08819378501V2.0

Elecsys AMH

cobas®

REF		Σ	SYSTEM
08819378190	08819378501	100	**cobas e** 402 **cobas e** 801

English

For use in the USA only

System information

Short name	ACN (application code number)
AMH	10190

Intended use

Elecsys AMH is intended for use in the in vitro quantitative determination of anti-Müllerian hormone (AMH) in human serum and lithium heparin plasma. The determination of AMH is used for the assessment of the ovarian reserve in women presenting to fertility clinics. This system is intended to distinguish between women presenting with AFC (antral follicle count) values > 15 (high ovarian reserve) and women with AFC values ≤ 15 (normal or diminished ovarian reserve). This system is intended to be used for assessing the ovarian reserve in conjunction with other clinical and laboratory findings before starting any fertility therapy. The Elecsys AMH system is not intended to be used for monitoring of women undergoing controlled ovarian stimulation in an Assisted Reproduction Technology program.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

The anti-Müllerian hormone is a homodimeric glycoprotein belonging to the transforming growth factor β (TGF-β) family. All members of this superfamily are involved in the regulation of tissue growth and differentiation. Prior to secretion, the hormone undergoes glycosylation and dimerization to produce an approximately 140 kDa precursor of 2 identical disulfide-linked 70 kDa subunits. Each monomer contains a large N-terminal pro-region and a much smaller C-terminal mature domain. In contrast to other TGF-β family members, AMH is thought to require the N-terminal domain to potentiate activity of the C-terminal domain to attain full bioactivity.[1,2]

A part of AMH is then cleaved at a specific site between the pro-region and the mature region during cytoplasmic transit to generate biologically active 110 kDa N-terminal and 25 kDa C-terminal homodimers which remain associated in a non-covalent complex. The AMH type II receptor (AMH RII) has the capacity of binding only the biologically active form of AMH.[2]

AMH plays an important role in ovarian folliculogenesis.[3] Follicle development in the ovaries comprises 2 distinct stages: initial recruitment, by which primordial follicles start to mature, and cyclic recruitment, which leads to the growth of a cohort of small antral follicles, among which the dominant follicle (destined to ovulate) is subsequently selected. FSH (follicle-stimulating hormone) directs the cyclic recruitment. AMH expression in granulosa cells starts in primary follicles and is maximal in granulosa cells of preantral and small antral follicles up to approximately 6 mm in diameter. When follicle growth becomes FSH-dependent, AMH expression diminishes and becomes undetectable. This pattern of AMH expression supports the inhibitory role of AMH at 2 distinct stages of folliculogenesis. First, AMH inhibits the transition of follicles from primordial into maturation stages and thereby has an important role in regulating the number of follicles remaining in the primordial pool. Second, AMH has inhibitory effects on follicular sensitivity to FSH and therefore has a role in the process of follicular selection.[4,5]

Serum levels of AMH are barely detectable at birth in females, reach their highest levels after puberty, decrease progressively thereafter with age, and become undetectable at menopause.[6,7] Serum AMH levels have been shown to be relatively stable during the menstrual cycle with substantial fluctuations being observed in younger women.[8,9,10] AMH levels further demonstrate lower intra- and inter-cyclic variation than baseline FSH.[9] Serum AMH levels decrease significantly during the use of combined contraceptives.[11] Measurement of serum AMH is clinically used for assessment of ovarian reserve reflecting the number of antral and pre-antral follicles, the so-called antral follicle count (AFC).[12,13]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 30 µL of sample, a biotinylated monoclonal AMH-specific antibody, and a monoclonal AMH-specific antibody labeled with a ruthenium complex[a)] form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack is labeled as AMH.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-AMH-Ab~biotin, 1 bottle, 7.2 mL:
Biotinylated monoclonal anti-AMH antibody (mouse) 1.0 mg/L; phosphate buffer 50 mmol/L, pH 7.5; preservative.

R2 Anti-AMH-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 7.2 mL:
Monoclonal anti-AMH antibody (mouse) labeled with ruthenium complex 1.0 mg/L; biotin scavenger antibody 1 mg/mL; phosphate buffer 50 mmol/L, pH 7.5; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing mist or vapours.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: 1-800-428-2336

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Performance data included was validated for measurements of AMH on days 2-4 of the menstrual cycle.

The measured AMH value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must, therefore, always contain a statement on the AMH assay method used. AMH values determined on patient samples by different testing procedures cannot be directly compared to one another and could be the cause of erroneous medical interpretations. Therefore, the results reported by the laboratory to the physician should always include: "The following results were obtained with the Elecsys AMH assay. Results from assays of other manufacturers cannot be used interchangeably."

The Elecsys AMH assay is intended to be used for assessing the ovarian reserve in conjunction with other clinical and laboratory findings before starting any fertility therapy (including pre-treatment such as gonadotropin-releasing hormone (GnRH) agonist down-regulation therapy) and should be used in conjunction with AFC. The Elecsys AMH assay is not intended to be used for monitoring of women undergoing controlled ovarian stimulation in an Assisted Reproduction Technology program.

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Specimen collection and preparation

Samples for AMH levels should be drawn on days 2-4 of the menstrual cycle.

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin plasma. Do not use EDTA plasma.

Criterion: Method comparison of Li-heparin plasma versus serum: slope of 0.9-1.1 + intercept within 0 ± 0.1 ng/mL + coefficient of correlation ≥ 0.95.

Stable for 3 days at 15-25 °C, 5 days at 2-8 °C, 6 months at -20 °C (± 5 °C). Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 09013326190, AMH CalSet, for 4 x 1.0 mL
- REF 06709966190, PreciControl AMH, for 4 x 2.0 mL
- REF 07299001190, Diluent Universal, 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against the Beckman Coulter AMH Gen II ELISA (unmodified version without predilution) assay.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer). Renewed calibration is recommended as follows:

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl AMH.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined

limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in ng/mL or in pmol/L).

Conversion factors: pmol/L x 0.14 = ng/mL

ng/mL x 7.14 = pmol/L

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1000 mg/dL
Rheumatoid factors	≤ 1000 IU/mL
IgG	≤ 2.5 g/dL
IgA	≤ 1.8 g/dL
IgM	≤ 0.5 g/dL

Biotin interference

This assay has no biotin interference in serum concentrations up to 1200 ng/mL. Pharmacokinetic studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per day[14] and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.[15]

In addition the following 20 pharmaceutical drugs were tested. No interference with the assay was found.

Active agent	Concentration (mg/L)
Acetylcysteine	150
Ampicillin-Na	75
Ascorbic acid	52.5
Cyclosporine	1.8
Cefoxitin	750
Heparin	3300 IU/L
Levodopa	7.5
Methyldopa + 1.5	22.5
Metronidazole	123
Phenylbutazone	321
Doxycycline	18
Acetylsalicylic acid	30
Rifampicin	48
Acetaminophen	156
Ibuprofen	219
Theophylline	60
Gonapeptyl	0.1
Metformin	2000
Folic acid	0.4
Levothyroxine	0.2

Criterion: Recovery within ± 10 % of initial value.

The following drugs may interfere with this test: Cetrotide, Ovitrelle, Endometrin and Follistatin: do not use this test to analyze samples from patients who have received 1 or more of these products within 1 to 2 weeks of testing.

There is no high-dose hook effect at AMH concentrations up to 1400 ng/mL.

Human Anti-Mouse Antibody (HAMA) interference testing was completed with low and high AMH analyte concentrations using a high HAMA human serum pool. There was no HAMA interference up to 17.1 ng/mL.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

0.03-23 ng/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as < 0.03 ng/mL. Values above the measuring range are reported as > 23 ng/mL (or up to 46 ng/mL for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.007 ng/mL (0.049 pmol/L)

Limit of Detection = 0.01 ng/mL (0.07 pmol/L)

Limit of Quantitation = 0.03 ng/mL (0.214 pmol/L)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with AMH concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the analyzer or manually). The concentration of the diluted sample must be > 71.4 pmol/L (> 10 ng/mL).

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Reference values measured in apparently healthy population

A reference range study was conducted to establish age-dependent reference ranges for AMH in 718 healthy females of reproductive age between 20 and 44 years. Native samples were collected by an external vendor and testing was conducted at two sites; one in Germany and one in Belgium. The values given are for information only and may vary from other published data.

Estimated Quantiles of Elecsys AMH						
Healthy Women (years)	N	2.5 %-q ng/mL (95 % CI)[b)16]	5 %-q ng/mL (95 % CI)	Median ng/mL (95 % CI)	95 %-q ng/mL (95 % CI)	97.5-q ng/mL (95 % CI)
20-24	150	1.22 (0.478-1.67)	1.52 (0.758-1.81)	4.00 (3.60-4.44)	9.95 (7.87-13.6)	11.7 (9.11-15.7)

Elecsys AMH

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Estimated Quantiles of Elecsys AMH						
Healthy Women (years)	**N**	**2.5 %-q ng/mL (95 % CI)[b)16]**	**5 %-q ng/mL (95 % CI)**	**Median ng/mL (95 % CI)**	**95 %-q ng/mL (95 % CI)**	**97.5-q ng/mL (95 % CI)**
25-29	150	0.890 (0.493-1.21)	1.20 (0.797-1.75)	3.31 (3.00-3.89)	9.05 (7.59-10.3)	9.85 (8.91-11.3)
30-34	138	0.576 (0.256-0.958)	0.711 (0.256-1.12)	2.81 (2.35-3.47)	7.59 (6.84-9.52)	8.13 (7.27-9.72)
35-39	138	0.147 (0.052-0.474)	0.405 (0.053-0.496)	2.00 (1.73-2.36)	6.96 (5.31-9.37)	7.49 (6.49-10.9)
40-44	142	0.030 (0.030-0.063)	0.059 (0.030-0.119)	0.882 (0.726-1.13)	4.44 (2.94-5.56)	5.47 (3.92-6.76)

b) CI = Confidence interval according to Hahn and Meeker, 1991

Summary of clinical performance

The use of AMH for the assessment of ovarian reserve was investigated in a multicenter, prospective, non-interventional study with n = 856 women presenting at fertility clinics for evaluation.[17] Patient BMI included in the study ranged from 14.76 to 39.99.

BMI	N
< 18.50	29
18.50-24.99	469
25.00-29.99	200
> 30.00-39.99	158

AMH values were correlated to the antral follicle count (AFC) of the women. AFC was determined by transvaginal ultrasonography (TVUS), which measures antral follicles (2-10 mm) of the ovaries. Both AFC and AMH were determined on days 2-4 of the same menstrual cycle. Female subjects were recruited at 13 different collection sites in the United States; AMH sample analyses of the collected, clinical samples were performed at 3 US testing sites.

Exclusion criteria for the clinical study included:
Major ovarian abnormalities, including subject with only 1 ovary and/or cysts and solid masses > 2 cm (as detected by TVUS).
A diagnosis of Polycystic Ovarian Syndrome (PCOS).
Body Mass Index (BMI) ≥ 40.
Endocrine or metabolic abnormalities, including diabetes and/or disease of the pituitary gland, adrenal gland, pancreas, liver, and/or kidney.
Ovarian surgery in the past 6 months.
Hormonal contraceptive use in the preceding 3 months.
Patient had taken any hormonal medication (including Clomid, aromatase inhibitors, all types of gonadotropins, estrogen-receptor inhibitors, tamoxifen, gonadotropin-releasing hormone (GnRH) agonists/GnRH antagonists) in the past 21 days. Note: Thyroid hormones were allowed.

Using the 1.77 ng/mL cutoff for serum AMH, the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) observed in the clinical study for predicting AFC > 15 are summarized in the following table:

	Result	**95 % CI**
Specificity	68.3 %	63.6 %, 72.8 %
Sensitivity	88.3 %	85.0 %, 91.2 %
Positive Predictive Value (PPV)	75.2 %	71.3 %, 78.8 %
Negative Predictive Value (NPV)	84.3 %	80.0 %, 88.1 %

Interpretation of results

Based on the AMH cutoff (c = 1.77 ng/mL), 2 AFC groups are defined: AFC ≤ 15 and AFC > 15.[18,19] Correlation of AMH and AFC is presented in the two-way frequency table below (relationship is shown in both absolute numbers and percentages per AMH group)[c)]

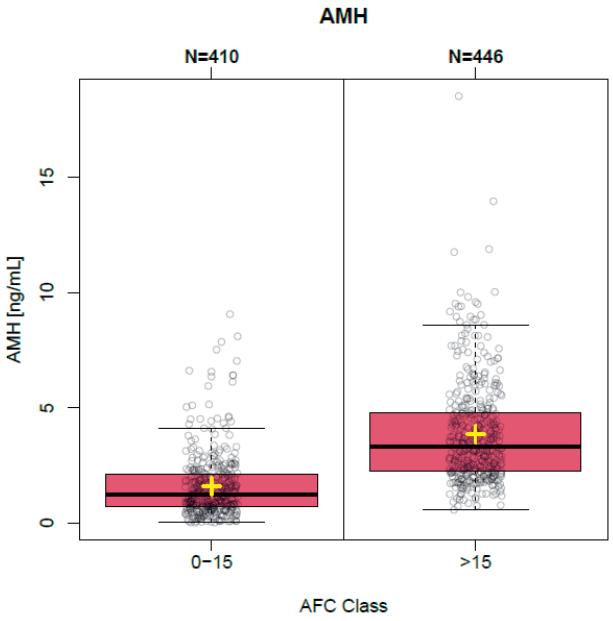
	AFC ≤ 15	**AFC > 15**	**N**
AMH ≤ 1.77 ng/mL	280 (84.3 %)	52 (15.7 %)	332
AMH > 1.77 ng/mL	130 (24.8 %)	394 (75.2 %)	524
N	410	446	856

- For a patient with an AMH value ≤ 1.77 ng/mL, the probability to have an AFC ≤ 15 is 84.3 %, and the probability to have an AFC > 15 is 15.7 %.
- For a patient with an AMH value > 1.77 ng/mL, the probability to have an AFC ≤ 15 is 24.8 %, and the probability to have an AFC > 15 is 75.2 %.

c) Given the site- and ultrasonographer-specific variations observed with AFC determinations, each site should assess the two-way frequency table for transferability to their own patient population.

AMH distribution in the 2 AFC groups

The following figure illustrates the Validation Arm AMH results, presented by AFC group/class (AFC ≤ 15 and AFC > 15).



x: AFC Class

y: AMH (ng/mL)

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Linearity

Linearity of the Elecsys AMH assay was assessed according to CLSI EP6-A. 3 high-level analyte serum samples (spiked human serum pools) were diluted with postmenopausal female serum, which can be considered to contain no AMH. 15 concentrations (dilutions) throughout the measuring range were prepared. Results were analyzed with regards to linear, quadradic, and cubic polynomials. Linearity results confirm the measuring range claim of 0.03 - 23 ng/mL for the Elecsys AMH assay.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.0497	0.001	2.1	0.002	3.8
Human serum 2	0.901	0.013	1.5	0.025	2.8
Human serum 3	4.64	0.072	1.5	0.167	3.6
Human serum 4	13.5	0.194	1.4	0.501	3.7
Human serum 5	21.4	0.405	1.9	0.686	3.2
PreciControl AMH 1	1.04	0.013	1.3	0.029	2.8
PreciControl AMH 2	5.14	0.042	0.8	0.147	2.9

Analytical specificity

The monoclonal antibodies used are highly specific to human AMH. The following cross-reactivities were found:

Cross-reactant	**Concentration tested**	**Cross-reactivity %**
Inhibin A	100 ng/mL	n. d.[d)]
Activin A	100 ng/mL	n. d.
LH	500 mIU/mL	n. d.
FSH	500 mIU/mL	n. d.

d) n. d. = not detectable

Method comparison

A comparison of the Elecsys AMH assay on the **cobas e** 801 analyzer (y) with the Elecsys AMH assay on the **cobas e** 601 analyzer (x) was performed. A total of 198 samples were measured.

The sample concentrations were between 0.125 and 21.5 ng/mL. The analysis is reported below:

Passing/Bablok[20]	Linear regression
y = 0.0854 + 0.968x	y = 0.133 + 0.958x
τ = 0.974	r = 0.999

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

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cobas®

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

Roche

Distribution in USA by:
Roche Diagnostics, Indianapolis, IN
US Customer Technical Support 1-800-428-2336