DCCT)
Measurement duration:	7 minutes
Operating conditions:	+15°C to +30°C
Electrical power supply:	Power supply adapter, 12 W
Recommended regular maintenance:	Every two years
Package contents:	InnovaStar analyzer, slider, power supply adapter, manual
Necessary equipment not included in the package:	10 µL capillaries, system solution, sample cups, controls TruLab HbA1c level 1 and 2, reagent cartridges

Table 2. Post analytical traceability

Is input of patient identification possible?	Yes
Is input of operator identification possible?	No
Can the instrument be connected to a bar-code reader?	Yes
Can the instrument be connected to a printer?	Yes
What can be printed?	Patient results, patient identifications, date, time and sample number
Can the instrument be connected to a PC?	Yes
Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	Yes No
Storage capacity and what is stored in the instrument?	50 results and patient identifications, date, time and sample number
Is it possible to trace/search for measurement results?	Yes

Table 3. Facts about the Reagent cartridge

Name of the reagent cartridge:	oneHbA1c IS
Stability in unopened sealed vial:	18 months
Stability in opened vial:	Not applicable
Package contents:	100 tests, 10 Cleaner Cups, package insert

Table 4. Quality control

Electronic self-check:	Yes, during start up
Recommended control materials:	TruLab HbA1c Level 1 and Level 2
Stability in unopened sealed vial:	15 months
Stability in opened vial:	15 months if after opening contamination and evaporation is avoided
Package contents:	reference value sheet and instruction for use • Small Package content 1 x 0,25 mL • Big Package content 4 x 0,25 mL

Attachment 3 Information about manufacturer, retailers and marketing

Marketing information

Manufacturer:	DiaSys Diagnostic Systems GmbH Alte Strasse 9 65558 Holzheim Germany Mail: info@diasys.de Tel.: +49 6432 9146 0
Retailers in Scandinavia:	Denmark: No Norway: Yes Med-Kjemi AS Drengsrudbekken 9 1383 Asker Norway Mail: firmapost@med-kjemi.no tel: +47 66 76 49 00 Sweden: No
In which countries is the system marketed:	Globally: no
Date for start of marketing the system in Scandinavia:	When the SKUP evaluation is completed
Date for CE-marking:	February 2010
In which Scandinavian languages is the manual available:	Norwegian

Attachment 4 Product information, InnovaStar HbA1c

InnovaStar HbA1c serial numbers

Instrument	Serial number	Used by
InnovaStar HbA1c	597	Nordsjællands Hospital
InnovaStar HbA1c	587	Hørsholm (centre 1)
InnovaStar HbA1c	614	Skibby (centre 2)
InnovaStar HbA1c	570	Nordsjællands Hospital, backup

The printers used had serial numbers 1041861C, 1041862C and 1041863C

InnovaStar HbA1cParamCard and reagent cartridges

oneHbA1c IS	Lot number	Kit lot	Expiry date	Used by
Lot	03 005 65	60089125	2014-11	Nordsjællands Hospital, Skibby
Lot	03 001 66	60089302	2014-11	Nordsjællands Hospital, Hørsholm
Lot	03 001 67	60089986	2014-11	Nordsjællands Hospital, Hørsholm Skibby

Control materials

TruLab HbA1c liquid	Batch	Lot	Expiry date	Used by
Level 1 (38,6 mmol/mol; 5,60 DCCT%)	18729	60089599	2014-09	All
Level 2 (106 mmol/mol; 11,8 DCCT%)	18731	60089598	2014-09	All

Other equipment used in the evaluation

Other equipment	Lot number	Expiry year	Used by
Greiner, K_2-EDTA 4 mL tube		2015	All
DiaCapil Sample Cups InnovaStar	254567	2015	All
System Solution InnovaStar		2015	All
Na-heparin End-to-end Kapillaren, ~ minicaps ~ Einmal-Kapillarpipetten ~ Disposable Capillaries from Hirschmann Laborgeräte, Germany	60089857	2015	All
Haemolance plus, Haemedic, Puncture depth: 1,4 mm	T42Y624G1	2018	All

Attachment 5 Statistical expressions and calculations

This chapter with standardised text deals with the statistical expressions and calculations used by SKUP. The chapter is a short extract of the comprehensive SKUP-document "Statistics in SKUP reports", presented atwww.skup.nu**,** under the option "The SKUP evaluation". The statistical calculations will change according to the type of evaluation. The descriptions in section 4.2 are valid for evaluations of quantitative methods with results on the ratio scale.

Statistical terms and expressions

The definitions in this section come from the ISO/IEC Guide 99; International Vocabulary of Metrology, VIM [a].

Precision

Definition: Precision is the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under stated specified conditions.

Precision is measured as *imprecision*. Precision is descriptive in general terms (good, poor e.g.), whereas the imprecision is expressed by means of the standard deviation (SD) or coefficient of variation (CV). SD is reported in the same unit as the analytical result. CV is usually reported in percent.

To be able to interpret an assessment of precision, the precision conditions must be defined.
Repeatability is the precision of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series).
Reproducibility is the precision of discontinuous measurements of the same component carried out under changing measuring conditions over time.

Trueness

Definition: Trueness is the closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value.

Trueness is inversely related to systematic measurement error. Trueness is measured as *bias*. Trueness is descriptive in general terms (good,poor e.g.), whereas the bias is reported in the same unit as the analytical result or in percent.

Accuracy

Definition: Accuracy is the closeness of agreement between a measured quantity value and the true quantity value of a measurand.

Accuracy is not a quantity and cannot be expressed numerically. A measurement is said to be more accurate when it offers a smaller measurement error. Accuracy can be illustrated in a difference-plot. Accuracy is descriptive in general terms (good, poor e.g.).

a. ISO/IEC Guide 99:2007, International vocabulary of metrology – Basic and general concepts and associated terms, VIM, 3rd edition, JCGM 200:2008

Statistical calculations

Statistical outliers
The criterion promoted by Burnett [b] is used for the detection of outliers. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is set to 5%. The segregation of outliers is made with repeated truncations, and all results are checked. Where the results are classified according to different concentration levels, the outlier-testing is carried out at each level separately. Statistical outliers are excluded from the calculations.

Calculation of imprecision
The precision of the field method is assessed by use of paired measurements of genuine patient sample material. The results are divided into three concentration levels, and the estimate of imprecision is calculated for each level separately, using the following formula [c,d]:

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$

d = difference between two paired measurements (formula 1)
n = number of differences

This formula is used when the standard deviation can be assumed reasonable constant across the concentration interval. If the coefficient of variation is more constant across the concentration interval, the following formula is preferred:

$$CV = \sqrt{\frac{\sum (d/m)^2}{2n}}$$

m = mean of paired measurements (formula 2)

The two formulas are based on the differences between paired measurements. The calculated standard deviation or CV is still a measure of the imprecision of single values. The imposed condition for using the formulas is that there is no systematic difference between the 1st and the 2nd measurement of the pairs. The CV is given with a 90% confidence interval.

Calculation of bias
The mean deviation (bias) at different concentration levels is calculated based on results achieved under optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results on the comparison method and the mean values of the duplicate results on the field method. The mean difference is shown with a 95% confidence interval.

Assessment of accuracy
The agreement between the field method and the comparison method is illustrated in a difference-plot. The x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on the field method and the mean value of the duplicate results on the comparison method. The number of results within the quality goal limits is counted and assessed.

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Attachment 6 Raw data HbA1c, comparison method results

Attachment 7 Raw data HbA1c, internal quality control, InnovaStar in the hospital laboratory

		TruLab HbA1c liquid, DiaSys							
date	**Reagent cartridge Lot no.***	**level 1**		**level 2**		**level 1**		**level 2**	
		mmol/mol				**DCCT%**			
30-11-2013	66	39,6	40,0	113	116	5,77	5,51	12,5	12,8
03-12-2013	66	38,9	41,8	109	112	5,71	5,97	12,1	12,4
04-12-2013	67	40,4	40,8	111	111	5,85	5,88	12,3	12,3
07-12-2013	67	39,3	39,6	113	111	5,74	5,77	12,5	12,3
09-12-2013	67	40,1	41,1	109	106	5,82	5,91	12,1	11,8
10-12-2013	67	39,7	39,7	108	110	5,78	5,79	12,0	12,2
11-12-2013	65	41,3	40,6	114	115	5,93	5,86	12,6	12,7
12-12-2013	65	41,0	39,7	113	111	5,90	5,78	12,5	12,3
13-12-2013	65	39,5	40,8	113	110	5,76	5,88	12,5	12,2
13-12-2013	65	40,9	40,0	111		5,89	5,81	12,4	
14-12-2013	66	39,1	39,4	106	108	5,73	5,75	11,8	12,0
15-12-2013	66	39,0	39,0	limh	limh	5,72	5,72	limh	limh
15-12-2013	66			109	112			12,1	12,4
16-12-2013	66	39,5	38,3	107	108	5,77	5,65	12,0	12,0
17-12-2013	66	39,9	40,4	107	111	5,81	5,84	11,9	12,3
18-12-2013	66	38,1	38,8	107	107	5,64	5,70	11,9	11,9
19-12-2013	66	40,7	38,9	110	105	5,88	5,71	12,2	11,8
20-12-2013	67	39,8	38,9	108	108	5,79	5,71	12,0	12,0
27-12-2013	66	38,1	39,6	109	108	5,64	5,77	12,2	12,0
30-12-2013	65	40,6	41,4	117	115	5,86	5,94	12,9	12,7
03-01-2014	66	39,8	41,8	114	109	5,79	5,98	12,6	12,1
06-01-2014	66	38,2	38,7	110	107	5,65	5,69	12,2	11,9
07-01-2014	67	39,7	40,4	112		5,79	5,84	12,4	

*only the last two numbers in the lot number is used, see attachment 4.

13-12-2013: End of first bottle of TruLab HbA1c liquid, DiaSys level 1.
15-12-2013: Use of second bottle of TruLab HbA1c liquid, DiaSys level 2. Repeated results were higher than the upper measuring range.
07-01-2014: Single measurement, no TruLab HbA1c liquid, DiaSys level 2 materials left

Attachment 8 Raw data HbA1c, InnovaStar results, in the hospital laboratory

Attachment 9 Raw data HbA1c, internal quality control, InnovaStar in the two primary health care centres

Primary Health Care Centre 1, Hørsholm

date	Reagent cartridge Lot no. *	TruLab HbA1c liquid, DiaSys level 1 mmol/mol	TruLab HbA1c liquid, DiaSys level 2 mmol/mol	TruLab HbA1c liquid, DiaSys level 1 DCCT%	TruLab HbA1c liquid, DiaSys level 2 DCCT%
02-12-2013	66	40,1		5,82	
03-12-2013	67	40,6	111	5,86	12,3
04-12-2013	67	38,9	110	5,71	12,2
05-12-2013	67	38,9	105	5,71	11,7
06-12-2013	66	40,0	107	5,81	11,9
09-12-2013	67	38,5	107	5,68	11,9
10-12-2013	67	39,4	105	5,75	11,8
11-12-2013	66	39,0	109	5,72	12,1
16-12-2013	66	39,4	108	5,75	12,1
17-12-2013	66	40,1	109	5,82	12,1
18-12-2013	66	39,6	109	5,77	12,1
19-12-2013	66		108		12,0

*only the last two numbers in the lot number is used, see attachment 4.

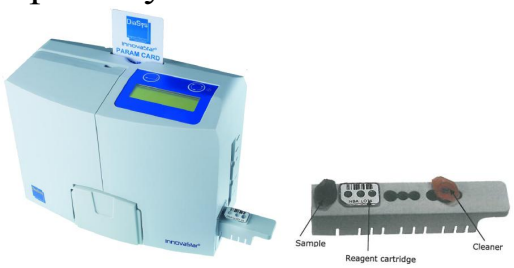
Primary Health Care Centre 2, Skibby

date	Reagent cartridge lot no.*	TruLab HbA1c liquid, DiaSys level 1 mmol/mol	TruLab HbA1c liquid, DiaSys level 2 mmol/mol	TruLab HbA1c liquid, DiaSys level 1 DCCT%	TruLab HbA1c liquid, DiaSys level 2 DCCT%
02-12-2013	66	40,8	40,2	5,83	
03-12-2013	65	39,9	35,5	5,80	5,40
04-12-2013	65	114	120	12,6	13,1
05-12-2013	65	41,6	42,3	5,95	6,02
09-12-2013	65	120	117	13,1	12,8
10-12-2013	65	115	114	12,7	12,6
11-12-2013	67	41,3	40,6	5,93	5,86
12-12-2013	67	116	112	12,7	12,4
17-12-2013	67	41,8	41,5	5,97	5,95
18-12-2013	67	126	119	13,7	13,1
19-12-2013	67	42,6	40,7	6,05	5,87

*only the last two numbers in the lot number is used, see attachment 4.

Attachment 10 Raw data HbA1c, InnovaStar results, from the two primary health care centres

Attachment 11 "SKUP-info". Summary for primary health care



InnovaStar til analyse af HbA1c fra DiaSys Diagnostic Systems GmbH
Sammendrag fra en afprøvning i regi af SKUP

Konklusion, Kvalitetsmål i de to lægehuse

- **CV≤3% (Coefficient of Variance, Variationskoefficient)**
  kapillære, patientprøver lægehus1: CV = 0,9 og 1,2% (kvalitetsmål opfyldes)
  patientprøver lægehus2: CV = 1,8 og 3,2% (opfyldes måske ikke)
- **Afvigelse fra sammenligningsmetoden: <±10%**
  kapillære prøver: 73 og 88% (opfyldes ikke)
- **Tilfredsstillende brugervenlighed (manual, tid, betjening af instrument)**
  Begge lægehuse var tilfredse med instrumentet
- **Kontrolmaterialet i 2 niveauer**
  lægehus1: CV<3% for begge niveauer (kvalitetsmål opfyldes)
  lægehus2: CV= 4,5 og 3,5% niveau 1 og 2 (kvalitetsmål opfyldes måske ikke)

InnovaStar Hba1c er beregnet til analyse af HbA1c. med-kjemi, Norge har bestilt afprøvningen.

Afprøvningen blev udført af bioanalytikere, sygeplejersker og læge på 128 kapillære og 102 venøse prøver i to lægehuse og en klinisk biokemisk afdeling på sygehus.

Resultater
InnovaStar Hba1c opfyldte kvalitetskravet (CV maks 3%) for analyseusikkerhed (imprecision) med **venøse og kapillære** prøver samt **kontroller** i sygehus og i lægehus1. Kvalitetskravet var også opfyldt for lave koncentrationer med middelkoncentration 36,9 mmol/mol i lægehus 2, men formentlig ikke opfyldt for høje koncentrationer med middelværdi 53,6 mmol/mol.
Kvalitetsmål er fastsat til afvigelse ≤±10% fra sammenligningsmetoden. Henholdsvis 88 og 67% (lægehuse) og 84% (sygehus) resultater fra kapillære prøver opfyldte kvalitetsmålet. For venøse prøveresultater med koncentration >37 mmol/mol blev kvalitetsmålet opfyldt for 94% i hospital.

Brugervenlighed
Manual, tidsfaktorer, kontrolmuligheder og betjening af instrumentet blev vurderet som tilfredsstillende af brugerne. Det kræver laboratorieerfaring at anvende instrumentet.

Yderligere information
Oplysninger om pris fås ved at kontakte med-kjemi, Norge, der har bestilt afprøvningen.
Hele rapporten fra afprøvningen af ***InnovaStar Hba1c***, SKUP/2014/101, findes på SKUPs hjemmeside www.skup.nu og på www.skup.dk, hvor den er farvekodet efter kvalitetskravet fra Laboratorieudvalget vedrørende almen praksis.

Attachment 12 List of previous SKUP evaluations

Summaries and complete reports from the evaluations are found at www.skup.nu. In addition, SKUP reports are published at www.skup.dk, where they are rated according to the national Danish quality demands for near patient instruments used in primary health care. SKUP summaries are translated into Italian by Centre for Metrological Traceability in Laboratory Medicine (CIRME), and published athttp://users.unimi.it/cirme. SKUP as an organisation has no responsibility for publications of SKUP results on these two web-sites.

The 30 latest SKUP evaluations

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2014/101	HbA1c	InnovaStar HbA1c	DiaSys Diagnostic Systems GmbH
SKUP/2014/105	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/87	Glucose[1]	Wellion Calla Light	Med Trust Handelsges.m.b.H.
SKUP/2013/100	Glucose[1]	Mylife Unio	Bionime Corporation
SKUP/2013/97	NT-proBNP	Cobas h 232 POC system	Roche Diagnostics GmbH
SKUP/2013/92	CRP	Eurolyser smart 700/340	Eurolyser Diagnostica GmbH
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/85	Glucose, β-Ketone	Nova StatStrip	Nova Biomedical Corporation, USA
SKUP/2013/96	Hemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB Marknadsbolag Sverige
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer Healthcare
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd
SKUP/2011/93*	Glucose	Accu-Chek Performa	Roche Diagnostics
SKUP/2011/90	CRP	*i*-Chroma	BodiTech Med. Inc.
SKUP/2011/84*	PT-INR	Simple Simon PT and MixxoCap	Zafena AB
SKUP/2011/86	Glucose[1]	OneTouch Verio	LifeScan, Johnson & Johnson
SKUP/2011/77	CRP	*Confidential*	
SKUP/2011/70*	CRP	smartCRP system	Eurolyser Diagnostica GmbH
SKUP/2010/83*	Glucose	*Confidential*	
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2010/80	PT (INR)	INRatio2	Alere Inc.
SKUP/2010/89*	Glucose	FreeStyle Lite	Abbott Laboratories
SKUP/2010/88*	HbA1c	*Confidential*	
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmBH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/67	Allergens	*Confidential*	
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB

*A report code followed by an asterisk indicates that the evaluation is not complete according to SKUP guidelines, since the part performed by the intended users was not included in the protocol, or the evaluation is a follow-up of a previous evaluation, or the evaluation is a special request from the supplier.
[1] Including a user-evaluation among diabetes patients

Attachment 13 List of previous HbA1c SKUP evaluations

SKUP HbA1c evaluations between 1999 and 2014

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2014/101	HbA1c	InnovaStar HbA1c	DiaSys Diagnostic Systems GmbH
SKUP/2012/91	HbA1c	Quo-Test	Quotient Diagnostics Ltd
SKUP/2010/88	HbA1c	*Confidential*	
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2009/76*	HbA1c	*Confidential*	
SKUP/2008/65	HbA1c	Afinion HbA1c	Axis-Shield PoC AS
SKUP/2006/58	HbA1c	*Confidential*	
SKUP/2006/41*	HbA1c	*Confidential*	
SKUP/2003/26*	HbA1c	*Confidential*	
SKUP/2003/25*	HbA1c	*Confidential*	
SKUP/1999/4	HbA1c	DCA 2000	Bayer
SKUP/1999/3	HbA1c	NycoCard HbA1c	Axis-Shield PoC AS

Attachment 14 Comments from DiaSys Diagnostic Systems GmbH

Comments about the SKUP report 2014/101:

"InnovaStar® analyzer - A system for measurement of HbA1c manufactured by DiaSys Diagnostic Systems GmbH"

First of all DiaSys Diagnostic Systems GmbH would like to thanks SKUP and all involved persons for the comprehensive evaluation study of the InnovaStar® POCT analyzer with the oneHbA1c IS assay.

DiaSys Diagnostic Systems GmbH is pleased to hear, that the participating users of the InnovaStar® assess the analyzer as "Satisfactory", which is the highest level in SKUP classification. We appreciate all the efforts which were done to perform the precision study as well as the method comparison study which revealed the excellent performance and the ease of use of the InnovaStar® system.

DiaSys would like to take the opportunity to give some comments about some issues reported in the SKUP evaluation:

Method comparison bias / outliers:

In method comparisons performed by SKUP, slightly higher results from InnovaStar® were observed compared to Tosoh HPLC method. Despite this shift, 94.3% of the results in the diagnostically interesting range above 37 mmol/mol had a deviation less than ±10% (goal from SKUP 95%).

Since the SKUP evaluation, DiaSys has made changes to its internal calibration procedure for the reagents. DiaSys now calibrates directly with a pool of fresh patient samples with calibration values assigned by reference methods. We therefore expect less deviation to Tosoh HPLC systems.

The very high outliers seen in the method comparison performed in the hospital laboratories were unexpected and further investigations have to be done on that issue. Therefore the raw data from the evaluation sites are mandatory. Since such outliers were not observed before, we would highly appreciate to receive such sample material causing high outliers for further investigations.

Error in the manual about handling of capillaries:

DiaSys Diagnostic Systems GmbH recommends the use of open end capillaries, which have to be broken at a predetermined point for very accurate volume handling. This procedure is correctly described in the user manual. Due to the fact that in Scandinavia such capillaries are not common, another type of capillaries (end to end) has been used. We will improve the user

manual for the Scandinavian market in local languages, which describes also the handling of the end to end capillaries.

In addition we will also supply each instrument in the Scandinavian market with a quick guide for instrument setup and also a quick guide for correct capillary blood sampling procedures.

For a more convenient handling of the small end to end capillaries DiaSys also offers a special capillary holder, which was not used during SKUP evaluation.

DiaSys is looking forward to offer the InnovaStar in the Scandinavian market to ease the treatment of the still growing number of diabetes patients.

DiaSys highly appreciates the opportunity to have participated in the SKUP evaluation since this increase the confidence in the InnovaStar system on operator's as well as on patients side.

Please note:
The quality goals have been tightened compared to previous SKUP evaluations and therefore results are hardly comparable.

David Ehlers
Product Manager Systems
DiaSys Diagnsotic Systems GmbH

2/2 21.11.2014