USER-EVALUATION
ASCENSIA CONTOUR Blood Glucose Meter System

Table of contents

Attachments with raw data are included only in the copy to Bayer AS.

Summary

Background
Acsensia Contour is a meter designed for glucose self-measurements by diabetic patients. The meter is produced by Bayer HealthCare and is supplied in Scandinavia by Bayer. Ascensia Contour was launched onto the Norwegian market in the autumn of 2003.
In order to give reimbursement for the test strips, The National Social Insurance Office (*Rikstrygdeverket*) in Norway instructs the companies to carry out an evaluation that includes a user-evaluation among diabetic patients. The evaluation of Ascensia Contour is done under the direction of SKUP during the spring of 2004.

The aim of the evaluation
The aim of the evaluation of Ascensia Contour is to

- reflect the analytical quality under standardised and optimal conditions (performed by two biomedical laboratory scientists)
- reflect the analytical quality by the users (app. 75 diabetics)
- compare the analytical quality before and after training and practice
- examine if hematocrit interferes with the measurements
- check the lot-variation of test strips
- evaluate Ascensia Contour regarding user-friendliness
- evaluate the Ascensia Contour user manual

Materials and methods
76 diabetic patients took part in the evaluation. All participants met twice at NOKLUS. At the first consultation the patients did a finger prick and performed two measurements on the Ascensia Contour meter, without further instructions. The biomedical laboratory scientist also took capillary samples of the diabetic patients and measured twice at Ascensia Contour. In addition, two capillary samples were taken to a designated comparison method. Then the diabetics were given a standardised instruction about the Ascensia Contour meter. In a practice period of approximately three weeks the diabetics used the meters at home, before they were called for a second consultation. The blood glucose sampling and measurement procedures at the first consultation were repeated, and in addition a sample for hematocrit was taken. Three different lots of test strips were used in the evaluation. All the participants finally answered questionnaires about the user-friendliness of the meter and about the user manual.

Results

- Ascensia Contour shows acceptable precision. The CV is < 5 % under standardised and optimal measuring conditions and approximately 5 % when the measurements are performed by diabetic patients.
- The agreement with a designated comparison method is good on certain conditions. Quality goals set in ISO 15197 and by ADA are achieved under standardised and optimal measuring conditions when using the first measurement of paired results. The second measurement in the pair is systematic higher than the first. When handled by the diabetic patients, Ascensia Contour shows good results initially. After three weeks of use at home the results are not as good as the initial ones. 80 % of these results are within the quality goals set in ISO 15197 and 90 % are within the “adjusted ISO-goal”. It is not clear why these results do not meet the quality goals.

- The three lots of test strips that were used showed no clinical significant bias from the comparison method.
- Glucose measurements on Ascensia Contour seem to be affected by the hematocrit values of the samples in a higher degree than described in the package insert. The glucose values are over-estimated when hematocrit is low and under-estimated when hematocrit is high. The hematocrit effect applies not only for high glucose values in combination with high hematocrit values, but is also true for glucose values below 11,1 mmol/L and for hematocrit values within the reference range. Although the glucose results under standardised and optimal conditions seem to be affected by the hematocrit, they were within ±15 % of the comparison method, as shown in figure 7.
- The diabetic patients summarise the Ascensia Contour device as easy to use. As a whole they were pleased with the device. The patients that had used the user manual were satisfied with the manual.

Conclusion

Glucose measurements on Ascensia Contour have acceptable precision. The results obtained under optimal measuring conditions are within the strict quality goals set by ADA. The measurements performed by the diabetic patients when the device is new are within the quality goals set in the ISO-guide 15197. After having been used at home and outside controlled conditions for three weeks, the device no longer performed satisfactorily. The results obtained after the practice period do no longer fulfil the quality goals. It has not been possible to find an explanation for this, but there is no reason to believe that the poor results are caused by user errors. The glucose results in this evaluation are affected by hematocrit in a higher degree than described in the package insert. The users say that the Ascensia Contour device is easy to use and they are quite satisfied with the device.

Comments from Bayer Diagnostics

A rebuttal to SKUP from Bayer HealthCare Self Testing Systems Division is found in attachment 12. An answer from SKUP is given in attachment 13.

Planning of the evaluation

Trine Setterberg from Bayer applied to *Scandinavian Evaluation of Laboratory Equipment for Primary Health Care*, SKUP, in the autumn of 2003 for an evaluation of the glucose meter Ascensia Contour. In October SKUP gave a written offer together with a preliminary suggestion regarding how to organise the evaluation. The offer was accepted by Torstein Myhre, representative from Bayer AS, in November 2003, and a contract was set up between SKUP and Bayer AS. The Laboratory at Haraldsplass Diaconal Hospital accepted to carry out the analytical part of the evaluation dealing with the reference samples. Two biomedical laboratory scientists, Wenche Eilifsen Hauge and Kjersti Østrem, were given the responsibility for the practical work with the comparison method at the laboratory.
The Ascensia Contour system was launched onto the market in Norway in November -03. SKUP carried out the user-evaluation of Ascensia Contour blood glucose meter system during the spring of 2004.

SKUP evaluations are made according to guidelines in the book "*Evaluation of analytic instruments. A guide particularly designed for evaluations of instruments in primary health care"* [1]. The evaluation of a self-monitoring blood glucose device follows the guidelines in the book, but the evaluation in primary health care is replaced by a user-evaluation conducted among diabetic patients based on the model by the NOKLUS-project "Diabetes – Self-measurements".

The evaluation comprises the following studies:

- examine analytical quality under standardised and optimal conditions done by two biomedical laboratory scientists
- examine analytical quality among 75 diabetic patients
- examine agreement between Ascensia Contour and a designated comparison method
- compare analytical quality among diabetic patients between first and final consultation
- examine if hematocrit effects the Ascensia Contour measurements
- examine lot-to-lot-variations
- evaluate user-friendliness of Ascensia Contour
- evaluate user-manual of Ascensia Contour

The blood sampling of the diabetic patients and the measurements on Ascensia Contour under standardised and optimal conditions were done by Camilla Eide Jacobsen, SKUP, and Åse Nilsen, NOKLUS. The statistical calculations are done by Åse Nilsen and Kari Nerhus, NOKLUS. The report is written by Grete Monsen, SKUP.

Analytical quality specifications

There are different criteria for setting quality specifications for analytical methods. Ideally the quality goals should be set according to the medical demands the method has to meet. For glucose it is natural that the quality specification is set according to whether the analysis is used for diagnostic purpose or for monitoring diabetes. Ascensia Contour is designed for monitoring blood glucose, and the quality goals must be set according to this.

For glucose meters designed for monitoring blood glucose one should point out the need of a method with good precision [2]. According to the American Diabetes Association (ADA) the total error for meters designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1,67 – 22,2 mmol/L [3]. The quality goal from ADA must be seen as an optimal goal for the analytical quality of these meters. According to ADA the imprecision of new glucose devices must be less than 5 %. Other authors also recommend an imprecision of 5 % or less [4].

The quality goal for the total error of Ascensia Contour comes from ISO 15197, In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus [5]. The ISO-Guide is an international protocol for evaluating meters designed for glucose monitoring systems.

ISO 15197 gives the following minimum acceptable accuracy requirement:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 0,83 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 20 % at glucose concentrations ≥ 4,2 mmol/L.

This is a quality goal for measurements by trained laboratory staff. Ideally, the same quality requirement should apply for measurements by the diabetic patients. Previous investigations under the direction of the NOKLUS-project ”Diabetes-Self-measurements”, and results from evaluations under the direction of SKUP, showed that none of the self-monitoring glucose meters that were tested met the ISO-requirements. The results by the diabetics therefore have to be discussed towards a *modified* goal suggested by NOKLUS, with a total error of 25 %. This modified goal has wide, and not ideal, limits. The modified requirements for diabetics will be tightened up over time as the meters improve due to technological development.

Quality demands, adjusted to the diabetics self-measurements:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 1,0 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 25 % at glucose concentrations ≥ 4,2 mmol/L.

Materials and methods

Ascensia Contour

Ascensia Contour is a blood glucose monitoring system based on electrochemical technology. The system consists of a meter and dry reagent test strips designed for capillary blood glucose testing by people with diabetes or by health care professionals. The system is calibrated to report glucose plasma values. The system does not require calibration by the user. The calibration and an electronic check are performed automatically when the meter is turned on by insertion of an Ascensia Microfill test strip. The test strip chemistry uses a pyrroloquinoline quinone-glucose dehydrogenase (PQQ-GDH). PQQ serves as a cofactor and this enzyme system offers the advantages to reduced sensitivity to oxygen compared to glucose oxidase based systems. The test strips are packaged in a plastic bottle with snap-top closure and desiccant. The system requires a blood volume of 0,6 µL and provides a result in 15 seconds. The meter has the capability of storing 240 results in memory and detects when a glucose measurement is performed with an Ascensia Microfill control solution. Ascensia Contour is cleared for multiple site testing. The meter can be used on less sensitive testing sites like the forearm, palm, abdomen or thigh. Bayer recommends to consult Healthcare Professional if use of multiple sampling sites. The Ascensia Microlet adjustable lancing device is used to form a drop of blood on the fingertip. The Ascensia WinGlucofacts Diabetes software is available to download the meters information to a computer through the meters data port.

Technical data from the manufacturer is shown in table 1.

Table 1. Technical data for Ascensia Contour

Ambient temperature	10 - 40º C
Sample volume	0,6 µL
Measuring range	0,6 – 33,3 mmol/L
Measuring time	15 s
Power supply	2x3V lithium battery supply (DL or CR2032)
Memory	240 tests
Operating time	Approximately 1000 tests (1 year consumption)
Dimensions	W=53 mm, H=74 mm, D=17,3 mm
Weight	52,3 g

The designated comparison method

Definition
A designated comparison method is a fully specified method, which, in the absence of a reference method, serves at the common basis for the comparison of a field method.

The designated comparison method in this evaluation
In this evaluation, the routine method for quantitative determination of glucose in human serum, plasma (lithium heparin) and urine at the Laboratory at Haraldsplass Diaconal Hospital was used as the designated comparison method. The method will be called the comparison method in this report. The comparison method is a photometric enzymatic method based on the method by Slein, utilising hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is implemented on the Advia 1650 Chemistry System from Bayer, with reagents and calibrators from Bayer.
The Advia 1650 Chemistry System Glucose Hexokinase II method is a two-component reagent. Sample is added to Reagent 1, which contains buffer, ATP and NAD. Absorbance readings of the sample in Reagent 1 are taken and are used to correct for interfering substances in the sample. Reagent 2 is added, which initiates the conversion of glucose and the development of absorbance at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration. The measuring principle in the Advia 1650 is as follows. Glucose is phosphorylated by ATP in the presence of hexokinase. The glucose-6-phosphate that forms is oxidised in the presence of glucose-6-phosphate dehydrogenate causing the reduction of NAD to NADH. The absorbance of NADH is measured as an endpoint reaction at 340 nm.

Quality assurance of the Advia 1650 comparison method during the evaluation period
The Autonorm Human Liquid Control Solutions at two levels from Sero were measured in duplicate every day in front and at the end of the analytical series of samples.
The results are summarised in table 5.

Verifying of trueness
The results from new SMBG-devices must be compared with a recognized comparison method. The comparison method should be a plasma method, hexokinase by preference. The method has to show traceability equivalent to that of an internationally accepted reference solution, such as the standards supplied by the National Institute of Standards & Technology, NIST. Unfortunately, the glucose standards from NIST were not available during the spring of 2004. As an adequate alternative, two materials from The International Measurement Evaluation Program, IMEP [6], were used. IMEP is a program for inter-laboratory comparison, founded, owned and co-ordinated by the European Commission's Institute for Reference Materials and measurements (IRMM). The mission of IRMM is to promote a common European measurement system. IMEP provides certified values with demonstrated traceability and uncertainty. In July 1999 IRMM launched the IMEP-17 [7], which focuses on twenty components in two human serum materials, of which glucose is one. The IMEP-17 samples were analysed several times during the evaluation period. In addition, the freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method at a Reference laboratory in Belgium [8].

Product information

Ascensia Contour blood glucose meter system
Manufactured by: Bayer Healthcare
Internet: www.ascensia.com

Suppliers of Ascensia Contour in the Scandinavian countries:

Denmark:	Norway:	Sweden:
Bayer A/S Diagnostics Nørgaardsvej 32 Postboks 2090 DK-2800 Kgs. Lyngby Denmark	Bayer AS Diagnostics Drammensveien 147B Postboks 14 N-0212 Oslo Norway	Bayer AB Diagnostics Drakegatan 1 Box 5237 S-402 24 Göteborg Sweden
Phone: +45 45 23 50 00 diagnostics.dk.dd@bayer.dk	Phone: +47 24 11 18 00 diagnostics.no.dn@bayer.no	Phone: +46 31 83 98 00 diagnostics.se.ds@bayer.se

During this user-evaluation 79 Ascensia Contour blood glucose meters were used.
Serial no. 1134229 (called meter A) and serial no. 1134238 (called meter B) were used by the biomedical laboratory scientist under the standardised and optimal conditions.
Attachment 1 gives serial numbers for the 77 meters that were used by the diabetics.

Ascensia Microfill blood glucose test strips

Lot-no. 3JB3A07	exp. 2005-09	range control normal 5,6-7,6 mmol/L
Lot-no. 3KB3A01	exp. 2005-10	range control normal 5,4-7,3 mmol/L
Lot-no. 3MB3A03	exp. 2005-12	range control normal 5,4-7,3 mmol/L

The Ascensia Microfill test strip has a two-year shelf life if used according to the manufacturer's specifications.

Ascensia Microfill Control normal
Lot-no. 9046083C exp. 2004-11

Microlet lancets
Lot-no. J0381 exp. 2008-07

Designated comparison method Advia 1650
Manufactured by: Bayer AS
Meter serial no. CA 175524-196

Reagents
Bayer Glucose Hexokinase methode II (B01-4597-01)
Lot-no 0473X exp. 2004-11

Calibrator
Chemistry Cal Bayer
Lot-no. V67400A1 exp. 2004-07 reference value = 13,90 mmol/L

Internal control
Seronorm Autonorm Human Liquid 1 and 2, Sero AS
Level 1: value = 5,3 ± 0,3 mmol/L lot-no. FE3086 exp. 2005-04
Level 2: value = 14,8 ± 1,34 mmol/L lot-no. FE3087 exp. 2005-04

NOKLUS control (ID-GCMS method; reference value from Laboratory for Analytical Chemistry, Belgium)
Level 1 ref.value = 7,04 mmol/L SEM* = 0,012 mmol/L
Level 2 ref.value = 11,10 mmol/L SEM = 0,014 mmol/L
(* Standard Error of the Mean)

IMEP-17 (International Measurement Evaluation programme) from IRRM (Institute for Reference Materials and Measurements)
Level 1 Certified value = 4,412 mmol/L SEM = 0,0165 mmol/L
Level 2 Certified value = 8,41 mmol/L SEM = 0,09 mmol/L

Tubes used for the designated reference method:
Microvette CB 300 LH, manufactured by Sarstedt AS
lot-no. 12685089 exp. 2004-09

Centrifuge
JOUAN A-14 High Speed Microcentrifuge, manufactured by JOUAN SA
Serial no. 30302345

Study design

Recruiting of the diabetics

The Ascensia Contour glucose meter was tested in use by 77 diabetic patients. The diabetic patients were recruited through two advertisements in the daily press and by mail inquiry sent to members of the local branch of the diabetes association. The group of diabetic patients was representative for diabetics who carry out self-monitoring of blood glucose (SMBG). The group included diabetic patients from across a range of self-monitoring frequencies, i.e. diabetics who perform self-monitoring often (one or more times a day) and those who perform self-monitoring less frequently (once a week).
Patient characteristics of the group are shown in table 2.

Table 2. Characteristics of diabetic patients included (n=77).

		Diabetic patients
Total		77
Sex	Men	41
	Women	36
Age (years), median and range		49 (10 – 73)
Diabetes	Type 1	26
	Type 2	49
	Don't know	2
Treatment	Insulin	44
	Tablets	23
	Diet	9
	Unspecified	1
Frequency of SMBG	Less than weekly	11
	1 -3 per week	8
	4 – 6 per week	8
	7 – 10 per week	15
	> 10 per week	32
	Doesn't measure	1
	Unspecified	2

The SMBG-devices that the diabetic patients use regularly were:
Accu-Chek (7), Accu-Chek Compact (5), Accu-Chek Plus (1), Accu-Chek Sensor (9), Ascensia Contour (1), Ascensia DEX/DEX2 (9), Ascensia Elite (6), OneTouch (1), OneTouch Ultra (10), InDuo (2), GlucoTouch (3), EuroFlash (1), ExacTech (1), MediSense Precision QID (3), Precision Xtra (6), FreeStyle (2), GlucoMen PC (1), doesn't do SMBG (1) and unspecified (8).

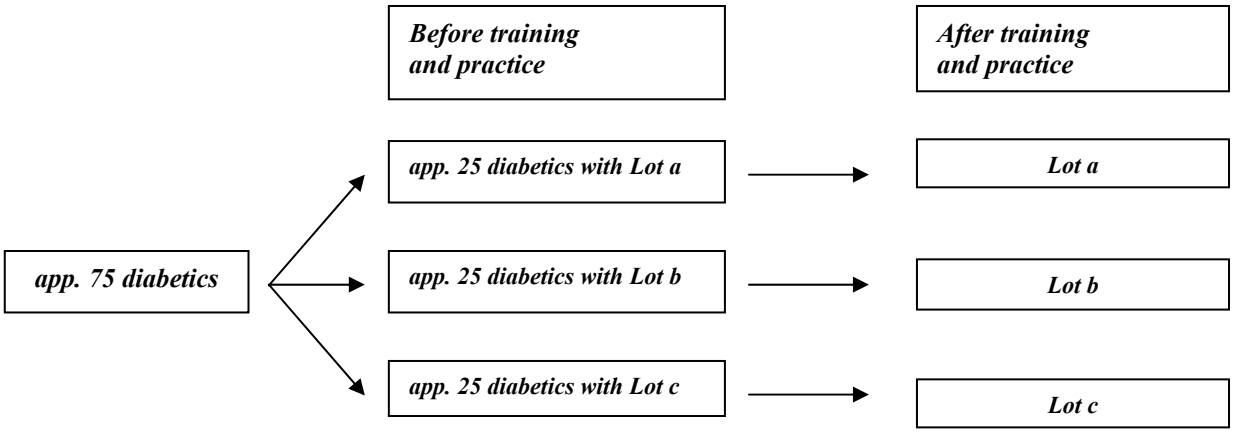
The practical work with the evaluation was carried out during ten weeks from February to April 2004 (from week number nine to week number 14). The diabetic patients had to meet at NOKLUS twice. For the first consultation they met two and two and for the second consultation they met one at the time. Appointments were arranged by phone and confirmed in writing. The first and second consultation overlapped in time. It took approximately 1 ½

months to complete the first consultation and nine weeks to complete the second consultation for all the diabetic patients.
The sampling and measuring procedures at the two consultations, the training-programme, the evaluation by the diabetic patients at NOKLUS and at home, and the measurements under standardised and optimal measuring conditions are described in the following.

The first consultation
At the first consultation the diabetic patients received the device along with test strips, lancet pen, lancets and user manual. Before they were trained in the use of the device, some samples were taken to assess the analytical quality of Ascensia Contour. The samples were taken and measured both by the diabetic patients themselves and by the biomedical laboratory scientist. After the training lesson the diabetic patients received an information letter with explanations regarding what to do with the Ascensia Contour device during the three weeks at home. The information letter is attached to the report (in Norwegian). See attachment 2.

The training programme
After the sampling and first measurements, the diabetic patients got instructions and a demonstration on how to use the Ascensia Contour device correctly. The training was done for two and two diabetics at the time. The responsibility for the training programme was undertaken by SKUP. Camilla Eide Jacobsen and Åse Nilsen were in charge of the training, after having been trained themselves by a representative from Bayer AS. The training programme was standardised and was carried out according to a check list set up by Bayer AS. It took approximately 1 ½ month to complete the first consultation and the training programme for all the participating diabetic patients. In this way, the distribution of the meters also was spread over a period of 1 ½ month.

Evaluation of three lots of test strips
Three lots of strips were distributed equally among the participating diabetic patients. In this way one lot was used by approximately 25 persons. The same three lots were also used by the biomedical laboratory scientist at meter B. At meter A one of the lots was used for all the measurements.
The distribution of the three lot numbers among the diabetic patients is shown in figure 1.
The number of samples for each lot of strips measured under standardised and optimal conditions is shown in table 3.



Figur 1. Distribution of the three lot numbers among the diabetics.

Table 3. The number of samples (n) for each lot of strips measured under standard and optimal conditions.

Ascensia Contour		Lot 3KB3A01 n	Lot 3MB3A03 n	Lot 3JB3A07 n	Total number
Meter A	1st consultation		77 x 2		77 x 2
	2nd consultation		76 x 2		76 x 2
Meter B	1st consultation	31 x 2	12 x 2	34 x 2	77 x 2
	2nd consultation	19 x 2	39 x 2	18 x 2	76 x 2
Total, Meter B		50 x 2	51 x 2	52 x 2	

Use of Ascensia Contour at home by the diabetic patients

The diabetic patients used the new devices at home for three weeks before being called for a second consultation. The length of this practice period at home ought not to exceed three weeks by more than a few days. Most users read the user manual at once when they receive the meter. As the diabetic patients are going to evaluate the user manual at the second consultation, it would be unfortunate if the practice period at home is too long. During the practice period the diabetic patients used Ascensia Contour in addition to their own glucose meter and they continued to carry out self-measurements with their own meter as normal.

The first and second week

The diabetic patients familiarised themselves with the new device during the first two weeks. Each patient used approximately 25 reagent strips to measure his/her blood glucose with Ascensia Contour. They could choose when to do the measurements themselves. Fasting was not necessary. If more convenient to them, they could perform the measurements at the same time as they measured their blood glucose with their own meter.

The third week

During the third week the diabetic patients performed five measurements in duplicate on Ascensia Contour on different days. The results were recorded on a provided form. They pricked a finger and made two consecutive measurements with blood from the same prick. When necessary they pricked another finger for the second measurement. They were free to choose when to perform the measurements, and it was not necessary to be fasting. They could choose whether to use the provided lancets or the lancets they use regularly. The diabetic patients are not familiar with control solutions for the self-measurements. Therefore they were not instructed to use control solution on Ascensia Contour in the evaluation. To document correct functioning of the Contour-meters used by the diabetic patients during the test period, the biomedical scientist in charge of the practical work controlled the meters by means of the control solution when the diabetics were called for the two consultations.

The second consultation

After the three week practice period at home, the diabetic patients were called for, one by one, to a second consultation. Each diabetic patient brought "their own" Ascensia Contour and the remaining test strips to this consultation. First the patient made two self-measurements at the Contour-meter. Within 5 minutes the biomedical laboratory scientist sampled a different finger and performed duplicate measurements on each of meter A and B, and in addition took the capillary samples to the comparison method, to which all results were compared. Finally, a venous sample for hematocrit was taken.

The questionnaires
After all the blood samples were collected and the measurements on Ascensia Contour were done, the diabetic patients filled out two questionnaires. The first questionnaire was about the user-friendliness of the Ascensia Contour device, the second about the user manual. The questionnaires (in Norwegian) are attached to the report. After the evaluation, the diabetic patients could choose whether to keep Asencia Contour or return it to the project.

Use of Ascensia Contour under standardised and optimal measuring conditions
The biomedical laboratory scientist examined Ascensia Contour by using the new device on samples from the diabetic patient at the first and the second consultation. The practice period between the two consultations was 3 weeks. The sampling and measuring period under standardised and optimal conditions lasted for approximately two months.

The biomedical laboratory scientist made use of two meters, called meter A and meter B. Meter A was used for one lot of test-strips for all measurements on all the diabetic patients. Meter B was used for the same three lots that were distributed among the diabetic patients. In this way, the variation between three lots, or more precisely, the agreement of the three lots to the comparison method, can be assessed.

Sampling and measurement order:

1. The first sample for the comparison method (approximately 300 µL)
2. Two samples for Ascensia Contour meter A and two samples for meter B
3. The second sample for the comparison method (approximately 300 µL)

As a rule, all the samples were taken from one finger prick. This means that the capillary samples were taken continuously from the same bleeding stream. At some occasions though, it was necessary to do another finger prick to fill up the last Microvette cup for the comparison method.

The first sample to the comparison method was taken before the measurements on meter A and B, and the second sample was taken directly afterwards. This should give a measure of the stability of the glucose concentration during the sampling time. The order of the sampling and measurements on meter A and B was altered between each patient, but the blood for the comparison method was always taken first and last, as proposed in ISO 15197. If the difference between the paired results at the comparison method exceeded 4 %, the samples were re-analysed. If the result from the re-run confirmed the difference, the difference has to be looked upon as a real difference in the glucose concentration in the two samples. Deviations > 10 % were regarded as not acceptable and such results would be excluded. The Ascensia Contour results carried out in the period between the two samples at the comparison method had to be excluded as well. If the deviation between the paired results was not confirmed by the re-run, the result from the re-run was used as the accepted result. Meter A and B were checked by means of the manufacturer's control solution every day they were used.

Statistical terms and expressions

Precision
The common used terms within-series imprecision and between-series imprecision are often misinterpreted. Especially the terms between-series and between-day imprecision are often not precisely defined. In this report, the terms are replaced by the precisely defined terms *repeatability and reproducibility*. Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability. The two terms are measured as imprecision and are commonly expressed by means of the coefficient of variation, CV %. Precision is descriptive in general terms (good, poor), whereas imprecision is an estimate, reported in the same unit as the measurand (or in %). The imprecision will be summarised in tables.

Accuracy
Accuracy is the closeness of agreement between the result of one measurement and the true value. Inaccuracy is a measure of a single measurements deviation from a true value, and implies a combination of random and systematic error (analytical imprecision and bias). Inaccuracy, as defined by a single measurement, is not sufficient to distinguish between random and systematic errors in the measuring system. Inaccuracy can be expressed as total error. The inaccuracy will be illustrated by difference plots with quality goals for the total error shown as deviation limits in percent.

Trueness
Trueness is the agreement between an average value obtained from a large number of measuring results and a true value. Trueness is measured as bias. Trueness is descriptive in general terms (good, poor), whereas bias is the estimate, reported in the same units as the measurand (or in %). The bias at different glucose concentration levels will be summarised in tables.

Calculations and number of samples

Number of samples

77 diabetic patients participated in the evaluation. They met at NOKLUS twice, and blood samples were taken at both consultations. This means that the total number of samples is 154. The two sets of 77 results are not statistically independent results, because the same diabetic patients participate twice. The sampling and measuring performance of each diabetic patients, and matrix-effects or interfering substances in the samples, may therefore affect some calculations twice if the results are treated as a whole. In most cases the results therefore are divided according to the first and second consultation and calculated and discussed as two separate parts. Under standardised and optimal conditions all the samples from both consultations are included in the calculations of imprecision. This will appear clearly at each separate calculation.

Statistical outliers

All results are checked for outliers according to Burnett [9], with repeated truncations. The model takes into consideration the number of observations included in the calculations, together with the statistical significance level for the test. The significance level is often set to 5 %, so also in this evaluation. Where the results are classified according to different glucose concentration levels, the outlier-testing is done at each level separately. Possible outliers will be commented on under each table.

Missing or excluded results

Besides the outliers, some results are missing or excluded for other reasons. They are summarised and explained here:

- ID number 6 had a difference > 10 % between the paired results on the comparison method in the first consultation. The difference was confirmed by a re-run. As a consequence of this, the results for ID 6 at the first consultation are excluded from calculations regarding the imprecision at the comparison method and at Ascensia Contour under standardised and optimal conditions. ID 6 is also excluded when Ascensia Contour is compared with the comparison method (accuracy and trueness).
- ID number 78 is omitted at the first consultation because the second sample of the duplicate was strongly hemolysed, and therefore there is no duplicate result from the comparison method. ID 78 is included in the calculations at Ascensia Contour.
- ID number 43 is missing in the second consultation because the diabetic patient was unable to meet for this appointment

Calculations based on duplicate results

Two capillary samples were taken of each diabetic patient. The imprecision was calculated by use of paired measurements, based on the following formula:

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

where d is the difference between the two measurements and n is the number of duplicate samples. The assumption for using this formula is that there is no systematic difference between the 1st and the 2nd measurement. Previous evaluations, both under the direction of SKUP and in the NOKLUS-project “Diabetes - self-measurements”, have shown that this assumption is met.

Comparing the 1st and the 2nd measurement at the comparison method by means of the t-test for paired values gives a measure of the stability of the glucose concentration during the time it took to take and measure the samples (up to five minutes). Only one result gave an unacceptable difference (ID number 6). This result is excluded as described earlier.

Table 4 shows that there is no significant difference in glucose concentration between the paired measurements on the comparison method (Advia). The results at Advia are shown as a whole, but the differences at three levels of glucose concentrations are not significantly different, either. Despite this, the second measurement at Contour surprisingly is higher than the first. The difference between the first and second measurement at Ascensia Contour is significant at all three levels of glucose concentrations. This applies to all the measurements, both under standardised and optimal conditions and for the measurements done by the diabetic patients. The reason for this systematic difference is not clear and is difficult to explain because of the stability between the values on the comparison method. This finding will unfortunately affect all the calculations of imprecision at Ascensia Contour, because these calculations are based on paired values. The problem with the calculations of imprecision at Ascensia Contour will be emphasised in the chapter "Results and discussion".

Table 4. Systematic differences between the 1st and the 2nd measurement. T-test for paired values.

Glucose instrument		Glucose range mmol/L	Mean 1st measurement mmol/L	Mean 2nd measurement mmol/L	Mean difference 2nd – 1st measurement mmol/L (95 % CI)	n
Advia		3,6 – 26,1	9,0	9,0	0 (-0,05 – +0,00)	151
Ascensia Contour	Meter A	3,3 – 26,8	9,0	9,3	0,3 (+0,25 – +0,45)	152
		< 7	5,7	5,8	0,1 (+0,03 – +0,16)	52
		7 – 10	8,2	8,5	0,3 (+0,16 – +0,44)	47
		> 10	13,3	13,9	0,6 (+0,42 – +0,90)	50
	Meter B	3,1 – 28,2	9,0	9,3	0,3 (+0,25 – +0,42)	152
	The diabetics' measurements at the 1st consultation	3,1 – 27,4	8,9	9,2	0,3 (+0,10 – +0,47)	76
	The diabetics' measurements at the 2nd consultation	3,2 – 22,9	10,0	10,4	0,4 (+0,19 – +0,57)	75

Results and discussion

Precision and trueness of the designated comparison method

The precision of the comparison method

The reproducibility of the comparison method is shown in table 5. The results are obtained with the internal control solution at two levels of glucose concentrations. The controls were analysed in duplicate in the beginning and at the end of each series of samples, giving a total number of more than 160 results. In table 5 only the first result in each series is included. All the results are shown in attachment 3.

Table 5. The comparison method. Reproducibility. Results with internal control solutions.

Control Solution	Target value glucose (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Autonorm 1	5,3	5,3	21	0	1,1 (0,9 – 1,6)
Autonorm 2	14,8	14,6	21	0	1,1 (0,9 – 1,6)

To get a representative measure of the repeatability of the comparison method, capillary samples from 77 diabetic patients were analysed in duplicate. The samples were taken by the biomedical laboratory scientist at the first and second consultation. The results from the first and second consultation are pooled before the calculation of repeatability. This should give a total number of 154 results. The repeatability of the comparison method is shown in table 6. Raw data is shown in attachment 4.

Table 6. The comparison method. Repeatability. Results with patient samples.

Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
< 7	5,7	52	1	1,3 (1,1 - 1,7)
7-10	8,3	54	0	1,4 (1,2 - 1,7)
>10	13,8	44	0	1,0 (0,8 - 1,2)

There are 150 counting results in table 6. ID number 21 was defined as an outlier at the first consultation and is excluded from the calculations. Three more results are missing. Please refer to the explanation in the previous chapter.

The trueness of the comparison method

Verifying the trueness of the comparison method is explained previously in the report, under the chapter “Material and methods”, in the section about the comparison method.
The agreement with target values from a reference laboratory in Belgium is shown in table 7.
The agreement with IMEP-17 from IRRM is shown in table 8.

Table 7. The comparison method. Bias. Control materials (frozen human serum) from NOKLUS' External Quality Assessment Program measured during the evaluation period.

Control (human serum)	Date	Target value from reference lab. in Belgium (mmol/L)	Mean value glucose (mmol/L)	n	CV % (95 % CI)	% deviation from target value
NOKLUS 1	17.03.2004	7,04	6,95	4	0,3 (0,1 – 0,9)	- 1,2 %
	19.03.2004		6,97	4	0,4 (0,2 – 1,5)	- 1,0 %
	31.03.2004		7,03	4	0,3 (0,2 – 1,0)	- 0,1 %
	13.04.2004		7,03	4	0,5 (0,3 – 2,0)	- 0,1 %
	14.04.2004		7,04	4	0,3 (0,2 – 1,2)	0,0 %
	22.04.2004		7,03	4	0,5 (0,3 – 1,8)	- 0,1 %
	Total		**7,01**	**24**	**0,6 (0,5 – 0,8)**	**- 0,4 %**
NOKLUS 2	17.03.2004	11,10	10,96	4	0,2 (0,1 – 0,7)	- 1,2 %
	19.03.2004		10,97	4	0,3 (0,1 – 1,0)	- 1,2 %
	31.03.2004		10,95	4	0,3 (0,1 – 1,0)	- 1,4 %
	13.04.2004		11,20	4	1,8 (1,0 – 6,8)	+ 0,9 %
	14.04.2004		11,07	4	0,2 (0,1 – 0,6)	- 0,3 %
	22.04.2004		11,06	4	0,2 (0,1 – 0,6)	- 0,4 %
	Total		**11,03**	**24**	**1,1 (0,8 – 1,5)**	**- 0,6 %**

Table 8. The comparison method. Bias. IMEP 17 Control material (frozen human serum) measured during the evaluation period.

Control	Date	Target value (mmol/L)	Mean value glucose (mmol/L)	n	CV % (95 % CI)	% deviation from target value
IMEP 17 material 1	11.03.2004	4,41	4,53	10	0,3 (0,2 – 0,5)	+ 2,6
	22.03.2004		4,47	4	0,2 (0,1 – 0,8)	+ 1,3
	26.03.2004		4,48	4	0,4 (0,2 – 1,4)	+ 1,6
	20.04.2004		4,52	4	0,2 (0,1 – 0,7)	+ 2,5
	Total		**4,51**	**22**	**0,6 (0,5 – 0,9)**	**+ 2,2**
IMEP 17 material 2	29.03.2004	8,41	8,36	10	0,4 (0,3 – 0,7)	- 0,6
	13.04.2004		8,48	4	0,2 (0,1 – 0,9)	+ 0,9
	16.04.2004		8,48	4	0,6 (0,3 – 2,1)	+ 0,9
	20.04.2004		8,49	4	0,2 (0,1 – 0,6)	+ 0,9
	Total		**8,43**	**22**	**0,8 (0,7 – 1,2)**	**+ 0,2**

Discussion

The precision of the comparison method is very good. The CV is about 1%. The control material from NOKLUS and the IMEP-17 materials together cover a glucose concentration range from 4,4 to 11,1 mmol/L. The comparison method bias from the true glucose value at four concentration levels is ignorable. The comparison method gives glucose values with a high degree of trueness.

Precision, accuracy and trueness of Ascensia Contour

Precision of Ascensia Contour

Reproducibility and repeatability under standardised and optimal measuring conditions
The results for reproducibility are obtained with the Ascensia Microfill Normal Control. The measurements are carried out on meter A and B during the whole evaluation period and at all the meters in use by the diabetic patients. All the control measurements are done by two biomedical laboratory scientists. The control measurements on the diabetics' meters were done with the test strips that were distributed to each diabetic patient. The control solution was kept at NOKLUS during the evaluation period.

The reproducibility of Ascensia Contour at meter A and B is shown in table 9.
The reproducibility at all the meters of the diabetic patients is shown in table 10.
Raw data is shown in attachment 5.
The repeatability obtained with patient samples under standardised and optimal conditions is shown in table 11 and 12.
Raw data is shown in attachment 6.

Be aware of the fact that the CV % in table 11 is calculated from paired values, were a small, but significant systematic difference between the first and second measurement is pointed out at all three levels of glucose concentration. It is most likely that these systematic differences lead to increased imprecision. The CVs are therefore firstly probably estimated too high, secondly the CVs are burdened with more uncertainty than usually. Consequently the CVs are given without 95 % confidential intervals. As an experiment, the average systematic difference will be subtracted from the values at meter A to get an idea of how this will affect the CV. The corrected results are shown in table 12.
The results in table 11 and 12 are sorted at three glucose concentration levels according to the first measurement at Ascensia Contour, because of the systematic shift of the values.

Table 9. Ascensia Contour. Reproducibility. Results with Ascensia Microfill Normal Control, measured by two biomedical laboratory scientists on meter A and B under standardised and optimal conditions.

Ascensia Contour	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	3JB3A07	5,6 – 7,6	6,3	27	0	2,2 (1,8 – 3,1)
Meter B	3JB3A07	5,6 – 7,6	6,3	9	0	1,6 (1,1 – 3,1)
	3KB3A01 3MB3A03	5,4 – 7,3	6,4	20	0	1,5 (1,1 – 2,2)

Table 10. Ascensia Contour. Reproducibility (results with Ascensia Microfill Normal Control) measured by the biomedical laboratory scientists on the diabetic patients' meters.

Ascensia Contour	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
1st consultation						
The diabetic patients' meters	3JB3A07	5,6 – 7,6	6,3	27	0	2,2 (1,7 – 2,9)
	3KB3A01	5,4 – 7,3	6,3	24	0	1,8 (1,4 – 2,6)
	3MB3A03	5,4 – 7,3	6,3	26	0	1,6 (1,3 – 2,2)
2nd consultation						
The diabetic patients' meters	3JB3A07	5,6 – 7,6	6,7	25	0	4,9 (3,8 – 6,8)
	3KB3A01	5,4 – 7,3	6,7	24	0	3,6 (2,8 – 5,0)
	3MB3A03	5,4 – 7,3	6,6	26	0	4,2 (3,3 – 5,8)

Table 11. Ascensia Contour. Repeatability. Patient samples measured under standardised and optimal conditions. Results from the first and second consultation as a whole.

Ascensia Contour	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV %
Meter A	< 7	5,7	53	1*	3,2
Meter B	< 7	5,7	54	0	3,3
Meter A	7 – 10	8,5	52	0	5,0
Meter B	7 – 10	8,5	54	0	5,2
Meter A	> 10	13,6	46	0	5,4
Meter B	> 10	14,1	44	0	4,5

* The outlier is ID 38 at the first consultation.

Table 12. "Corrected repeatability". Ascensia Contour. Patient samples measured under standardised and optimal conditions at meter A. In rows marked "after correction" the mean bias between 1st and the 2nd measurement is subtracted from the difference.

Ascensia Contour		Correction	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV %
Meter A	Before correction		< 7	5,7	53	1	3,2
Meter A	After correction	- 0,1 mmol/L	< 7	5,7	53	0	3,0
Meter A	Before correction		7 – 10	8,5	52	0	5,0
Meter A	After correction	- 0,3 mmol/L	7 – 10	8,3	52	0	4,2
Meter A	Before correction		> 10	13,9	46	0	5,4
Meter A	After correction	- 0,6 mmol/L	> 10	13,6	46	0	4,5

Discussion
The reproducibility at Ascensia Contour meter A and B is good when measured with an internal control solution. The CV is approximately 2 %.
At the diabetics' meters the reproducibility was good at the first consultation when meters and test strips were new. The CV was approximately 2 %. The results from the second consultation were not as good as the initial results, with a CV slightly more than 4 %. Still this imprecision is partly acceptable. At the second consultation these meters have been used at home by the diabetic patients for three weeks. The diabetic patients had been trained in how to use the meter correctly and how to handle the test strips. Therefore there is no reason to believe that most of them have treated the device wrongly. This result is therefore surprising and not easy to explain. The poorer performance of the system (meter and test strips) after three weeks of use can be confirmed or disproved when looking at the diabetic patients' own results obtained with blood samples, shown as the total error in the difference plots, figure 4 and 5.
The repeatability is acceptable when measured with capillary blood samples. The measure for this imprecision is burdened with extra uncertainty because of a shift in the glucose concentration between the first and the second of two duplicate measurements on Ascensia Contour. The CV at meter A and B before correction is somewhere between 3 and 5,5 %. The precision is slightly better after the correction. The actual CV is most likely somewhere between 3 and 5 %, at least it seems to be < 5 %.

Repeatability obtained by the diabetic patients
The repeatability obtained by the diabetic patients with capillary blood samples is shown in table 13. The table gives the results from the measurements at the first and second consultation, together with the results they obtained at home. The results obtained at home of course have a higher degree of uncertainty since it is impossible to control what has actually been done. The reporting of these home-values also reveals that some of the diabetic patients did not quite understand "the recipe" on how to perform and report the five duplicate measurements they were supposed to carry out according to the written instruction they had received. One should also be aware of the fact that the CVs in the table are calculated from paired values were a small, but significant systematic difference is pointed out at all three levels of glucose concentration.
Raw data from the diabetic patients' measurements at NOKLUS is shown in attachment 7.
Raw data from the diabetic patients' measurements at home is shown in attachment 8.

Table 13. Repeatability, Ascensia Contour. Results with patient samples measured by the diabetic patients at the 1st consultation (before training and practise), at home and at the 2nd consultation.

Ascensia Contour Diabetic measurements	Consultation	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV %
At NOKLUS	1st	< 7	5,6	29	1	5,1
	2nd	< 7	5,4	15	1	2,6
At home		< 7	5,3	103	3	5,0
At NOKLUS	1st	7 – 10	8,3	26	0	5,5
	2nd	7 – 10	8,3	26	1	6,1
At home		7 – 10	8,4	132	3	6,6
At NOKLUS	1st	> 10	14,6	21	0	6,5
	2nd	> 10	13,9	33	0	5,0
At home		> 10	13,9	111	3	6,7

Discussion

The precision obtained by the diabetic patients at NOKLUS are slightly poorer than the precision achieved by the biomedical laboratory scientists. The CV % is between 5 and 6. Despite the limitations in the statistical calculations because of the systematic difference between the duplicates, the precision at Ascensia Contour seems acceptable. The results at home show that the diabetic patients have been practising with the new system according to the instructions, but one should not give greater weight to the calculated CV values.

Trueness

To measure the trueness of the measurements on Ascensia Contour, the average bias at three glucose concentration levels is calculated based on the results obtained under standardised and optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results at the comparison method and the first result at Ascensia Contour meter A (because the second measurement is significantly higher than the first). The calculations are shown in table 14 for the results from the first consultation only. The results from the second consultation give the same conclusion.

Table 14. Bias. Mean difference between Ascensia Contour and the comparison method. Results from the 1st consultation at meter A under standardised and optimal measuring conditions.

	< 7 mmol/L		7 – 10 mmol/L		> 10 mmol/L	
	The comparison method	**Meter A**	**The comparison method**	**Meter A**	**The comparison method**	**Meter A**
Mean glucose, mmol/L	5,7	5,7	8,3	8,4	15,1	14,8
Mean bias, mmol/L Ascencia – the comparison method (95 % CI)	0,0 (-0,11 - +0,09)		0,1 (-0,04 - +0,30)		- 0,3 (-0,68 - +0,15)	
n	30		26		19	
Outliers	0		0		0	
p-value	0,832		0,138		0,202	

Discussion

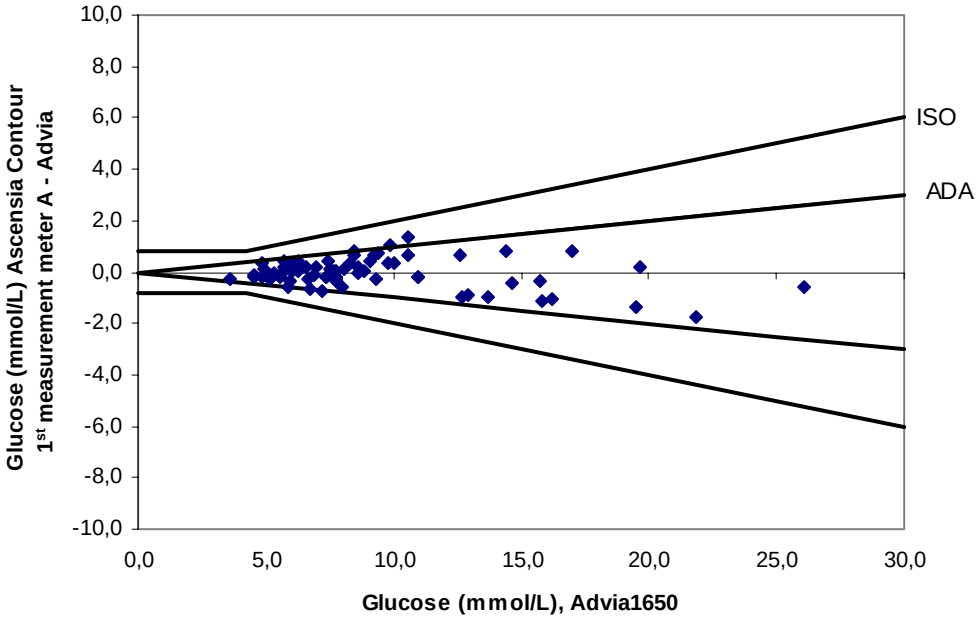
The agreement between Ascensia Contour and the comparison method is good. There is no significant bias between the two methods at three different levels of glucose concentrations.

Accuracy

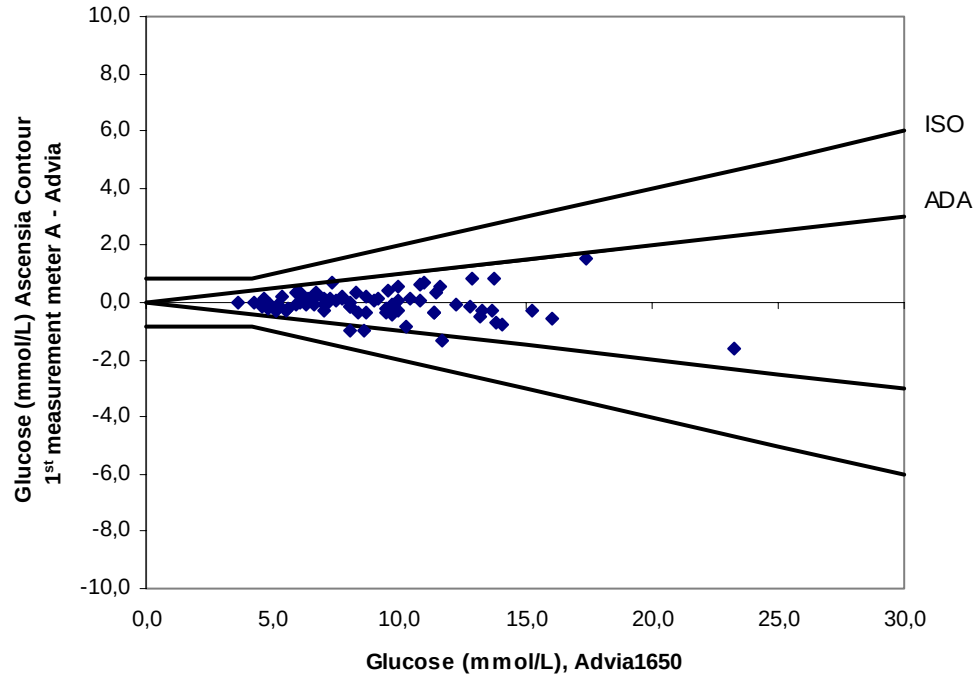
To evaluate the accuracy of the results at Ascensia Contour, the agreement between Ascensia Contour and the comparison method is illustrated in four difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Ascensia Contour and the mean value of the duplicate results at the comparison method. The difference plots give a picture of both random and systematic deviation and reflect the total measuring error at Ascensia Contour. The total error is demonstrated for the first measurements of the paired results, only. The second measurements show significantly systematic higher values, and consequently poorer agreement compared to the comparison method. At meter A only one lot of test strips were used. At meter B three different lots were used. The same three lots were randomly distributed between the diabetic patients.

The limits in the plots are based upon the quality goals discussed in a previous chapter of this report. Under standardised and optimal measuring conditions the goal from ADA at 10 % and the ISO-goal at 20 % are used. For the diabetic patients' self-measurements the goal from ADA and the "adjusted ISO-goal" at 25 % are used.

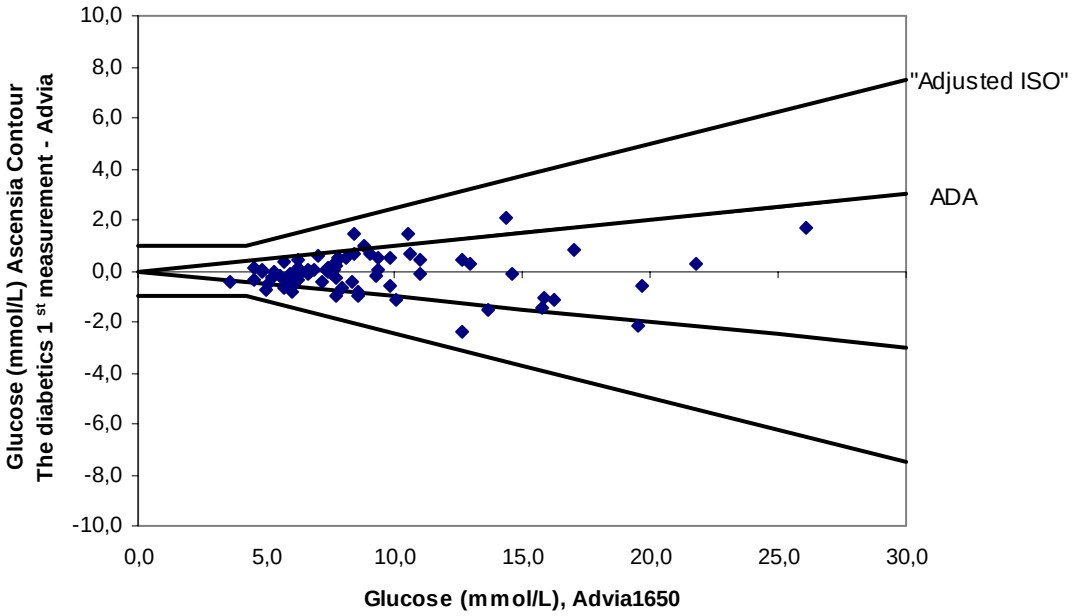
The total error, Ascensia Contour meter A, under standardised and optimal measuring conditions, with the first measurements at the first consultation is shown in figure 2.
The total error, Ascensia Contour meter A, under standardised and optimal measuring conditions, with the first measuremnet at the second consultation is shown in figure 3.
The total error, Ascensia Contour, as measured by the diabetic patients with the first measurement at the first consultation is shown in figure 4.
The total error, Ascensia Contour, as measured by the diabetic patients with the first measurement at the second consultation is shown in figure 5.
The results from the four difference plots are summarised in table 15 and discussed afterwards. The results from all the second measurements are also shown in the table.



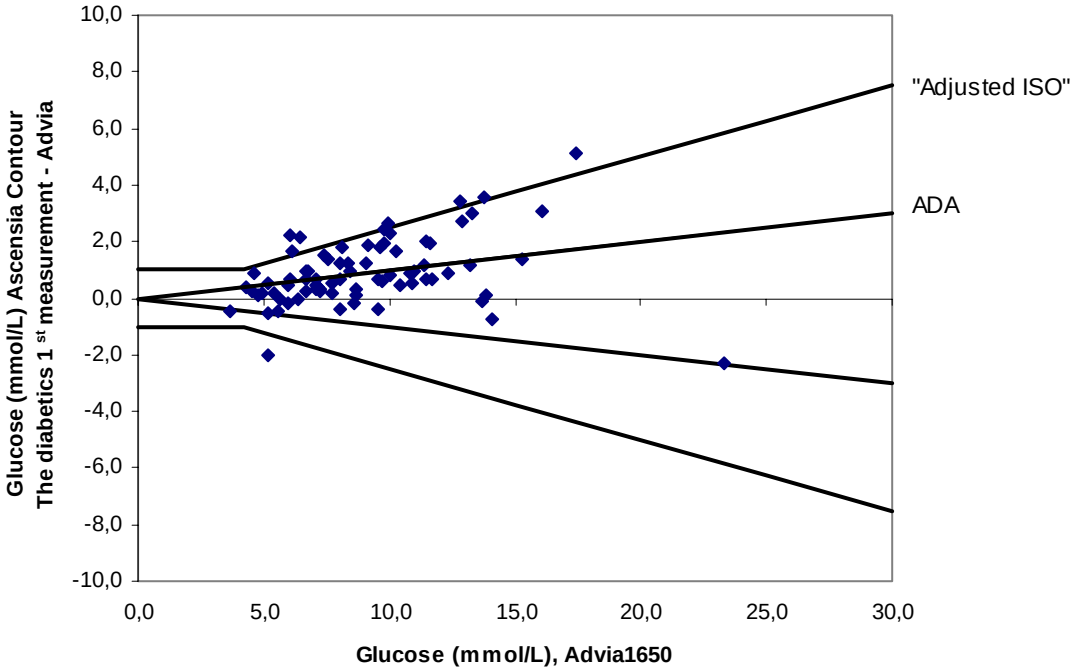
Figur 2. Total error. Ascensia Contour meter A (one lot of test strips) under standardised and optimal measuring conditions at the first consultation. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Ascensia Contour and the mean value of the duplicate results at the comparison method. N = 75.



Figur 3. Total error. Ascensia Contour meter A (one lot of test strips) under standardised and optimal measuring conditions at the second consultation. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Ascensia Contour and the mean value of the duplicate results at the comparison method. N = 76.



Figur 4. Total error. The diabetic patients' self-measurements at the first consultation. Three lots of test strips. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Ascensia Contour and the mean value of the duplicate results at the comparison method. N = 75.



Figur 5. Total error. The diabetic patients' self-measurements at the second consultation. Three lots of test strips. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Ascensia Contour and the mean value of the duplicate results at the comparison method. N = 76.

Table 15. Total error of Ascensia Contour results compared to the comparison method.

Number of Ascensia Contour results in percent within the limits.

Measurements done by	Consultation	Meter	n	Number of results (%) within the quality goals			Shown in figure
				< ADA < ± 10 %	**< ISO** < ± 20 %, and < ± 0,83 mmol/L at consentrations ≤ 4,2	**< "adjusted ISO"** < ± 25 %, and < ± 1,0 mmol/L at consentrations ≤ 4,2	
Biomedical laboratory scientist	1st	A 1st measurement	75	97	100		2
		A 2nd measurement	75	80	100		not shown
		B 1st measurement	75	93	100		not shown
		B 2nd measurement	75	85	99		not shown
Biomedical laboratory scientist	2nd	A 1st measurement	76	96	100		3
		A 2nd measurement	76	87	100		not shown
		B 1st measurement	76	93	100		not shown
		B 2nd measurement	76	91	100		not shown
Diabetic patients at NOKLUS	1st	1st measurement	75	**81**	**100**	**100**	4
		2nd measurement	75	76	95	96	not shown
	2nd	1st measurement	76	**58**	**80**	**90**	5
		2nd measurement	76	37	63	82	not shown

Discussion

Figure 2 shows that all the results obtained under standardised and optimal measuring conditions are within the ISO-limits. The summing up in table 15 shows that all the first measurements at the first consultation are within the ISO-limits. The results are within the limits recommended by ADA, also. Figure 3 looks exactly like figure 2 and the summing up in table 15 gives the same good results.

Figure 4 shows that the diabetic patients' first self-measurements at the first consultation fulfil the "adjusted ISO-goal" and also the ISO-goal. The results from the second consultation (figure 5) are considerably poorer. The results from the second consultation do not fulfil the quality goals from ADA, ISO or the "adjusted ISO". Only 80 % of these results are within the ISO-limits. The second measurements of the duplicates are even poorer.

The poorer performance of the system (meter + test strips) after three weeks of use at home was pointed out already when discussing the reproducibility results with the internal control solution in table 10. The finding is confirmed by the accuracy plots.

There is no reason to believe that the poorer results at the second consultation are caused by user errors. All the diabetics were trained in how to use the meter correctly and how to handle the test strips. It is not likely that most of them treated the device wrongly at home. All the measurements performed by the diabetics at NOKLUS were overlooked by the biomedical laboratory scientist. Therefore, the poorer results after having been used in "real life" conditions probably have something to do with the robustness of the meter or test strips.

Conclusion
The Ascensia Contour device fulfils the quality goals set in the ISO 15197 when used under standardised and optimal conditions. When handled by the diabetic patients, the device shows good results initially, but after three weeks of use at home the results no longer fulfil the quality goals. It is difficult to find a reasonable explanation to this occurrence.

Lot-to-lot variations

The measurements on meter B were performed with three different lot numbers of test strips. All of the measurements on meter A were performed with one of the three lots. The three lots were also distributed among the diabetic patients. To measure the variation between the three lots, all the first glucose results at Ascensia Contour obtained under standardised and optimal conditions at meter B were compared with the mean of the paired values from the comparison method (paired t-test). The reason for not using the mean of paired values at Ascensia Contour is the fact that the second measurements on Ascensia Contour were significantly higher than the first measurements, as shown in table 4.
The results are shown in table 16.

Table 16. Lot variation, test strips. T-test for paired values between three lots at meter B and the comparison method under standardised and optimal conditions.

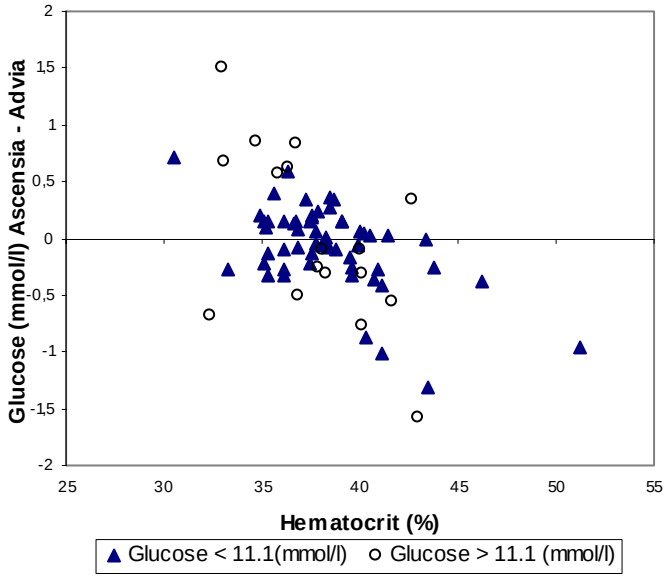
	The reference method	**Meter B Lot 3JB3A07**	**The reference method**	**Meter B Lot 3KB3A01**	**The reference method**	**Meter B Lot 3MB3A03**
Mean glucose, mmol/L	9,2	9,3	9,0	8,8	8,8	8,7
% deviation from the comparison method (95 % CI)	1,0 (-0,9 – (+2,9))		-1,7 (-3,2 – (-0,2))		-1,4 (-3,1 – (+0,2))	
n	51		50		50	
Outliers	0		0		0	
p-value	0,278		0,025		0,078	

Discussion
The differences between the comparison method and lot 3JB3A07 and 3MB3A03 are not statistically significant. Lot 3KB3A01 gives significantly lower values than the comparison method, but the difference is small. The measured differences have no clinical significance.

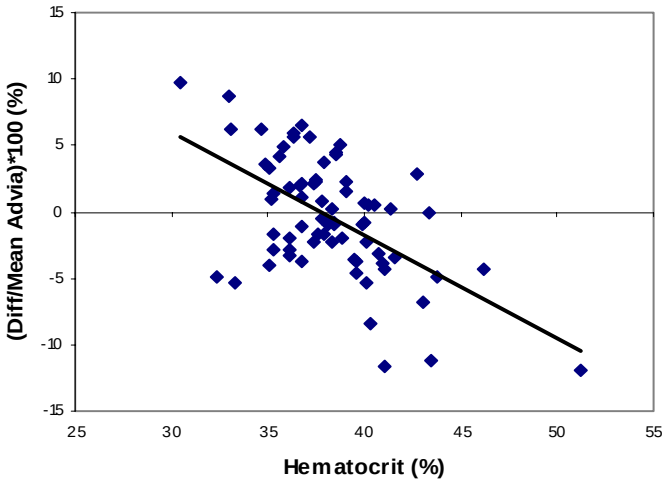
Effect of hematocrit

In the package insert of Ascensia Microfill test strips it is told that normal glucose concentrations are not significantly affected by hematocrit-values between 20 and 60 %. At glucose concentrations higher than 11,1 mmol/L, hematocrit more than 55 % will give too low glucose values, also according to the insert.
To measure the effect of hematocrit at Ascensia Contour, a venous sample was taken of the diabetic patients (voluntary) at the second consultation. All the diabetics were willing to have a sample for hematocrit taken. Out off the 76 diabetic patients that met for the second consultation, the sampling to hematocrit was successful in 73 cases.
The measurements on Ascensia Contour are performed under standardised and optimal measuring conditions. The glucose concentration range in the samples was from 4,3 to 21,7 mmol/L. The hematocrit range was 32 – 51%.

The effect of hematocrit is shown in two difference plots. The x-axis in the plots shows the hematocrit value.
In Figure 6 the y-axis shows the difference in glucose concentration in mmol/L between Ascensia Contour and the comparison method (Ascensia Contour – the comparison method). The glucose values < 11,1 mmol/L and > 11,1 mmol/L are drawn with different symbols.
In Figure 7 the y-axis shows the difference in glucose concentration between Ascensia Contour and the comparison method in percent.
Raw data is shown in attachment 9.



Figur 6. The effect of hematocrit at glucose measurements (in mmol/L) at Ascensia Contour under standardised and optimal conditions. The x-axis shows the hematocrit value in percent. The y-axis shows the difference in glucose concentration between Ascensia Contour and the comparison method (Ascensia Contour – the comparison method) in mmol/L.



Figur 7. The effect of hematocrit at glucose measurements on Ascensia Contour under standardised and optimal conditions. The x-axis shows the hematocrit value in percent. The y-axis shows the difference in glucose concentration between Ascensia Contour and the comparison method (Ascensia Contour – the comparison method) in percent.

Discussion

The trend-line in figure 7 shows that the glucose measurements on Ascensia Contour are affected by the hematocrit value of the samples. This applies not only for high glucose values in combination with high hematocrit values, but is true also for glucose values below 11,1 mmol/L and for hematocrit values within the reference range, as shown in figure 6. The glucose values at Ascensia Contour are over-estimated when the hematocrit is below 35 %, and the glucose values are under-estimated when hematocrit is more than 40 - 45 %.

Practical points of view

Questionnaires

Each diabetic patient filled out a questionnaire about the user manual and a questionnaire about the user-friendliness of Ascensia Contour when they attended the second consultation (n = 76). Some patients needed assistance in filling out the questionnaires.
Questionnaire about the user-friendliness (in Norwegian), see attachment 10.
Questionnaire about the user manual (in Norwegian), see attachment 11.

Evaluation of user-friendliness of Ascensia Contour

The questionnaire about the user-friendliness had nine questions concerning Ascensia Contour and one question concerning Microlet lancet pen. In addition, each patient should state the name of the blood glucose meter he/she uses regularly on the same questionnaire. The answers to these questions are summarized in table 17 and 18.

Table 17 summarizes six questions where the patients were asked to rank the answers on a scale from 1 to 6, where 1 is difficult and 6 is simple. The mean is 5,8 and 6,0 on the questions about inserting a strip into the meter and about filling the strip with blood, respectively. This indicates that the patients seemed satisfied with use of the test strip. The patients also seemed satisfied with use of the meter. The mean is between 5,7 and 5,9 on the questions about reading the figures in the display, recognizing the meters' sound signal and operating the meter, all in all. Regarding Microlet lancet pen the mean is 5,3, which indicates that the patients were satisfied with the lancet pen too.

Table 17. Ascensia Contour - Questions about the meter and about Microlet lancet pen.

Questions about Ascensia Contour and about Microlet lancet pen		mean	range	Not answered (% of total)	Total number
How will you rank the following questions on a scale from 1 to 6, where 1 is difficult and 6 is simple:	1. To insert a strip into the meter	5,8	4 – 6	0	76
	2. To fill the strip with blood	6,0	5 - 6	0	76
	3. To read the figures in the display	5,9	4 - 6	0	76
	4. To recognize the meters' sound signal?	5,7	1 - 6	0	76
	5. All in all, to operate the meter	5,7	3 - 6	0	76
	6. To operate Microlet lancet pen	5,3	1 - 6	8	76

Table 18 summarizes two other questions about Ascensia Contour. On the Norwegian market at present, Ascensia Contour is the only meter with single test strips with automatic calibration. 64 % of the patients think that automatic calibration is important and 28 % think it less important. 5 % of the patients answered that they had technical problems with the meter during the testing period. Except for one patient, written comments indicate that the problems were not technical problems. The meter in question showed error message E 7 once during the home period and was replaced.

Table 18. Ascensia Contour – Questions about the meter.

Questions about Ascensia Contour	Important (%)	Less important (%)	No importance (%)	Not answered (%)	Total number
How important do you think it is that Ascensia Contour has automatic calibration?	64	28	5	3	76
	Yes	No	Not answered		Total number
Did you have any technical problems with the meter during the testing period?	5	89	5		76

65 patients reported one or more advantages with Ascensia Contour. The reported advantages are distinctly grouped as follows:

1. simple operating of the meter (25)
2. the meter/strip needs little blood sample volume (20)
3. the meter has short measuring time (21)
4. the small size of the meter (13)
5. PC connection/memory feature (10)
6. the automatic calibration of the meter (7)

40 patients reported one or more disadvantages with Ascensia Contour. The reported disadvantages are not as distinctly grouped as the advantages. The interesting fact is that one of the mentioned advantages also is reported as a disadvantage. This refers to the measuring time (15 seconds), which seems too long for some of the patients. Another reported disadvantage is that the test strips are placed in bottles. Some of the patients indicated that it is difficult to get the strips out of the bottle and others indicated that it is more convenient with individually packed test strips. The two remaining disadvantages are concerning the case and the Microlet lancet pen. The case seems too large for some of the patients, but at the same time the case seems to have too little inner space for others. The Microlet lancet pen seems inconvenient to use for some patients as much as the needles were too large or difficult to replace. Ten of the patients reported that Ascensia Contour seemed “inaccurate”. For some of them the difference between two subsequent results on Contour was larger than they expected and for others the values on Contour seemed to be higher than the results on their own meter. Ascensia Microfill reports plasma results. It is not likely that some of the patients’ own meters are referenced to match whole blood results. From the first of January 2004 only plasma-calibrated test strips get reimbursed in Norway. In the questionnaires the diabetics give information about their own meters. Only two patients reported to have a meter that might not have been changed to plasma-values.

Evaluation of the user manual for Ascencia Contour

On the questionnaire about the user manual each patient first was asked whether he/she had used the manual. If not, they were to ignore the rest of the questions in the questionnaire.

Table 19 shows that 75 % of the patients had used the user manual, i.e. 60 of the 76 patients that participated in the study. Approximately 40 % of them had read the entire manual and approximately 60 % had consulted the manual when they needed. The 60 patients that had been reading in the user manual seemed satisfied with the manual. 92 % answered they were satisfied with the description of how to perform a blood glucose measurement with this meter. None of them thought the manual had essential shortcomings and 93 % were quite satisfied with the user manual.

Table 19. Ascensia Contour – Questions about the user manual.

Questions about the user manual	Yes (%)	No (%)	Not answered (%)	Number
Have you been reading in the user manual?	75	22	3	76
If yes, did you read the entire user manual?	42	47	12	60
And/or did you only consult the user manual when needed?	62	13	25	60
1. Are you satisfied with the description of how to perform a blood glucose measurement with this meter?	92	0	8	60
2. Do you think the user manual has essential shortcomings?	0	88	12	60
3. All in all, are you satisfied with the user manual?	93	0	7	60

References

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9. Burnett RW. "Accurate Estimation of Standard Deviations for Quantitive Methods Used in Clinical Chemistry". *Clinical Chemistry* 1975; 21 (13): 1935 – 1938.

Attachments

1. Serial numbers, Ascensia Contour meters
2. Information letter to the diabetic patients (in Norwegian)
3. Raw data, internal quality control, Advia
4. Raw data, Advia results, diabetic patients
5. Raw data, internal quality control, Ascensia Contour
6. Raw data, Ascensia Contour results under standardised conditions, diabetic patients
7. Raw data, Ascensia Contour results, the diabetics measurements at NOKLUS
8. Raw data, Ascensia Contour results, the diabetics measurements at home
9. Raw data, hematocrit
10. Questionnaire, user-friendliness (in Norwegian)
11. Questionnaire, user manual (in Norwegian)
12. Bayer Healthcare Self Testing Systems Division. Rebuttal to SKUP
13. An answer from to SKUP to Bayer's comments.

Attachments with raw data are included only in the report to Bayer AS.

Serial numbers, Ascensia Countour instruments used by medical scientist **Attachment 1**

Instrument	Serialnumber
A	1134229
B	1134238

Serial numbers, Ascensia Countour instruments used by diabetics

ID	Serialnumber
2	1134231
6	1134232
9	1134187
12	1134181
13	1134186
14	1134196
16	1134201
17	1134216
18	1134207
19	1134182
21	1134192
22	1134197
23	1134183
24	1134204
25	1134218
27	1134220
29	1134188
30	1134189
32	1134202
34	1134230
35	1134235
36	1134225
37	1134239
38	1134215
39	1134210
40	1134219
41	1134205
42	1134221
43	1134226
44	1134222
45	1134227
46	1134211
47	1134212
48	1134217
49	1134203
50	1134241
51	1134246
53	1134251
54	1134256

ID	Serialnumber
55	1134208
56	1134191
58	1134209
59	1134240
61	1134234
62	1134185
67	1134195
68	1134198
72	1134199
74	1134190
75	1134193
78	1134116
81	1134184
86	1134237
87	1134224
89	1134228
92	1134233
95	1134242
98	1134252
101	1134257
103	1134243
105	1134163
106	1134173
109	1134168
120	1134174
121	1134146
122	1134141
123	1134179
124	1134165
126	1134178
131	1134162
132	1134167
133	1134172
134	1097118
140	1097112
141	1097120
142	1097114
146	1097104

NORSK KVALITETSFORBEDRING AV LABORATORIEVIRKSOMHET UTENFOR SYKEHUS

NOKLUS

Mars 2004

Utprøving av nytt blodsukkerapparat

Du har fått utlevert en eske med:

- 1 Ascensia Contour blodsukkerapparat i etui
- 1 boks Ascensia Microfill teststrimler for glukose (á 50 stk.)
- 1 Microlet prøvetakingspenn
- 25 lansetter
- Brukerveiledning

Du skal bruke dette hjemme i en periode på ca. 3 uker. I denne prøveperioden skal du bruke det nye apparatet **i tillegg** til ditt eget apparat. Det betyr at du skal utføre blodsukkermålingene med ditt vanlige apparat så ofte som du ellers ville ha gjort. **Når du skal vurdere ditt eget blodsukker, skal du bruke resultatene fra ditt vanlige apparat.** Det nye apparatet skal du bruke slik det står beskrevet nedenfor:

1. og 2. uke:

De to første ukene skal benyttes til å bli kjent med det nye apparatet. I løpet av disse to ukene skal du bruke ca. 25 strimler til å måle ditt eget blodsukker med det nye apparatet.

Du kan selv velge når på dagen du vil gjøre disse målingene (du trenger ikke å være fastende). Passer det best slik, kan du utføre blodsukkermålingen med Ascensia Contour samtidig som du måler med ditt vanlige apparat. Dersom du ønsker det, kan du benytte ditt eget utstyr for prøvetaking i stedet for Microlet prøvetakingspenn.

3. uke:

Etter at du har brukt de 25 første strimlene, skal du i løpet av den tredje uken måle blodsukkeret med Ascensia Contour på 5 forskjellige dager. Du kan selv velge når på dagen du vil gjøre disse målingene (du trenger ikke å være fastende). Hver av disse 5 dagene skal du: Stikke deg i fingeren og **måle blodsukkeret to ganger rett etter hverandre** med blod fra samme stikk. Dersom du ikke får nok blod til å utføre begge målingene, kan du stikke deg på nytt til andre måling. Resultatene føres i skjemaet på baksiden.

NOKLUS Senter | Seksjon for allmennmedisn | UNIFOB AS | Boks 6165 Postterminal | 5892 Bergen
Telefon: 55 58 67 00 | Telefaks: 55 58 67 10 | E-post: noklus@isf.uib.no | www.noklus.no

ID-nr:
Lot nr. teststrimler:
Serienr. apparat:

Dato	Ascensia Contour Svar 1 (mmol/L)	Ascensia Contour Svar 2 (mmol/L)	Er målingene gjort med blod fra samme/forskjellige stikk? Stryk det som ikke passer.
Dag 1:			Samme / forskjellige
Dag 2:			Samme / forskjellige
Dag 3:			Samme / forskjellige
Dag 4:			Samme / forskjellige
Dag 5:			Samme / forskjellige

Har du brukt Microlet prøvetakingspenn til prøvetakingen? □ Ja □ Nei □ Noen ganger

Av de 50 strimlene du fikk sammen med apparatet, skal du nå ha ca. 10 strimler igjen. Du må spare 5 stykker av disse til målingene du skal gjøre når du kommer hit til NOKLUS for den avsluttende utprøvingen. Da skal du ta med det nye apparatet, Ascensia Contour, sammen med resten av strimlene og Microlet prøvetakingspenn med lansetter. Du skal da utføre egne målinger med det nye apparatet, samtidig med at bioingeniøren stikker deg to ganger i fingeren og til slutt tar en blodprøve fra armen. Du vil også bli bedt om å svare på noen spørsmål mht. apparatets brukervennlighet og om brukerveiledningen. Det hele vil ta ca ½ time.

Har du spørsmål, enten før du starter, eller i løpet av prøveperioden, er det bare å ringe 55 58 61 68 (Camilla) eller 55 58 67 02 (Grete), mellom kl. 08.00 og 16.00.

Lykke til!

Med vennlig hilsen

Sverre Sandberg
Prosjektansvarlig (sign.)

Grete Monsen
Prosjektleder (sign.)

Camilla Eide Jacobsen
Avdelingsingeniør (sign.)

Raw data, internal quality control (Autonorm), Advia 1650 **Attachment 3**

Date	Serial-	Res. Autonorm 1	Res. Autonorm 1	Res. Autonorm 2	Res. Autonorm2
08.mar	Start	5,36	5,36	14,7	14,71
	End	5,34	5,31	14,7	14,69
09.mar	Start	5,39	5,35	14,78	14,9
	End	5,33	5,33	14,69	14,73
11.mar	Start	5,33	5,33	14,67	14,7
	End	5,31	5,3	14,6	14,67
12.mar	Start	5,35	5,27	14,72	14,7
	End	5,33	5,28	14,76	14,68
16.mar	Start	5,27	5,25	14,56	14,5
	End	5,26	5,28	14,49	14,45
17.mar	Start	5,22	5,25	14,51	14,59
	End	5,22	5,25	14,54	14,54
19.mar	Start	5,32	5,29	14,73	14,69
	End	5,25	5,25	14,7	14,72
22.mar	Start	5,26	5,27	14,51	14,58
	End	5,25	5,2	14,46	14,52
22.mar	Start	5,28	5,25	14,53	14,51
	End	5,24	5,27	14,56	14,48
26.mar	Start	5,23	5,26	14,5	14,51
	End	5,26	5,22	14,54	14,56
29.mar	Start	5,1	5,16	14,16	14,12
	End	5,17	5,16	14,18	14,15
31.mar	Start	5,29	5,3	14,69	14,66
	End	5,3	5,24	14,6	14,63
13.apr	Start	5,3	5,3	14,93	14,87
	End	5,29	5,27	14,85	14,81
13.apr	Start	5,32	5,29	14,48	14,5
	End	5,3	5,27	14,46	14,44
13.apr	Start	5,28	5,34	14,62	14,62
	End	5,33	5,33	14,67	14,63
14.apr	Start	5,34	5,33	14,57	14,6
	End	5,29	5,32	14,6	14,59
15.apr	Start	5,28	5,25	14,61	14,58
	End	5,25	5,24	14,62	14,58
16.apr	Start	5,3	5,29	14,69	14,69
	End	5,29	5,29	14,66	14,69
20.apr	Start	5,28	5,27	14,77	14,76
	End	5,26	5,26	14,75	14,82
22.apr	Start	5,32	5,3	14,39	14,46
	End	5,28	5,26	14,47	14,49
27.apr	Start	5,28	5,29	14,76	14,74
	End	5,32	5,26	14,76	14,67

Raw data, hematocrit **Attachment 9**

ID	Hematocrit
2	0,353
6	no blood sample
9	0,351
12	0,361
13	0,403
14	0,358
16	0,384
17	0,372
18	0,391
19	0,374
21	0,381
22	0,438
23	0,405
24	0,430
25	0,361
27	0,368
29	0,396
30	0,411
32	0,363
34	0,375
35	0,409
36	0,396
37	0,356
38	0,434
39	0,330
40	0,435
41	0,379
42	0,512
43	Utgår
44	0,367
45	0,400
46	no blood sample
47	0,411
48	0,323
49	0,366
50	0,383
51	0,383
53	0,353
54	0,385

ID	Hematocrit
55	0,388
56	0,333
58	0,376
59	0,385
61	0,400
62	0,368
67	0,381
68	0,347
72	0,375
74	0,374
75	0,378
78	0,395
81	no blood sample
86	0,363
87	0,368
89	0,361
92	0,462
95	0,414
98	0,401
101	0,353
103	0,349
105	0,399
106	0,367
109	0,416
120	0,361
121	0,305
122	0,378
123	0,402
124	0,352
126	0,351
131	0,384
132	0,427
133	0,407
134	0,379
140	0,331
141	0,401
142	0,391
146	0,387

ID 43 didn’t meet to the 2’nd consultation when blood sample was collected. We didn’t manage to collect blood sample of three diabetic persosns.

ID-nummer (diabetiker):_____

Ascensia Contour

Spørreskjema om blodsukkerapparatets brukervennlighet

Hvordan vil du rangere følgende på en skala fra 1 til 6, der 1 er *vanskelig* og 6 er *enkelt*:

1. Å sette strimmel inn i apparatet

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

2. Å fylle strimmelen med blod

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

3. Å lese tallene i displayet

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

4. Å oppfatte lydsignal fra apparatet

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

5. Å betjene apparatet, totalt sett

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

6. Å betjene Microlet lansettpenn (skal kun besvares hvis Microlet lansettpenn er benyttet i utprøvingen)

Vanskelig *Enkelt*

1	2	3	4	5	6
☐	☐	☐	☐	☐	☐

Snu arket

7. Hvor viktig synes du det er at Ascensia Contour har automatisk koding?

☐ **Viktig** ☐ **Mindre viktig** ☐ **Ingen betydning**

8. Var det tekniske problemer med apparatet i utprøvingsperioden? ☐ **Ja** ☐ **Nei**

Hvis ja, kan du beskrive problemet/ene:_____

_____

_____

9. Synes du det er noen fordeler ved Ascensia Contour?

- _____
- _____
- _____

10. Synes du det er noen ulemper ved Ascensia Contour?

- _____
- _____
- _____

11. Hvilket blodsukkerapparat benytter du til vanlig? _____

Evt. andre kommentarer:_____

_____

_____

_____

ID-nummer (diabetiker):_____

Ascensia Contour

Spørreskjema om brukerveiledning til apparatet

Har du lest i brukerveiledningen? ☐ **Ja** ☐ **Nei**

Hvis du svarer nei, skal du ikke svare på resten av spørsmålene på dette arket.

Hvis du svarer ja:

- har du lest gjennom hele brukerveiledningen? ☐ **Ja** ☐ **Nei**

- og/eller har du slått opp i den ved behov? ☐ **Ja** ☐ **Nei**

1. **Er du fornøyd med beskrivelsen av hvordan man skal utføre en blodsukkermåling med dette apparatet?** ☐ **Ja** ☐ **Nei**

   Hvis nei, kan du beskrive hva du ikke er fornøyd med: _____

   _____

   _____

2. **Mener du at det er vesentlige mangler i brukerveiledningen?** ☐ **Ja** ☐ **Nei**

   Hvis ja, kan du beskrive hva som mangler: _____

   _____

   _____

3. **Totalt sett, er du fornøyd med brukerveiledningen?** ☐ **Ja** ☐ **Nei**

   Hvis nei, kan du beskrive hva du ikke er fornøyd med: _____

   _____

   _____

   Evt. andre kommentarer:_____

   _____

   _____

   _____

Attachment 12

Bayer HealthCare Self Testing Systems Division Rebuttal to SKUP

The Self Testing Systems Division of Bayer HealthCare is not in a position to explain the inconsistent results from the second consultation of the SKUP trial. As with all blood glucose testing, many factors can affect the results including but not limited to the protocol, the physiological state of the subjects, the attention to detail and the proper storage and handling of the meters and reagent strips. We are not at liberty to comment on what happened to the patient samples or results. SKUP conducted the trial based on their internal protocol and expertise. Any number of factors could be responsible for the discrepant results.

To summarize, results from the first consultation were fine for both the subjects and the scientists at SKUP. At the second consultation, the results with materials in the hands of SKUP were found to perform satisfactorily. Unfortunately, some meters and some samples returned by the patients after three weeks, were found to give results that were ten percent high, on average, when compared to the laboratory method. In addition, testing of the patient samples with aqueous control solutions showed twice the amount of imprecision than was observed from the first consultation. In effect, the aqueous solutions indicated that the patient samples were somewhat compromised either through storage, exposure or otherwise, such that the results cannot be attributed to the nature of blood as a matrix for testing. The Ascensia CONTOUR®/Ascensia MICROFILL® system has been rigorously tested in-house by Bayer personnel and by outside agencies before and after it was launched. The authorities at SKUP may want to consider re-evaluating the process and procedures used in the study to determine why samples in the hands of patients did not give acceptable results. Retention samples maintained by SKUP under controlled conditions were found to perform satisfactorily with both blood and aqueous control solutions for both consultations.

The Ascensia CONTOUR/Ascensia MICROFILL product has performed as expected and in accordance with the labeling approved by the Food and Drug Administration. Since the product's market introduction in April 2003, tens of thousands of Bayer HealthCare customers are successfully employing the Ascensia CONTOUR/Ascensia MICROFILL system in their

daily regimen of blood glucose monitoring and find the product to be of high quality. The product meets or exceeds the performance standards as set forth by ISO 15197 as denoted by the CE Mark.

Since the Ascensia CONTOUR/Ascensia MICROFILL system was just recently launched worldwide, external study results have not been published in peer review journals. Results from additional studies have been submitted to ***Diabetes Technology & Therapeutics*** and ***Diabetes Research & Clinical Practice*** for publication in the next few months. The Bayer HealthCare Self Testing Systems Division intends to provide white papers on the performance of the system in different areas to further support the packaging and labeling in the product manual and reagent inserts.

Attachment 13

Comments from SKUP to the letter "Bayer HealthCare Self Testing Systems Division Rebuttal to SKUP"

Bayer Diagnostics commented the SKUP report in a letter handed over to SKUP the 29th of October 2004. In the letter the test strips confusingly seem to be referred to as 'patient samples' which make some of the arguments difficult to follow.

Factors that affect the glucose result
Many factors affect the glucose result. Still, there is no reason to believe that these factors differed from the first to the second consultation. The physiological state of the subject would most likely be the same, and the diabetics' attention to details was probably not changed noticeably. SKUP therefore has difficulties in explaining the poorer results at the second consultation based on these factors.

The protocol for the evaluation of Ascensia Contour
The protocol used for the evaluation of Ascensia Contour is not an internal SKUP-protocol. The protocol is based on a standard protocol for user evaluations of Self-Monitoring Blood Glucose (SMBG) test strips. This standard protocol is in use as the official requirements for documenting the analytical quality in Norway, in order to achieve test strip reimbursement by the National Office for Social Insurance (RTV). The standard protocol was adapted to the specific evaluation of Ascensia Contour, and was furthermore commented on and approved by Bayer in advance of the evaluation.

The results achieved by the diabetic patients at the second consultation
All the measurements performed by the diabetic patients were observed by a professional laboratory technologist. After the first consultation, all the diabetic patients were trained in how to handle and take care of the system properly. From having achieved the quality goals set by ISO 15197 at the first consultation, the results at the second consultation no longer met the quality goals. When they met for the second consultation, the diabetic patients had kept the meters (a total of 79 meters) and bottles of test strips at home for three weeks. SKUP has no reason to believe that the poorer results at the second consultation were caused by user errors. By means of the internal quality control solution, SKUP also could support the finding that the quality of the meters or test strips had decreased after having been kept "out-house" for three weeks.

In-house testing by Bayer versus the SKUP evaluation
According to the letter from Bayer, Ascensia Contour has been rigorously tested in-house by Bayer personnel, and also by "outside agencies", with satisfying results. This is of course very important. SKUP evaluates instruments and methods under standardised and optimal conditions by laboratory personnel, to reveal the analytical quality of the system. In addition, a SKUP-evaluation consists of an evaluation by the users in a "real life" situation, to document user-friendliness and the robustness of the system. This evaluation of Ascensia Contour illustrates that independent evaluations sometimes give discrepant results compared to in-house evaluations, and that evaluations among the users can reveal new and important information about the system.

“Bayer HealthCare customers are successfully employing Ascensia Contour”
Most often the diabetics will be satisfied with their blood glucose monitor as long as they get the measurement results without trouble. However, the diabetic patients can not evaluate analytical quality themselves. In fact, this is the reason why SKUP organises evaluations were the users also participate. The analytical quality achieved under standard and optimal conditions most often differs from the results obtained by the users. This is the finding in this study as well.

The CE-mark and the standards set forth by ISO 15197
In Europe SMBG-device is regulated by the IVD Directive. The CE-mark is the visible sign for meeting the requirements in this directive. However, there are no explicit analytical quality requirements in the directive, and the directive gives no quality guarantee. In general, the CE-mark therefore does not necessarily amount for meeting the quality goals set forth by ISO 15197. In the user-evaluation organised by SKUP, the goals set by ISO are achieved at the first consultation. For some reason the diabetic patients’ results at the second consultation did not meet the goals. It has not been possible, neither for SKUP, nor for Bayer, to explain the discrepant results between the first and the second consultation. In contrast to Bayer, however, SKUP does not believe that this is a user-related problem, but more likely associated with properties of test strips and measuring device.