Trial number	KF6005/04
Title of trial	A randomized 4-week Phase IIa trial evaluating the efficacy, safety, and tolerability of GRT6005, a new centrally acting analgesic, in subjects with pain due to diabetic polyneuropathy
Trial design	A randomized, multi-center, double-blind, placebo-controlled, parallel-group, multiple-administrations, fixed dose, 4-week treatment Phase IIa trial
Development phase	Phase IIa
EudraCT number	2010-022557-42
Publication number	430409 (ClinicalTrials.gov)
Indication	Moderate to severe pain due to diabetic polyneuropathy
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Coordinating investigator	[redacted] 55116 Mainz, Germany
Trial sites	Bulgaria (1 site), Germany (15 sites), Romania (5 sites)
Trial period	First subject enrolled: 04 May 2011 Last subject completed: 05 Jan 2012

Objectives

The primary objective was to evaluate the analgesic efficacy of fixed doses of 25 µg, 75 µg, and 200 µg GRT6005 once daily compared to placebo in subjects with moderate to severe pain due to diabetic polyneuropathy (DPN). Secondary objectives were to evaluate the safety and tolerability of fixed doses of 25 µg, 75 µg and 200 µg GRT6005 once daily compared to placebo in subjects with moderate to severe pain due to DPN, to explore the relationship between exposure to GRT6005 and analgesic efficacy and tolerability, and to describe multiple-dose kinetics of GRT6005 over 4 weeks in subjects with pain due to DPN.

Investigational medicinal products

The following batches of GRT6005 hard gelatin capsules (liquid filled with self-emulsifying drug delivery system [SEDDS] 0708) containing 25 µg, 50 µg, or 200 µg GRT6005 for oral administration and matching placebo capsules were used.

Substance	Strength	Batch no.	Retest date	Collective batch no.	Expiry date
GRT6005	25 µg	KGVY01	01/2012	061210	01/2012
		LGVY03	01/2013	260911	01/2013
	50 µg	KGWH01	02/2012	061210	01/2012
		LGWH02	01/2013	260911	01/2013
	200 µg	KLWA04	04/2012	061210	01/2012
		LGWA05	01/2013	260911	01/2013
Placebo	-	KGWB02	01/2012	061210	01/2012
	-	KGWB03	01/2012	061210	01/2012
	-	LGWB05	01/2013	260911	01/2013

Rescue medication

The following batch of paracetamol was used as rescue medication.

Substance	Strength	Batch no.	Retest date	Collective batch no.	Expiry date
Paracetamol	500 mg	612M091	11/2014	081210, 050811, 101210, 060811	11/2014

Treatments

The total daily doses of GRT6005 during the 4-week treatment period were 25 µg (1 x 25 µg capsule + 1 x placebo), 75 µg (1 x 25 µg capsule + 1 x 50 µg capsule), or 200 µg (1 x 200 µg capsule + 1 x placebo) in the first, second, and third treatment arm, respectively. Placebo was taken in the fourth treatment arm (2 capsules). The investigational medicinal products (IMPs) had to be taken starting on the day of the Baseline Visit (Visit 3), and the last dose was to be taken on the morning of the Final Visit (Visit 7) that was planned for Day 28. Since 2 capsules were required to achieve daily dose of 75 µg, all subjects took 2 IMP capsules orally once daily in the morning to maintain the blinding. On the visit days, subjects took their IMP at the trial site. The IMPs had to be taken orally with a glass of water after the intake of food and after the subjects had assessed and documented their pain intensity in the electronic diary. No dose adjustment of the IMPs was allowed. In case of intolerable adverse events (AEs) or lack of efficacy, the subjects had to discontinue their trial participation.

Subjects were allowed to take up to 3000 mg of paracetamol (tablets containing 500 mg paracetamol for oral administration) per day as rescue medication for the treatment of pain due to diabetic polyneuropathy, except for the last 3 days before the Baseline Visit.

Trial population

Male or female subjects aged 18 years to 75 years inclusive with a diagnosis of type 1 or type 2 diabetes mellitus (controlled by a diet, oral anti-hyperglycemic medication, and/or insulin for at least 3 months prior to enrolling in the trial) and a documented clinical diagnosis of painful DPN with symptoms and signs present for at least 3 months and pain present at the Enrollment Visit were included. Subjects had to be on stable analgesic medications for their condition with a regular intake

of analgesics for at least 3 months prior to enrollment according to their medical history and had to be dissatisfied with their current analgesic treatment in terms of efficacy and/or tolerability.

During the last 3 days prior to treatment allocation, subjects had to complete at least 5 of 6 possible pain intensity assessments. After a washout of any previous analgesic treatment, their daily average pain intensity score had to be ≥4 on the 11-point numeric rating scale (NRS) without any intake of rescue medication.

Subjects with any scheduled surgery or painful procedure during the course of the trial, with significant vascular disease, with a need for treatment with prohibited medication, with a clinically relevant history of hypersensitivity, allergy, or contraindications to any of the IMP's excipients as well as to opioids or paracetamol were excluded as were subjects with the presence of conditions other than painful DPN that could contribute to pain or confound the assessment of self-evaluation of pain, for instance fibromyalgia, complex regional pain syndrome, phantom pain, significant skin conditions such as abscesses, significant osteoarthritis, low back pain, inflammation (e.g., rheumatoid arthritis, ankylosing spondylitis), and vasculitis.

Methodology

This was a randomized, multi-center, double-blind, placebo-controlled, parallel-group, multiple-administrations, fixed-dose, 4-week treatment, Phase IIa trial. It consisted of an Enrollment Period, a treatment period, and a Follow-up Period.

Every day during the whole trial, starting in the evening of the Enrollment Visit and ending in the morning of the Follow-up Visit, the subjects were asked in the morning and in the evening to record their current pain intensity score (as rated on an 11-point NRS) as well as their average pain intensity during the last 12 hours.

The Enrollment Period lasted a minimum of 7 days and maximum of 20 days and comprised a Washout Phase (up to 14 days) and a Baseline Phase (4 days to 6 days). A washout of previous analgesic medication was performed as instructed in the respective Summary of Product Characteristics of the previous analgesic medication, and the baseline pain intensity score was assessed. The intake of rescue medication had to be documented in the eDiary and on a rescue medication intake sheet each evening during the Enrollment Period. The use of rescue medication during the last 3 days prior to Baseline Visit was considered a major protocol deviation and resulted in an exclusion of subjects from the Per Protocol Set.

The double-blind treatment period was the time span from the intake of the first dose of IMPs at the Baseline Visit (Visit 3) to the Final Visit (Visit 7) and was scheduled for 28 days of treatment. Blood samples for pharmacokinetic analyses were taken pre-dose and post-dose as planned and a blood sample for pharmacogenetic analyses was taken from subjects who had consented.

The Follow-up Period was the time span from the day after the Final Visit (Visit 7) to the Follow-up Visit (Visit 8). The Follow-up Visit at the site was scheduled within 3 days to 5 days following the last intake of the IMP. At the Follow-up Visit, a single blood sample was taken for pharmacokinetic analysis. In Bulgaria only, the Follow-up Period lasted for 10 days to 14 days and included an additional Follow-up Visit II.

Data collected

Efficacy

Subject-documented pain intensity was assessed on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine). Current pain intensity and average pain intensity over the last 12 hours were assessed and recorded in an electronic diary twice a day in the morning and in the evening.

Scores from Short-form Brief Pain Inventory (SF-BPI), Short-form-12 Health Survey (SF-12), EuroQol-5 Dimension (EQ-5D) quality of life questionnaire, Neuropathic Pain Scale (NPS), allodynia testing (cotton swab and brush-evoked pain), Leeds Sleep Evaluation Questionnaire (LSEQ), Patient's Global Impression of Change (PGIC), and Clinician's Global Impression of Change (CGIC) were collected.

Rescue medication intake.

Pharmacokinetics

Plasma concentrations of GRT6005.

Population pharmacokinetics/pharmacodynamics

Data on the correlation between drug exposure and therapeutic effect, concerned tolerability, and safety aspects of GRT6005.

Pharmacogenetics

DNA polymorphisms in genes associated with absorption, distribution, metabolism, and excretion of drugs.

Safety

Physical examination, clinical laboratory (biochemistry and hematology) and urinalysis, 12-lead electrocardiogram (ECG), vital signs (pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation), pregnancy tests, urine drug screening, Clinical Opiate Withdrawal Scale (COWS), and AEs.

Statistical methods

Descriptive statistics

All data collected in this trial were presented by summary statistics given by descriptive measures of location and variability for continuous variables (N, mean, standard deviation [SD], minimum, first quartile, median, third quartile, maximum), and absolute and relative frequencies for categorical variables, as appropriate.

Efficacy

The primary efficacy analysis was performed in the Full Analysis Set (FAS), i.e., a subset of the Safety Set that includes all subjects who had at least 1 pain intensity assessment after IMP intake. The primary efficacy endpoint was summarized by descriptive statistics and the primary evaluation was done by means of mixed-model repeated measures (MMRM) assuming a normal distribution. The longitudinal mixed effect model included fixed effects of baseline, treatment, day, and treatment-by-day interactions. A first order autoregressive AR(1) structure was planned and used for the covariance matrix. Similar statistical models were used for the analysis of the secondary endpoints.

Safety

The analysis of safety data was performed for the Safety Set. The Safety Set includes all subjects taking any amount of IMP. For all comparisons of the safety laboratory parameters, vital signs (including pulse oximetry), and ECG, the last values available before first intake of IMP served as baseline. Adverse events were coded using Version 14.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Summary of results

Subject disposition

This trial enrolled 189 subjects with chronic moderate to severe pain due to diabetic polyneuropathy; more than half of all subjects were enrolled in 15 active trial sites in Germany (n = 123), the remaining subjects in 5 active sites in Romania (n = 64) and 1 active site in Bulgaria (n = 2). A total of 123 subjects were allocated to treatment, thereof 72 in Germany, 51 in Romania, but no subject in Bulgaria. In total, 66 subjects were not allocated to treatment.

Overall, the subjects allocated to treatment (n = 123) were equally distributed among the treatment arms with 30 or 31 subjects per arm. One subject who was an enrollment failure was allocated by mistake but did not receive IMP; therefore the Safety Set comprised 122 subjects. A total of 108 of 122 subjects completed the treatment period and attended a Follow-up Visit. Premature discontinuation was highest in the arm of subjects taking 200 µg GRT6005 per day (7 subjects) or placebo (5 subjects). The main reason for discontinuation in subjects taking 200 µg GRT6005 was treatment emergent adverse event (TEAE) (in 4 subjects).

Parameter	Placebo N (%)	GRT6005 25 µg N (%)	GRT6005 75 µg N (%)	GRT6005 200 µg N (%)	GRT6005 Overall N (%)	Overall N (%)
Subjects enrolled						189
Subjects allocated to treatment	31 (100)	31 (100)	31 (100)	30 (100)	92 (100)	123 (100)
Subjects evaluated						
Safety Set	30 (96.8)	31 (100)	31 (100)	30 (100)	92 (100)	---
Full Analysis Set	30 (96.8)	31 (100)	31 (100)	30 (100)	92 (100)	---
Per Protocol Set	26 (83.9)	25 (80.6)	28 (90.3)	20 (66.7)	73 (79.3)	---
Subjects completing the trial	26 (83.9)	29 (93.5)	30 (96.8)	23 (76.7)	82 (89.1)	108 (87.8)
Subjects allocated and prematurely discontinued	5 (16.1)	2 (6.5)	1 (3.2)	7 (23.3)	10 (10.9)	15 (12.2)
Reason for discontinuation						
Adverse event	0	0	1 (3.2)	4 (13.3)	5 (5.4)	5 (4.1)
Lack of efficacy	0	1 (3.2)	0	1 (3.3)	2 (2.2)	2 (1.6)
Protocol deviation	2 (6.5)	0	0	0	0	2 (1.6)
Withdrawal by subject [a]	3 (9.7)	0	0	2 (6.7)	2 (2.2)	5 (4.1)
Other reasons	0	1 (3.2)	0	0	1 (1.1)	1 (0.8)

a) Withdrawal of informed consent.

Demographics and baseline characteristics

A total of 122 subjects (38 women and 84 men) aged 33 years to 75 years were treated in the trial (Full Analysis Set). The mean age of subjects ranged from 56.8 years to 60.9 years in the different treatment arms. About 30% of subjects in all treatment arms were >65 years except for the arm taking 25 µg GRT6005 per day where subjects >65 years of age accounted for 16.1%. The treatment arms were largely similar concerning further demographic data: mean height ranged from 1.703 m to 1.742 m, mean weight ranged from 90.7 kg to 101.0 kg, and mean body mass index ranged from 30.97 kg/m^2 to 33.75 kg/m^2. There were more men (about two thirds) than women (about one third) in all treatment arms.

All subjects had pain in their lower extremities and 17.2% of subjects in addition had pain in their upper extremities at enrollment. Pain had been present for a mean of 58.8 months (range 4 months to 256 months). The average 12-hour average pain intensity (11-point NRS) at enrollment was 6.54, with a range of 4.3 to 9.5. The mean intensity score (Question 1) of the NPS at baseline was 6.7 with a range of 3 to 10. The mean total score of the SF-BPI at baseline was 4.91 with a range between 1.5 and 9.0.

The majority of subjects in the FAS had Type II diabetes (overall 92.6%) and 7.4% had Type I diabetes. The mean duration of diabetes (i.e., time since diagnosis) was 126.9 months (range 9 months to 472 months) before Visit 1. Diabetic polyneuropathy was diagnosed on average 53.5 months before enrollment (minimum 2 months, maximum 203 months before enrollment). Similar frequencies of subjects reported burning sensation (65.6%), tingling or prickling (72.1%), and paresthesias (70.5%). Fewer subjects had a painful heat or cold sensation (35.2%).

The most frequently used prior treatments in the FAS were analgesics (62 subjects, 50.8%). Prior opioid treatment was reported for 11 subjects (9.0%) overall, other analgesics and antipyretics in 56 subjects (45.9%).

Efficacy

Based on the MMRM analysis for the primary endpoint, the 3 doses of GRT6005 (25 µg, 75 µg, or 200 µg) did not show a statistically significant or clinically relevant improvement in average pain intensity.

In addition, exploratory ad-hoc analyses on the primary endpoint using mixed models with site specific covariance and/or with site-by-dose interaction generally showed better goodness of fit and potentially improved effects for 75 µg and 200 µg GRT6005 and a trend for dose effect relationship.

Results of the MMRM analysis for the FAS for the entire 4 weeks of treatment indicate that, numerically, there was a better pain reduction in the treatment arm taking 200 µg GRT6005 per day (MMRM estimate -0.4188) than in the arms taking 25 µg or 75 µg GRT6005 when compared to placebo.

The overall picture obtained from the MMRM analyses for the average 12-hour average pain intensity for the other time points matches the results obtained for the fourth week and for the overall treatment period. Changes from baseline for the average 12-hour average pain intensity, the morning, and the evening pain intensity in the last 24 hours before the Follow-up Visit generally indicate an increase in subjects' pain again during the Follow-up Period.

Numerically, a larger percentage of subjects in all treatment arms taking GRT6005 were responders with a pain reduction of at least 30% already after the first week of treatment and up to the Final Visit (i.e., at Visit 4, 5, 6, and 7) when compared to the placebo treatment arm. But the responder rates did not indicate a dose-response trend for treatment with GRT6005.

In the Leeds Sleep Evaluation Questionnaire, no improvement and no worsening were seen under treatment with GRT6005 compared to placebo.

No changes or differences between doses were observed in the amount of rescue medication taken, in the allodynia testing and in the SF-BPI total scores or pain interference score. For the SF-BPI pain severity scores, differences to placebo at Visit 7 were numerically larger than for the rest of the SF-BPI scores, with -0.73 in subjects who took 25 µg GRT6005 per day and -0.99 in subjects who took a daily dose of 200 µg.

Numerically, the largest changes from baseline in any SF-12 domain for all subjects (FAS) with 16.1 points were reported for the domain “bodily pain” under treatment with GRT6005 (25 µg or 200 µg) at Visit 7.

There was no relevant improvement and no worsening in the quality of life during treatment with GRT6005 as can be seen from the weighted EQ–5D health score index changes from baseline to Visit 7. Changes with placebo treatment or treatment with 25 µg GRT6005 were larger than with a treatment with 75 µg or 200 µg GRT6005. The analysis of the EQ-5D health state at the Final Visit revealed an improvement by a mean of 15.0, 6.5, and 11.1 points from baseline for a treatment with 25 µg, 75 µg, and 200 µg GRT6005 compared to 1.2 points in the placebo arm.

The evaluation of the secondary endpoints PGIC, CGIC, and NPS showed a trend towards a separation of GRT6005 from placebo, indicating analgesic efficacy. In subjects who completed the trial as planned, results obtained after treatment with 200 µg GRT6005 per day were numerically better than for placebo or for 25 µg and 75 µg GRT6005 per day but did not indicate a dose-response trend.

- The PGIC indicated a dose-dependent improvement of the subject’s condition (“very much and much improved”) at Visit 4 and – in trial completers – also at Visit 7. When the evaluation at Visit 7 was restricted to subjects completing the trial according to protocol, 11.5% of the subjects taking placebo rated that their overall impression of change compared to baseline was “very much improved and much improved”. The percentages of subjects taking 25 µg, 75 µg, and 200 µg GRT6005 per day were higher at 31.0%, 40.0%, and 47.8%, respectively.
- The assessment of the investigators (CGIC) was similar to the PGIC results: after 4 weeks of treatment, the clinicians of subjects who completed the trial stated that 34.6% of subjects who took placebo, 34.5% of subjects who took a daily dose of 25 µg GRT6005, 43.3% who took 75 µg, and 52.2% of subjects who took 200 µg had “very much improved and much improved” when compared to baseline. The investigators reported that only 1 subject taking 75 µg GRT6005 per day experienced a worsening (“much worse and very much worse”) since they began trial treatment.

- For the NPS, a reduction of the scores of the pain characteristics at Visit 7 compared to baseline was observed for all items (pain intensity, sharpness, heat, unpleasantness, intensity of deep pain, and intensity of surface pain) in all treatment arms. This reduction was numerically larger in subjects who took 200 µg GRT6005 than in subjects who took placebo for all questions but for sharpness which was best in subjects who took 25 µg GRT6005 per day. Compared to placebo treatment, the differences exceeded 1 point for sharpness (at Visit 4 and at Visit 7 for 25 µg or 200 µg GRT6005), dullness (at Visit 4 and at Visit 7 for 25 µg, at Visit 7 for 200 µg GRT6005), and for unpleasantness (at Visit 7 for 200 µg GRT6005) but no dose-response trend was observed.

Pharmacokinetics

A descriptive analysis of GRT6005 plasma concentrations showed that the GRT6005 exposure was in line with previous predictions: exposure increased with dose, steady state was reached after 2 weeks of treatment, and an approximate 2-fold accumulation was observed.

The results of the population pharmacokinetics/pharmacodynamics analysis will be presented in a separate report.

Exposure

Overall, the mean exposure was 24.5 to 28.1 IMP doses within 4 weeks of the double-blind treatment period; the mean compliance (defined as actual exposure to IMP relative to planned intake of IMP) was 93.8% to 100%. Mean intake and compliance were reduced in subjects taking 200 µg GRT6005 due to the higher number of subjects with early discontinuation in this arm compared with the other treatment arms. For subjects discontinuing prematurely, the day of the last intake of IMP mostly was before the day of the investigator's decision to exclude the subject; the latter, however, was used for the compliance calculations.

Safety and tolerability

Overall, 92 subjects were exposed to GRT6005 and 30 subjects to placebo in this trial.

The use of GRT6005 over a period of 4 weeks was safe within range of fixed daily doses of 25 µg, 75 µg, or 200 µg GRT6005 per day for the treatment of pain due to DPN.

The most frequent TEAEs (occurring in at least 5% of the subjects in any treatment arm) were constipation, dizziness, nausea, vomiting, nasopharyngitis, dyspepsia, flatulence, pruritus, AST increased, GGT increased, back pain, pain in extremity, and headache. No serious TEAE occurred. There were no deaths and no pregnancies in this trial.

Fourteen subjects who took GRT6005 and 1 subject who took placebo experienced TEAEs that were related to laboratory parameters. There was no consistent pattern in within these TEAEs indicative for any drug related effect.

Highest discontinuation rates (13.3%) were observed for the treatment arm taking the highest dose (200 µg) of GRT6005. In analogy, the frequency of TEAEs of at least moderate intensity was highest for the 75 µg and 200 µg treatment arms. The main reasons for trial discontinuation were nausea, dizziness, and vomiting. The majority of the TEAEs occurred within 4 hours to 12 hours after the first intake of IMP and led to trial discontinuation in the first or second week of treatment.

There were no clinically relevant changes in the mean values of vital signs, oxygen saturation, and ECG. No systemic changes of safety laboratory parameters were observed.

The abrupt cessation of the 4-week treatment with GRT6005 led to mild opioid withdrawal symptoms in only 1 subject allocated to the 25 µg treatment arm of GRT6005 (as assessed by the use of the COWS score).

The tolerability of fixed doses of GRT6005 was good for the tested doses up to 200 µg GRT6005 per day.

Conclusion

GRT6005 was found to be safe in the dose range tested. No serious TEAE occurred in this trial.

The tolerability of oral doses up to and including 200 µg GRT6005 per day was good. Future dosing up to and including 200 µg GRT6005 per day without titration can be supported.

Overall, efficacy in the treatment arm taking 200 µg GRT6005 per day was numerically better than placebo (MMRM estimate equaling -0.38 point on the NRS scale in FAS); efficacy in the treatment arms taking 25 µg and 75 µg GRT6005 per day did not substantially differentiate from placebo. Factors such as exposure were comparable to a previous trial in DPN and do therefore not explain the efficacy data. Results of a post-hoc subgroup analysis (especially based on countries) and analysis of secondary endpoints indicate that the current trial is inconclusive and might be affected by the high variability in placebo responses and different use of rescue medication in the placebo treatment arm by subgroups.

Based on the efficacy results obtained in this trial, conclusion concerning recommended future doses of GRT6005 cannot be simply made and other consideration must be taken into account in subjects suffering from pain due to DPN.

KF6005/04
ICTR SYNOPSIS SUPPLEMENT

Original ICTR date / DMS version:	10 Dec 2012	DMS-ver. 2.0
ICTR synopsis supplement date / DMS version:	17 Apr 2014	DMS-ver. 1.0

1 SUPPLEMENT CONTENT

This document contains information about the trial that is not already covered in the synopsis of the corresponding clinical trial report.

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There were 3 amendments to the protocol:

Amendment 01 (valid for Europe) was signed on 08 Apr 2011. This amendment incorporated a number of general and Germany-specific requests of the independent ethics committee into the protocol:

- As an additional precautionary safety measure, a stopping criterion was added to limit the use of paracetamol/rescue medication. Subjects who took a daily dose of 3000 mg or more of paracetamol on 3 or more consecutive days or twice on 2 consecutive days within 2 weeks now had to be withdrawn.
- The requirements for the HbA_{1c} value at the Enrollment Visit were changed from 11.0% to 9.5% for Germany only due to a different treatment paradigm. This change was not considered to have a significant impact on the subjects' safety or the scientific value of the trial.
- A sensitivity analysis was added for the primary endpoint to account for the introduction of the new stopping criterion.
- The COWS questionnaire attached to the original protocol version was missing 1 answer to Question 11 and 1 answer to Question 7 was corrected. The questionnaire was replaced by a corrected version.
- Additionally, because of a change in standard operating procedures at the sponsor, the signature pages were adapted and the sponsor's medically qualified person was defined in Section 6.2.1 of the protocol.

Amendment 02 (valid for Germany) was signed on 10 Jun 2011 and extended the new stopping criterion introduced with protocol amendment 01. In Germany, this stopping rule as per amendment applied to the Enrollment Period up to Day -4 and the treatment period, and not only to the treatment period.

Amendment 03 (valid for Bulgaria) was signed on 31 Aug 2011 and extended the Follow-up Period for Bulgarian subjects based on the request from the Bulgarian competent authorities. A second follow-up visit (Follow-up Visit II/Visit 9) was added as a precautionary safety measure to the Follow-up Period to assess adverse events and concomitant medication, and to perform an abbreviated physical examination.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was not subjected to a clinical hold or early termination.

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

The names of principal investigators for all initiated sites are not here listed because consent for public disclosure was not obtained.

Site ID	Site
4101	(Name not given, since no consent given), 10177 Berlin Germany
4102	(Name not given, since no consent given), 23562 Lübeck Germany
4103	(Name not given, since no consent given), 55116 Mainz Germany
4104	(Name not given, since no consent given), 30167 Hannover Germany
4105	(Name not given, since no consent given), 48145 Münster Germany
4106	(Name not given, since no consent given), 24119 Kiel Germany
4107	(Name not given, since no consent given), 20253 Hamburg Germany
4108	(Name not given, since no consent given), 30159 Hannover Germany
4109	(Name not given, since no consent given), 32545 Bad Oeynhausen Germany
4110	(Name not given, since no consent given), 13125 Berlin Germany
4111	(Name not given, since no consent given), 01307 Dresden Germany
4112	(Name not given, since no consent given), 63739 Aschaffenburg Germany
4113	(Name not given, since no consent given), 19055 Schwerin Germany
4116	(Name not given, since no consent given), 88239 Wangen Germany
4117	(Name not given, since no consent given), 22587 Hamburg Germany
4401	(Name not given, since no consent given), 540139 Targu-Mures Romania
4402	(Name not given, since no consent given), 011025 Bucuresti Romania
4405	(Name not given, since no consent given), 010496 Bucuresti Romania
4406	(Name not given, since no consent given), 300594 Timisoara Romania
4407	(Name not given, since no consent given), 550166 Sibiu Romania
4502	(Name not given, since no consent given), 1431 Sofia Bulgaria