Weight reduction in obesity under bromocriptine therapy
Bromocriptine therapy depending on the
FTO genotype:
A randomised, double-blind, stratified trial

Test substance: bromocriptine
Eudra CT number: 2011-005628-16
DRKS number: 00003349
Short name: GAB-FTO

Synopsis

(Final) 2.0
Date: 20.06.2016
Supplemented Version 2.1 / Date: 13.09.2018

Sponsor of the clinical trial:
University of Cologne, represented by.
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Sponsor ID: Uni-Koeln-1473

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Study start - study completion
(Data from inclusion of the 1st patient - regular completion)
06.05.2013 - 03.06.2015

Title of the study:
Weight reduction in obesity during therapy with bromocriptine
with bromocriptine in relation to the FTO genotype

Amendments
Amendment I (22.11.2012): Adjustment of timetable, various minor linguistic corrections
Amendment II (15.05.2013): Advertising measures to recruit participants recruitment of study participants, submission therefore only to the responsible local ethic committee
Amendment III (04.06.2013): Adjustment of an exclusion criterion, amendment of the summary of product characteristics of the test substance
Amendment IV (04.12.2013): Increase in number of cases due to drop-out rate and drop-out rate and adjustment of the time schedule

Type of trial
Phase IIa clinical trial according to the AMG (German Medicine Act)

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Study centres:
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Study period
06.05.2013 - 03.06.2015

Study objectives
Obesity is a widespread and increasing disease with increasing prevalence and is associated with severe sequelae diseases. Up to now, the aetiology of the disease, independent of a

positive energy balance, is not yet understood. There is increasing evidence that an addictive component of food intake plays an important pathophysiological role, as well as the reward effect of food intake (in the sense of a secondary, non-essential reward). Current studies show a correlation between FTO risk allele carrier status (rs9939609) and obesity as well as reward behaviour by influencing dopamine neurotransmission. Based on this, a balancing of dopaminergic neurotransmission in FTO risk allele carriers seems to influence reward behaviour and thus food intake and consequently weight positively (in the sense of weight loss). The clinical trial of bromocriptine is intended to elucidate a genotype-specific and therefore individualised therapeutic approaches for obesity. The object of the trial is to elucidate the influence of the dopamine agonist therapy on weight loss in obesity as a function of the FTO (rs993960). The greatest weight loss is expected in homozygous risk allele carriers.

Primary outcome parameter
Reduction of the body mass index (BMI), as it is an established marker of weight reduction.

Secondary outcome parameters
The secondary objectives of the study are to elucidate the genotype-specific changes in reward and eating behaviour and the change in body composition under therapy with bromocriptin.

The reward behaviour is to be assessed with the help of the paradigm for "delay discounting". The ability to tolerate a delay in reward is examined. Delayed discounting describes the phenomenon that the experienced value of a reward decreases with the time until it is received (delay-to-reward). The degree of the decline in subjective valuation over time varies between individuals and can also be used as an empirical indicator of the ability to control impulsiveness. Addictive disorders such as smoking, gambling addiction or opiate addiction are associated with impaired ability to forego an immediate, smaller reward in favour of a delayed but greater reward. It is assumed that there is a lower temporal discounting on patients with risk allele carriers receiving dopamine agonistic therapy (in comparison to placebo therapy) and consequently a therapy-dependent increase in the tolerance to reward deferral.

Eating behaviour is assessed using a specific questionnaire (FEV Pudel & Westenhöfer, 1989). The questionnaire enables to capture essential psychological dispositions of human eating behaviour:
1.) cognitive control of eating behaviour, restrained eating behaviour
2.) Disruptibility of eating behaviour and
3.) experienced feelings of hunger and their behavioural correlates.
The questionnaire has been tested on more than 80,000 people and is a reliable and validated method for assessing eating behaviour.

Body composition is measured using a Bio-impedance analysis. The fat-free mass and the fat mass, as well as their distribution is investigated. The primary aim of the study is the change in BMI, which is determined by the change in body mass, while size remains the same. With the determination of the body composition and fat distribution pattern, a more specific statement about the body mass lost is possible. This is particularly important, while a

loss of fat mass (and in particular truncal fat mass) results in a reduction in metabolic and cardiovascular disease risk.

Study design

In a preliminary phase, inclusion and exclusion criteria were checked.
If subjects they were suitable for the study, a blood sample for genotyping the FTO risk allele status was taken after informed consent.
The examination was carried out (in a blinded manner) at the Max Planck Institute for Metabolism, Cologne. The result leaded to the allocation to 3 different strata of the study (homozygous risk allele (AA), homozygous wild type (TT) and heterozygous risk allele (AT). The aim was to include 10 subjects into each stratum. The result of the genotyping remained unknown to subjects and investigators for the duration of the study and was only transmitted anonymously to the Institute for Medical Statistics at the University Hospital of Cologne, where the computer-assisted 1:1 randomisation to verum or placebo within each strata is was executed. During the initial visit anthropometric data, laboratory chemical examinations, eating behaviour, reward behaviour and psychological tests were recorded. After that, the treatment with verum or placebo (see also section treatment/intervention) for a total of 18 weeks was initiated.

In interim visits laboratory and anthropometric data were recorded and, in the final visit, eating and reward behaviour were tested again

Trial medication/ treatment

Trade name: Bromocriptine ratiopharm®

Gerneric name: Bromocriptine mesylate

Dosage form: Capsules for oral administration
Dose: 1 capsule contains: 1.435 mg bromocriptine mesilate (equivalent to 1.25 mg bromocriptine mesylate, equivalent to 1.25 mg bromocriptine, corresponding to 1/2 tablet of Bromocriptine ratiopharm® 2.5 mg).

Original manufacturer: ratiopharm GmbH

Contract manufacturer:
Apotheke de Universitätsmedizin der
Johannes-Gutenberg University Mainz,
Study Centre-
Langenbeckstr. 1
55131 Mainz
Tel.: 06131 / 17-5359
Fax: 06131 / 17-3439

Composition: Each tablet contains 2.87mg bromocriptine mesilate, corresponding to 2.5 mg bromocriptine, for the preparation in the clinical trial half a tablet of bromocriptine was used for the preparation of a capsule used in the clinical trial.
In the trial the content of half a tablet of bromocriptine 2.5mg was used, giving a dosage of 1.25mg per capsule.

Other ingredients: Lactose monohydrate, maize starch, povidone, K25, maleic acid, magnesium stearate, (Ph.Eur.), highly dispersed silicon dioxide.

Shelf life: the shelf life of the capsules was one year.

Preparation of the test medication:
The study medication was prepared and blinded in the pharmacy of the University of Mainz. Commercially available bromocriptine mesilate (ratiopharm GmH) was used to manufacture the verum capsules. For the placebo capsules white 7 mm P-Lichtenstein tablets (drug-free) were used.

Storage of the test medication:
The test medication was stored according to the manufacturer's datal in a lockable shrink in the Centre for Endocrinology, Diabetology and Preventive Medicine at the University Cologne University Hospital at room temperature (<25°C). The temperature was checked and documented regularly.

Treatment/intervention

The trial was a two-armed placebo-controlled trial, stratified according to the FTO genotype. Treatment was either with bromocriptine (bromocriptine-mesilate, 1 capsule containing 1.25 mg) or placebo (capsule did not contained any active substance).
Starting dose was 1.25 mg per day (1 Capsule). The dose was increased in steps of 1.25 mg to a maximum of 5 mg per day (5 Capsules) if tolerated. The same was performed with the placebo capsules. The assigned mediation (verum or placebo) was administered in the morning immediately after getting up. From the first dose, the mediation was administered daily for a period of 18 weeks ending with the last dose at final visit. 2 weeks after taking the last mediation, a telephone visit followed to check for possible AES or SAEs. Two further follow-up examinations were scheduled in weeks 30 and 42.

Comparative condition/medication

Placebo:
Trade name: P-tablets white 7mm Lichtenstein®

Dosage form: capsules to be taken per os

Dose: not applicable

Original manufacturer: Winthrop Arzneimittel

Contract manufacturer:
Apotheke der Universitätsmedizin der
Johannes-Gutenberg University Mainz,
Study Centre-
Langenbeckstr. 1
55131 Mainz
Tel.: 06131 / 17-5359
Fax: 06131 / 17-3439

Composition:
For preparation of a capsule used in the clinical trial half a tablet of P-tablets white 7mm Lichtenstein® was used, which containing no active substance.

Other ingredients:
Lactose monohydrate, magnesium stea-.
rat (Ph. Eur.), cellulose powder and microcrystalline cellulose.

Shelf life: The expiry date for the capsules is the shortest usability period of the placebo tablets contained in the capsules, up to a maximum of 3 years.

Total number of patients

Planned number of cases: 30 (10 per stratum)
Increase of the planned number of cases to 60 by Amendment 4
Screened patients: 79
Patients included: 47
Randomised patients: 37 (ITT population)
Drop-outs: 12
PP population: 25

Study population

79 subjects were screened. Of these, 5 subjects did not fulfil the inclusion and exclusion criteria (2 subjects had high blood pressure values, one subject had an inadmissible concomitant medication, 1 subject had not signed the consent form and
1 subject had not signed the consent form and also high blood pressure values).
Recruitment was terminated before reaching the planned number of cases, as no more suitable subjects were available.

27 subjects fulfilled the inclusion and exclusion criteria, but could not be included in the study, because after genotyping revealed that they belonged to a strain that had already been filled.

Of the remaining 47 subjects, 7 subjects withdrew their consent before receiving the first study medication and another 2 subjects were excluded from the study before receiving the first study medication while exclusion criteria were discovered (coronary heart disease (1), elevated scores in a depression questionnaire (1).
One subject did not appear again without giving reasons.

37 subjects were randomised (ITT-population) finally. Of these, 18 received placebo and 19 verum.

The strata were filled as follows:

- homozygous for the risk allele (AA): 7
- heterozygous for the risk allele (AT): 17
- homozygous for the wild type (TT): 13
-

12 subjects terminated the study prematurely (before week 18). The most frequent reasons given were timing problems in keeping the visit appointments and
disappointment that the hoped-for weight reduction had not been achieved.
No respondent discontinued the study due to adverse effects of the trial medication.

The per to protocol (PP) collective was 25.

Inclusion criteria

- Diagnosis: obesity (BMI ≥ 30kg/m^2).

<u>Main inclusion criteria:</u>

- ≥ BMI ≥ 30kg/m^2
- Age ≥ 18 years
- Signed informed consent

Exclusion criteria

- Known hypersensitivity to bromocriptine or other ingredients of the study drug or placebo
- Diabetes mellitus type 1 and type 2 (excluded by determination of HbA1c in screening; exclusion in case of HbA1c > 6.5%)
- Presence of hypothyroidism or hyperthyroidism (excluded by determination of TSH, fT3 and fT4)
- Pregnancy or breastfeeding
- Known presence of uncontrolled hypertension (systolic blood pressure values, if applicable under antihypertensive therapy, > 140mmHg or diastolic blood pressure values under antihypertensive therapy > 90mmHg, (> 160mmHg systolic and >100mmHg diastolic after Amendment III respectively)
- Presence of coronary heart disease (CHD)
- Presence of peripheral arterial disease
- Presence of any of the following liver diseases

    - acute and chronic viral hepatitis, cirrhosis of the liver
- Presence of moderately severe chronic renal insufficiency; corresponding to a glomerular filtration rate (GFR) ≤ 59ml/min (calculated according to the MDRD formula).
    - Presence of Parkinson's disease
- Current presence of, or positive history of any of the following psychiatric disorders:
    - depression or mania
    - anxiety or panic disorder,
    - obsessive-compulsive disorder, schizophrenia, psychosis, addictive disease
- Presence of any of the following pituitary disorders
    - hormone-active pituitary microadenoma,
    - pituitary macroadenoma, pituitary inflammation
- Prior therapy with bromocriptine in the last 12 months
- Presence of dementia
- Presence of gastric or intestinal ulcers
- Presence of malignant disease in the last 5 years
- Presence of cardiac insufficiency NYHA III or IV
- Exceeding the limits of normal of laboratory parameter
    - Creatinine> 2.0 mg/dl
    - Urea > 100 mg/dl
    - Uric acid > 10 mg/dl
    - Alkaline phosphatase > 250 U/l (female) > 450 U/l (male)
    - GOT > 150 U/l
    - GPT > 150 U/l
    - Gamma-GT > 150 U/l
    - CK > 8500/l
    - HCG (female) ≥ 50/l

- Co-medication with the following drugs
    - Methyldopa
    - Levodopa
    - Dopamine antagonists
    - Metoclopramide
    - Domperidone
    - Glycerol nitrate
    - Griseofulvin
    - Azole antifungals
    - Macrolide antibiotics
    - Octreotide
    - Orlistat
    - Tamoxifen
- Wearing a pacemaker
- Participation in other interventional trials and receipt of any other investigational medication in the last 21 days
- Persons in a dependency/employment relationship with the sponsor or investigator
- Placement in an institution due to a court or official order
- Lack of safe contraceptive measures. As safe contraceptive measures are Methods with a Pearl index of less than 1%:

- oral hormonal contraception
- dermal hormonal contraception,
- vaginal hormonal contraception (NuvaRing®)
- contraceptive patches,
- long-term injectable contraceptives,
- progesterone-releasing implant (Implanon®),
- tubal ligation (female sterilisation),
- hormone-releasing intrauterine device ("hormone-releasing IUD"),
- double barrier methods

Demography and baseline characteristics

The key demographic and baseline characteristics of the ITT population are shown in the following table:

	Total population (n=37)	Placebo (n=18)	Verum (n=19)
Mean Age (years=	45,2	46,3	44,2
Male/female	18/19	8/10	10/9
Co-Medication (%)	86,5	83,3	85,5
BMI (kg/m^2)	38,1	37,1	39,1

The data show that despite the overall rather small study a homogeneous distribution between the placebo and verum groups. The high proportion of co-mediation in both groups illustrates the high rate of comorbidity rate in obesity. The baseline characteristics genotype strata are shown in the following table:

	Homozygous for FTO-risk allele (AA) n=7	Heterozygous for FTO-risk allele (AT) n=17	Homozygous for wildtype (TT) n=13
Mean age (years)	41,6	45,7	46,5
Male/female	3/4	8/9	7/6
BMI (kg/m^2)	41,8	38,7	35,4

As expected, the highest BMI levels are found in the group of homozygous carriers of the FTO risk allele, the lowest in the wild-type group.

Efficacy

The compliance of the subjects in relation to study-medication adherence was assessed by the return of surplus study medication or empty study medication containers.
Accordingly, the study medication was used in the PP population amounted 80-120% which indicates good compliance.
Disregarding the genotypes, no effect of bromocriptine in relation to the primary endpoint was observed. However, in the homozygous genotype (AA), an opposite effect was observed. In the heterozygous genotype (AT) there was no effect.
In the wild type (TT), the weight loss is greater in the bromocriptine group. Due to the small numbers this effect is not statistically significant (as expected).

Safety

During the entire study period, there was no unpredictable serious adverse reaction (SUSAR) associated with the study medication. Also, there were no serious, expected adverse reactions associated with the study drug medication (SAR).

A total of 3 serious adverse events (SAE) occurred, all of which were not associated with the study medication (ankle fracture, neck strain, swallowing of a blister).
Complete recovery was achieved in all cases.

There were 88 mild adverse events, 7 of which were possibly related to the study medication. These were adverse events listed in the study drug information leaflet, such as mild nausea, loss of appetite and orthostatic complaints.

Statistical methods:

10 patients were intended to be allocated to each stratum (FTO genotype). The allocation of test medications (bromocriptine, placebo) within the strata was block randomized. This was to guarantee balanced allocation to the treatments.

Evaluation of the primary outcome variables:
The primary outcome variable is the change in BMI (difference) from the beginning to the end of the treatment phase. This is compared between treatment groups using exploratory evaluation techniques and is used to determine an effect for the following confirmatory study. The evaluation of the change within the genotype subgroups, as well as the evaluation of the secondary target parameters, is exploratory.

Giving the number of cases of 15 patients per treatment group, the one-sided significance level α = 5% and a power (1-β) = 80% a large effect (δ= 0.93) can be statistically demonstrated by the t-test. Since the main purpose of the pilot study is to show that the is on the right side, i.e. the BMI-reduction in the bromocriptine group is higher than in the placebo group (equivalent to a one-sided α = 50%), small effects (δ=0.31) can be detected. In the genotype groups, medium effects (δ= 0.53) still can be detected.

SUMMARY:

RESULTS EFFECTIVENESS:

In the present pilot study, there was no statistically significant effect of bromocriptine on BMI in the overall population. The change in BMI (kg/m2) for the bromocriptine group (ITT population) was -0.25 (95% confidence interval -0.86 to 0.35) and for the placebo group -0.42 (95% confidence interval -0.86 to 0.35).

There was no significant difference between the groups with a p-value of 0.45 (ANCOVA). Similarly, there were no significant effects on the secondary endpoints change in eating behaviour and change in body composition. However, there was an effect/trend depending on the genotype of the test persons. Contrary to the original hypothesis, bromocriptine therapy led to a moderate weight gain in the group of the carriers of the homozygous risk allele (AA) compared to placebo (BMI change 1.25). (BMI - change 1.25 (95% confidence interval: - 0.20 to 2.70) in the bromocriptine group; BMI change-0.08 (95% confidence interval -1.19 to 1.03) in the placebo group), whereas there was no effect in the group heterozygous for the risk allele (AT). (Change in the bromocriptine group -0.34 (95% confidence interval: - 0.98 to 0.30); BMI-change in the placebo group - 0.60 (95% confidence interval: - 1.76 to 0.57)).

In the wild-type group (TT), there was a decrease in BMI with bromocriptine compared to placebo. (BMI change in the bromocriptine group - 1.13 (95% confidence interval: -2.36 to 0.10); BMI change in placebo group -0.35 (95% confidence interval: -0.91 to 0.20).

SAFETY RESULTS:

Only a few mild adverse events occurred during treatment with bromocriptine, which has been approved for many years. These adverse events were all known and listed in the drug information sheet. In this respect, there were no new safety concerns regarding to the study medication.

CONCLUSION:

In this pilot study, therapy with bromocriptine in people with obesity did not result in any detectable reduction in BMI in the whole study population. This result is not particularly surprising, as several published studies on the use of bromocriptine for weight reduction in obese people had shown very heterogeneous results. It therefore seems remarkable that in the pilot study here, a genotype-specific effect/trend was discernible. According to this, subjects who were not carriers of the FTO risk allele benefited from the therapy, while homozygous carriers of the risk allele gained weight despite the therapy.

Concordant with this result, the group of heterozygous allele carriers showed no effect. Even if this result is in contradiction to what we postulated, the genotype, regarding the FTO risk allele, seems to influence the response to weight-reducing therapy.

This encourages us to investigate in a confirmatory study whether this genotype-specific effect can be confirmed in a larger cohort and may apply to other weight-reducing interventions.