2. SYNOPSIS

Name of Sponsor: Janssen Pharmaceutical K.K.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: To be determined		
Name of Active Ingredient: CNTO 3649		

Title of study:
Safety, Pharmacokinetics, and Pharmacodynamics of a Single Subcutaneous Dose of CNTO 3649 in Healthy Adult Men and Multiple Subcutaneous Doses of CNTO 3649 in Patients With Type 2 Diabetes Mellitus

Investigators:
Part 1
Yukikuni Sakata, Director, Hakata Clinic
Part 2
Takashi Eto, Clinical Director, PS Clinic

Study sites:
Part 1
Hakata Clinic
Part 2
PS Clinic

Publication (reference):
None

Study period:	**Phase of development:**
Date of informed consent for first subject: 22 July 2009 Date of last observation for last subject: 17 March 2010	Phase 1
	Type of study: Clinical pharmacology study

Objectives:

Part 1

Primary objective
The primary objective was to investigate the safety (adverse events, weight, blood pressure, pulse rate, body temperature, abdominal ultrasonography, standard 12-lead electrocardiography, and laboratory tests) of CNTO 3649 when administered once by subcutaneous injection in healthy adult Japanese men.

Secondary objectives
A secondary objective was to investigate the pharmacokinetics of CNTO 3649 when administered once by subcutaneous injection in healthy adult Japanese men, using the serum CNTO 3649 concentration as an indicator. Other secondary objectives were to investigate the pharmacological effects using blood glucose, serum insulin concentration, and serum C-peptide concentration as indicators and to investigate the immune response using anti-CNTO 3649 antibodies as an indicator.

Part 2

Primary objective
The primary objective was to investigate the safety (adverse events, weight, blood pressure, pulse rate, body temperature, abdominal ultrasonography, standard 12-lead electrocardiography, and laboratory

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tests) of CNTO 3649 when administered by subcutaneous injection once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus.

Secondary objectives
A secondary objective was to investigate the pharmacokinetics of CNTO 3649 when administered by subcutaneous injection once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus, using the serum CNTO 3649 concentration as an indicator. Other secondary objectives were to investigate the pharmacological effects using blood glucose, hemoglobin A1C (HbA_{1C}), serum insulin concentration, and serum C-peptide concentration as indicators and to investigate the immune response using anti-CNTO 3649 antibodies as an indicator.

Method of administration:

Part 1
CNTO 3649 (10, 30, 100, or 300 µg/kg) or placebo was administered once by subcutaneous injection.

Part 2
CNTO 3649 (30 or 100 µg/kg) or placebo was administered once a week for 4 weeks by subcutaneous injection.

Number of subjects:

Part 1
Healthy adult Japanese men: 40 (planned and analyzed)

Part 2
Japanese patients with type 2 diabetes mellitus: 24 (planned and analyzed)

Subjects and main criteria for inclusion:

The subjects were patients who met all of the following inclusion criteria and none of the following exclusion criteria (Part 1: healthy adult Japanese men, Part 2: Japanese patients with type 2 diabetes mellitus).

Inclusion criteria

Part 1
1. Is able to personally give voluntary written consent after being fully informed about the study agent and the study before participating in the study.
2. Is between 20 and 39 years of age on the day of informed consent.
3. Weighs ≥50 kg and <100 kg and has a body mass index (BMI) (BMI = [weight in kg]/[height in m]^2) of ≥18.5 and <25.0 at the time of screening tests.
4. Is a non-smoker, or is able to refrain from smoking from 2 days before screening tests until completion of posttreatment examinations or follow-up investigations.
5. Is able to refrain from consuming alcohol from 2 days before screening tests until completion of screening tests, from 2 days before hospitalization (Day −4) until after discharge (Day 8), from 2 days before clinic visits (Days 13 and 20) until completion of tests at clinic visits (Days 15 and 22), and from 2 days before posttreatment examinations or follow-up investigations until completion of posttreatment examinations or follow-up investigations.
6. Has agreed to use a medically acceptable form of contraception (eg, condoms) from the day of

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hospitalization (Day −2) until completion of posttreatment examinations or follow-up investigations.
7. Has no clinically problematic abnormalities in medical examinations and tests before study treatment.

Part 2
1. Is able to personally give voluntary written consent after being fully informed about the study agent and the study before participating in the study.
2. Is between 20 and 64 years of age on the day of informed consent.
3. Weighs ≥50 kg and <100 kg and has a BMI of ≥18.5 and <37.0 at the time of screening tests.
4. Was diagnosed with type 2 diabetes mellitus at least 3 months before screening tests and this is being stably managed with dietary modification, exercise therapy, or sulfonylureas or biguanides. If sulfonylureas or biguanides are being used, these have been used at a fixed dosage to stably manage the disease since at least 3 months before screening tests.
5. If the subject has hyperlipidemia, this has been stably managed with antihyperlipidemic drugs at a fixed dosage since at least 3 months before screening tests.
6. If the subject has hypertension, this has been stably managed with antihypertensive drugs at a fixed dosage since at least 3 months before screening tests.
7. Is a non-smoker, or is able to refrain from smoking during the hospitalization period and from 1 day before clinic visit days until completion of tests.
8. Is able to refrain from consuming alcohol during the hospitalization period and from 1 day before clinic visit days until completion of tests.
9. Has agreed to use a medically acceptable form of contraception (eg, condoms) from the day of hospitalization (Day −2) until completion of posttreatment examinations or follow-up investigations.
10. Has no clinically problematic abnormalities in medical examinations and tests before starting study treatment.

Exclusion criteria

Part 1
1. Has or has had hepatic, renal, central nervous system (including psychiatric), cardiovascular, respiratory, gastrointestinal, hematopoietic, ophthalmic, infectious, or endocrine disease that would make the patient unsuitable as a study participant.
2. Has had a malignant tumor within 5 years before study treatment.
3. Has undergone surgery that would make the patient unsuitable as a study participant within 12 weeks before screening tests.
4. Has or had acute disease that occurred within 7 days before study treatment.
5. Has or has had an eating disorder (pathological anorexia or bulimia).
6. Regularly drinks ≥1,200 mL of coffee, cola, or hot chocolate per day.
7. Has been vaccinated (live or inactivated vaccine) within 30 days before study treatment.
8. Has had heart disease such as ischemic heart disease or arrhythmia, or currently has heart disease sporadically.
9. Has a family history of long QT syndrome.
10. Has a QTcB or QTcF of <340 msec or ≥450 msec in the standard 12-lead electrocardiogram at the time of screening tests.
11. Has participated in another clinical study and received a study agent within 120 days before study treatment.

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12. Has had ≥200 mL of blood collected (eg, blood donation) within 30 days before study treatment or ≥400 mL within 90 days, or has had a total of more than 1,200 mL of blood collected in the past year.
13. Has a history of drug allergy or drug hypersensitivity (immediate or delayed allergy) that would make the patient unsuitable as a study participant.
14. Has previously had an allergic reaction to infusion of sucrose, tromethamine, or polysorbate 80.
15. Has previously had a clinically problematic injection site reaction (eg, rash, itching, pain, swelling).
16. Has or is suspected of having a history of alcohol, drug, or narcotic addiction (determined from history, physical findings, and urine drug tests).
17. Has a positive result for human immunodeficiency virus antigen or antibodies, hepatitis C virus antibodies (third-generation assay), hepatitis B surface antigen, or a serological test for syphilis (*Treponema pallidum* antibodies and rapid plasma reagin method).
18. Used a drug (other than cold remedies for common cold; analgesics to relieve pain caused by toothache etc; and plasters, ointments, creams, nasal sprays, eye drops, etc, that do not have systemic effects) or supplement within 14 days before study treatment.
19. Contracted a serious disease within 90 days before study treatment.
20. Is not eligible as a subject in this study for some other reason in the opinion of the investigator or subinvestigator.

Part 2

1. If only dietary modification and exercise therapy are being used, fasting blood glucose is <130 mg/dL or ≥270 mg/dL in screening tests and at hospitalization (Day −1). If oral antihyperglycemic drugs are being used, fasting blood glucose is <100 mg/dL or ≥240 mg/dL at the time of screening tests and <120 mg/dL or ≥270 mg/dL at hospitalization (Day −1).
2. If only dietary modification and exercise therapy are being used, HbA_{1C} at the time of screening tests is <6% or ≥10%. If oral antihyperglycemic drugs are being used, HbA_{1C} at the time of screening tests is <6% or ≥9%.
3. Has blood pressure or a pulse rate that is outside of the following ranges, or has hypertension and blood pressure or a pulse rate that is outside of the following ranges despite taking an antihypertensive drug at the same dosage since at least 3 months before screening tests.
   - Supine or standing systolic blood pressure is ≥95 mmHg and ≤160 mmHg at screening and hospitalization (Day −1).
   - Supine or standing diastolic blood pressure is ≥50 mmHg and ≤95 mmHg at screening and hospitalization (Day −1).
   - Supine or standing pulse rate is ≥40 beats per minute at screening and hospitalization (Day −1).
4. Has or has had hepatic, renal, central nervous system (including psychiatric), cardiovascular, respiratory, gastrointestinal, hematopoietic, ophthalmic, infectious, or endocrine disease that would make the patient unsuitable as a study participant.
5. Has or has had type 1 diabetes mellitus.
6. Has or has had autoimmune diabetes mellitus.
7. Used insulin for ≥4 days within 3 months before the start of study treatment.
8. Took a thiazolidinedione (eg, rosiglitazone, pioglitazone) or α-glucosidase inhibitor (eg, acarbose, miglitol) within 3 months before the start of study treatment.
9. Has received a pancreas transplant.
10. Has or has had chronic pancreatic disease that would make the patient unsuitable as a study participant.

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11. Has diabetic complications (retinopathy, nephropathy, neuropathy, gastroparesis, coma) that would make the patient unsuitable as a study participant.
12. Has undergone a gastrectomy or has or has had a clinically significant gastrointestinal disorder.
13. Has had clinically significant hypoglycemia or hypoglycemia-like symptoms.
14. Has or has had hypertriglyceridemia (≥500 mg/dL), gallbladder disease, or gallstones that would make the patient unsuitable as a study participant.
15. Used corticosteroids (oral or non-oral) that have systemic effects within 3 months before the start of study treatment or is expected to use corticosteroids during the study period.
16. Took aspirin (≥325 mg/day), nonsteroidal anti-inflammatory drugs, or anticoagulants for a long period (continuously for ≥8 days) within 3 months before the start of study treatment, or is expected to take any of these drugs for a long period during the study period.
17. Has a history of chronic disease (eg, hypertension or hyperlipidemia that does not meet the inclusion criteria, hypercholesterolemia, asthma) requiring the administration of prescription drugs that would make the patient unsuitable as a study participant.
18. Has had a malignant tumor within 5 years before the start of study treatment.
19. Has undergone surgery that would make the patient unsuitable as a study participant within 6 months before the start of study treatment.
20. Has or had clinically significant acute disease that occurred within 14 days before the start of study treatment.
21. Has been hospitalized because of clinically significant disease within 3 months before the start of study treatment.
22. Has or has had an eating disorder (pathological anorexia or bulimia).
23. Regularly drinks ≥1,200 mL of coffee, cola, or hot chocolate per day.
24. Has been vaccinated (live or inactivated vaccine) within 30 days before the start of study treatment.
25. Has had heart disease such as ischemic heart disease or arrhythmia, or currently has heart disease sporadically.
26. Has a family history of long QT syndrome.
27. Has a QTcB or QTcF of <340 msec or ≥450 msec in the standard 12-lead electrocardiogram at the time of screening tests.
28. Has participated in another clinical study and received a study agent within 120 days before the start of study treatment.
29. Has had ≥200 mL of blood collected (eg, blood donation) within 30 days before the start of study treatment or ≥400 mL within 90 days, or has had a total of more than 1,200 mL of blood collected in the past year.
30. Has a history of drug allergy or drug hypersensitivity (immediate or delayed allergy) that would make the patient unsuitable as a study participant.
31. Has previously had an allergic reaction to infusion of sucrose, tromethamine, or polysorbate 80.
32. Has previously had a clinically problematic injection site reaction (eg, rash, itching, pain, swelling).
33. Has or is suspected of having a history of alcohol, drug, or narcotic addiction (determined from history, physical findings, and urine drug tests).
34. Has a positive result for human immunodeficiency virus antigen or antibodies, hepatitis C virus antibodies (third-generation assay), hepatitis B surface antigen, or a serological test for syphilis (*Treponema pallidum* antibodies and rapid plasma reagin method).
35. Took a drug (other than cold remedies for common cold; analgesics to relieve pain caused by toothache etc; and plasters, ointments, creams, nasal sprays, eye drops, etc, that do not have

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systemic effects) or supplement within 15 days before the start of study treatment (excluding the permitted concomitant drugs shown in Section 9.3.10.2.1 "Concomitant Drugs").
36. If the subject is female, has a positive pregnancy test result at the time of screening tests and at hospitalization (Day −1).
37. Is not eligible as a subject in this study for some other reason in the opinion of the investigator or subinvestigator.

Study agents and manufacturing codes:

Study agents

CNTO 3649 vial
The CNTO 3649 vial was a lyophilized formulation containing 11.3 mg of CNTO 3649 per vial. The excipients were sucrose, tromethamine, and polysorbate 80.
Placebo vial
Each placebo vial contained 8 mL of an injection solution that did not contain CNTO 3649. The excipients were sucrose, tromethamine, and polysorbate 80.

Manufacturing codes

CNTO 3649 vial: 01II
Placebo vial: 02II

Study period:

Part 1
The study period for each subject from receipt of informed consent to completion of posttreatment examinations was set at a maximum of 57 days. However, the study period was extended if the subject required follow-up investigations.

Part 2
The study period for each subject from receipt of informed consent to completion of posttreatment examinations was set at a maximum of 92 days. However, the study period was extended if the subject required follow-up investigations.

Screening period
Part 1: From 28 days before to 3 days before study treatment
Part 2: From 42 days before to 16 days before study treatment

From hospitalization of subject to posttreatment examinations
Part 1: 31 days
Part 2: 52 days

Endpoints:

Safety
Adverse events, weight, blood pressure, pulse rate, body temperature, abdominal ultrasonography, standard 12-lead electrocardiography, and laboratory tests (hematology, blood coagulation tests, biochemistry, and urinalysis)

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Pharmacokinetics
Time course of the serum CNTO 3649 concentration, and pharmacokinetic parameters

Pharmacological effects
Blood glucose, serum insulin concentration, serum C-peptide concentration, and HbA_{1C} (Part 2 only)

Immune response
Anti-CNTO 3649 antibodies

Analysis sets:

Analysis set for safety
The analysis set for safety was defined as subjects who received the study agent at least once.

Analysis set for pharmacokinetics
The analysis set for pharmacokinetics was defined as subjects who received the study agent and for whom measurement results for the serum CNTO 3649 concentration were obtained.

Analysis set for pharmacological effects
The analysis set for pharmacological effects was defined as subjects who received the study agent and for whom measurement results for pharmacological effects were obtained.

Analysis set for immune response
The analysis set for immune response was defined as subjects who received the study agent and for whom measurement results for anti-CNTO 3649 antibodies were obtained at least once.

Analytical methods:

Evaluation of safety

Adverse events, weight, blood pressure, pulse rate, body temperature, abdominal ultrasonography, standard 12-lead electrocardiography, and laboratory tests (hematology, biochemistry, and urinalysis) were tabulated and analyzed. The frequency of deviation from the reference range was also tabulated. Descriptive statistics were calculated for change in weight, blood pressure, pulse rate, body temperature, and laboratory test variables that are measured using continuous values, as compared with before treatment (baseline).

Investigation of pharmacokinetics

Pharmacokinetics was evaluated as follows using the measured values for individual serum CNTO 3649 concentrations in the analysis set for pharmacokinetics.

- Graphs of the time course of the serum CNTO 3649 concentration (mean or median) were prepared for each treatment group and at each scheduled blood collection time.
- Pharmacokinetic parameters were calculated by noncompartmental analysis on the basis of actual blood collection times using WinNonlin® pharmacokinetic analysis software (Version 5.2.1, Pharsight Corporation). The pharmacokinetic parameters calculated were the maximum serum CNTO 3649 concentration (C_{max}), time to reach the C_{max} (t_{max}), elimination half-life in the terminal phase ($t_{1/2}$), area under the serum concentration-time curve from 0 to the last measurable concentration (AUC_{last}), AUC from 0 to the dosing interval (AUC_{τ}), AUC from 0 to infinity (AUC_{∞}), apparent total body clearance (CL/F), and apparent volume of distribution (V_z/F).

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- Descriptive statistics were calculated by treatment group and by scheduled blood collection time using the serum CNTO 3649 concentration that was obtained for each subject. Similarly, descriptive statistics were calculated by treatment group from the pharmacokinetic parameters for each subject.
- The correlation between the dose and the C_{max} and AUC was shown in graph form, and dose proportionality was evaluated visually (Part 1 only).

Investigation of pharmacological effects

Pharmacological effects were analyzed as follows using blood glucose, serum insulin concentration, serum C-peptide concentration, and HbA_{1c} (Part 2 only) for each subject.

- Descriptive statistics were calculated for the serum concentration by treatment group and scheduled blood collection time and for change (absolute change and percentage change) from baseline. The time course of the serum concentration (mean) or change from baseline was shown in graph form.
- Weighted average blood glucose (WAG) (WAG = AUC_{24}/24 hr) the day before the first injection and on treatment Day 24 (Week 4, third day) was calculated in Part 2. An analysis of covariance was conducted using WAG at baseline as a covariate, as necessary.

Summary - Conclusions:

(The mean was used for representative values unless specified otherwise.)

Safety results

Part 1

Safety was investigated when CNTO 3649 (10, 30, 100, or 300 µg/kg) or placebo was administered once by subcutaneous injection in healthy adult Japanese men.

1. No serious adverse events occurred.
2. Four adverse events occurred in 4 of the 40 subjects who were given the study agent. The adverse events in the CNTO 3649 groups were gastroenteritis (1 event in 1 subject, 30 µg/kg), blood creatine phosphokinase increased (1 event in 1 subject, 100 µg/kg), and urinary tract infection (1 event in 1 subject, 300 µg/kg). Gastroenteritis (1 event in 1 subject) occurred in the placebo group. All of the events were mild and resolved within the study period.
3. No abnormal changes or abnormal findings were seen in laboratory tests, weight, vital signs, standard 12-lead electrocardiography, or abdominal ultrasonography, apart from abnormal changes related to adverse events.
4. The frequency and severity of adverse events were not dependent on the dose.
5. CNTO 3649 was well-tolerated when administered once by subcutaneous injection at a dose of 10, 30, 100, or 300 µg/kg in healthy adult Japanese men.

Part 2

Safety was investigated when CNTO 3649 (30 or 100 µg/kg) or placebo was administered by subcutaneous injection once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus (men and women).

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1. No serious adverse events occurred.
2. After starting study treatment, 6 adverse events occurred in 4 of the 24 subjects who were given the study agent. The adverse events in the CNTO 3649 groups were blood triglycerides increased (1 event in 1 subject, 30 µg/kg), blood amylase increased (2 events in 2 subjects, 100 µg/kg), and lipase increased (2 events in 2 subjects, 100 µg/kg). Herpes simplex (1 event in 1 subject) occurred in the placebo group. All of the events were mild and resolved within the study period. Diabetic retinopathy (1 event in 1 subject, placebo) also occurred before starting study treatment, and it had not resolved at the time of posttreatment examinations.
3. No abnormal changes or abnormal findings were seen in laboratory tests, weight, vital signs, standard 12-lead electrocardiography, or abdominal ultrasonography, apart from abnormal changes related to adverse events.
4. The frequency and severity of adverse events were not dependent on the dose.
5. CNTO 3649 was well-tolerated when administered by subcutaneous injection at a dose of 30 or 100 µg/kg once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus.

Pharmacokinetics results

Part 1

The pharmacokinetics of serum CNTO 3649 was investigated when CNTO 3649 was administered at a dose of 10, 30, 100, or 300 µg/kg once by subcutaneous injection in healthy adult Japanese men.

1. At each dose, the serum CNTO 3649 concentration reached C_{max} (28.37 to 901.52 ng/mL) at 48.0 hours after administration (median), and the drug was then eliminated with a $t_{1/2}$ of 88.2 to 110.1 hours.
2. The C_{max} for serum CNTO 3649 increased almost dose-proportionally. The AUC_{last} for serum CNTO 3649 increased more than dose-proportionally at doses of 10 to 30 µg/kg and 30 to 100 µg/kg, but at 100 to 300 µg/kg, it increased dose-proportionally and the relationship between the AUC_{last} and dose was almost linear. These results suggest pharmacokinetic dose-proportionality in the dose range above 30 µg/kg (100 to 300 µg/kg).

Part 2

The pharmacokinetics of serum CNTO 3649 was investigated when CNTO 3649 was administered by subcutaneous injection at a dose of 30 or 100 µg/kg once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus (men and women).

1. The serum CNTO 3649 concentration reached C_{max} (42.46 and 151.17 ng/mL, respectively) at 48.0 to 72.0 hours (median) after the first injection at a dose of 30 or 100 µg/kg. After the fourth injection, the C_{max} (67.16 and 225.80 ng/mL, respectively) was reached at 48 hours (median) and the drug was eliminated with a $t_{1/2}$ of 114.7 and 114.8 hours, respectively.
2. The serum CNTO 3649 trough concentration did not differ greatly from the third injection (336, 504, and 672 hours after the first injection), suggesting that steady state is reached before the third injection. The accumulation ratio calculated from the AUC_{τ} and C_{max} was approximately 1.6 to 1.8.
3. The C_{max} and AUC_{τ} for serum CNTO 3649 increased almost dose-proportionally at the time of the first and fourth injections, suggesting pharmacokinetic dose-proportionality in the dose range of 30 to 100 µg/kg.

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Results for pharmacological effects

Part 1

The pharmacological effects were investigated when CNTO 3649 (10, 30, 100, or 300 µg/kg) or placebo was administered once by subcutaneous injection in healthy adult Japanese men.

1. Mean percentage change in blood glucose values, serum insulin concentration, and serum C-peptide concentration from baseline did not differ appreciably between the CNTO 3649 groups and the placebo group or between the CNTO 3649 groups.

Part 2

The pharmacological effects were investigated when CNTO 3649 (30 or 100 µg/kg) or placebo was administered by subcutaneous injection once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus (men and women).

1. Mean percentage change in blood glucose values, serum insulin concentration, and serum C-peptide concentration from baseline did not differ appreciably between the CNTO 3649 groups and the placebo group or between the CNTO 3649 groups during the investigation period.
2. The results of an analysis of covariance of change (Day 24 − Day −1) in WAG from the day before initiation of study treatment (Day −1) to Day 3 after the fourth injection (Day 24) using WAG on Day −1 as a covariate showed no significant difference when compared with the placebo group, as the two-sided 95% confidence interval for the difference from the placebo group included 0 in both the 30 µg/kg group and the 100 µg/kg group.
3. Change in HbA_{1c} from baseline on Days 36 and 50 did not differ appreciably between the CNTO 3649 groups and the placebo group for a dose of either 30 or 100 µg/kg.

Results for immune response

Part 1
All subjects tested antibody-negative when CNTO 3649 was administered once by subcutaneous injection at a dose of 10, 30, 100, or 300 µg/kg in healthy adult Japanese men.

Part 2
All subjects tested antibody-negative when CNTO 3649 was administered by subcutaneous injection at a dose of 30 or 100 µg/kg once a week for 4 weeks in Japanese patients with type 2 diabetes mellitus.

Date of report: 30 September 2010

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