MEANS AND METHODS FOR IMPROVED TREATMENT USING "SETRONES"

The present invention relates to the use of "setrones" for the preparation of a pharmaceutical composition for treating and/or preventing "setrone-treatable diseases" in a patient having a genotype with a first or second variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first and/or second variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from "setrone-treatable diseases" as well as to methods of treatment for treating and/or preventing "setrone-treatable diseases".
Means and methods for improved treatment using ‘setrones’

The present invention relates to the use of setrone drugs i.e. ondansetron (1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one) or tropisetron (1[alpha]H,5H-tropan-3-yl indole-3-carboxylate), dolasetron ((2a,6a,8a,9ab)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethane-sulfonate), granisetron (endo-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide) for the preparation of a pharmaceutical composition for treating and/or preventing postoperative nausea and/or vomiting, or nausea and/or vomiting secondary to cancer chemotherapy, radiation therapy, migraine, acetaminophen poisoning, prostacyclin therapy, and opioid treatment, spinal or epidural opioid-related pruritus, acute levodopa-induced psychosis, bulimia nervosa, fibromyalgia, chronic fatigue syndrome, obsessive-compulsive disorders, schizophrenia, alcoholism, cocaine addiction, opioid withdrawal syndrome, drug withdrawal phenomena, anxiety disorders, cognitive disturbances, neuroleptic-induced tardive dyskinesia, tourette's syndrome, migraine, headache, and gastrointestinal motility disorders in a patient having a genotype with a first, a second or a first and a second variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, a second or a first and a second variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from postoperative nausea and/or vomiting, or nausea and/or vomiting secondary to cancer chemotherapy, radiation therapy, migraine, acetaminophen poisoning, prostacyclin therapy, and opioid treatment, spinal or epidural opioid-related pruritus, acute levodopa-induced psychosis, bulimia nervosa, fibromyalgia, chronic fatigue syndrome, obsessive-
compulsive disorders, schizophrenia, alcoholism, cocaine addiction, opioid withdrawal syndrome, drug withdrawal phenomena, anxiety disorders, cognitive disturbances, neuroleptic-induced tardive dyskinesia, tourette's syndrome, migraine, headache, and gastrointestinal motility disorders as well as to methods of treatment for treating and/or preventing 'setrone-treatable diseases'.

Nausea and vomiting are severe side effects of cancer chemotherapy and the incidence of these adverse effects frequently influences the success of the individual cancer therapy (Stewart, Can J Physiol Pharmacol 68 (1990), 304-313). Three different forms of vomiting or nausea induced by cancer chemotherapy can be distinguished: the acute emesis within the first 24 hours, the delayed emesis after the first 24 hours up to 6 days and the anticipatory emesis (Andrews and Davis. In Andrews PL SG (ed): Emesis in anti-cancer therapy. London, Chapman and Hall, 1993, pp 113-161). Various mechanisms contribute to these effects, as shown by the following examples: Cisplatinum, one archetypical emetogenic drug leads to increased the release of serotonin from enterochromaffin cells of the gut, which in turn increases the number of episodes of emesis (Cubeddu, N Engl J Med 322 (1990), 810-816). This effect can partially be counteracted by interference with the serotonin system: For example, lower serotonin concentrations, and in consequence less emesis were observed when patients had been pretreated with an inhibitor of serotonin synthesis (Alfieri, Br J Cancer 71 (1995), 629-632). Metoclopramide, which shows serotonin antagonist properties at higher therapeutic doses, as well as the treatment with serotonin (5-hydroxytryptamine) receptor type 3 antagonist (5-HT₃ antagonist), can reduce emesis significantly (Cunningham, Lancet 1 (1987), 1461-1463; Kris, J Clin Oncol 6 (1988), 659-662).

The molecular mechanism of acute emesis seems to be a peripheral and/or central serotonin release with consecutive activation of 5-HT₃ receptors on peripheral vagal fibers and central regions as the area postrema and ncl. tractus solitarii (Tyers, Oncology, 49 (1992), 263-268; Miller and Leslie, Front Neuroendocrinol, 15 (1994), 301-320; Gregory, Drugs 55 (1998),173-189). This correlation between serotonin release and nausea and vomiting had also been observed during treatment with

Other anticancer drugs like cyclophosphamide may not by themselves directly increase the serotonin release in humans, but the induced emesis is still sensitive to 5-HT$_3$ receptor antagonists (Cubeddu, Br J Cancer 72 (1995), 1033-1038, Minami, Res Commun Mol Pathol Pharmacol 97 (1997), 13-24).

The prophylactic administration of 5-hydroxytryptamine (5-HT$_3$) receptor antagonists, a class of drugs with similar structural properties that can be summarized as 'setrones' (e.g. ondansetron, tropisetron, granisetron or dolasetron), plays a major role in the current antiemetic treatment (Gralla, J Clin Oncol 17 (1999), 2971-2994). The application of 'setrones' results in a significant improvement of cancer therapy, as well as quality of live in cancer patients (Cunningham, Lancet 1 (1987),1461-1463; Jantunen, Eur J Cancer 33 (1997), 66-674).

In addition to the emetogenic level of the chemotherapeutic agents, individual factors such as female sex, younger age, alcohol consumption and pre-existing nausea correlate with the individual risk of acute vomiting, which can be treated with 5-HT$_3$ receptor antagonists. While 'setrones' are effective in many patients, about 20-30% of the patients do not respond satisfactorily to 5-HT$_3$ receptor antagonists (Gregory, Drugs 55 (1998),173-189).

All currently known 5-HT$_3$ receptor antagonists are metabolized by the cytochrome P450 (CYP) enzymes: tropisetron and dolasetron predominantly by CYP2D6, ondansetron partially by CYP2D6 but also by CYP3A4, CYP2E1, or CYP1A2 and granisetron mainly by CYP3A4 (Fischer, Drug Metab Dispos 22 (1994), 269-2674, Sanwald, Drug Metab Dispos 24 (1996), 602-609, Corrigan, Drug Metab Dispos 27 (1999), 110-112, Dixon, Drug Metab Dispos 23 (1995),1225-1230, Firkusny, Biochem Pharmacol 49 (1995), 1777-1784, Bloomer, Br J Clin Pharmacol 38 (1994), 557-566). For the genetically polymorphic enzyme CYP2D6, several alleles have been detected which result in defective, qualitatively altered, diminished or enhanced activity (http://www.imm.ki.se/CYPalleles/cyp2d6.htm; Sachse, Am J Hum
Genet, 60 (1997), 284-295). About 5%-10% of Caucasians, the so-called poor metabolizers (PMs) of the model substrates debrisoquine and sparteine, completely lack CYP2D6 activity, and about 2% of Caucasians are so-called ultrarapid metabolizers with more than two active genes due to a duplication or even an amplification of the CYP2D6 gene (Johansson, Proc Natl Acad Sci U S A 90 (1993), 11825-9). The proportion of poor and ultrarapid metabolizers varies between different populations (Ingelman-Sundberg, Trends Pharmacol Sci 20 (1999), 342-349). An inverse correlation was demonstrated between CYP2D6 activity, measured by the sparteine metabolic ratio, and the bioavailability of oral tropisetron, i.e. PMs had higher tropisetron Cmax and AUC levels and showed longer halflifes (Kees, Br J Clin Pharmacol 52 (2001), 705-707). However, drug response does not necessarily correlate with pharmacokinetics. Although CYP2D6 genotypes have been shown to correlate with plasma levels of CYP2D6-metabolized anti-retroviral drugs, no association could be detected between CYP2D6 genotype and therapeutic outcome (Fellay, Lancet 359 (2002), 30-36). So far, a correlation between CYP2D6 genotype, phenotype, and antiemetic efficacy of ‘setrones’ has not been demonstrated, even though the polymorphic CYP2D6 system has been known to experts in the field for many years, and has been analyzed for a variety of drugs for many medical indications.

CYP2D6 is not the only factor which might influence the efficacy of antiemetic therapy with ‘setrones’. Other factors that could interfere with the therapeutic efficacy of antiemetic drugs which target the ‘serotonin system’ are the regulatory regions and genes that provide the molecular target for the action of ‘setrones’, as well as genes that control the uptake and distribution and excretion of ‘setrones’ and their metabolites.

The serotonin receptor (5-HT₃ receptor) might serve as one example: The 5-HT₃ receptor antagonists act through specific binding to the 5-HT₃ receptor. This receptor belongs to the family of ligand-gated ion channels, which after activation becomes permeable preferentially for monovalent cations like Na⁺, K⁺ and divalent cations like Ca²⁺ (Maricq, Science 254 (1991), 432-437; Jackson, Annu Rev Physiol 57 (1995), 447-468). Two subunits of the 5-HT₃ receptor, the 5-HT₃A, 5-HT₃B and
two human brain splice variants of the 5-HT$_{3A}$ receptor have been identified (Belelli, Mol Pharmacol 48 (1995), 1054-1062; Miyake, Mol Pharmacol 48 (1995), 407-416; Bruss, Ann N Y Acad Sci 861 (1998), 234-235; Davies, Nature 397 (1999), 359-363; Dubin, J Biol Chem 274 (1999), 30799-30810). The 5-HT$_3$ receptor channel itself is an oligomeric complex of five of these subunits (Boess and Martin, Neuropharmacology 33 (1994), 275-317; Boess, J Neurochem 64 (1995), 1401-1405). Until now, it is not finally clarified if the 5-HT$_3$ receptor is either homo- or heteropentameric in his native status (Bruss, Naunyn Schmiedebergs Arch Pharmacol 362 (2000), 392-401). The in vitro expression of a homopentameric 5-HT$_{3A}$ receptor leads to a functional ion channel, but only with small single conductance in contrast to neuronal 5-HT$_3$ receptors (Fletcher, Trends Pharmacol Sci 19 (1998), 212-215). However, heteropentameric 5-HT$_3$ receptors composed of both subunits assemble to functional 5-HT-gated channels but with a similar high single-channel conductance, low permeability to calcium ions and current-voltage relationship as the native 5-HT$_3$ channels (Davies, Nature 397 (1999), 359-363; Dubin, J Biol Chem 274 (1999), 30799-30810). Moreover, 5-HT$_{3A}$ and 5-HT$_{3B}$ receptor subunits have been detected in anatomical structures which seem to be involved in the mechanism of chemotherapy induced nausea like the area postrema, amygdala, hippocampus, and the small intestine and colon (Davies, Nature 397 (1999), 359-363; Dubin, J Biol Chem 274 (1999), 30799-30810). The 5-HT$_{3B}$ receptor (HTR3B) gene resides on the long arm of chromosome 11 at band 23.1, has nine exons, coding for a 441 amino acid residues and spans at least 55 kb (Davies, Nature 397 (1999), 359-363). So far, hereditary polymorphisms or variants of the 5-HT$_{3B}$ receptor (HTR3B) gene, which correlate with the activity or non-activity of indole-containing 5-hydroxytryptamine (5-HT$_3$) receptor antagonists (e.g. ondansetron, tropisetron, granisetron or dolasetron) have not been described.

Means and methods for improving the efficacy of the currently available antiemetic therapies and avoiding the aforementioned insufficient activity or non-activity, which are accompanied with the said therapies are not available yet but are nevertheless highly desirable. However, a correlation of genetic factors and the efficacy of antiemetic setrone therapy, or assays that predict the therapeutic efficacy of
serotonin-antagonist therapy based upon the genetic influence has not been made available yet.

Thus, the technical problem underlying the present invention is to provide improved means and methods for the efficient treatment and/or the prevention of 'setrone-treatable diseases'.

The technical problem underlying the present invention is solved by the embodiments characterized in the claims.

Accordingly, the present invention relates to the use of 'setrones' for the preparation of a pharmaceutical composition for treating and/or preventing 'setrone-treatable diseases' in a subject having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6 polypeptide.

The term "setrones" as used in accordance with the present invention refers to substances characterized by the general structural formula which is based on the indole-containing chemical structure of 5-hydroxytryptamin shown below or to variants thereof (e.g. Granisetron) which are obtainable by chemical modifications. The setrones encompass ondansetron, tropisetron, dolasetron, granisetron, azasetron, itasetron, ramosetron, palonosetron, lerisetron, zatosetron, clinasetron, alosetron hydrochloride and ricasetron, which act as serotonin receptor antagonists.
Further variants and modifications of setrones are described in US patents: 4,695,578; 4,753,789; 5,578,628; 5,955,488; 6,063,802; 4,886,808; 6,294,548; 5,360,800 and 4,906,755 and are herewith incorporated by reference.


Also encompassed by the use of the present invention are derivatives of those substances which are obtainable by way of any chemical modification, wherein said derivatives are equally well therapeutically suited for the use of the present invention. To determine whether a derivative of the substances of the invention is equally well therapeutically suited for the use of the invention biological assays well known in the art can be performed. It has been shown that ondansetron, tropisetron, dolasetron, granisetron are particularly well suited for the treatment and/or prevention of 'setrone-treatable diseases'. Thus, more preferably the substances used according to the present invention are ondansetron, tropisetron, dolasetron,
granisetron, azasetron, itasetron, ramosetron, palonosetron, lerisetron, zatosetron, clinasetron, alosetron hydrochloride and ricasetron. Most preferably the substances used according to the present invention are ondansetron and tropisetron.

The term "pharmaceutical composition" as used herein comprises the substances of the present invention and optionally one or more pharmaceutically acceptable carrier. The substances of the present invention may be formulated as pharmaceutically acceptable salts. Acceptable salts comprise acetate, methylester, HCl, sulfate, chloride and the like. The pharmaceutical compositions can be conveniently administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The substances may be administered in conventional dosage forms prepared by combining the drugs with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are phosphate buffered saline solution, syrup, oil such as peanut oil and olive oil, water, emulsions, various types of wetting agents, sterile solutions and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

The substance according to the present invention can be administered in various manners to achieve the desired effect. Said substance can be administered either alone or in the formulated as pharmaceutical preparations to the subject being treated either orally, topically, parenterally or by inhalation. Moreover, the substance can be administered in combination with other substances either in a common pharmaceutical composition or as separated pharmaceutical compositions.
The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. A therapeutically effective dose refers to that amount of the substance according to the invention which ameliorate the symptoms or condition. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50.

The dosage regimen will be determined by the attending physician and other clinical factors; preferably in accordance with any one of the above described methods. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Progress can be monitored by periodic assessment.

A typical dose can be, for example, in the range of 5 to 100 mg however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. Generally, the regimen as a regular administration of the pharmaceutical composition should be in the range of 1 μg to 10 mg units per day. If the regimen is a continuous infusion, it should also be in the range of 1 μg to 10 mg units per kilogram of body weight per minute, respectively. Progress can be monitored by periodic assessment. However, depending on the subject and the mode of administration, the quantity of substance administration may vary over a wide range to provide from about 0.01 mg per kg body mass to about 10 mg per kg body mass, usually 0.1 to 1 mg per kg body mass.

The pharmaceutical compositions and formulations referred to herein are administered at least once in accordance with the use of the present invention. However, the said pharmaceutical compositions and formulations may be
administered more than one time, for example from one to four times daily up to a non-limited number of days.

Specific formulations of the substance according to the invention are prepared in a manner well known in the pharmaceutical art and usually comprise at least one active substance referred to herein above in admixture or otherwise associated with a pharmaceutically acceptable carrier or diluent thereof. For making those formulations the active substance(s) will usually be mixed with a carrier or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other suitable containers or vehicles. A carrier may be solid, semisolid, gel-based or liquid material which serves as a vehicle, excipient or medium for the active ingredients. Said suitable carriers comprise those mentioned above and others well known in the art, see, e.g., Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania. The formulations can be adopted to the mode of administration comprising the forms of tablets, capsules, suppositories, solutions, suspensions or the like.

The dosing recommendations will be indicated in product labeling by allowing the prescriber to anticipate dose adjustments depending on the considered patient group, with information that avoids prescribing the wrong drug to the wrong patients at the wrong dose.

The present invention also encompasses all embodiments described in connection with pharmaceutical compositions in US patents: 4,695,578; 4,753,789; 5,578,628; 5,955,488; 6,063,802; 4,886,808; 6,294,548; 4,906,755.

The term “treating” refers to a statistically significant (p value less than 0.05) cure or alleviation of the diseases in subjects or disease populations which have been treated. Said cure or alleviation of the diseases can be monitored by the degree of the clinical symptoms accompanied with the disease. Whether said number of subjects is significant can be determined by statistical tests such as the Student’s t-test, the chi²-test, the U-test according to Mann and Whitney, the Kruskal-Wallis-test (H-Test), Jonckheere-Terpstra-test or the Wilcoxon-test.

The term “preventing” refers to a successful prevention or alleviation of the occurrence of the diseases in a statistically significant (p value less than 0.05)
number of subjects or disease population to which the setrones have been administered. Said prevention or alleviation of the disease can be monitored by the degree of the clinical symptoms accompanied with the disease. Whether said number of subjects is significant can be determined by statistical tests such as the Student’s t-test, the chi²-test, the U-test according to Mann and Whitney, the Kruskal-Wallis-test (H-Test), Jonckheere-Terpstra-test or the Wilcoxon-test.

The term “setrone-treatable diseases” comprise diseases and dysregulations related to the central and peripheral nervous system or secondary to drug treatment. Preferred diseases encompassed by the use of the present invention are postoperative nausea and/or vomiting, or nausea and/or vomiting secondary to cancer chemotherapy, radiation therapy, migraine, acetaminophen poisoning, prostacyclin therapy, and opioid treatment, spinal or epidural opioid-related pruritus, acute levodopa-induced psychosis, bulimia nervosa, fibromyalgia, chronic fatigue syndrome, obsessive-compulsive disorders, schizophrenia, alcoholism, cocaine addiction, opioid withdrawal syndrome, drug withdrawal phenomena, anxiety disorders, cognitive disturbances, neuroleptic-induced tardive dyskinesia, tourette’s syndrome, migraine headache, and gastrointestinal motility disorders. Said diseases and dysregulations are well known in the art and the accompanied symptoms are described, e.g., in standard text books such as Stedman. Particularly preferred, the ‘setrone-treatable diseases’ are nausea and/or vomiting secondary to cancer chemotherapy, and radiation therapy.

The term “subject” as used in the sense of the present invention comprises animals, preferably those specified herein after, and humans.

In the context of the present invention the term “polynucleotides” or “polypeptides” refers to different variants of a polynucleotide or a polypeptide specified in accordance with the uses of the present invention. Said variants comprise a reference or wild type sequence of the polynucleotides or polypeptides specified herein as well as variants which differ therefrom in structure or composition. The term “polynucleotide” as used herein preferably encompasses the nucleic acid sequence specifically referred to by SEQ ID NOs and as well as polynucleotides
comprising the reverse complementary nucleic acid sequence thereto. Reference or wild type sequences for the CYP2D6 polynucleotides are Genbank accession No.: GI:181303 or Genbank accession No.: GI:181304 for the CYP2D6 polypeptide. The differences in structure or composition usually occur by way of nucleotide or amino acid substitution(s), addition(s) and/or deletion(s). Details about the differences in structure or composition of the polynucleotides and polypeptides referred to in the present invention are state of the art and are described for example for different CYP2D6 alleles at http://www.imm.ki.se/CYPalleles/cyp2D6.htm. Preferred deletions in accordance with the invention are a deletion of the whole functional CYP2D6 gene resulting in a polynucleotide comprising SEQ ID No: 47, or a T deletion at a position corresponding to position 3326 or an AG deletion at a position corresponding to position 4232 to 4234 (Genbank accession No.: GI:181303), preferred insertion is a T insertion at a position corresponding to position 1756/1757 of the CYP2D6 gene (Genbank accession No.:GI:181303). Preferably, said nucleotide substitution(s), addition(s) or deletion(s) referred to in accordance with the use of the present invention result(s) in one or more changes of the corresponding amino acid(s) of the polypeptides. The variant polynucleotides also comprise fragments of said polynucleotides or polypeptides. The present invention also encompasses all embodiments described in connection with polynucleotides in PCT/EP01/00954, PCT/EP01/01456, PCT/GB96/02360, United state patents 5,981,174; 6,183,963; 5,648,482; 5,912,120; and 5,719,026. The term “corresponding” as used herein means that a position is not only determined by the number of the preceding nucleotides and amino acids, respectively. The position of a given nucleotide or amino acid in accordance with the use of the present invention which may be deleted, substituted or comprise one or more additional nucleotide(s) may vary due to deletions or additional nucleotides or amino acids elsewhere in the gene or the polypeptide. Thus, under a “corresponding position” in accordance with the present invention it is to be understood that nucleotides or amino acids may differ in the indicated number but may still have similar neighboring nucleotides or amino acids. Said nucleotides or amino acids which may be exchanged, deleted or comprise additional nucleotides or amino acids are also comprised by the term “corresponding position”. Said nucleotides or amino acids may for instance together with their neighbors form sequences which may be involved in the regulation of
gene expression, stability of the corresponding RNA or RNA editing, as well as encode functional domains or motifs of the protein of the invention. By, e.g., "position 4232 to 4234" it is meant that said polynucleotide comprises one or more deleted nucleotides which are deleted from position 4232 to position 4234 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format. By, e.g., "position 1756/1757" it is meant that said polynucleotide comprises one or more additional nucleotide(s) which are inserted from position 1756 to position 1757 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format, i.e. two consecutive position numbers separated by a slash (/).

The term "functional CYP2D6 polypeptide" as used herein refers to a polypeptide with wildtype CYP2D6 activity corresponding to the polypeptide of Genbank accession No.: GI: 181304 which forms the *1 (wildtype) allele or to a polypeptide encoded by the *2 allele as depicted infra. Preferred methods for diagnosing a CYP2D6 duplication are described below in more detail. The phenotype of each subject (enzymatic CYP2D6 activity) can be determined e.g. by measuring the sparteine oxidation, the dextromethorphan and debrisoquine metabolic ratio as described in Bock, Pharmacogenetics 4 (1994), 209-218; Griese, Pharmacogenetics 8 (1998), 15-26 and Sachse, Am J Hum Genet 60 (1997), 284-295. Most preferably, the polynucleotide of the use of the present invention is the CYP2D6*1 or *2 allele referred to herein.

In accordance with the present invention, the mode and population distribution of genetic variations in the CYP2D6 gene - the different alleles of the CYP2D6 gene - have been analyzed by sequence analysis of relevant regions of the human said gene from many different individuals. It is a well known fact that genomic DNA of individuals, which harbor the individual genetic makeup of all genes, including the CYP2D6 gene, can easily be purified from individual blood samples. These individual DNA samples are then used for the analysis of the sequence composition of the alleles of the CYP2D6 gene that are present in the individual which provided
the blood sample. The sequence analysis was carried out by PCR amplification of relevant regions of said genes, subsequent purification of the PCR products, followed by automated DNA sequencing with established methods (e.g. ABI dye terminator cycle sequencing), allelic discrimination assays using Taq Man or allele specific polymerase chain reaction (AS PCR) analysis.

A preferred and convenient method to be used in order to determine the presence or absence of one or more of the above specified polynucleotides is to isolate blood cells from a subject and to perform a PCR based assay on genomic DNA isolated from those blood cells, whereby the PCR is used to determine whether said polynucleotides specified herein above or parts thereof are present or absent. Most preferably, said method for diagnosing a duplication of a functional CYP2D6 polynucleotide is by Xbal RFLP analysis, allele specific polymerase chain reaction (ASPCR) analysis as described in more detail in Bock, Pharmacogenetics 4 (1994), 209-218; Griese, Pharmacogenetics 8 (1998), 15-26; Johannsson, Proc Natl Acad Sci USA 90 (1993), 11825-11829; Johannsson, Pharmacogenetics 6 (1996), 351-355 and Sachse, Am J Hum Genet 60 (1997), 284-295 or allelic copy number determination using 5’nuclease assay technology such as the TaqMan PCR detection system, or the Invader™-Assay technology.

Furthermore, the presence of three or more copies of a polynucleotide encoding a functional CYP2D6 polypeptide is also referred to as duplication or multiplication of active CYP2D6 genes. Initially only the CYP2D6*2 allele appears to be duplicated but more recent findings indicate a duplication of CYP2D6*1 (Dahl, J Pharmacol Exp Ther 274 (1995), 516-20; Bernal, Pharmacogenetics 9 (1999), 657-60.) and *35 (http://www.imm.ki.se/CYPalleles/cyp2d6.htm). CYP2D6*35 corresponds to a polypeptide encoded by the *2 allele as depicted infra in addition to an amino acid substitution of Val to Met at a position corresponding to position 11 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304). Since the enzyme activity of CYP2D6*35 is comparable to wildtype activity it is regarded as a functional CYP2D6 polypeptide belonging to a subgroup of *2. It appears that the CYP2D6*2x2 is the most common duplication among Caucasians. Furthermore, there can be a variable number of active CYP2D6 alleles; up to 13 copies of the *2 have been described
(Johansson, Proc Nati Acad Sci U S A 90 (1993), 11825-9; Bertilsson, Br J Clin Pharmacol 53 (2002), 111-22.). Whereas the multiplication of active genes leads to an ultra-rapid metabolizer phenotype (UM phenotype), the duplication of the inactive CYP2D6*4 allele in combination with a second poor-metabolizer allele (PM allele) results in a poor-metabolizer phenotype (PM phenotype).

Moreover, the presence of three or more copies of a polynucleotide encoding a functional CYP2D6 polypeptide can be determined by determining the presence of a polynucleotide comprising SEQ ID NO: 48 in the genome of the said subject. Consequently, a subject having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6 polypeptide is lacking in its genome a polynucleotide having SEQ ID NO: 48.

One important parameter that has to be considered in the attempt to determine the individual genotypes and identify novel variants of the CYP2D6 gene by direct DNA-sequencing of PCR-products from human blood genomic DNA is the fact that each human harbors (usually, with very few abnormal exceptions) two gene copies of each autosomal gene (diploidy). Because of that, great care has to be taken in the evaluation of the sequences to be able to identify unambiguously not only homozygous sequence variations but also heterozygous variations. The details of the different steps in the identification and characterization of the polymorphisms in the CYP2D6 gene (homozygous and heterozygous) are described in the Examples below.

Over the past 20 years, genetic heterogeneity has been increasingly recognized as a significant source of variation in drug response. Many scientific communications (Meyer, Ann. Rev. Pharmacol. Toxicol. 37 (1997), 269-296 and West, J. Clin. Pharmacol. 37 (1997), 635-648) have clearly shown that some drugs work better in some patients than in others or may even be highly toxic and that such variations in patients’ responses to drugs can be correlated to a molecular basis. This “pharmacogenomic” concept spots correlations between responses to drugs and genetic profiles of patient's (Marshall, Nature Biotechnology, 15 (1997), 954-957; Marshall, Nature Biotechnology, 15 (1997), 1249-1252). In this context of population
variability with regard to drug therapy, pharmacogenomics has been proposed as a tool useful in the identification and selection of patients which can respond to a particular drug without side effects. This identification/selection can be based upon molecular diagnosis of genetic polymorphisms by genotyping DNA from leukocytes in the blood of a patient, for example, and characterization of disease (Bertz, Clin. Pharmacokinet. 32 (1997), 210-256; Engel, J. Chromatogra. B. Biomed. Appl. 678 (1996), 93-103). For the founders of health care, such as health maintenance organizations in the US and government public health services in many European countries, this pharmacogenomics approach can represent a way of both improving health care and reducing costs related to health care caused by the development of unnecessary drugs, by ineffective drugs and by side effects due to drug administration.

The mutations in the variant genes of the invention sometimes result in amino acid deletion(s), insertion(s) and in particular in substitution(s) either alone or in combination. It is of course also possible to genetically engineer such mutations in wild type genes or other mutant forms. Methods for introducing such modifications in the DNA sequence of said genes are well known to the person skilled in the art; see, e.g., Sambrook, Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y.

Usually, said amino acid deletion, addition or substitution in the amino acid sequence of the protein encoded by the polynucleotide referred to in accordance with the use of the present invention is due to one or more nucleotide substitution(s), insertion(s) or deletion(s), or any combinations thereof. Preferably said nucleotide substitution may result in an amino acid substitution of Pro to Ser at a position corresponding to position 34 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304) and/or Gly to Arg at a position corresponding to position 42 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304) and/or His to Gly at a position corresponding to position 258 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304) and/or Arg to Cys at a position corresponding to position 296 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304) and/or His to Pro at a position corresponding to position 324 of the CYP2D6
polypeptide (Genbank accession No.: GI: 181304) and/or Ser to Thr at a position corresponding to position 486 of the CYP2D6 polypeptide (Genbank accession No.: GI: 181304). The polypeptides encoded by the polynucleotides referred to in accordance with the use described herein have altered biological properties due to the mutations referred to in accordance with the present invention. Examples for said altered properties are stability of the polypeptides which may be effected, an altered substrate specificity or substrate binding or an altered catalytic activity resulting in, e.g. an altered catalytic activity characterized by an insufficiency in drug metabolism, a complete loss of the capability to metabolize drugs or an enhanced capacity to metabolize drugs as described in the present invention.

The mutations in the CYP2D6 gene detected in accordance with the present invention are listed in Tables 1 and 2. As is evident to the person skilled in the art, the genetic knowledge of the polynucleotides specified herein above can be used to exactly and reliably characterize the genotype of a patient. An partial response or nonresponse to a treatment and/or prevention of a diseases, such as ‘setrone-treatable diseases’ referred to herein, which is associated with an enhanced CYP2D6 catalytic activity can be predicted based on the genetic knowledge.

Advantageously, preventive or therapeutical measures which are based on ‘setrones’ can be more efficiently applied when taking into consideration said genetic knowledge. Undesirable side effects of said substances can be avoided and an effective but not harmful dosage can be calculated individually due the knowledge of the genetic makeup of the subject. Moreover in accordance with the foregoing, in cases where a given drug causes an unusual effect, a suitable individual therapy can be designed based on the knowledge of the individual genetic makeup of a subject. The use of the present invention, therefore, provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein above since it is possible to individually treat the subject with an appropriate dosage and/or an appropriate derivative of said substances. Furthermore, the use of the present invention provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein
above since it is possible to identify those subject prior to onset of drug therapy and treat only those subjects with an appropriate dosage and/or an appropriate derivative of said substances who are most likely to benefit from therapy with said substances. Thereby, the unnecessary and potentially harmful treatment of those subjects who do not respond to the treatment with said substances (nonresponders) can be avoided. In these patients, e.g. those which are ultrarapid metabolizers, a different antiemetic approach is required.

In a preferred embodiment of the use of the present invention said subject is having in its genome at least one first variant allele which comprises a polynucleotide selected from the group consisting of: the allele CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*11, CYP2D6*12 and CYP2D6*15. The explanations and definitions of the terms made above apply mutates mutandis. The term "first variant allele" as used herein refers to a polynucleotide comprising one or more of the polynucleotides described herein corresponding to a CYP2D6 gene. Each individual subject carries at least two alleles of the CYP2D6 gene, wherein said alleles are distinguishable or identical. In accordance with the use of the present invention a variant allele comprises at least one or more of the polynucleotides specified herein above. Said polynucleotides may have a synergistic influence on the regulation or function of the first variant allele. Preferably, a variant allele in accordance with the use of the present invention comprises at least two of the polynucleotides specified hereinafter. Such variant alleles comprising at least two of the polynucleotides of the present invention encompass the following haplotypes which are defined by certain combinations of single nucleotide polymorphisms (SNPs):

The 4168A nucleotide deletion (SEQ ID NO 15) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *3 allele, the 3465G>A nucleotide substitution (SEQ ID NO 13) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *4 allele, the deletion of the entire coding sequence of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *5 allele (SEQ ID 47), the deletion of nucleotide T at position 3326 (SEQ ID NO 09) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *6 allele, the 4554A>C substitution (SEQ ID NO 21) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *7
allele, the 3377G>T nucleotide substitution (SEQ ID NO 11) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *8 allele, the 4469C>T nucleotide substitution (SEQ ID NO 19) of the CYP2D6 gene (Genbank accession No.: GI:181303) in combination with the nucleotide substitutions 1743G>A (SEQ ID NO 3) and 5799G>C (SEQ ID NO 23) of the CYP2D6 gene (Genbank accession No.: GI:181303) is responsible for the *12 allele, the 2502G>C nucleotide substitution (SEQ ID NO 07) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *11 allele, and the insertion of nucleotide T at position 1756/1757 (SEQ ID NO 05) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *15 allele. Furthermore, the present invention also encompasses first variant alleles which comprise polymnucleotides which are capable of hybridizing to the polymnucleotides having the above referenced SEQ ID Nos and which have a nucleotide deletion, substitution or insertion on a position corresponding to the positions referred to above. The term “hybridizing” is explained in detail below. The explanations apply mutates mutandis for the polymnucleotides referred to herein forming the CYP2D6 alleles.

In a preferred embodiment of the use of the present invention said subject is having in its genome at least one first variant allele which comprises a polymnucleotide selected from the group consisting of: the allele CYP2D6*1, CYP2D6*2, CYP2D6*9, and CYP2D6*10.

The explanations and definitions of the terms made above apply mutates mutandis.

The following haplotypes which are defined by certain combinations of single nucleotide polymorphisms (SNPs) form the aforementioned alleles:

The *1 allele of CYP2D6 has been described above and shown in SEQ ID NO: 49 and the combination of nucleotide substitutions 4469G>C (SEQ ID NO 19) with 5799G>C (SEQ ID NO 23) of the CYP2D6 gene (Genbank accession No.: GI:181303) is responsible for the *2 allele. Furthermore, the deletion of nucleotides AGA at positions 4232 to 4234 (SEQ ID NO 17) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *9 allele, and the combination of the 1719C>T (SEQ ID NO 01) with the 5799G>C (SEQ ID NO 23) nucleotide substitutions of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *10 allele.
The invention furthermore relates to the use, preferably the use as defined supra, of ‘setrones’ for the preparation of a pharmaceutical composition for treating and/or preventing ‘setrone-treatable diseases’ in a subject having in its genome a second variant allele which comprises at least one

a) polynucleotide having the nucleic acid sequence of SEQ ID NO: 026, and

b) polynucleotide capable of hybridizing to a HTR3B gene, wherein said polynucleotide is having at a position corresponding to position 36678 to 36680 of the HTR3B gene (Genbank accession No.: GI:17425234) an AAG.

The term “second variant allele” refers to an allele of a second gene being different from said first gene corresponding to the first allele described herein above. According to the present invention said second variant allele corresponds to a HTR3B gene comprising one or more of the polynucleotides specified above. Dependent on the polynucleotide specified above the individuals can be subgrouped into a non-responder group and a responder group or partial responder group. According to the present invention the subjects carrying two deletion polynucleotides (del/del) are subgrouped as non-responders and subjects carrying at least one insertion polynucleotide as responder or partial responder. More preferably, the subject has in its genome one or two second variant alleles comprising a polynucleotide having the nucleic acid sequence shown in SEQ ID NO: 26. Most preferably, the subject having in its genome one or two second variant alleles comprising a polynucleotide having the nucleic acid sequence shown in SEQ ID NO: 26 is lacking two second variant alleles comprising a polynucleotide having a nucleic acid sequence as shown in SEQ ID NO: 25.

The term “hybridizing” as used herein refers to polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a HT3RB dysfunction or dysregulation. Thus, said hybridizing polynucleotides are also associated with said dysfunctions and dysregulations. Preferably, said polynucleotides capable of hybridizing to the aforementioned polynucleotides or parts thereof which are associated with HT3RB dysfunctions or dysregulations are at least 70%, at least 80%, at least 95% or at least 100% identical to the polynucleotides or parts thereof which are associated with HT3RB dysfunctions or
dysregulations. Therefore, said polynucleotides may be useful as probes in Northern or Southern Blot analysis of RNA or DNA preparations, respectively, or can be used as oligonucleotide primers in PCR analysis dependent on their respective size. Also comprised in accordance with the use of the invention are hybridizing polynucleotides which are useful for analyzing DNA-Protein interactions via, e.g., electrophoretic mobility shift analysis (EMSA). Preferably, said hybridizing polynucleotides comprise at least 10, more preferably at least 15 nucleotides in length while a hybridizing polynucleotide to be used as a probe preferably comprises at least 100, more preferably at least 200, or most preferably at least 500 nucleotides in length.

It is well known in the art how to perform hybridization experiments with nucleic acid molecules, i.e. the person skilled in the art knows what hybridization conditions s/he has to use in accordance with the present invention. Such hybridization conditions are referred to in standard text books, such as Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y. Preferred in accordance with the use of the present inventions are polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a HT3B dysfunction or dysregulation under stringent hybridization conditions, i.e. which do not cross hybridize to unrelated polynucleotides such as polynucleotides encoding a polypeptide different from the polypeptides of the invention.

Moreover, methods for determining whether a subject comprises a polynucleotide referred to herein above are well known in the art. To carry out said methods, it might be necessary to take a sample comprising biological material, such as isolated cells or tissue, from said subject. Further, the methods known in the art could comprise for example, PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP) analysis, denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5’-nuclease assay-based techniques.

In accordance with the present invention said first variant allele corresponding to the CYP2D6 gene and a second variant allele corresponding to the HTR3B gene as
specified above, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of 'setrones'. Hence, in accordance with the use of the present invention the diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be more efficiently predicted compared to the state of the art.

As has been found in accordance with the present invention, the pharmacokinetics of a drug which is based on 'setrones' and the pharmacological response of a subject is mainly governed by the polypeptides encoded by the CYP2D6 and HTR3B genes. Therefore, in order to increase the predictability and/or efficiency of therapeutic or preventive measures applied in accordance with the present invention, the genetic constitution of a subject as regards the present or absence of the first and second variant alleles referred to herein has to be determined and based on that knowledge an individual therapy can be developed which is therapeutically most effective. Thereby, mistreatment of patients based on wrong medications and the results thereof, such as anticipatory vomiting, insufficient compliance to chemotherapy with subsequent failure to anticancer treatment can be efficiently avoided.

In a preferred embodiment of the use of the present invention the deletion, addition and/or substitution of one or more nucleotides comprised by said polynucleotide results in an altered expression of the first variant allele compared to the corresponding wild type allele.

As discussed above, the alleles referred to in accordance with the use of the present invention correspond to the CYP2D6 and HTR3B gene. It is well known in the art that genes comprise structural elements which encode an amino acid sequence as well as regulatory elements which are involved in the regulation of the expression of said genes. Structural elements are represented by exons which may either encode an amino acid sequence or which may code for RNA which is not encoding an amino acid sequence but is nevertheless involved in RNA function, e.g.
by regulating the stability of the RNA, RNA processing, translation efficiency or the nuclear export of the RNA.

Regulatory elements of a gene may comprise promoter elements or enhancer elements both of which could be involved in transcriptional control of gene expression. It is very well known in the art that a promoter is to be found upstream of the structural elements of a gene. Regulatory elements such as enhancer elements, however, can be found distributed over the entire locus of a gene. Said elements could reside, e.g., in introns, regions of genomic DNA which separate the exons of a gene. Promoter or enhancer elements correspond to polynucleotide fragments which are capable of attracting or binding polypeptides involved in the regulation of the gene comprising said promoter or enhancer elements. For example, polypeptides involved in regulation of said gene comprise the so called transcription factors.

Said introns may comprise further regulatory elements which are required for proper gene expression. Introns are usually transcribed together with the exons of a gene resulting in a nascent RNA transcript which contains both, exon and intron sequences. The intron encoded RNA sequences are usually removed by a process known as RNA splicing. However, said process also requires regulatory sequences present on a RNA transcript. Said regulatory sequences may be encoded by the introns.

In addition, besides their function in transcriptional control and control of proper RNA processing and/or stability, regulatory elements of a gene could be also involved in the control of genetic stability of a gene locus. Said elements control, e.g., recombination events or serve to maintain a certain structure of the DNA or the arrangement of DNA in a chromosome.

Therefore, single or multiple nucleotide polymorphisms, insertions and/or deletions can occur in exons of an allele of a gene which encode an amino acid sequence as discussed supra as well as in regulatory regions which are involved in the above discussed process. The polymorphisms comprised by the polynucleotides referred to in accordance with the use of the present invention can influence the expression level of CYP2D6 protein via mechanisms involving enhanced or reduced transcription of the CYP2D6 gene, stabilization of the gene’s RNA transcripts and alteration of the processing of the primary RNA transcripts.
Methods for the determination of an altered expression of a variant allele when compared to its wild type counterpart are well known in the art and comprise inter alia those referred to herein above, e.g. Northern blot analysis, Reverse transcriptase PCR based techniques (RT-PCT), Ribonuclease protection assays, Western Blot, Dot Blot, ELISA techniques, primer extension based techniques and Real Time PCR (TaqMan) assays. It might be necessary to obtain a sample comprising biological material, such as isolated cells or tissue from the subject prior to perform said methods for determination of the expression levels of the wild type and the variant alleles, respectively. An altered expression in accordance with the use of the present invention means that the expression of the wild type allele differs significantly from the expression of the variant allele. A significant difference can be determined by standard statistical methods, such as Student’s t-test, chi$^2$-test or the U-test according to Mann and Whitney. Moreover, the person skilled in the art can adopt these and other statistical method known in the art individually without an undue burden.

In a more preferred embodiment of the use of the invention said altered expression is decreased expression.

To determine whether the expression of an allele referred to in accordance to the present invention is increased or decreased in comparison to the corresponding wild type allele well known methods such as Northern blot analysis, Reverse transcriptase PCR based techniques (RT-PCT), Ribonuclease protection assays, Western Blot, Dot Blot, ELISA techniques, primer extension based techniques and Real Time PCR (TaqMan) assays can be applied. As discussed above, it might be necessary to obtain a sample comprising cells or tissue from the subject in order to determine the expression level of the variant allele referred to in the use of the invention. A decrease of the expression is characterized by a significant difference in the expression level of the variant versus the wild type allele in those assays. Also encompassed by decreased expression is the absence detectable expression of a variant allele.
In a furthermore preferred embodiment of the use of the present invention a deletion, addition and/or substitution of one or more nucleotides comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first variant allele compared to the polypeptide encoded by the corresponding wild type allele.

As discussed supra, the variant alleles comprising those polynucleotides specified herein which correspond to coding regions of the CYP2D6 gene effect the amino acid sequences of the polypeptides encoded by said variant alleles. The variant polypeptides, therefore, exhibit altered biological and/or immunological properties when compared to their corresponding wild type counterpart. Preferred variant polypeptides in accordance with the use of the invention are those, which exhibit an altered biological activity, i.e., an altered enzymatic function resulting in reduced, enhanced or complete loss of catalytic activity. It might be necessary to obtain a sample comprising biological material such as isolated cells or tissue from the subject prior to perform said methods for determination of the activities of the wild type and the variant polypeptides, respectively. Whether a variant polypeptide has an altered activity compared to its wild type corresponding counterpart can be determined by standard techniques well known in the art. Such standard techniques may comprise, e.g., ELISA based assays, RIA based assays, HPLC-based assays, LC/MS based assays, mass spectroscopy-based assays or assays which are known in the art and described in Brockmöller, Clin Pharmacokinet 1 27 (1994), 216-248; Mahgoub, Lancet 2 (1997), 584-586; Kutt, Neurology 14 (1964), 542-8; Scott, Diabetes 28 (1997), 41-51; Küpfer and Preisig, Eur J Clin Pharmacol 26 (1984), 753-759; Westlind, Biochem Biophys Res Commun 259 (1999), 201-205; Brockmöller, Clin Pharmacol Ther 61 (1997), 171; Chang, Pharmacogenetics 5 (1995), 358-63; Haining, Arch Biochem Biophys 333 (1996), 447-458; Takanashi, Pharmacogenetics 10 (2000), 95-104, Heils, J Neurochem 6 (1996), 2612-24; Heils, J Neural Transm 104 (1997), 1005-1014; Greenberg, Am J Med Genet 88 (1999), 83-87, Fuller, Life Sci 15 (1974), 1161-1171; Griese, Pharmacogenetics 8 (1998), 15-26 and Sachse, Am J Hum Genet 60 (1997), 284-295. An altered activity in accordance with the use of the present invention means that the activity of the wild type polypeptide differs significantly from the variant polypeptide. A significant
difference can be determined by standard statistical methods referred to herein above.

Most preferably, said altered activity is decreased activity. As discussed for the decrease of expression, a decrease of the activities is characterized by a significant difference in the activity of the variant versus the wild type polypeptide in the assays referred to herein. Also encompassed by decreased activity is the absence of activity of a variant allele.

Moreover, in a further preferred embodiment of the use of the present invention said subject is an animal. As described supra, the subject in accordance with the use of the present invention encompasses animals. The term “animal” as used herein encompasses all animals, preferably animals belonging to the vertebrate family, more preferably mammals. Moreover, the animals can be genetically engineered by well known techniques comprising transgenesis and homologous recombination in order to incorporate one or more of the polynucleotides referred to supra into the genome of said animals. Said animals comprising the genetically engineered animals can be used to study the pharmacological effects of drugs or pro-drugs which are based on the substances or derivatives thereof referred to herein, preferably ‘setrones’.

Moreover, in another preferred embodiment of the use of the present invention said subject is a human. In particular, the present invention is applicable to humans as is evident from the above. The use of the present invention is to be applied in order to treat or prevent patients which suffer from ‘setrone-treatable diseases’. The pharmacological effects of the above substances or derivatives thereof are well described in humans. However, the conventional therapies do not take into account the individual genetic makeup of the patient. Ethnical populations have different genetic backgrounds, which can also influence the function, regulation or expression of a variant allele and thereby alter the pharmacological response of a patient to a substance or derivative used as a basis for a drug or pro-drug in accordance with the invention.
In light of the foregoing, more preferably, said human is Asian, most preferably, Chinese.

The Chinese population shows compared to Caucasians a higher frequency of the CYP2D6 poor metabolizer phenotype (30% versus 9% in the Caucasian population) and are therefore more likely to respond to setrone treatment. On the other hand, the multiplication of CYP2D6 gene copies which causes the ultrarapid metabolizer phenotype is very common in Ethiopians (30% versus 2% in Caucasians and Chinese) who are therefore more likely to suffer from therapeutic failure. Thus, Ethiopians are more susceptible to insufficient treatment or non-response to setrone treatment and can particularly benefit from uncovering the genetic background (Population frequency data are from the OMIM database).

In another preferred embodiment the invention relates to the use of "setrones" for the preparation of a pharmaceutical composition for treating and/or preventing "setrone-treatable diseases" in a subject having in its genome a polynucleotide associated with an ultrarapid metabolizer phenotype of CYP2D6.

The term "associated with" in the content of the present invention means the coexistence of a polymorphism and a phenotype in a population. A polymorphism is said to be associated with a specific phenotype when its frequency is significantly higher among one phenotype group compared to its frequency in another.

The term "ultrarapid metabolizer phenotype of CYP2D6" is well known to experts in the field and further described supra and in the examples. Duplicate or multiple copies of functional active CYP2D6 genes cause the ultrarapid metabolizer phenotype of CYP2D6. The amplification of CYP2D6 copies causes the expression of an increased amount of CYP2D6 protein resulting in an increased metabolic CYP2D6 capacity as described in Johansson, Proc Natl Acad Sci U S A, 90 (1993), 11825-11829; Daly, Pharmacogenetics 6 (1996),193-201; Sachse, Am J Hum Genet 60 (1997), 284-295; Gaedigk, Pharmacogenetics 9 (1999), 669-682; and Kubota, Br J Clin Pharmacol 50 (2000), 31-34. Debrisoquine, dextromethorphan, metoprolol and sparteine are the most common probe drugs to assess CYP2D6 function in vivo. For example, using debrisoquine as a substrate a debrisoquine/4-hydroxydebrisoquine metabolic ratio (MR) of less than 0.15 defines the UM

The present invention also relates to a method for selecting a suitable therapy for a subject suffering from 'setrone-treatable diseases', wherein said method comprises:

(a) determining whether a subject is having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6;

(b) optionally determining the presence or absence of a first and/or second variant allele in the genome of a subject in a sample obtained from said subject; and

(c) selecting a suitable therapy for said subject based on the results obtained in (a).

The definitions and explanations of the terms made above apply mutatis mutandis to the above method.

The term "suitable therapy" as used herein means that a substance according to the invention is selected and said substance being administered in a certain dosage to a subject, wherein said substance and said dosage are selected based on the knowledge of the presence of the numbers of the copies of a polynucleotide encoding a functional CYP2D6 and/or the presence or absence of a first and/or second variant allele referred to in accordance with the use of the invention. Said substance and said dosage of the substance are selected in a way that on one hand they are most effective in treating and/or preventing 'setrone-treatable diseases' on the other hand they do not cause toxic or undesirable side effects. Based on the knowledge of the presence of the numbers of the copies of a polynucleotide encoding a functional CYP2D6 and/or the presence or absence of a first and/or second variant allele referred to in accordance with the use of the invention the preferred suitable therapy referred to in accordance with the present invention is administration of setrones in a therapeutically effective amount.

As is evident from the above, a prerequisite for selecting a suitable therapy is the knowledge of the numbers of the copies of a polynucleotide encoding a functional CYP2D6 and/or the presence or absence of a first and/or second variant allele referred to in accordance with the use of the invention. Therefore, the method of the present invention encompasses the determination of the presence or absence of said variant alleles in a sample which has been obtained from said subject. The sample which is obtained by the subject comprises biological material which is
suitable for the determination of the presence or absence of said variant alleles, such as isolated cells or tissue. Methods for the determination of the presence or absence of the variant alleles of the method of the invention comprise those methods referred to herein above.

The present invention also relates to a method of treating and/or preventing ‘setrone-treatable diseases’ comprising:
(a) determining whether a subject is having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6;
(b) optionally determining the presence or absence of a first and/or second variant allele comprising a polynucleotide referred to herein; and
(c) administering to a subject a therapeutically effective dosage of ‘setrones’.

The definitions used in accordance with the use of the present invention apply mutatis mutandis to the methods mentioned supra and infra. Further, all embodiments described in accordance with the use of the present invention can be applied mutatis mutandis to the methods of the present invention. Moreover, also encompassed by the methods of the present invention are any further developments of said methods which the person skilled in the art can make without undue burden based on its knowledge and the prior art.

It is furthermore envisaged that the present invention relates to a method for treating and/or preventing ‘setrone-treatable diseases’ in a subject which comprises:
(a) determining if the subject has one or more variant alleles of the CYP2D6 and/or 5HTR3B gene in a sample; and
(b) administering to the subject having one or more of such variant alleles an amount of setrone which is sufficient to treat a subject having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the subject’s alleles in the CYP2D6 and/or 5HTR3B gene.

Additionally, the present invention also relates to a method of preventing and/or treating ‘setrone-treatable diseases’ in a subject which comprises internally administering to the subject an effective amount of ‘setrones’, wherein the treatment
regimen is modified based upon the genotype of the subject's CYP2D6 and/or HTR3B gene.

Moreover, in another embodiment the present invention relates to a method for determining whether a subject is at risk for non-response to treatment with 'setrones' which comprises determining if the subject has one or more variant alleles of the CYP2D6 and/or HTR3B gene.

In a preferred embodiment of the present invention, the methods for treating and/or preventing 'setrone-treatable diseases' are postoperative nausea and/or vomiting, or nausea and/or vomiting secondary to cancer chemotherapy, radiation therapy, migraine, acetaminophen poisoning, prostacyclin therapy, and opioid treatment, spinal or epidural opioid-related pruritus, acute levodopa-induced psychosis, bulimia nervosa, fibromyalgia, chronic fatigue syndrome, obsessive-compulsive disorders, schizophrenia, alcoholism, cocaine addiction, opioid withdrawal syndrome, drug withdrawal phenomena, anxiety disorders, cognitive disturbances, neuroleptic-induced tardive dyskinesia, tourette's syndrome, migraine headache, and gastrointestinal motility disorders.
Particularly preferred 'setrone-treatable diseases' are nausea and/or vomiting secondary to cancer chemotherapy, and radiation therapy.

In another preferred embodiment of the present invention, the 'setrones' administered in the above mentioned methods for treating and/or preventing 'setrone-treatable diseases' in a subject are ondansetron, tropisetron, dolasetron, granisetron, azasetron, itasetron, ramosetron, palonosetron, lerisetron, zatogetron, clinasetron, alosetron hydrochloride and ricasetron.
Most preferably said 'setrones' are ondansetron and tropisetron.

In a preferred embodiment of the method of the invention the subject does not have in its genome a polynucleotide associated with an ultrarapid metabolizer phenotype of CYP2D6.
In another preferred embodiment the subject has in its genome less than three copies of a polynucleotide encoding a functional CYP2D6 polypeptide.

In a furthermore preferred embodiment the subject is having in its genome a
(a) polynucleotide having the nucleic acid sequence of SEQ ID NO: 026, and
(b) polynucleotide capable of hybridizing to a HTR3B gene, wherein said polynucleotide is having at a position corresponding to position 36678 to 36680 of the HTR3B gene (Genbank accession No.: GI:17425234) an AAG.

Thanks to the method of the present invention, it is possible to identify non-responders to antiemetic therapy on a pharmacogenetic basis and to efficiently select a suitable therapy for a subject, preferably a human, suffering from 'setronetreatable diseases'. Thereby, mistreatment of patients based on wrong medications and the results thereof, such as anticipatory vomiting, insufficient compliance to chemotherapy with subsequent failure to anticancer treatment, and increased costs in health care, can be efficiently avoided. Furthermore, patients that are at high risk can be excluded from therapy prior to the first dose and/or dosage can be adjusted according to the individual’s genetic makeup prior to the onset of drug therapy. Thus, treatment failure can be avoided and the optimal drug level can be reached faster without time-consuming and expensive drug monitoring-based dose finding. This can reduce costs of medical treatment and indirect costs of disease (e.g. shorter time and less frequent hospitalization of patients).

Several documents are cited throughout the text of this specification by name. Each of the documents cited herein (including any manufacturer's specifications, instructions, etc.) are hereby incorporated by reference; however, there is no admission that any document cited is indeed prior art as to the present invention.
The Figures show

**Fig. 1:** Proportion of patients with nausea and vomiting as function of the emetogenic level.

**Fig. 2:** Serum concentrations of tropisetron as function of the number of active genes of CYP2D6 (three and six hours after administration). Given are box plots of plasma concentrations in ng/ml. The difference between concentration of poor metabolizers and all others was significant ($p<0.02$, Mann-Whitney U-test).

**Fig. 3:** Mean values of vomiting in as function of the number of active genes of CYP2D6. Individuals with three active genes had significant more vomiting at both observation periods than all other patients ($p<0.001$, $p<0.02$, Mann-Whitney-U test). A similar observation was made for nausea. The x-axis indicates the number of active CYP2D6 genes. The y-axis of the upper two panels indicate the mean episodes of vomiting. The y-axis of the lower two panels indicate the mean of VAS for nausea (% of scale).

**Fig. 4:** Intensity of vomiting or nausea as a function of the CYP2D6 genotype for patients treated with tropisetron or ondansetron between the 5 to 24 hours after administration of the chemotherapy. The x-axis indicates the number of active CYP2D6 genes. The y-axis indicates the mean episodes of vomiting.

**Fig. 5:** Shows the genomic structure and the polymorphisms found by sequencing of the 5-HT$_{3B}$ receptor gene in 242 cancer patients. Boxes represent the exons and numbers below, the respective number of the exon. Transmembrane domains (TM 1-4) were characterized by black boxes. All polymorphisms are indicated with their respective localization (A of ATG is +1) according to the published sequence (Genbank accession No AP001874.4 (GI: 17425234)).
Fig. 6: Mean values of vomiting with SEM 0 to 4 hours and 5 to 24 hours after administration of the chemotherapy as function of the different genotypes of the -100AAG deletion variant of the 5-HT$_{3B}$ receptor gene. Individuals homozygous for the -100AAG deletion had significant more vomiting at both observation periods than all other patients. A similar observation was made for nausea.
The present invention is illustrated by reference to the following biological Examples which are merely illustrative and are not to be constructed as a limitation of the scope of the present invention.

Example 1

The CYP2D6 polymorphisms are serving as genetic markers for the CYP2D6 metabolic capacity. Haplotypes are defined by certain combinations of SNPs, i.e. the 4168A nucleotide deletion (SEQ ID NO 15) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *3 allele, the 3465G>A nucleotide substitution (SEQ ID NO 13) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *4 allele, the deletion of the entire coding sequence of the CYP2D6 gene (SEQ ID NO 47) forms the *5 allele, the deletion of nucleotide T at position 3326 (SEQ ID NO 09) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *6 allele, the 4554A>C substitution (SEQ ID NO 21) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *7 allele, the 3377G>T nucleotide substitution (SEQ ID NO 11) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *8 allele, the 4469C>T nucleotide substitution (SEQ ID NO 19) of the CYP2D6 gene (Genbank accession No.: GI:181303) in combination with the nucleotide substitutions 1743G>A (SEQ ID NO 03) and 5799G>C (SEQ ID NO 23) of the CYP2D6 gene (Genbank accession No.: GI:181303) is responsible for the *12 allele, the 2502G>C nucleotide substitution (SEQ ID NO 07) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *11 allele, and the insertion of nucleotide T at position 1756/1757 (SEQ ID NO 05) of the CYP2D6 gene (Genbank accession No.: GI:181303) forms the *15 allele all of which are associated with a loss of CYP2D6 enzyme function. Furthermore, the deletion of nucleotides AGA at positions 4232 to 4234 (SEQ ID NO 17) of the CYP2D6 gene (Genbank accession No.: GI:181303) which forms the *9 allele, the combination of nucleotide substitutions 4469G>C (SEQ ID NO 19) with 5799G>C (SEQ ID NO 23) of the CYP2D6 gene (Genbank accession No.: GI:181303) which is responsible for the *2 allele and the combination of the 1719C>T (SEQ ID NO 01) with the 5799G>C (SEQ ID NO 23) nucleotide substitutions of the CYP2D6 gene (Genbank accession No.: GI:181303) which forms the *10 allele, are both associated with the
"intermediate metabolizer" (IM) phenotype, who shows a decreased but still detectable CYP2D6 metabolic activity. The allele lacking all these genetic markers is depicted as *1 or wildtype allele and is associated with the "extensive metabolizer" (EM) phenotype. The current state of the art suggests that EMs are homozygous carriers of *1 alleles or of the heterozygous genotypes *1/*2, *1/*9, and *1/*10. Individuals with two IM-associated alleles (*2, *9, and *10) or heterozygous genotypes consisting of one *1 and one PM-related allele (*3, *4, *5, *6, *7, *8, *11, *12, and *15) are of IM phenotype and individuals with two PM-related alleles are of the PM phenotype. Furthermore, ultrarapid metabolism phenotype (UM) is caused by duplicate or multiple copies of functional active CYP2D6 genes resulting in the presence of a polynucleotide comprising SEQ ID NO: 48 (1xN; 2xN). The amplification of CYP2D6 copies causes the expression of an increases amount of CYP2D6 protein resulting in an increased metabolic CYP2D6 capacity (Johansson, Proc Natl Acad Sci U S A, 90 (1993), 11825-11829; Daly, Pharmacogenetics 6 (1996),193-201; Sachse, Am J Hum Genet 60 (1997), 284-295; Gaedigk, Pharmacogenetics 9 (1999), 669-682; Kubota, Br J Clin Pharmacol 50 (2000), 31-34). By genetic testing prior to onset of treatment with 'setrones', the CYP2D6 metabolic activity of the patients can be predicted and the patients can be classified as either ultra rapid, extensive, intermediate (IM), or poor metabolizers. Based on pharmacokinetic data (Kees, Br J Clin Pharmacol 52 (2001), 705-707; Cox, J Pharmacokinet Biopharm 27 (1999), 625-644; Wada, Bio Pharm Bull 24 (2001), 432-435) and on the experience with other drugs (e.g. amitryptiline, clomipramine, fluvoxamine) which are substrates of CYP2D6 (Brockmöller, Pharmacogenomics 1 (2000), 125-151), the initial dose of 'setrones' for PMs of CYP2D6 should be 50 to 70%, for EMs 100 to 120%, and for UM's >120%, of the average recommended dose to achieve optimal setrone plasma level and therapeutic efficacy. This example is illustrated to merely illustrate the use of pharmacogenetic testing to improve therapeutic use of 'setrones' and are not to be constructed as a limitation of the scope of the present invention.
Example 2
Correlation of effectivity of antiemetic treatment with 5-HT₃ receptor antagonists with CYP2D6 genotypes

PATIENTS: To analyze the effect of CYP2D6 polymorphisms, a prospective non interventional cohort study was performed to analyze the impact of functional polymorphisms of CYP2D6 on the antiemetic efficacy of tropisetron or ondansetron in cancer patients. From April 1998 to September 2000 consecutive adult patients scheduled to receive moderately to highly emetogenic chemotherapy either for the first time, or the first course of a chemotherapy after relapse, were enrolled in the study. We included 270 patients (116 males, 154 females, 157 outpatients and 113 inpatients) at the Universitätsklinikum Charité and the community hospital Krankenhaus Moabit, Berlin, Germany. Mean age of the patients was 53.7 years (range from 18-83 years, standard deviation, SD 13.3). From these, 32.5% suffered from breast cancer, 15.4% from lung cancer, 14.2% from non-Hodgkin's lymphoma, 4.9% from multiple myeloma, 4.9% from Hodgkin's disease and 28.1% from miscellaneous other tumors. Patients who met one of the following criteria were excluded from participation: presence of nausea or vomiting before the chemotherapy, the use of antiemetics, benzodiazepines, neuroleptics or radiation therapy in the 24 hours before administration of the chemotherapy, use of opioids within the last two weeks, regular use of inducers of CYP2D6 (e.g. rifampicin) or inhibitors of CYP2D6 (e.g. quinidine, fluoxetine, haloperidol). We also excluded all patients with presence of concomitant diseases which might cause nausea or vomiting (e.g. severe heart failure, ulcerations or obstructions of the upper gastrointestinal system, severe hepatic or renal dysfunction, brain metastases, patients with artificial stoma or pregnancy). From 286 patients primarily enrolled in the study, 16 patients had later to be excluded for predefined reasons e.g. administration of antiemetics other than ondansetron or tropisetron, missing of antiemetic drug treatment at day one of the chemotherapy or because patients did not complete all questionnaires. Seven patients delivered incomplete data.

TREATMENT AND SIDE EFFECTS: Emetogenic level at the day of the administered anticancer drugs was calculated according to the emetogenic classification scheme of (Hesketh, J Clin Oncol, 15 (1997),103-109, Hesketh,
Oncologist, 4 (1999),191-196) and patients were grouped in five different emetogenic levels 1-5 (level 1: n= 2, level 2: n= 55, level 3: n= 22, level 4: n= 94, level 5: n= 95). Cyclophosphamide was administered to 98 patients (mean dosage 1524 mg) either alone or in combination with various other cytostatic drugs. Cisplatin (mean dosage 90 mg) and carboplatin (mean dosage 448 mg) were given to 27 patients and 29 patients, respectively. All other patients (n= 116) received miscellaneous chemotherapeutic drugs. Glucocorticoids were administered to 151 patients either as a part of the antineoplastic therapy or as additional antiemetic treatment. Tropisetron (Navoban®, Novartis, Switzerland) was given in a dosage of 5 mg once daily (n=96), ondansetron (Zofran®, GlaxoWellcome, UK) was administered in a dosage of 8 mg twice daily (n=174). Measurement of nausea and vomiting were performed immediately before the chemotherapy started, four hours after administration of chemotherapy (observation period 1) and then within the next 20 hours (5th to the 24th hour, observation period 2) at day one of the chemotherapy. The timing within the first 24 hours and number of retching and vomiting episodes were recorded by the patients on diary cards. The intensity of nausea was assessed with the help of visual analogue scales (VAS, which ranged from no nausea at 0 mm to most extensive nausea at 100 mm). An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Vomiting or retching had to be absent for at least one minute to calculate different episodes of emesis according to the definition of the Italian Group for Antiemetic Research (Italian Group for Antiemetic Research, J Clin Oncol, 16 (1998), 2937-42). Protection from nausea was regarded as incomplete when emetic episodes occurred or when nausea intensity was 20% above the baseline level. The study was approved by the ethic committee of the Universitätsklinikum Charité (Humboldt-Universität zu Berlin) and all patients gave written informed consent.

PHARMACOGENETIC AND PHARMAKOKINETIC ANALYSES: To determine the CYP2D6 genotype of the above mentioned study cohort, high-molecular-weight genomic DNA was prepared from venous blood using the standard phenol chloroform extraction. All laboratory staff were blind to the clinical observations. CYP2D6 genotyping was carried out according to Sachse et al. (Sachse, Am J Hum Genet, 60 (1997), 284-295). PCR-products were separated by agarose gel electrophoresis and stained with ethidium bromide for visualization. Alleles *3, *4, *5
and *6 of CYP2D6 were considered to predict the deficient (poor metabolizer, PM) phenotype, whereas the allele *1 and the duplication (2x*1 or 2x*2) of the gene are coding for the active enzyme. By definition, PMs are carriers of two of the alleles *3, *4, *5, and *6 of CYP2D6, intermediate metabolizers (IM) have one active allele *1 (wild type), extensive metabolizers (EM) have two active alleles *1 or one defective allele and one duplication allele, and ultrarapid metabolizers (UM) have one active allele *1 and one duplication allele or even two duplication alleles. Therefore, with respect to the genotype we were able to group the patients into four subgroups which we briefly termed as subjects with no active, one, two or three active genes, also termed as poor metabolizers, intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers. To analyze possible correlations between CYP2D6 genotype, phenotype, and Tropisetron serum concentrations, three hours and six hours after the administration of the 5-HT₃ antagonist tropisetron blood samples were drawn at the arm that had not been used for drug administration. Tropisetron hydrochloride was provided by Novartis Pharma (Basel, Switzerland). Tropisetron was extracted with dichloromethane under alkaline conditions, separated at room temperature on a Phenomenex Luna™ C18 HPLC-column (5 μm, 250 x 4.6 mm I.D., Phenomenex, Aschaffenburg, Germany) and quantified by UV detection at 284 nm. The mobile phase consisted of 20% of acetonitrile and 80% 0.05 M sodium hydrogen phosphate buffer, pH 5.0, the flow rate was 1.5 ml/min. Intra- and inter-assay coefficients of variation ranged from 1.5 to 7.5% and from 5.3 to 13.7% respectively. The lower limit of quantification was 1.25 ng tropisetron/ml.

CYP2D6 GENOTYPE CORRELATION WITH DRUG EFFICACY: Within the first 24 hours after administration of the chemotherapy, vomiting was observed in 58 out of 270 patients (22.1%) and nausea in 94 out of 270 patients (35.9%). The mean number of vomiting episodes and the mean degree of nausea were compared with the Kruskal-Wallis or with the Mann-Whitney-U-tests. The pairwise comparison between groups was performed with the Wilcoxon rank-sum test (SPSS version 8.01). The limit of significance was set to 0.05.

The mean number of vomiting episodes of all 270 patients was 1.0 (range from 0 to 22) and the mean percentages of the VAS for nausea was 15.6% (range from 0.0% to 98%). Fig. 1 shows the data on acute nausea and vomiting stratified for the different emetogenic levels of chemotherapy as classified according to (Hesketh, J
Clin Oncol 15 (1997), 103-109; Hesketh, Oncologist 4 (1999): 191-196). The percentage of patients with incomplete protection from nausea or vomiting appeared to be independent of the respective emetogenic level of the chemotherapy: vomiting ($\geq 1$ episode) was observed in 19.1% of the patients treated with anticancer drugs of the high-emetogenic level five and in 18.9% of the patients treated with the low emetogenic level two (Hesketh, J Clin Oncol 15 (1997), 103-109; Hesketh, Oncologist 4 (1999): 191-196). Nausea occurred in 40.4% of the patients treated with high-emetogenic drugs (level four) and in 37.7% of the patients receiving a low-emetogenic therapy (level two). The results were similar in in- and outpatients. Patients treated with glucocorticoids either as part of their therapeutic regime or as additional antiemetic therapy had a better protection from nausea than patients without glucocorticoids (73.6% versus 51.8%, $p<0.001$, chi-square test). A similar trend was observed for vomiting and for the combined event of nausea and vomiting (detailed data not shown). When stratifying the patients for the emetogenic levels (Table 1), patients treated with a high-emetogenic level 4 chemotherapy without glucocorticoids experienced a two-fold higher intensity of nausea in observation period 1 (mean value 12.8% versus 6.8%, $p<0.02$, Mann-Whitney-U-test) and in observation period 2 (mean value 23.1%, versus 11.9%, $p=0.01$, Mann-Whitney-U-test), than patients with glucocorticoid treatment. A similar trend was observed for vomiting. As shown in Fig. 2, patients deficient for CYP2D6 activity had significantly higher serum concentrations of tropisetron six hours after the administration compared to patients with one or more active alleles (median of the concentration 15.3 ng/ml versus 4.9 ng/ml, $p<0.03$, Mann-Whitney-U-test). The result was similar three hours after the administration (median of concentration of 13.5 ng/ml versus 8.0 ng/ml).

Genotyping for CYP2D6 revealed that 7.8% of the 270 patients were deficient for the CYP2D6 gene (poor metabolizers), 32.6% had one active allele, 58.1% had two active alleles (extensive metabolizers) and 1.5% had three active genes (ultrarapid metabolizers). As shown in Fig. 3, patients with three active CYP2D6 genes (ultrarapid metabolizers) had a significantly higher mean number of vomiting episodes than all other patients in observation period 1 (mean value of episodes of vomiting of 2.3, SD: 2.5 versus 0.2, SD: 1.0, $p<0.001$, Mann-Whitney-U-test) and in observation period 2 (mean value of episodes of vomiting of 3.3, SD 3.5 versus 0.8,
SD: 2.4, p<0.03). A similar trend was observed for nausea: ultrarapid metabolizers had more severe nausea in the two study periods (mean value of nausea 22.3%, SD: 25.9 versus 9.6%, SD: 16.4 and 46.8%, SD: 44.9 versus 15.1%, SD: 22.2, respectively) than all other patients. These results were similar for vomiting and emesis in the group of patients receiving glucocorticoids at both observation periods and in the group of patients who did not receive glucocorticoids.

The effects of the CYP2D6 polymorphisms seen in the whole group of patients were similar in tropisetron treatment and after treatment with ondansetron (Fig. 4), extensive metabolizers had the highest intensity of vomiting or nausea in both groups and observation periods and poor metabolizers showed the lowest intensity of vomiting and emesis during the first observation period. None of the PMs in the tropisetron group showed vomiting, indicating that the diagnosis of CYP2D6 can be utilized to predict together with other genetic factors- the efficacy of antiemetic therapy with Serotonin antagonists. Poor CYP2D6 metabolizers have the highest concentration of 5-HT₃ receptor antagonists in blood and, consequently, the best protection from nausea and vomiting, whereas ultrarapid metabolizers have worse protection from nausea and vomiting when given the standard dose. Because of the observed association between CYP2D6 genotype and nausea and vomiting, CYP2D6 genotyping before starting the chemotherapy provides an improvement over the current therapeutic applications of these antagonists.

Example 3
Correlation of effectiveness of antiemetic treatment with 5-HT₃ receptor antagonists with polymorphisms in the gene encoding the human 5-HT₃B receptor

PATIENTS, STUDY COHORT: We conducted a prospective non interventional cohort study to analyze the impact of genetic polymorphisms on the antiemetic efficacy of the 5-HT₃ receptor antagonists tropisetron and ondansetron in cancer patients. From April 1998 to September 2000 consecutive adult patients scheduled to receive moderately to highly emetogenic chemotherapy either for the first time or the first course of a chemotherapy after relapse were enrolled in the study. We
included 242 patients (105 males, 137 females, 145 outpatients and 97 inpatients) at the Universitätsklinikum Charité and the community hospital Krankenhaus Moabit. Mean age of the patients was 53.3 years (range from 18-83 years, standard deviation, SD 13.6). From these, 32.0% suffered from breast cancer, 16.0% from lung cancer, 15.1% from non-Hodgkin's lymphoma, 5.5% from Hodgkin's disease, 4.6% from multiple myeloma, 4.1% from ovarian carcinoma and 22.7% from miscellaneous other tumors. Patients who met one of the following criteria were excluded from participation: presence of nausea or vomiting within 24 hours prior to chemotherapy, the use of antiemetics, benzodiazepines, neuroleptics or radiation therapy in the 24 hours prior to administration of the chemotherapy, use of opioids within the last two weeks, use of inducers of CYP2D6 (e.g. rifampicin) or inhibitors of CYP2D6 (e.g. quinidine, fluoxetine, haloperidol) which modify the pharmacokinetics of the 5-HT₃ antagonists. We also excluded all patients with presence of concomitant diseases which might cause nausea or vomiting (e.g. severe heart failure, ulcerations or obstructions of the upper gastrointestinal system, severe hepatic or renal dysfunction, brain metastases, patients with artificial stoma or pregnancy). From 258 patients primarily enrolled in the study, 16 patients had later to be excluded for predefined reasons e.g. administration of antiemetics other than ondansetron or tropisetron, missing of antiemetic drug treatment at day one of the chemotherapy or that patients did not completed all questionnaires.

TREATMENT AND SIDE EFFECTS: Emetogenic level at the day of the administered anticancer drugs was calculated according to the emetogenic classification scheme (Hesketh, J Clin Oncol 15 (1997), 103-109; Hesketh, Oncologist 4 (1999): 191-196) and patients were grouped in five different emetogenic levels 1-5 (level 1: n= 1, level 2: n= 50, level 3: n= 17, level 4: n= 83, level 5: n= 91). Cyclophosphamide was administered to 91 patients (mean dosage 1554 mg) either alone or in combination with various other cytostatic drugs. Cisplatin (mean dosage 88 mg) and carboplatin (mean dosage 424 mg) were given to 25 patients and 27 patients, respectively. All other patients (n= 99) received miscellaneous chemotherapeutic drugs. Glucocorticoids were administered to 141 patients either as a part of the antineoplastic therapy or as additional antiemetic treatment. Tropisetron (Navoban®, Novartis, Switzerland) was given in a dosage of 5 mg once daily (n= 84), ondansetron (Zofran®, GlaxoWellcome, UK) was
administered in a dosage of 8 mg twice daily (n= 158). Measurement of nausea and vomiting were performed immediately before administration of the chemotherapeutic agents, four hours after administration of chemotherapy (observation period 1) and then within the next 20 hours (5th to the 24th hour, observation period 2) at day one of the first course of chemotherapy. The timing within the first 24 hours and number of retching and vomiting episodes were recorded by the patients on diary cards. The intensity of nausea was assessed with the help of visual analogue scales (VAS, which ranged from no nausea at 0 mm to most extensive nausea at 100 mm). An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Vomiting or retching had to be absent for at least one minute to calculate different episodes of emesis. Protection from nausea was regarded as incomplete when emetic episodes occurred or when nausea intensity was 20% above the baseline level. Nine patients delivered incomplete data, so that the efficiency of the antiemetic treatment could be analyzed in 233 patients. The study was approved by the ethic committee of the Universitätsklinikum Charité (Humboldt-Universität zu Berlin) and all patients gave written informed consent.

POLYMORPHISMS IN THE 5-HT3B RECEPTOR GENE: High-molecular-weight genomic DNA was prepared from venous blood using the standard phenol chloroform extraction. All laboratory staff were blind to the clinical observations. All sequencing analysis were performed with PCR technology, as is known in the art, from genomic DNA amplification reactions. As shown in Fig. 1, we first amplified exons 1-2, exons 3-6 and exons 7-9. A total number of 242 unrelated subjects were screened for genomic DNA polymorphisms of the 5-HT3B receptor gene by sequencing of the protein coding exons including the exon-intron junctions. This revealed an extensive genetic variation in the 5-HT3B receptor gene (Fig. 1, Table 1, 2). A total number of 13 variations was found and confirmed by repeated analysis. Genotype frequency of the variations varied between 0.4 % and 47.6%. All except for one polymorphism were found in several unrelated subjects. Two of the mutations were amino acid exchanges located in exon five (Tyr129Ser) and in exon six (Ala223Thr). Moreover, two deletion variations, a 3-bp deletion variant (-100AAG deletion) in the promoter region and a 2-bp deletion in intron 5, were found. Particularly frequent were the 26946A>G and the 27721CA insertion/deletion polymorphism with an allele frequency of the more rare allele of 0.4. The Tyr129Ser
polymorphism had a respective allele frequency of 0.3, the 28671A>G of 0.2 and the
-100AAG deletion allele of 0.1. In contrast, the Ala154Ala and the Ala223Thr were less
frequent and were not found in any subject in the homozygous combination.

GENOTYPE_PHENOTYPE CORRELATION: Vomiting, vomiting episodes, and the
degree of side effects were determined for the individuals of the study cohort and
these data were correlated to the identified 5-HT3 receptor genotypes. The
significance of frequency differences of the different genotypes was assessed by
Pearson’s χ² test or, if any cell count was less than 5, by Fisher’s exact test. The
limit of significance was set to 0.05. The mean number of vomiting episodes and the
mean degree of nausea were compared with the Kruskal-Wallis or with the Mann-
Whitney-U-tests. Linkage disequilibrium and estimated haplotypes were assessed
using the linkage utility program Equilibrium HaploType (EH) (Terwilliger and Ott,
Handbook of human genetic linkage. The Johns Hopkins University Press, Baltimore
and London, 1994). The statistical analyses regarding potential genotype-phenotype
associations based on the data that vomiting was observed in 55 out of 233 patients
(22.7%) and nausea in 84 out of 233 patients (35.9%) within the first 24 hours after
administration of the chemotherapy. The mean number of vomiting episodes of all
233 patients in the first and in the second observation period was 0.2 (range from
0.0 to 10) and 0.9 (range from 0.0 to 22). The mean percentages of the VAS for
nausea in the first and in the second observation period was 9.5% (range from 0.0% to
74.0%) and 15.9% (range from 0.0 to 98.0%). Table 3 presents the genotypes
found and relates them with the observed nausea and vomiting during
chemotherapy. Increasing nausea and vomiting was observed with increasing
number of variant alleles for the -100AAG deletion variant and for the 26945 T
variant. The association with the -100AAG deletion variant was clearly statistically
significant.

Patients homozygous for the -100AAG deletion variant showed significantly more
episodes of vomiting than all other patients in the first observation period (mean
value of episodes of vomiting of 1.0, SEM: 0.58 versus 0.23, SEM: 0.07, p< 0.001,
Mann-Whitney-U-test). The same was seen in the second observation period (mean
value of episodes of vomiting of 4.0, SEM: 2.3 versus 0.83, SEM: 0.2, p< 0.04,
Mann-Whitney-U-test). A similar but statistically not significant trend was observed
for nausea in the first observation period: patients homozygous for the deletion
variant suffered from more severe nausea than all other patients (mean value of nausea 42.6%, SEM: 21.3 versus 9.1%, SEM: 1.0). These findings could be observed in patients treated with ondansetron and in patients treated with tropisetron.

ADDITIVE TREATMENT WITH GLUCOCORTICOIDS: Glucocorticoids are a frequent co-medication during antiemetic and cancer therapy. Therefore, it is important to know, whether the function of the -100AAG deletion variant of the 5-HT₃B receptor gene might have an influence on the therapeutic effect of an additive treatment with glucocorticoids: the mean episodes of vomiting increased from patients homozygous for the insertion variant over heterozygous patients to patients which were homozygous for the deletion variant at observation period 1 (0.2, SD: 0.8; 0.3, SD: 1.2; 1.0, SD: 1.0, p< 0.001, Kruskal Wallis-test) and at observation period 2 (0.5, SD: 1.5; 1.3, SD: 3.1; 4.0 SD: 5.3, p < 0.03, Kruskal Wallis-Test, Table 4). Table 4 also illustrates, that the association of the -100AAG deletion variant with the antiemetic outcome is not the result of differences in the emetogenic level of the chemotherapy: only patients homozygous for the deletion variant had the highest scores of vomiting or nausea when receiving a combined chemotherapy of the emetogenic level of four or five. All other patients with the same emetogenic level showed had lower intensities of vomiting and nausea. In conclusion of table 4, the effect of the -100AAG deletion variant is not due to confounding influences by drug metabolism, steroid medication or emetogenic potential.

HAPLOTYPE ANALYSES: Not only single functional polymorphisms, but also the pattern of linkage of polymorphisms, represented in individual haplotypes (known to experts in the field) can be important in determining the activity or inactivity of medications. For the haplotype analyses of the 5-HT₃B receptor gene, we included only those variants in the linkage analysis with a frequency higher than 1% for the heterozygous genotype. These eleven polymorphisms within or near the 5-HT₃B receptor gene are partially linked. The Tyr₁₂₉Ser variant was in strong linkage disequilibrium with all other mutations except the Ala₁₅₄Ala, 27978A>T and the 37912C>T variation. The -100AAG deletion variant however was only linked with the 26946A>G, Tyr₁₂₉Ser, 27721CA deletion and the 27978A>T polymorphism.
### Table 1

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### Table 2

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Table 3. Polymorphisms genotype frequency in all patients and efficacy of the antiemetic treatment as function of the 5-HT\textsubscript{3} polymorphisms at both observation periods (0-4 and 5-24 hours). Given are the mean value and standard deviation (SD).

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Ins., insertion; del., deletion.
Table 4. Confounding effect of CYP2D6 genotypes, administration of glucocorticoids and emetogenic level of the chemotherapy. Given are the mean value and standard deviation (SD).

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0= no active CYP2D6 gene, 1 = one active-, 2 = two active-, 3 = three active CYP2D6 gene. **Emetogenic level of the combined chemotherapy according to Hesketh, J Clin Oncol 15 (1997), 105-109 and Hesketh, Oncologist 4 (1999), 191-196. Ins., insertion; del., deletion.
49

Claims

1. Use of 'setrones' for the preparation of a pharmaceutical composition for treating and/or preventing 'setrone-treatable diseases' in a subject having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6 polypeptide.

2. The use of claim 1, wherein said subject is having in its genome at least one first variant allele selected from a group consisting of: the allele CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*11, CYP2D6*12 and CYP2D6*15.

3. The use of claim 1 or 2, wherein said subject is having in its genome at least one first variant allele selected from a group consisting of: the allele CYP2D6*1, CYP2D6*2, CYP2D6*9 and CYP2D6*10.

4. Use, preferably of any one of claims 1 to 3, of 'setrones' for the preparation of a pharmaceutical composition for treating and/or preventing 'setrone-treatable diseases' in a subject having in its genome a second variant allele which comprises at least one
   a) polynucleotide having the nucleic acid sequence of SEQ ID NO: 026, and
   b) polynucleotide capable of hybridizing to a HTR3B gene, wherein said polynucleotide is having at a position corresponding to position 36678 to 36680 of the HTR3B gene (Genbank accession No.: GI:17425234) an AAG.

5. The use of any one of claims 1 to 3, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first variant allele compared to the corresponding wild type alleles.

6. The use of claim 5, wherein said altered expression is decreased expression.
7. The use of any one of claims 1 to 3, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first variant allele compared to the polypeptide encoded by the corresponding wild type allele.

8. The use of claim 7, wherein said altered activity is decreased activity.

9. The use of any one of claims 1 to 8, wherein said subject is an animal.

10. The use of any one of claims 1 to 8, wherein said subject is a human.

11. The use of claim 10, wherein said human is Asian.

12. The use of claim 11, wherein said Asian is Chinese.

13. Use of ‘setrones’ for the preparation of a pharmaceutical composition for treating and/or preventing ‘setrone-treatable diseases’ in a subject not having in its genome a polynucleotide associated with an ultrarapid metabolizer phenotype of CYP2D6.

14. A method for selecting a suitable therapy for a subject suffering from ‘setrone-treatable diseases’, wherein said method comprises:
   (a) determining whether a subject is having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6;
   (b) determining the presence or absence of a first and/or second variant allele in the genome of a subject in a sample obtained from said subject; and
   (c) selecting a suitable therapy for said subject based on the results obtained in (a).

15. A method of treating and/or preventing ‘setrone-treatable diseases’ comprising:
   (a) determining whether a subject is having in its genome less than three copies of a polynucleotide encoding a functional CYP2D6;
(b) optionally determining the presence or absence of a first and/or second variant allele comprising a polynucleotide referred to herein; and

(c) administering to a subject a therapeutically effective dosage of 'setrones'.

16. A method of preventing and/or treating 'setrone-treatable diseases' in a subject which comprises internally administering to the subject an effective amount of 'setrones', wherein the treatment regimen is modified based upon the genotype of the subject's CYP2D6 and/or HTR3B gene.

17. A method for determining whether a subject is at risk for non-response to treatment with 'setrones' which comprises determining if the subject has one or more variant alleles of the CYP2D6 and/or HTR3B gene.

18. The method of any one of claims 15 to 17 wherein treating and/or preventing 'setrone-treatable diseases' are postoperative nausea and/or vomiting, or nausea and/or vomiting secondary to cancer chemotherapy, radiation therapy, migraine, acetaminophen poisoning, prostacyclin therapy, and opioid treatment, spinal or epidural opioid-related pruritus, acute levodopa-induced psychosis, bulimia nervosa, fibromyalgia, chronic fatigue syndrome, obsessive-compulsive disorders, schizophrenia, alcoholism, cocaine addiction, opioid withdrawal syndrome, drug withdrawal phenomena, anxiety disorders, cognitive disturbances, neuroleptic-induced tardive dyskinesia, tourette's syndrome, migraine headache, and gastrointestinal motility disorders.

19. The method of any one of claims 15 to 17 wherein 'setrones' are ondansetron, tropisetron, dolasetron, granisetron, azasetron, itasetron, ramosetron, palonosetron, lerisetron, zatosetron, clinasetron, alosetron hydrochloride and ricasetron.

20. The method of any one of claims 15 to 17 wherein the subject does not have in its genome a polynucleotide associated with an ultrarapid metabolizer phenotype of CYP2D6.
21. The method of any one of claims 15 to 17 wherein the subject has in its genome less than three copies of a polynucleotide encoding a functional CYP2D6 polypeptide.

22. The method of any one of claims 15 to 17 wherein the subject having in its genome a
(a) polynucleotide having the nucleic acid sequence of SEQ ID NO: 026, and
(b) polynucleotide capable of hybridizing to a HTR3B gene, wherein said polynucleotide is having at a position corresponding to position 36678 to 36680 of the HTR3B gene (Genbank accession No.: GI:17425234) an AAG.
Fig. 1

Nausea

- All patients

Vomiting

- All patients

Emetogenic level

% of patients with nausea
Fig. 2

3 hours after administration

Tropisetron serum conc., µg/l

Number of active CYP2D6 genes

6 hours after administration

p < 0.03

Number of active CYP2D6 genes
Fig. 6

0-4 hours after chemotherapy

5-24 hours after chemotherapy
EPIDAUROS Biotechnologie AG

Means and methods for improved treatment using 'setrones'

G1818PCT

EP 02011491.4
2002-05-24

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PatentIn version 3.1

1
21
DNA
Homo sapiens

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2
21
DNA
Homo sapiens

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3
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**Homo sapiens**
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### INTERNATIONAL SEARCH REPORT

**International Application No**

**PCT/EP 03/05366**

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#### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC.

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbol)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

| EPO-Internal, WPI Data, PAJ |

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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#### Date of the actual completion of the international search

24 September 2003

#### Date of mailing of the international search report

08/10/2003

**Name and mailing address of the ISA**

European Patent Office, P.O. Box 5000 2280 AG, NL-2280 HU, The Hague

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**Authorized officer**

Stienon, P

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