(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2012 (15.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/154779 A1

(51) **International Patent Classification**:
*A61K 31/216* (2006.01) *A61K 9/00* (2006.01)
*A61K 31/4178* (2006.01) *A61P 13/10* (2006.01)

(21) **International Application Number**:
PCT/US2012/037014

(22) **International Filing Date**:
9 May 2012 (09.05.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/484,662 10 May 2011 (10.05.2011) US

(71) **Applicant** *(for all designated States except US)*: **THERAVIDA. INC.** [US/US]; 800 West El Camino Real, Suite 180, Mountain View, CA 94040 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **PABORJI, Mehdi** [US/US]; 10351 Byrne Ave., Cupertino, CA 95014 (US). **DUCHIN, Kenneth, L.** [US/US]; 9236 Isles Cay Drive, Delray Beach, FL 33446 (US). **HERNANDEZ, Wendy, Jade, Limayo** [US/US]; 11 Alverno Court, Redwood City, CA 94061 (US). **FLUGEL, Roger, S.** [US/US]; 11 Alverno Court, Redwood City, CA 94061 (US).

(74) **Agent**: **TAHMASSEBI, Sam, K.**; TechLaw LLP, 10755 Scripps Poway Parkway, Suite 465, San Diego, CA 92131 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

— *with international search report (Art. 21(3))*

WO 2012/154779 A1

(54) **Title**: COMBINATIONS OF OXYBUTYNIN AND SALIVARY STIMULANTS FOR THE TREATMENT OF OVERACTIVE BLADDER

(57) **Abstract**: Disclosed herein are pharmaceutical compositions comprising a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof. Also disclosed herein are methods of treating a patient suffering from overactive bladder, the method comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof. Also disclosed herein are methods of alleviating a side effect of treatment for overactive bladder in a patient suffering therefrom, the method comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof.

# COMBINATIONS OF OXYBUTYNIN AND SALIVARY STIMULANTS FOR THE TREATMENT OF OVERACTIVE BLADDER

## RELATED APPLICATIONS

**[001]** This application claims priority to U.S. Provisional Application No. 61/484,662, filed May 10, 2011, by Mehdi Paborji et al., and entitled "COMBINATIONS OF OXYBUTYNIN AND SALIVARY STIMULANTS FOR THE TREATMENT OF OVERACTIVE BLADDER," which is incorporated herein by reference in its entirety.

## FIELD OF THE INVENTION

**[002]** The present invention is in the field of pharmaceutical compositions and methods of using the same for the treatment of overactive bladder and reduction of various side effects thereof.

## BACKGROUND OF THE INVENTION

**[003]** Overactive bladder (OAB) is characterized by involuntary contractions of the detrusor muscle during bladder filling. These contractions may be asymptomatic or may cause the three common symptoms that clinically define OAB: frequency of urination; urgency; and urge, or reflex incontinence. Frequency is an increase in the number of micturitions, to as many as eight or more a day. Urgency is the strong and sudden desire to urinate. Urge incontinence, or reflex incontinence, is the situation where the urge to urinate cannot be controlled and the patient wets his/her clothing. Nocturia, or nighttime urinary frequency that disturbs sleep (more than twice a night), is often included as a fourth symptom. The symptoms of OAB may appear individually or together, and it is not known whether they have a pathologic or neurogenic cause.

**[004]** Several classes of medications have been used to treat and manage OAB, including antimuscarinic agents. Antimuscarinic agents, which exert their effects at muscarinic receptors and suppress or diminish the intensity of involuntary detrusor muscle contractions, are the first-choice pharmacotherapy for OAB, and may be the only therapy available whose efficacy is not in question. Oxybutynin chloride is an extensively studied antimuscarinic agent. A major limitation of the use of oxybutynin is that it lacks specificity for bladder tissue, with resultant bothersome side effects, such as dry mouth, constipation, effects on cognition, impaired sleep, etc.

## SUMMARY OF THE INVENTION

**[005]** Disclosed herein are pharmaceutical compositions comprising a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist. Also disclosed herein are methods of treating a patient suffering from overactive bladder, the method comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of extended release oxybutynin (e.g. Ditropan® XL), or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist. Also disclosed herein are methods of alleviating a side effect of treatment for overactive bladder in a patient suffering therefrom, the method comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[006]** Figure 1 is a graph showing the results of a clinical study on saliva formation when the subject was given a) no drug (▲); b) 10 mg Ditropan® XL (•); and c) 10 mg Ditropan® XL followed by 10 mg of pilocarpine 6 hours after the administration of oxybutynin (◆).

**[007]** Figure 2 is a graph showing the results of a clinical study on saliva formation when the subject was given a) no drug (▲); b) 10 mg Ditropan® XL (•); and c) 10 mg Ditropan® XL followed by 10 mg of pilocarpine 3.5 hours after the administration of oxybutynin (■).

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

**[008]** The major limitations of treatment of overactive bladder (OAB) are the dry mouth and constipation side effects. The current approach to address the dry mouth is development of sustained release of the active moiety, such as oxybutynin in the form of Ditropan® XL, which is disclosed in U.S. Patent 6,262,115, incorporated by reference herein in its entirety. However, patients taking the long-acting sustained release formulation of oxybutynin still suffer from these side effects and thus their quality of life is hampered significantly to the extent that the majority of patients discontinue the mediations after about 4-6 months.

**[009]** Thus, in the first aspect, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a sustained release formulation of oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist.

**[0010]** Oxybutynin, which has the chemical name 4-diethylaminobut-2-ynyl2-cyclohexyl-2-hydroxy-2-phenyl-ethanoate, is a muscarinic receptor antagonist and is the active ingredient found in the product Ditropan® XL (as oxybutynin chloride).

**[0011]** Within the context of the present disclosure, a "muscarinic agonist" is a compound that modulates, i.e., agonizes, the activity of a muscarinic receptor either directly or indirectly. A muscarinic agonist acts directly on the muscarinic receptors when the muscarinic agonist itself binds to the muscarinic receptor and modulates its activity. A muscarinic agonist acts indirectly on the muscarinic receptors when the muscarinic agonist stimulates the production of an endogenous muscarinic agonist, which in turn agonizes the muscarinic receptors. An endogenous muscarinic agonist is a natural binding partner of the muscarinic receptors and is produced by the body of the subject itself. An example of an endogenous muscarinic agonist is acetylcholine.

**[0012]** In certain embodiments, the muscarinic agonists selected from the group consisting of pilocarpine, cevimeline, anethole trithione, aclatonium napadisilate, and yohimbine, or a pharmaceutically acceptable salt or prodrug thereof. In further embodiments, the muscarinic agonist is pilocarpine, or a pharmaceutically acceptable salt or prodrug thereof. In other embodiments, the second compound is cevimeline, or a pharmaceutically acceptable salt or prodrug thereof.

**[0013]** The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, succinic acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as

dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl) methylamine, and salts thereof with amino acids such as arginine, lysine, and the like.

**[0014]** Throughout the present disclosure, when a particular compound is named, it is understood that the name refers to both the free base, or free acid, of the compound, and the pharmaceutically acceptable salts thereof. Thus, for example, the scope of the term "oxybutynin" covers both the free base of oxybutynin, i.e., 4-diethylaminobut-2-ynyl2-cyclohexyl-2-hydroxy-2-phenyl-ethanoate, and its various pharmaceutically acceptable salts, for example oxybutynin chloride.

**[0015]** The compounds useful for the compositions and methods described herein may be used in various formulations. Certain formulations affect the rate at which the compound enters the blood stream of the patient. Thus, some formulations are immediate release formulations while other formulations are delayed release, sustained release, or extended release formulations.

**[0016]** Thus, in some embodiments, disclosed herein are combinations where oxybutynin, or a pharmaceutically acceptable salt thereof, is in an extended release formulation, while the muscarinic agonist is in an immediate release formulation. In other embodiments, both oxybutynin, or a pharmaceutically acceptable salt thereof, and the muscarinic agonist are in an extended release formulation.

**[0017]** By "extended release formulation" of oxybutynin it is meant a formulation of oxybutynin, similar to that found in Ditropan® XL, where oxybutynin is administered once a day.

**[0018]** The compositions described herein are particularly useful in alleviating the major side effects in the treatment of OAB, namely dry mouth, discomfort around the mouth, difficulty speaking secondary to dry mouth, degree of difficulty chewing food secondary to dry mouth, and/or lack of quality of sleep, improving tolerability, and enhancing patient compliance while increasing the patient's quality of life.

**[0019]** In another aspect, the present invention relates to a method of treating a patient comprising administering to a patient in need thereof a therapeutically effective amount of a sustained release formulation of oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist.

**[0020]** A patient in need of the treatment methods disclosed herein may be a patient who suffers from overactive bladder. The patient may also be one who finds current therapies for overactive bladder uncomfortable and/or the side effects of the

therapy, such as the dry mouth, intolerable enough so as to require adjunct therapy to alleviate the side effects. The patient may also be one who is considering discontinuing therapy for overactive bladder due to the side effects of the therapy. In some embodiments, a patient who is recently diagnosed with overactive bladder but yet has not been treated therefor is a patient in need of the treatment methods and compositions disclosed herein. In these embodiments, the patient begins the therapy using the methods and combinations disclosed herein so that the patient does not experience any of the side effects, or experience the side effects to a lesser degree.

**[0021]** In some embodiments oxybutynin, or a pharmaceutically acceptable salt thereof, and the muscarinic agonist are administered more or less simultaneously. In other embodiments oxybutynin, or a pharmaceutically acceptable salt thereof, is administered prior to the muscarinic agonist. In yet other embodiments, oxybutynin, or a pharmaceutically acceptable salt thereof, is administered subsequent to the muscarinic agonist.

**[0022]** It should be noted that simply taking commercially available the muscarinic agonist, e.g., pilocarpine HCl, e.g., Salagen® tablets, or any other salivary gland stimulants in conjunction with an OAB drug is not effective to alleviate the dry mouth side effect. The disclosed methods of therapy and therapeutic combinations are directed to matching the pharmacokinetic profile of the muscarinic agonist with the pharmacokinetic profiles of oxybutynin, or a pharmaceutically acceptable salt thereof.

**[0023]** The present inventors have surprisingly discovered that if the extended release formulation of oxybutynin, or a pharmaceutically acceptable salt thereof, and the muscarinic agonist are administered such that the peak plasma concentration for oxybutynin occurs at nearly the same time after administration as the peak plasma concentration for the muscarinic agonist, then the patient will not receive the most efficacious combination of the two compounds. That is, in this situation, the patient still suffers from dry mouth and the related side effects that would render the patient uncomfortable. Instead, if the two compounds are administered such that the peak plasma concentration for the muscarinic agonist occurs at a time before the peak plasma concentration for oxybutynin, then the patient receives the maximum therapeutic effect of the combination.

**[0024]** Similarly, if the extended release formulation of oxybutynin, or a pharmaceutically acceptable salt thereof, and the muscarinic agonist are administered

such that the time point at which the lowest saliva flow occurs because of the action of oxybutynin nearly corresponds to the time point at which the highest saliva flow occurs because of the action of the muscarinic agonist, then the patient will not receive the most efficacious combination of the two compounds. Instead, if the two compounds are administered such that the time point at which the lowest saliva flow occurs because of the action of oxybutynin after the time point at which the highest saliva flow would have occured because of the action of the muscarinic agonist in the absence of oxybutynin, then the patient receives the maximum therapeutic effect of the combination.

**[0025]** In some embodiments in the above methods, oxybutynin, or a pharmaceutically acceptable salt thereof, and the muscarinic agonist are administered such that the ratio of their plasma concentrations, at a given point in time following their administration, is a predetermined value. Those of ordinary skill in the art recognize that the ratio of plasma concentrations is not necessarily the same as the ratio of the amount of compound administered. Compounds are digested differently in the gut, pass the gut wall differently, and have a different rate of first-pass metabolism in the liver. Furthermore, the clearance rate by the kidney is different for various compounds. Thus, for example, even if two compounds are administered in equivalent molar amounts, their plasma concentrations at a point in time after the administration may be significantly different. The methods disclosed herein take into account the pharmacokinetics of drug intake and metabolism, such that the ratio of the two compounds at the time of administration is adjusted so that the two compounds would have a predetermined concentration ratio in the plasma.

**[0026]** Thus, the two compounds may be administered simultaneously, but be formulated such that the delay in their release causes maximum therapeutic effect for the patient. In some of the embodiments when the two compounds are administered simultaneously, the two compounds are within one dosage form.

**[0027]** In some embodiments the dosage form is designed as sustained release of one agent combined with either sustained release or immediate release of the second agent to ensure maximum therapeutic effect. Further the dosage from can be designed based on the pharmacokinetic profiles where the peak plasma concentration of one compound, for example the muscarinic agonist, corresponds to maximum amount of mouth dryness caused by oxybutynin.

**[0028]** Thus, in another aspect, the present invention relates to a method of increasing intrinsic bladder capacity, comprising administering to a patient in need thereof a therapeutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a muscarinic agonist.

**[0029]** The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as diluents, lubricants, bulking agents, desentegrant or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound, for example oral, exist in the art. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

**[0030]** The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

**[0031]** The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

**[0032]** In certain embodiments, the same substance can act as a carrier, diluent, or excipient, or have any of the two roles, or have all three roles. Thus, a single additive to the pharmaceutical composition can have multiple functions.

**[0033]** The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

**[0034]** The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

**[0035]** Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen and desired pharmacokinetic profiles of each component of combination therapy. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

**[0036]** For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

**[0037]** Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

**[0038]** Many of the compounds used in the pharmaceutical combinations of the invention may be provided as salts with pharmaceutically compatible counterions.

Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, and the like. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acids or base forms.

**[0039]** Typically, the dose range of the composition administered to the patient can be from about 0.010 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. Note that for oxybutynin and the muscarinic agonist, human dosages for treatment of at least some condition have been established. For example, for oxybutynin the preferred dosage is between 0.1 mg to 50 mg, and the more preferred dosage is between 1 mg to 30 mg. Other dose ranges include between 1 to 20 mg, between 2 mg to 17 mg, between 5 to 15 mg, between 7 mg to 15 mg. The dose may also be at 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, or 20 mg. For pilocarpine, the preferred dosage is between 0.1 mg to 50 mg, and the more preferred dosage is between 1 mg to 30 mg. Other dose ranges include between 2 to 20 mg, between 3 to 25 mg, and between 4 to 20 mg. The dose may also be at 1 mg, 2 mg, 3 mg, 4 mg, or 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 13 mg, and 15 mg.

**[0040]** Although the exact dosage can be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.001 mg and 1000 mg of each ingredient, preferably between 0.01 mg and 500 mg, for example 1 to 200 mg or each ingredient of the pharmaceutical compositions of the present invention or a pharmaceutically acceptable salt thereof calculated as the free base or free acid, the composition being administered 1 to 4 times per day or per week. Alternatively the compositions of the invention may be administered by continuous delivery such as sustained, delayed, or extended release, preferably at a dose of each ingredient up to 500 mg per day. Thus, the total daily dosage by oral administration of each ingredient will typically be in the range 0.1 mg to 2000 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a day, a week or more, or for months or years.

**[0041]** The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, , the manner of administration and the judgment of the prescribing physician.

**[0042]** It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present invention. Therefore, it should be clearly understood that the forms of the present invention are illustrative only and are not intended to limit the scope of the present invention.

## Examples

**[0043]** The examples below are non-limiting and are merely representative of various aspects of the invention.

### Example 1: Case Study for a Combination of Oxybutynin and Pilocarpine

**[0044]** In this study, the effect of oxybutynin (Ditropan® XL), pilocarpine, the combination of the two, and placebo was measured in separate, yet identical, studies in a single individual.

### Study Protocol:

**[0045]** The following protocol was for a pilot human study to evaluate the extent of saliva flow rate following the administration of 10 mg Ditropan® XL capsule and 10 mg pilocarpine HCl tablet after about 3.5 or 6 hrs from oxybutynin administration. The subject was a healthy, white, male, 53 years old. The subject performed the following:

1. Fast the night before.
2. No coffee or soda 8 hrs prior to taking the first dose.
3. Record time voiding and measure urine if possible.
4. Record extent of dryness of the mouth (Very dry, dry, and not dry).
5. Record any adverse event.
6. Chew a 1" X 1" piece of Parafilm (American National Can (Neenah, WI 54956) Bar code No. 7-466676999) over 2 minutes.
7. Collect wetted Parafilm and saliva into a tared container (pre-weighed container).
8. Measure the amount of saliva collected.

9. Plot Saliva collected per 2 min time intervals against time.

**[0046]** The subject fasted overnight, but had 240 mL of water 1 hr prior to dose. The water continued ad lib until 1 hr pre and 1 hr post dose, other than 120 mL with Ditropan® XL and 120 mL with 5 mg Salagen tablet. For lunch, the subject consumed a light sandwich. No coffee or soda or alcohol beverages was consumed.

**[0047]** Figure 1 shows three separate lines. The first (▲) is the baseline corrected saliva output for the subject during the course of 12 hours. The subject in this case did not take any medications, but followed the study protocol outlined above with respect to food and fluid intake. As the graph shows, there is a natural variation of less than about ±0.5 g/2 minutes of saliva during the course of the study. The second line (•) is the corrected saliva output for the subject having taken 10 mg Ditropan® XL during the course of 12 hours. The graph shows the extent of saliva output depression caused by oxybutynin. The maximum dry mouth occurs at about 6 hours after the administration of oxybutynin. The third line (◆) shows the corrected saliva output for the subject having taken 10 mg Ditropan® XL followed by 10 mg of pilocarpine 6 hours after the administration of oxybutynin. As can be seen, there is saliva output depression at about the same time as the placebo line and having about the same magnitude. This output depression is followed by an increase in saliva output.

**[0048]** Figure 2 also shows three lines. The first two lines (▲ and •) are identical to those of Figure 1. The third line (■) shows the corrected saliva output for the subject having taken 10 mg Ditropan® XL followed by 10 mg of pilocarpine 3.5 hours after the administration of oxybutynin. As can be seen, the corrected saliva output for the third line follows that of the placebo line, indicating that this combination stabilizes the saliva generation.

**[0049]** The data in the Figures 1-2 are shown in tabular format below. Table 1 lists the absolute values of the weight of the collected saliva (g/2 min) at the various time points for the different study arms.

Table 1

| Time, Hrs | 10D[a] | 10D-10P-3[b] | 10D-10P-6[c] | Baseline | |
|---|---|---|---|---|---|
| | | | | Time Hrs | Weight |
| 0 | 2.485 | 2.400 | 2.480 | 0 | 2.64 |
| 1 | 2.395 | 2.69 | 2.590 | 1 | 3.07 |
| 2 | 2.585 | 2.49 | 2.395 | 2 | 3.04 |
| 2.5 | 2.145 | 2.38 | 2.680 | 3 | 3.12 |
| 3 | 2.58 | 2.235 | 2.260 | 4 | 2.98 |
| 3.5 | 2.705 | 2.61 | 2.400 | 4.5 | 2.87 |
| 4 | 2.41 | 3.235 | 2.390 | 5 | 3.5 |
| 4.5 | 2.09 | 2.785 | 1.725 | 5.5 | 3.3 |
| 5 | 1.8 | 2.59 | 1.900 | 6 | 3.55 |
| 5.5 | 1.69 | 2.36 | 1.500 | 7 | 3.23 |
| 6 | 1.52 | 2.555 | 1.850 | 8 | 2.81 |
| 7 | 2.17 | 2.405 | 3.075 | 9 | 3.02 |
| 8 | 2.265 | 2.5 | 2.785 | 10 | 3.40 |
| 10 | 2.68 | 2.29 | 2.795 | 12 | 2.83 |
| 11 | 2.605 | 2.505 | 2.380 | | |

a: 10D = 10 mg Ditropan® XL
b: 10D-10P-3 = 10 mg Ditropan® XL followed by 10 mg pilocarpine 3.5 hrs after Ditropan® XL.
c: 10D-10P-6 = 10 mg Ditropan® XL followed by 10 mg pilocarpine 6 hrs after Ditropan® XL.

**[0050]** Table 2 lists the baseline corrected values shown in Table 2. To obtain the values in Table 2, the value for time = 0 hours in Table 1 is subtracted from the values for the other time points in each column.

Table 2

| Time, Hrs | 10D[a] | 10D-10P-3[b] | 10D-10P-6[c] | Baseline | |
|---|---|---|---|---|---|
| | | | | Time Hrs | Weight |
| 0 | 0 | 0.000 | 0.000 | 0 | 0 |
| 1 | -0.09 | 0.290 | 0.110 | 1 | 0.426 |
| 2 | 0.1 | 0.090 | -0.085 | 2 | 0.39 |
| 2.5 | -0.34 | -0.020 | 0.200 | 3 | 0.48 |
| 3 | 0.095 | -0.165 | -0.220 | 4 | 0.33 |
| 3.5 | 0.22 | 0.210 | -0.080 | 4.5 | 0.222 |
| 4 | -0.075 | 0.835 | -0.090 | 5 | 0.855 |
| 4.5 | -0.395 | 0.385 | -0.755 | 5.5 | 0.655 |
| 5 | -0.685 | 0.190 | -0.580 | 6 | 0.905 |
| 5.5 | -0.795 | -0.040 | -0.980 | 7 | 0.585 |
| 6 | -0.965 | 0.155 | -0.630 | 8 | 0.164 |
| 7 | -0.315 | 0.005 | 0.595 | 9 | 0.37 |
| 8 | -0.22 | 0.100 | 0.305 | 10 | 0.754 |
| 10 | 0.195 | -0.110 | 0.315 | 12 | 0.184 |
| 11 | 0.12 | 0.105 | -0.100 | | |

**[0051]** As can be seen from the data, the maximum saliva depression point for Ditropan® XL occurs at about 6 hours after its administration. Previous studies, for example Figure 1 of 7,678,821, which figure and the related discussion in the specification are incorporated by reference herein, have shown that maximum saliva output due to 5 mg of pilocarpine occurs about 30 minutes after its administration. One would expect for pilocarpine to retard the saliva depression of Ditropan® XL most effectively, pilocarpine would need to be administered about 30 minutes before the maximum depression point due to Ditropan® XL. That is, one would expect that pilocarpine would need to be administered about 5.5 hours after the administration of Ditropan® XL. However, the results presented herein show unexpectedly that best results are obtained when pilocarpine is administered at about 3.5 hours after the administration of Ditropan® XL.

Example 2: Clinical Study Protocol Synopsis

**[0052]** A study was conducted to evaluate the effect of oxybutynin (Ditropan® XL) and pilocarpine in overactive bladder patients. The objectives of the study were to determine degree of dry mouth after oral administration of oxybutynin and pilocarpine, and to determine the effect of the combination on number of voids, and number of incontinence episodes.

**[0053]** Subjects who have reasonable control of OAB symptoms (urinary frequency $\leq$13 voids/day and $\leq$ 1 incontinence episode/day) and have good tolerability (excluding dry mouth) while taking a stable dose of Ditropan® XL (10 mg/day) were recruited to participate in this evaluation. All subjects were administered Ditropan® XL for at least 4 to 6 weeks before being administered the combination therapy. The subjects were asked to record their OAB symptoms and status of dry mouth symptoms in a 3-day diary.

**[0054]** The subjects were asked to take pilocarpine (5 mg) at 3.5 hours after Ditropan® XL is taken. The combination was given for at least 2 weeks (Period 1) and then continued for another two weeks (Period 2). At the end of each 2-week period, a 3-day diary for voiding function, incontinence episodes, and dry mouth evaluation was collected.

**[0055]** Data related to voiding information were collected in diaries that were recorded over 3 consecutive days at the end of each treatment period. Self-assessments of dry mouth and other related activities/functions were made using validated 100 mm visual analog scales (VAS) that were completed on each of the three diary days. On the VAS, the value of 0 mm meant that there was no adverse symptom, whereas the value of 100 mm meant that the adverse symptom was at a highly intolerable level. The average value obtained over the 3 days was used as the value for the treatment period whether it was baseline (Ditropan® XL alone) or the study periods (combination of Ditropan® XL and pilocarpine).

**[0056]** The mean value ($\pm$ standard deviation (SD)) for each 3-day measurement for each patient was calculated. The data point before the commencement of Period 1 was considered to be baseline. Baseline correction was applied by subtracting the baseline value from the data point at the end of Periods 1 and 2. The baseline corrected values are shown in the tables below.

**[0057]** Table 3 shows the baseline corrected value for the number of voids (micturitions) per day and the number of incontinence episodes (IE) per day. As can be seen, the addition of pilocarpine to Ditropan® XL does not adversely affect the efficacy of Ditropan® XL, because the number of micturitions and IEs do not worsen after the introduction of pilocarpine. Therefore, the addition of a muscarinic agonist to the muscarinic antagonist therapy does not alter the mechanism of action of the antagonist.

**Table 3: Variation of Change from Baseline in Micturition and Incontinence Episodes of Oxybutynin (Ditropan® XL) with Treatment**

| **Subject No.** | **Change from Baseline in Micturition Per Day*** | | | **Change from Baseline in Incontinence Episodes** | |
|---|---|---|---|---|---|
| | **Baseline** | **Period 1** | **Period 2** | **Period 1** | **Period 2** |
| 001 | 0.0 | 1.7 | 1.0 | -0.3 | -0.3 |
| 002 | 0.0 | 1.0 | 0.3 | 0.7 | -0.7 |
| 003 | 0.0 | -1.0 | -1.7 | 0.0 | 0.0 |
| **Mean** | **0.0** | **0.6** | **-0.1** | **0.1** | **-0.3** |
| **SD** | **0.0** | **1.4** | **1.4** | **0.5** | **0.3** |

*Each value represents mean of micturition value per day collected over a 3-consecutive day period.

**[0058]** More significantly, the dry mouth and the related adverse symptoms decrease significantly. Table 4 shows the baseline corrected VAS values for dry mouth. As can be seen, at the end of both Period 1 and Period 2 the VAS value decreases significantly. The data clearly show that pilocarpine can effectively negate the adverse dry mouth effect of Ditropan® XL in this study. It is significant to note that the change from baseline VAS did not change from Period 1 to Period 2, showing that the effect of the addition of pilocarpine to Ditropan® XL-therapy is consistent throughout the study.

**Table 4: Variation of Change from Baseline in VAS Values of Dry Mouth of Treatment with Oxybutynin (Ditropan® XL)**

| Subject No. | Change from Baseline in VAS* | | |
|---|---|---|---|
| | Baseline | Period 1 | Period 2 |
| 001 | 0.0 | -37.7 | -54.0 |
| 002 | 0.0 | -33.3 | -11.7 |
| 003 | 0.0 | -42.0 | -41.3 |
| **Mean** | **0.0** | **-37.7** | **-35.7** |
| **SD** | **0.0** | **4.3** | **21.7** |

*Each value represents mean of VAS scores of dry mouth collected over a 3-consecutive day period.

**[0059]** Table 5 shows the VAS values for other, secondary adverse symptoms related to dry mouth. These include the general feeling in the mouth, quality of sleep, ease of speaking, and ease of swallowing. As the data show, all of these metrics also improved in a sustained and consistent way when pilocarpine was added to Ditropan® XL-therapy.

**Table 5: Variation of Change from Baseline in VAS Values of other Dry Mouth Related Adverse Symptoms of Treatment with Oxybutynin (Ditropan® XL)**

| Subject No. | | Feeling in Mouth | | Sleeping | | Speaking | | Swallowing | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 | Period 1 | Period 2 |
| 001 | 0.0 | -31.7 | -48.7 | -45.7 | -53.0 | -53.3 | -59.7 | -42.3 | -45.3 |
| 002 | 0.0 | -32.7 | -10.7 | -28.7 | -35.7 | -22.7 | -19.0 | -20.0 | -14.7 |
| 003 | 0.0 | -42.7 | -37.3 | -45.7 | -44.0 | -41.0 | -36.3 | -55.0 | -51.0 |
| **Mean** | **0.0** | **-35.7** | **-32.2** | **-40.0** | **-44.2** | **-39.0** | **-38.3** | **-39.1** | **-37.0** |
| **SD** | | **6.1** | **19.5** | **9.8** | **8.7** | **15.4** | **20.4** | **17.7** | **19.5** |

*Each value represents mean of VAS scores collected over a 3-consecutive day period

Example 3: Clinical Study Protocol Synopsis

**[0060]** A study is conducted to evaluate the effect of single doses of extended release formulation of oxybutynin (Ditropan® XL) and pilocarpine, alone and in combination versus placebo on salivary output in healthy volunteers. The objectives of the study are to determine salivary flow and degree of dry mouth after oral administration of Ditropan XL and pilocarpine, alone and in combination, vs. placebo, and to determine the effect of Ditropan XL and pilocarpine, alone and in combination, on urine volume/void and vital signs.

**[0061]** At each treatment period, following an overnight fast, subjects enter the clinic and after baseline measurements have been made, they are randomized to one of the following groups:

- Ditropan® XL (10 mg) followed 3.5 hours later by placebo
- Pilocarpine (5 mg) followed 3.5 hours later by placebo
- Placebo followed 3.5 hours later by placebo
- Ditropan® XL (10 mg) followed 3.5 hours by pilocarpine (5 mg)
- Ditropan® XL (10 mg) followed 6 hours by pilocarpine (5 mg)

**[0062]** The following measurements are made just prior to and at frequent intervals for up to 12 hours post dose:

- Salivary flow is determined by chewing a piece of Parafilm for 2 minutes
- Degree of dry mouth is determined by visual analog scale (VAS)
- Urine volume/void and frequency over 12 hours post dose is measured
- Blood samples are taken for pharmacokinetics at pre-dose, and at , 1, 2, 4, 6, 10, 12 and 24 hours post dose
- Food and water intake are standardized over the first 12 hour period

**[0063]** The study is a double blind, randomized, placebo-controlled, with sequences (5 treatments over 5 weeks) with the drugs being administered orally as a single dose. There is a one-week washout between treatments. The study population is chosen as follows:

- Healthy volunteers
- 12 subjects
- ≥18 years males or non-pregnant females
- Weight 18-28 kg/$m^2$ BMI
- No known allergy to antimuscarinic agents

- No previous history of glaucoma, urinary retention, cardiac arrhythmias
- No OTC medications, nutriceuticals or vitamins within 10 days of study enrollment and throughout the study

**[0064]** Assessments (except for urine output) is performed at: 0.5 hr and within 10 minutes pre-dose, 1, 2, 4, 8, 12, and 24 hours post dose. The following are assessed:

1) Stimulated salivary flow
2) Degree of dry mouth (VAS)
3) Urine volume/void over 12 hours post dose
4) Pharmacokinetics of oxybutynin, active metabolite and pilocarpine

**[0065]** The standard safety precautions, such as physical exam, medical history, con-meds, ECG, hematology, clinical chemistry, urinalysis performed at screening and study termination, urine drug/alcohol screening at pre-dose for each period, vital signs (HR and BP) at: pre-dose, and at 2 hour intervals for 12 hours, and an awareness of adverse events throughout and between study period, are taken.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof.

2. The composition of claim 1, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, and pilocarpine, or a pharmaceutically acceptable salt thereof, are together disposed in the same dosage form.

3. The composition of claim 1, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

4. The composition of claim 1, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, or 20 mg.

5. The composition of claim 1, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

6. The composition of claim 1, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2 mg, 3 mg, 4 mg, or 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 13 mg, and 15 mg.

7. The composition of claim 1, further comprising a pharmaceutically acceptable carrier, diluent, or excipient.

8. A method of treating a patient suffering from overactive bladder, the method comprising

identifying a patient in need thereof, and

administering to the patient a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, and pilocarpine, or a pharmaceutically acceptable salt thereof, are together disposed in the same dosage form.

10. The method of claim 8, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, and pilocarpine, or a pharmaceutically acceptable salt thereof, are administered separately.

11. The method of claim 8, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

12. The method of claim 8, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, or 20 mg.

13. The method of claim 8, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

14. The method of claim 8, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2 mg, 3 mg, 4 mg, or 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 13 mg, and 15 mg.

15. A method of alleviating a side effect of treatment for overactive bladder in a patient suffering therefrom, the method comprising

identifying a patient in need thereof, and

administering to the patient a therapeutically effective amount of extended release oxybutynin, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of pilocarpine, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, and pilocarpine, or a pharmaceutically acceptable salt thereof, are together disposed in the same dosage form.

17. The method of claim 15, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

18. The method of claim 15, wherein oxybutynin, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, or 20 mg.

19. The method of claim 15, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose of between 0.1 mg to 50 mg.

20. The method of claim 15, wherein pilocarpine, or a pharmaceutically acceptable salt thereof, is present in a dose selected from the group consisting of 1 mg, 2

mg, 3 mg, 4 mg, or 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 13 mg, and 15 mg.

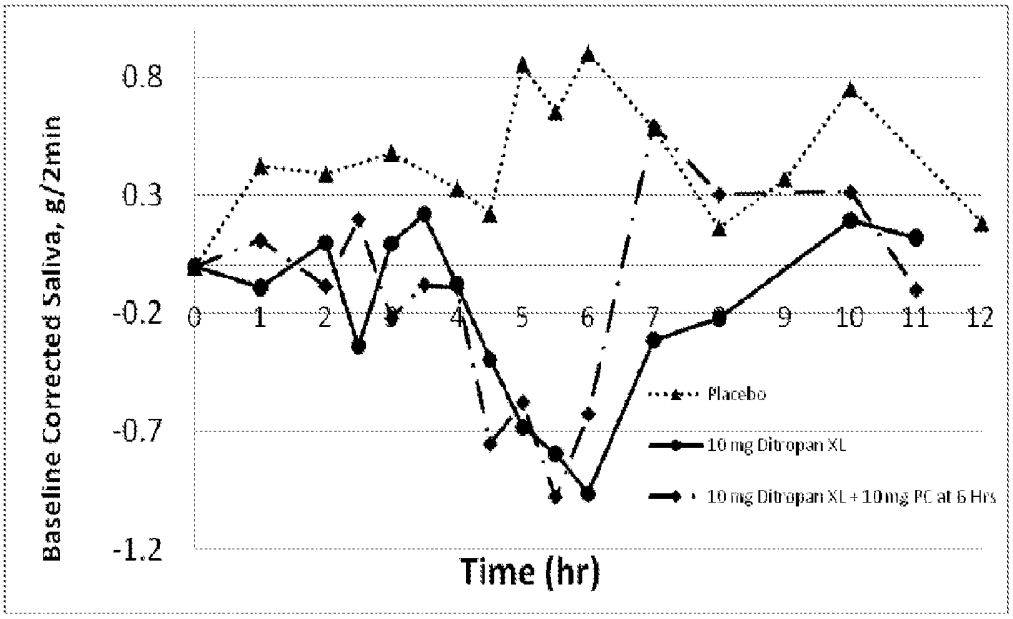


FIGURE 1

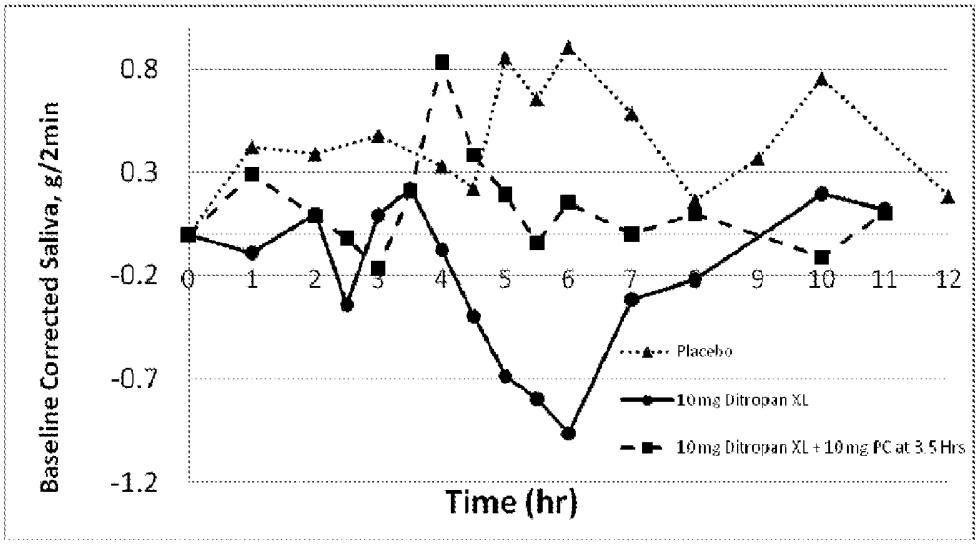


FIGURE 2

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/037014

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/216 A61K31/4178 A61K9/00 A61P13/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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 practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2007/053995 A1 (PABORJI MEHDI [US])<br>8 March 2007 (2007-03-08)<br>page 6, paragraphs 75, 76, 78,79<br>pages 9,10; examples 1, 3, 4<br>page 5, paragraph 56<br>page 6, paragraphs 68,69<br>page 8, paragraph 108<br>----- | 1-20 |
| X,P | WO 2011/123815 A1 (THERAVIDA INC [US];<br>PABORJI MEHDI [US]; FLUGEL ROGER S [US])<br>6 October 2011 (2011-10-06)<br>page 8, paragraph 32<br>pages 11,12, paragraph 45<br>pages 2,3, paragraph 10<br>page 16, paragraph 67<br>pages 10,11, paragraphs 41,42<br>-----<br>-/-- | 1-20 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 27 June 2012 | 04/07/2012 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Opravz, Petra |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/037014

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,P | WO 2011/123836 A2 (THERAVIDA INC [US]; PABORJI MEHDI [US]; TUOHY III ROBERT V [US]; FREED) 6 October 2011 (2011-10-06)<br>page 1, paragraph 2<br>page 2, paragraphs 6,7<br>page 15, paragraph 49<br>----- | 1-20 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/037014

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2007053995 A1 | 08-03-2007 | AT 506059 T | 15-05-2011 |
| | | AU 2006284940 A1 | 08-03-2007 |
| | | BR PI0615432 A2 | 17-05-2011 |
| | | CA 2619565 A1 | 08-03-2007 |
| | | CN 101287462 A | 15-10-2008 |
| | | DK 1933833 T3 | 25-07-2011 |
| | | EP 1933833 A1 | 25-06-2008 |
| | | ES 2365161 T3 | 23-09-2011 |
| | | JP 2009507021 A | 19-02-2009 |
| | | KR 20080059155 A | 26-06-2008 |
| | | NZ 565840 A | 29-07-2011 |
| | | PT 1933833 E | 08-07-2011 |
| | | US 2007053995 A1 | 08-03-2007 |
| | | US 2009275629 A1 | 05-11-2009 |
| | | US 2009318522 A1 | 24-12-2009 |
| | | US 2010137392 A1 | 03-06-2010 |
| | | US 2010152263 A1 | 17-06-2010 |
| | | WO 2007027675 A1 | 08-03-2007 |
| | | ZA 200802811 A | 30-09-2009 |
| WO 2011123815 A1 | 06-10-2011 | US 2011245294 A1 | 06-10-2011 |
| | | WO 2011123815 A1 | 06-10-2011 |
| WO 2011123836 A2 | 06-10-2011 | AU 2010201841 A1 | 20-10-2011 |
| | | GB 2479213 A | 05-10-2011 |
| | | KR 20110116174 A | 25-10-2011 |
| | | SG 174658 A1 | 28-10-2011 |
| | | US 2011244051 A1 | 06-10-2011 |
| | | WO 2011123836 A2 | 06-10-2011 |