SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Emselex. For information on changes after approval please refer to module 8.

1. Introduction

Novartis Pharma AG has submitted a Marketing Authorisation Application through the Centralised Procedure, for the medicinal product EMSELEX, containing darifenacin hydrobromide. The applied indication is "symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome"

This is a complete and independent marketing authorisation application, as stated in Art. 8 (3) of Directive 2001/83/EC, as amended. The provided data cover all aspects of the clinical characterization of safety and efficacy of darifenacin. The applicant has submitted the results of non-clinical and clinical studies carried out for the application.

Urinary incontinence is defined by the International Continence Society[1] as the complaint of any involuntary leakage of urine. It is a common and chronic condition in women. While not life-threatening, it can have a significant negative impact on the psychological well-being, social functioning and overall quality of life of those affected.

The ability to hold urine and maintain continence is dependent on normal function of the lower urinary tract, the kidneys, and the nervous system. The bladder's ability to fill and store urine requires a functional sphincter and a stable bladder wall muscle (detrusor).

Two phases are involved in the process of urination: the filling and storage phase and the emptying phase.

Undesired bladder muscle contraction may occur as the result of a break in the neurological pathway from the brain to the bladder. It can also occur if the bladder is irritated and the normal neurological impulses to inhibit urination are insufficient to keep the bladder relaxed as it fills.

Incontinence can be broadly divided into two main types: stress (effort) and urge incontinence. The term mixed incontinence denotes the concomitant appearance of stress and urge incontinence.

Stress urinary incontinence is defined by the International Continence Society as the complaint of involuntary leakage of urine on effort or exertion, or on sneezing or coughing.

Urge urinary incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. The overactive bladder (OAB) syndrome is defined by the symptoms of urinary urgency with or without urge urinary incontinence, usually associated with urinary frequency and nocturia. It is said that about one third of people with OAB have urinary incontinence[2].

Urge incontinence is basically a storage problem in which the bladder muscle contracts inappropriately. Often these contractions occur regardless of the amount of urine that is in the bladder. Urge incontinence may result from neurological injuries (such as spinal cord injury or stroke), neurological diseases (such as multiple sclerosis), infection, bladder cancer, bladder stones, bladder inflammation, or bladder outlet obstruction. The majority of cases are classified as idiopathic.

Recently available epidemiologic studies in which OAB was defined as a symptomatic diagnosis compose of the symptoms of frequency, urgency, and urge incontinence, occurring singly or in combination have found a prevalence of OAB of approximately 16% in adult men and 17% in adult women. [3] However, sex-specific prevalence differed substantially by severity of symptoms. In women, prevalence of urge incontinence increased with age from 2.0% to 19% with a marked increase after 44 years of age, and in men, increased with age from 0.3% to 8.9% with a marked increase after 64 years of age.

[1] Abrams et al. Neurourol Urodyn 2002; 21: 167-178
[2] Herbison et al. BJM 2003; 326.
[3] Staskin et al. Urology 2002 (S5A); 1-6.

Available treatments

- Medicinal products are aimed at relaxing the involuntary contraction of the bladder and include: anticholinergic agents (propantheline), antispasmodic medications (oxybutynin, tolterodine, flavoxate), tricyclic antidepressants (imipramine, doxepin), and beta agonist (terbutaline).

  Oxybutynin and tolterodine are antispasmodic medications and are the most commonly used.

- Surgery.
- Diet: Controlled fluid intake
- Bladder training: Management of urge incontinence usually begins with a program of bladder retraining
- KEGEL exercises. Pelvic muscle training exercises called Kegel exercises are primarily used to treat patients with stress incontinence.
- Biofeedback and electrical stimulation.

EMSELEX 7.5 mg and 15 mg prolonged-release tablets contain the active substance darifenacin hydrobromide or UK-88,525-04, (S)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide equivalent to 7.5 mg and 15 mg of darifenacin, respectively.

Darifenacin is a muscarinic M3 selective receptor antagonist, which is intended for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome

Antimuscarinic agents work on the principle of blocking the binding of acetylcholine to muscarinic receptors. Published data in human bladder tissue show that acetylcholine-induced contractions are mediated by M3 receptors. Parasympathetic muscarinic activity results in a coordinated detrusor contraction and relaxation of the bladder outlet. The symptoms of OAB have been attributed to involuntary contractions of the bladder detrusor muscle during the filling phase of the micturition cycle. This supports the rationale for using a drug that antagonizes the M3-mediated parasympathetic excitation of the detrusor smooth muscle contraction.

The recommended posology is a starting dose of 7.5 mg daily without regard to meals. For those patients requiring greater symptom relief, the dose may be increased to 15 mg daily as early as 2 weeks after starting therapy.

No formal scientific advice has been given by the CPMP for this medicinal product.

Scientific recommendation was given in May 1999 by Sweden and The Netherlands.

A paediatric development programme has been performed but is not included in the actual application for this medicinal product.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

EMSELEX prolonged-release (PR) tablets contain darifenacin hydrobromide equivalent to 7.5 mg and 15 mg of darifenacin free base. Considering the clinical use of the product, the choice of a modified release dosage form is justified on the basis of the intrinsic pharmacokinetics (PK) characteristics and data from a colonic intubation study.

The tablets are round and are differentiated by colour and debossing. The 7.5 mg tablets are white and the 15 mg tablets are light peach. Both tablets are debossed with DF on one side and the strength on the other. The SPC gives details of the formulation excipients, packaging and available presentations.

Active Substance

Darifenacin hydrobromide is described as a white to almost white crystalline powder, slightly soluble in water (6.03 mg/ml). Its aqueous solubility has been found to be pH dependent, with a maximum solubility (8,75 mg/ml) at a pH of 5,0. The molecule has a chiral centre and the S-enantiomer has been selected for commercial development (see pharmaceutical development).

Studies on polymorphism have been carried out and demonstrate that this drug substance is monomorphic and solvated forms have never been detected. The chemical structure is well characterised by means of elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry, X-ray diffractometry. These studies are considered suitable to establish the structure of this active substance.

- Manufacture

Darifenacin hydrobromide is manufactured using a six-step process , five of them involve chemical reactions and the other corresponds to a purification and recrystallisation step. Chiral starting materials are used where appropriate.

- Specification

Apart from the assay (HPLC non-chiral), general tests (IR, optical rotation, residue on ignition, heavy metals and water) are carried out according to well described in-house and PhEur methods.

A reasoned discussion about potential impurities, as indicated in the ICH Guideline Q3A (R), including their origin according to the manufacturing process described and the main degradation pathways, is also provided. All the impurities, except the R-enantiomer, are determined by a well-described HPLC method with a gradient elution system and detection at 230 nm. The R-enantiomer is determined by an isocratic HPLC method using a chiral stationary phase. Butan-2-one as residual solvent is checked by a well-described headspace GC method.

Whilst not having a critical effect on bioavailability, the particle size distribution is also controlled in the specification, in the interests of uniformity.

The specifications established for toxicological batches were less restrictive than the current specifications, and the impurities have been qualified with reference to these tox. studies.

In general, the specification of the active substance was set according to ICH Q3A(R), Q3C and Q6A Guidelines on the base of 15 batches of darifenacin HBr manufactured by the proposed commercial route of synthesis, and is suitable to control the quality of the active substance on a routine basis.

- Stability

Formal stability studies have been performed in accordance with the ICH Q1A (R) guideline.

Long term, intermediate condition and accelerated stability studies have been carried out over 3 batches in relevant containers for marketing. The tests performed were stability indicating (appearance, assay, water, impurities and microbiological examination). The analytical methods used were the same as those used for routine controls. A photostability study was also carried out according to ICH Q1B.

Results up to 24 months for the long term and intermediate conditions studies and up to 6 months for accelerated conditions, using the two packaging materials proposed, are presented. All the results comply with the specifications established and justify the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The decision to select the S-enantiomer of the active substance was based on its potency and selectivity. Subsequently, this isomer has been used throughout the development program. In addition, it does not have the modest interaction with other receptors (α_1 and 5-HT_2), which the R-enantiomer has.

The choice and development of a matrix tablet was justified as follows:

- It was apparent that patients would require dosing three times a day with an immediate-release (IR) formulation to maintain therapeutic plasma concentrations over the entire day. An MR product improved patient compliance.
- Data from a colonic intubation study (study number 137-214) indicated that darifenacin was rapidly and well absorbed from the colon thus offering the opportunity for the drug to be delivered using a modified release formulation.
- A clinical study (study number 137-212) to compare fast, medium and slow releasing MR darifenacin hydrobromide products with an IR capsule demonstrated the benefits to be gained from a MR product. This study concluded that a MR product would provide increased bioavailability, reduced plasma concentration peak : trough ratio and potentially fewer adverse effects than an IR product.

The hypromellose included in the tablet core modifies the release of darifenacin hydrobromide from the matrix tablet formulation and hence is the critical excipient in the formulation. The choice of the concentration and the grade of hypromellose (2208), have been selected on the basis of a clinical study (number 137-212). In addition, comparative dissolution profiles have demonstrated that ± 10% changes in hypromellose concentration have no adverse influence on the in vitro dissolution performance of the tablet.

Also, the impact of various parameters on the dissolution performance of formulation has been studied (e.g. moisture content, particle size distribution, hardness).

- Manufacture of the Product

The manufacturing process is a dry granulation method, via roller-compaction. All clinical batches of the MR tablet formulation have been produced by this roller compacted method.
The manufacturing process involves the blending, screening and blending of all the excipients (except for magnesium stearate), lubrication with 0.5% w/w of the magnesium stearate and dry granulation (by roller compaction and milling). The resultant granules are blended and lubricated with the remaining 0.5% w/w magnesium stearate prior to tabletting on a suitable tablet machine. Finally, the tablets are film-coated.

- Product Specification

The specification for each strength includes criteria to ensure darifenacin hydrobromide MR tablets are well defined and its quality is appropriate for their intended commercial use. The limits are proposed in accord with ICH Quality Guidelines (Q3B and Q6A) and in accord with results obtained for batches manufactured by the proposed commercial manufacturing process at release and the stability programme.

- Stability of the Product

The stability programme was designed to cover 7.5 mg,15 mg and 30 mg tablets in HDPE bottles, Aclar UltRx 2000 and Aclar Rx 160 blisters, according to current ICH guidelines. Although the 30 mg tablets will not be commercialised, data from this strength were provided as supporting information.
Stress testing studies were conducted both in the solid state and in aqueous suspension. The primary degradation products observed on darifenacin hydrobromide MR tablets are the same as those seen in darifenacin hydrobromide drug substance with the following exceptions. Tablets exposed to 5% H_2O_2 and 5% H_2O_2 /1M NaOH resulted in the formation of certain known degradation products, but in elevated amounts as expected. These are detectable by the methodology employed in the formal stability programme.

Nineteen batches under stability study were manufactured using the proposed commercial process, at batch sizes between 9 % and 100% of the intended commercial batch size. Samples were stored under standard ICH accelerated, intermediate and long-term conditions and results up to 24 months were reported in the first evaluation phase, supplemented by additional data up to 36 months in the second phase.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and product are defined and characterised in an acceptable way, typical for a modified release tablet. The product has been developed in a rational way and there are no special characteristics which need additional routine control to be imposed, other than those required by the product release specification.

At the time of the CHMP opinion, a number of minor quality issues having no impact on the benefit/risk balance were unresolved; the applicant committed to resolve these as follow up measures within an agreed timeframe and to submit amending variations if necessary

3. Part III: Toxico-pharmacological aspects

Pharmacology

The Applicant has performed and submitted a number of *in vitro* and *in vivo* studies, covering all aspects non-clinical pharmacology of darifenacin.

- Primary pharmacodynamics

Acetylcholine muscarinic receptors belong to the superfamily of G-protein-coupled receptors. Five subtypes of muscarinic receptors exist in rodents as well as humans and are encoded by distinct genes. The M1, M3 and M5 subtypes are coupled to $G_{q/11}$ and phospholipase C activation, whereas M2 and M4 receptors are coupled to $G_{i/o}$ and *inter alia* adenylyl cyclase inhibition. Although several muscarinic receptor subtypes are expressed in the bladder, it is the M3 subtype that plays a dominant role in the parasympathetic stimulation of its contraction.

- *In vitro* **studies**

Darifenacin has been shown to exhibit M3 receptor selectivity, using radioligand binding and functional studies *in vitro*.

The blockade of muscarinic M3 receptors is the pharmacological basis for the inhibition of involuntary bladder contraction and voiding in OAB patients which in turn attenuates the typical symptoms of OAB, i.e. urinary urgency with or without urge urinary incontinence, usually associated with urinary frequency and nocturia. Therefore, the effectiveness of darifenacin in the treatment of

overactive bladder is linked to its inhibition of involuntary bladder contraction and voiding in OAB patients.

- *In vivo* **studies**

Results from *in vivo* studies in dog and rat also support the *in vitro* observations that darifenacin is a muscarinic antagonist in the bladder.

In anaesthetised dogs, darifenacin i.v. inhibited the bladder contraction induced either by electrical stimulation of nerves or by betanechol i.v. The ID_{50} was 6.7 µg/kg, to be compared to the 100-200 µg/kg oral dose recommended for patients. Inhibition of salivation required 10-fold higher doses, while no increase in heart rate was noticed up to 100 µ/kg i.v. By comparison, for atropine the ID_{50} was 3.9 µg/kg for bladder contraction and 4.7 for salivation, while half-maximal effect on heart rate was obtained at 12.2 µg/kg. In conscious dogs, bladder capacity was measured by cystometry. Its reduction by bethanecol s.c. was inhibited by oral darifenacin in the 0.3-3 mg/kg range. Similar results were obtained in rats, and they were consistent with the antagonism of darifenacin on the bladder.

Darifenacin exhibits functional muscarinic antagonist effects in human and guinea pig bladder and is selective for M3 over M1, M2, M4 and M5 mediated responses. Darifenacin is also active at M3 receptors in the gastrointestinal tract, salivary gland and in the lung. Therefore, adverse effects related to this inhibition cannot be discarded.

Beside the use of more or less specific antagonists and studies of subtype localization in different organs (RT-PCR, immunodetection), gene targeting in mice has been instrumental in defining the physiopathological roles of the various muscarinic receptor subtypes. In particular M3-null mice display bladder distension and impaired contractile response of the detrusor muscle to carbachol (Matsui et al, 2000), a finding consistent with the development of M3 antagonists for treatment of bladder overactivity symptoms.

- Secondary pharmacodynamics

These studies were focused on muscarinic responses in organs other than bladder where M3 receptors are expressed, essentially: gastrointestinal tract, salivary glands, airways and eye

On the gastrointestinal tract, darifenacin is likely to inhibit gastrointestinal motility at the same doses as it inhibits bladder contractility, because both effects are mediated by M_3 receptors. Thus, in the anaesthetised dog, the doses of darifenacin that reduced small intestinal and colonic were similar to those that inhibited bladder contractions. Darifenacin was also a potent inhibitor of food-stimulated small bowel motility when it was administered orally to conscious dogs. These effects are consistent with the potency of darifenacin in the isolated guinea pig ileum.

Darifenacin was, however, comparatively weaker on other parameters of gastrointestinal function that were studied in the pharmacology programme. The results showed that orally administered darifenacin was less potent on all other parameters of gastrointestinal function that were measured – compared to effects on food stimulated motility.

On the salivary gland, darifenacin reduced salivation in anaesthetised and conscious dog studies and in the conscious rat. However, darifenacin was less potent on the salivary gland than on the bladder in both *in vitro* and *in vivo* studies in dog and rat.

Muscarinic M_3 receptors also mediate cholinergic contractile responses of bronchial smooth muscle (Eglen *et al.,* 1996). Darifenacin exerts a potent antagonism of these responses both *in vitro* and *in vivo*. However, this is unlikely to cause side effects in man, as antimuscarinic agents are not reported to cause adverse pulmonary effects in humans. There were no effects of darifenacin on respiration or blood gas exchange in the rat or on respiratory rate in the anaesthetised dog.

- Safety pharmacology

Most of the safety pharmacology studies were not performed in compliance with GLP regulations as they pre-dated the ICH S7A Guidelines on Safety Pharmacology Studies for Human Pharmaceuticals. However, some of the later studies (IC/009/01, IC/012/01, CG/017/01 and IC/001/02) were GLP-compliant. These studies were conducted in response to draft ICH S7B guidelines for assessing the potential for delayed ventricular repolarization by human pharmaceuticals.

The Applicant has developed a range of *in vitro* and *in vivo* studies concerning darifenacin effects on cardiac repolarisation. The results obtained from in vitro studies are apparently contradictory; darifenacin produced a concentration-related inhibition of the amplitude of the hERG potassium current with an IC50 of 77nM. Given these effects, it might be anticipated that darifenacin would also prolong action potential duration (APD) in the canine isolated Purkinje fibre. However, darifenacin caused a concentration-related reduction of APD. Further studies in vivo showed a slight prolongation of the QT intervain dogs, which was observed only at concentrations almost 100-fold above therapeutic levels (8.1% at 25 nM). Moreover, this effect on action potential duration showed no linearity, since a 4-fold increase in exposure to darifenacin resulted in an additional prolongation of 2.9%. These findings suggest that darifenacin has no effects on cardiac repolarisation at therapeutic levels in non clinical trials, the cardiovascular safety margin being enough, and are supportive of the safe use of darifenacin from the cardiovascular point of view.

The haemodynamic effects of darifenacin were evaluated in six studies. No effects were observed at therapeutic dose levels suggesting that antagonism of muscarinic M_3 receptors causes no cardiovascular effect. However, at concentrations above those that will be attained in therapeutic use, darifenacin has the potential to prolong ventricular repolarisation (>86-fold therapeutic levels), and to decrease heart rate and cardiac contractility (>190-fold).

There were no effects of darifenacin on appearance and behaviour in the rat, locomotor activity in the mouse, convulsions in mice induced by electroshock, strychnine or pentetrazole, motor co-ordination in the mouse or alcohol-, pentobarbitone- or hexobarbital-induced sleeping times in the mouse.

In conclusion, darifenacin appears to be devoid of effects on other targets and in particular the possible actions on cardiac channels have been adequately addressed.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction study has been conducted to assess potential interactions of darifenacin with possibly co-administered drugs. The lack of such studies in animals is considered justified taking into account the battery of interaction studies conducted in humans.

- Summary of salient findings

Darifenacin is a selective antagonist of M3 muscarinic receptors of acetylcholine. It is proposed for the treatment of symptoms of overactive bladder, a syndrome defined by urinary urgency with or without urge urinary incontinence, usually associated with urinary frequency and nocturia.
The blockade of muscarinic M3 receptors is the pharmacological basis for the inhibition of involuntary bladder contraction and voiding in overactive bladder (OAB) patients, which in turn attenuates the typical symptoms of OAB (urgency and incontinence).
There is a strong rationale to use M3-selective antagonists for the treatment of symptoms of overactive bladder instead of non-selective antagonists: a similar efficacy but a better tolerance are indeed expected (reduction of some side effects observed with non-selective muscarinic antagonists, especially tachycardia and cognitive dysfunction).

A number of pharmacological studies have been performed to elucidate the antimuscarinic effects of darifenacin in both *in vitro* and *in vivo* test. The *in vivo* studies conducted in rats and dogs show that darifenacin produces antimuscarinic effects on the bladder, and also in digestive tract, salivary gland and lungs in both species. Although adverse events related to the selective inhibition of M3 muscarinic receptors in those organs cannot be discarded, safety studies concerning darifenacin effects on cardiac repolarization do not raise any concern and supports its use in humans, as well as additional studies targeting others systems and organs.

Pharmacokinetics

The nonclinical pharmacokinetic program for darifenacin comprised detailed single dose studies in all toxicology species to define the basic pharmacokinetic parameters and absolute oral bioavailability. This program was supplemented by sampling during repeat-dose toxicology studies to confirm the pharmacokinetics of darifenacin under the actual conditions of safety evaluation. Tissue distribution, metabolism and excretion studies in animal species were also conducted. *In vitro* metabolism studies were used to support the *in vivo* studies, to characterise the enzymes involved in the metabolism of darifenacin and to determine the potential for drug-drug interactions.

Pharmacokinetic studies were performed in mouse, rat, rabbit and dog. The concentration of darifenacin and its metabolites was determined by validated methods: HPLC with UV or fluorescence detection, HPLC-mass spectrometry and TFC (turbulent flow chromatography)-mass spectrometry. [^{14}C]-darifenacin was used in some studies: its radiochemical purity was greater than 95%.

- Absorption- Bioavailability

According to the absorption studies conducted, darifenacin is well absorbed from the gastrointestinal tract in animals and humans and at low doses exhibits extensive first-pass extraction leading to incomplete oral bioavailability mainly in humans. However, in the mouse and the dog as the dose is increased, the hepatic extraction of the compound becomes saturated leading to an increase in the apparent oral bioavailability. Similarly, on multiple administrations to the dog there is a reduction in the hepatic clearance of darifenacin (and hence increased apparent bioavailability).

- Distribution

The plasma protein binding in animal species and human was determined in vitro by equilibrium dialysis at concentrations, which were considered relevant to the concentrations observed in the clinic. Darifenacin was highly bound in the plasma of mouse, rat, dog and human. In rabbit plasma, the free fraction of darifenacin was 0.24.
Darifenacin has been shown to bind predominantly to human α-1-acid glycoprotein in plasma, with a component of binding to serum albumin. According to tissue distribution studies in pigmented rats, darifenacin distributes extensively into tissues despite its high plasma protein binding. Such extensive distribution into tissues is consistent with the lipophilic and basic nature of darifenacin.
Darifenacin presents affinity to melanin, since foci of radioactivity were associated with retina, skin and substantia nigra. This is a common observation for many lipophilic bases, which reversibly bind to tissues containing melanin, and no toxicity has been reported related to this for other substances.

- Metabolism

Darifenacin is extensively metabolized. Studies have been undertaken *in vivo* to identify excreted metabolites and the most significant circulating metabolites in human and toxicology species. *In vitro* studies have been used to identify the cytochrome P450 enzymes involved in darifenacin metabolism, and to examine the potential for drug interactions.

- *In vivo* studies

The human metabolism of darifenacin proceeded by three primary routes. Route A was monohydroxylation in either the dihydrobenzofuran ring to produce UK-148,993 (12% of the dose) or in the phenyl ring (5% of the dose). Route B was dihydrobenzofuran ring opening to produce the diol UK-156,981 (8% of the dose) or the zwitterion UK-222,247 (21% of the dose). Route C was N-dealkylation to produce UK-73,689 (4% of the dose). The latter was further metabolised by glycine conjugation to UK-297,101 (4% of the dose). Further metabolism of UK-148,993 (N-dealkylation) produced a major acidic metabolite UK-346,036 (20% of the dose).

N-dealkylation of darifenacin (route C) splits the molecule into two fragments. UK-73,689 contains the radiolabelled centre. The non-radiolabelled portion, UK-88,862, was determined in urine by a specific assay. The proportion of the dose excreted in human urine as UK-88,862 was 24% in molar terms.
The metabolism of darifenacin in toxicology species was qualitatively similar to that in humans with all three routes apparent. All the metabolites identified in human excreta were present in the excreta of the mouse, the rat and the dog. Thus, the animals used in toxicity testing for darifenacin were exposed to the same metabolites as humans.
Analysis of human plasma identified that the main circulating components following darifenacin administration are UK-73,689, UK-88,862, UK-148,993 and unchanged darifenacin. These components were also identified in animal plasma following darifenacin administration.

- *In vitro* studies

In hepatic microsomal incubations, darifenacin was rapidly metabolised with disappearance half-life values of 6, 15 and 6 minutes in rat, dog and human respectively. This is consistent with the *in vivo* studies, where metabolism has been shown to be the predominant route of clearance for darifenacin. The only metabolites of darifenacin that were formed in human liver microsomes were UK-148,993 and UK-88,862. Further studies showed that the formation of UK-148,993 in human liver microsomes was mediated by high and low affinity components. Inhibition studies showed that the high affinity component comprised of CYP2D6 and CYP3A4 whereas the low affinity component was exclusively CYP3A4. Similar studies on the metabolism of darifenacin to UK-88,862 showed that this route of metabolism is mediated by CYP3A4 only.
Thus, both CYP3A4 and CYP2D6 mediate a large proportion of the human metabolism of darifenacin. As a consequence, the pharmacokinetics of darifenacin are likely to be altered by co-administration of drugs that inhibit either CYP3A4 or CYP2D6. The likely outcome is an increased darifenacin exposure. A number of clinical interaction studies have been performed to investigate this possibility.
Other *in vitro* studies have shown that darifenacin has the potential to inhibit both CYP2D6 and CYP3A4, and UK-148,993 may also inhibit CYP2D6.

- Excretion

The excretion of [14C]-darifenacin has been investigated in the toxicology species at doses within the range used in safety evaluation, and also in male human volunteers. Overall, there were no major differences in the qualitative pattern of excretion between species, genders and routes of administration.
In the rat, the rabbit and the dog, the predominant route of excretion was in the faeces. This probably reflects extensive biliary elimination of darifenacin and its metabolites. This was confirmed in a separate study in the isolated perfused rat liver where 41% of a dose of [14C]-darifenacin was excreted in the bile. In mouse and human, excretion of radioactivity was balanced between urine and faeces.
[14C]-darifenacin and UK-148,993 were secreted in rat milk where concentrations were similar to those in plasma. This is likely to be the case in humans.

- Pharmacokinetic drug interactions

The effect of darifenacin and its circulating metabolites on cytochrome P450 activity has been investigated *in vitro* using a series of substrates. According to the results darifenacin is a potent inhibitor of CYP2D6-mediated metabolism *in vitro*. UK-148,993 also inhibited CYP2D6 metabolism but was 10-fold weaker than darifenacin. UK-88,862 did not inhibit CYP2D6.

Darifenacin also inhibited CYP3A4 and UK-148,993 was found to be a weak inhibitor of CYP3A4. Neither UK-88,862 nor UK-73,689 inhibited CYP3A4 metabolism *in vitro*.
Thus the in vitro data shows that interactions can be expected with the co-administration of CYP3A4 and CYP2D6 substrates/inhibitors with darifenacin. A program of interaction studies has been pursued in the clinical part.

- Summary of pharmacokinetic parameters

The Applicant has performed a classical program of pharmacokinetic studies. Studies were performed in mouse, rat, rabbit and dog. Animal species used in the studies were sufficiently exposed to darifenacin and its metabolites, in relation to highest exposure expected in clinical situation.
Darifenacin shows good oral absorption but extensive first-pass effect, extensive distribution without accumulation, limited distribution in brain, clearance by hepatic metabolism involving CYP3A4 and CYP2D6. *In vitro* studies have shown that darifenacin has the potential to inhibit both CYP2D6 and CYP3A4, and UK-148,993 may also inhibit CYP2D6. In addition, *in vitro* studies show that interactions could be observed upon co-administration of CYP3A4 substrates or inhibitors. Consequently a comprehensive series of clinical drug interaction studies have been performed, since drug interactions are expected.

Toxicology

A complete nonclinical toxicology evaluation programme was carried out with darifenacin in several animal species. The compound was administered as the hydrobromide salt in all studies apart from range-finding studies (repeat-dose, non-pivotal studies) in rats and dogs where the base was used and one of the bacterial mutagenicity assays where the tartrate salt was used. Additional studies were performed with UK-73,689 to comply with the Worker Safety Testing (WST) and Notification of New Substances (NONS), since this compound is a starting material and metabolite of darifenacin in all animal species tested and man. The metabolism of darifenacin in toxicology species was qualitatively similar to that in humans with all three routes apparent. Thus, the animals used in toxicity testing for darifenacin were exposed to the same metabolites as humans.

- Single dose toxicity

The Applicant has conducted a number of studies in mice and rats concerning the single-dose toxicity of darifenacin and its metabolite UK-73,689.
The minimal lethal dose of darifenacin was about 100mg/kg in mice and between 100 and 200mg/kg in rats following single oral administration. Similar clinical signs (tremors, ataxia, depression, dyspnoea, mydriasis and partially closed eyes) were observed in both species, and disappeared within 24 hours, with the exception of mydriasis. The lethal doses were 333-and 667-fold higher in mice and rats respectively, than the maximum recommended human dosage. The non-lethal doses in mice (62.5mg/kg) and rats (100mg/kg) were associated with only minor clinical signs.
Following single intraperitoneal administration, the minimal lethal dose was between 50 and 100mg/kg in mice and about 50mg/kg in rats. Clinical signs were similar to those observed by the oral route. These doses were 333 and 167-fold higher in mice and rats respectively, than the maximum recommended human dosage.
No relevant effects were observed in rats following oral administration of UK-73,689 up to 2000mg/kg

- Repeat dose toxicity

The Applicant has submitted a number of repeat-dose studies, carried out over a dose range of 0.5-100mg/kg in rats and dogs. Most clinical signs observed in treated animals were consistent with the pharmacological activity of the compound.

Adverse effects observed in rats included mydriasis and ptosis from 3mg/kg, hypersecretion of the Harderian gland from 10mg/kg, and difficulties introducing the gavage catheters when dosing from 30mg/kg. Since the Harderian gland is absent in humans, this finding was not considered clinically relevant. Bacterial overgrowth of the non-glandular stomach was considered to be linked to the non-selective antimuscarinic effects on gastric emptying, gastrointestinal motility and/or drying of the mucous membranes. Mortality showed a low incidence (3/5 at 100mg/kg, 2/20 at 50mg/kg and 5/40 at 30mg/kg), and is considered to be associated with the pharmacological activity of the compound. There was a reduction in body weight and food consumption in both sexes, and an increase in water consumption from 10mg/kg in males and from 30mg/kg in females, probably to compensate for the drying of the mucous membranes and to aid chewing of the food. The increase in relative liver weights were not accompanied by any histopathologic changes, and are considered an adaptive response of the liver to enzyme induction. The Applicant considers the effects observed on cardiac parameters such as bradycardia and increase in PR, QRS and RT intervals as a consequence of the poor condition of the animals, including hypothermia. Administration of UK-73,689 produced effects only at 1000 mg/kg/day, and therefore is not considered a toxicological concern.
In repeat-dose studies in dogs mild clinical signs occurred from 1mg/kg (dry mouth, mydriasis, conjunctival redness, regurgitation and emesis), from 3mg/kg (inhibition of the pupillary reflex), or at 16mg/kg (difficulty in swallowing, transient absence of faeces). Increases in relative liver weight were noted from 1mg/kg. Oral administration for one year produced no evidence of new toxicological findings, with the addition of increased heart rate at 6mg/kg. Corneal changes (neovascularisation and opacities etc.) were limited to the high dose, and have been described previously in dogs treated with anticholinergic or antispasmodic agents (Gopinath et al.,1987; Majeed et al.,1983).
Overall, sporadic mortality occurred from doses of 30mg/kg in rats and from 10mg/kg in dogs, representing darifenacin plasma exposures at least 43 and 197-fold greater than those seen at the maximum recommended human dosage, and has been ascribed to the exaggerated pharmacology of the compound. Darifenacin has been shown to inhibit salivation in rats and dogs and to produce dry mouth in dogs. This effect on salivation, together with the decrease of motility of the upper digestive tract hinders feeding and swallowing and facilitates the entry of food into the respiratory airways, leading to asphyxia. The exaggerated effect on salivation and gastric motility in these studies leading to sporadic mortality is not considered a risk to humans as it occurs at plasma concentrations which are many times higher than seen in humans.
The Applicant has conducted a number of toxicokinetic studies, where the plasma exposure to darifenacin at the maximum therapeutic dose (15mg, 0.3mg/kg) has been compared to reference doses in animal studies. Overall, in toxicity studies at doses of darifenacin which caused no toxicological consequences (NOAEL), animals were exposed to total amounts of darifenacin and its metabolites which exceeded several fold those encountered at the highest clinical dose of darifenacin (dose range of 1.25-100mg/kg). The exposure multiples for darifenacin indicate an acceptable multiple between C_{max} and AUC for the drug in humans and the equivalent values associated with no adverse effects in mouse, rat and dog.

- Genotoxicity *in vitro* and *in vivo*

Darifenacin has been evaluated in in vitro and in vivo genotoxicity tests in two salt forms, the tartrate and the hydrobromide. Darifenacin does not display mutagenic activity in any in vitro test system when tested up to cytotoxic concentrations in either the absence or presence of exogenous metabolic activation, and does not cause chromosomal aberrations in vivo. Additionally, in the in vivo assay carried out, no evidence of clastogenicity was seen.
The mutagenic potential of UK-85,069, an intermediate of synthesis of darifenacin and UK-73,689 were tested according to the Worker Safety Testing regulations. Both compounds were neither mutagenic nor clastogenic in vitro.

- Carcinogenicity

Range-finding and long-term studies have been conducted by the Applicant to study the carcinogenic profile of darifenancin in mice and rats. Darifenacin had no effects on the survival of the animals. The decreased body weight validates the high dose selection. Furthermore these high doses are associated with an exposure higher than that in human subjects receiving the highest recommended

dose (see toxicokinetics). Some findings (mydriasis and increased secretion of Harderian gland) have been noticed consistently in repeat-dose studiesThe only findings in terms of carcinogenicity were the increased incidence of adrenocortical adenomas in high dose female rats and of haemangiosarcomas in high dose male rats. These findings were however not considered to be related to treatment.

- Reproductive and developmental studies

Reproductive and developmental toxicity studies carried out with darifenacin

Study type	Specie	Dose
Preliminary reproduction study	Rat	3, 10, 50
Fertility	Rat	3, 10, 50
Maternal toxicity	Rat	10, 30, 50
Teratology	Rat	3, 10, 50
Maternal toxicity	Rabbit	10, 30, 50
Teratology	Rabbit	3, 10, 30
Peri & postnatal development	Rat	3, 10, 50
Pre & postnatal study	Rat	3, 10, 50

The effects of darifenacin on fertility have been evaluated in rats. Darifenacin has no effect on copulation rate, and effects on pregnancy rate observed were mild and only appeared at high doses. Darifenacin at 50mg/kg was toxic to adult male and female rats, and thereby the post-implantation loss is a consequence of maternal toxicity. In conclusion, darifenacin had no effect on male or female fertility, or any effect in the reproductive organs of either sex.

Foetotoxicity studies carried out in rats demonstrated maternal toxicity (reduced body weight) and slight foetotoxicity at 50mg/kg (reduced foetal weights and delays in ossification). In the rabbit, darifenacin produced maternal toxicity (reduced body weight and abortions) and embryo- and foetotoxicity at 30mg/kg (increased post-implantation loss and decreased number of viable foetuses per litter). Adverse effects on embryos and foetuses were seen at darifenacin doses which induced maternal toxicity and, in both species, these effects occurred at maternal free plasma exposures that are 28-59 times those obtained in humans at the maximum recommended human dosage. Therefore, darifenancin was not considered teratogenic in rats or rabbits.

Metabolism data have demonstrated that darifenacin is excreted in milk; however, darifenacin was not detected in the plasma of pups. Perinatal and postnatal toxicity (delays in physical development of pups), together with signs of maternal toxicity, were observed at 50mg/kg, that were above the maximum recommended human dosage (87 times the human free AUC). In peri and post natal studies in rats, dystocia, increased foetal deaths in utero, and toxicity to post natal development (pup body weight and development land marks) were observed at systemic exposure levels up to 11 times higher than the expected clinical exposure. Furthermore, the adverse effects of the compound on the length of gestation, littering and lactation were not observed in a previous fertility study. Therefore, darifenacin would not pose a toxicological risk on prenatal and postnatal development at the recommended human dosage. However, the CHMP considered that, darifenacin should not be recommended during pregnancy, as stated in the SPC.

- Local tolerance

Darifenacin and its metabolite UK-73,689 produced evidence of skin sensitisation in the rat and rabbit species; furthermore, darifenacin and UK-73,689 produced eye irritation in the rabbit. Although, darifenacin would pose a dermotoxicity risk it is not expected any concern due to the oral route intended to be used in humans.

- Other toxicity studies

Darifenacin did not induce an active systemic anaphylaxis reaction or a passive cutaneous anaphylaxis reaction in guinea pigs. Therefore, darifenacin has no antigenic potential under the conditions of this study.

- Summary of salient findings

The observed toxicity of darifenacin in repeat-dose studies is at least in part the consequence of its pharmacological activity on M3 receptors: in particular decreased food intake, decreased body weight and some deaths could be explained by decreased salivation that makes feeding and swallowing difficult and facilitates the entry of food in the respiratory airways. Darifenacin had no effect on fertility and no teratogenic action. In peri and post natal studies in rats, dystocia, increased foetal deaths in utero, and toxicity to post natal development (pup body weight and development land marks) were observed at systemic exposure levels up to 11 times higher than the expected clinical exposure. However, the CHMP considered that darifenacin should not be recommended during pregnancy, as stated in the SPC.
Darifenacin was neither mutagenic nor clastogenic and had no carcinogenic activity.

Ecotoxicity/environmental risk assessment

As a result of consumer use, darifenacin is mainly excreted as metabolites mainly in urine (58%) and feces. Only 3% of the dose is excreted as unchanged darifenacin, 2% in urine and 1% in feces. Excretions are collected with other wastes in public waste water systems and are processed by sewage treatment plants. Darifenacin and its metabolites residing in the hydraulics of sewage treatment plants are directly released into the external aquatic environment, while that bound to the wastewater biomass may be indirectly released to the soil environment as a result of wasting sludge. Once released into the aquatic environment, effluent concentrations of darifenacin and its metabolites are further diluted (approximately 1:10) by the receiving waters. Soil concentrations of darifenacin resulting from sludge amendments to soil are negligible, such as release to the atmospheric compartment. No unusual toxicity was observed for those species tested as representative of the water and soil compartments.

Discussion on the non-clinical aspects

The extent and scope of the documentation provided in this application are appropriate to support the non-clinical pharmacology profile of darifenacin

Darifenacin is a selective antagonist of M3 muscarinic receptors of acetylcholine. Darifenacin is intended for the treatment of symptoms of overactive bladder, defined by urinary urgency with or without urge urinary incontinence, usually associated with urinary frequency and nocturia.

The rational for the use M3 selective antagonists is based on expected better tolerance while achieving similar efficacy.

Various pharmacological studies demonstrate the antimuscarinic effect of the compound in the bladder, and explore other effects related to the inhibition of M3 muscarinic receptors in other organs.

Pharmacokinetics studies were performed in mouse, rat, rabbit and dog. The animals were exposed to darifenacin, in relation to the highest exposure expected in the clinical situation. Darifenacin showed extensive absorption by oral route, and presented an important first-pass effect. It is extensively distributed. Metabolism occurs namely in the liver, involving CYP3A4 and CYP2D6, to which darifenacin and its metabolites have the potential to inhibit. A number of potential clinical interactions are derived from this fact, in it has been further addressed in the clinical part.

In the rat, the rabbit and the dog, the predominant route of excretion was in the faeces, while in mouse and human, excretion of radioactivity was balanced between urine and faeces.

A complete toxicology programme was performed, and did not raise special concern, although darifenacin is not recommended during pregnancy. The observed toxicity is in part consequence of its pharmacological activity on M3 receptors. Adequate genotoxicity and carcinogenicity studies did not anticipate any potential hazard for the use of darifenacion in humans.

A Phase I Environmental Risk Assessment has been carried out to assess the environmental risk of darifenacin. The results of this study show that there are no potential risks to the environment from the use or storage of darifenacin.

4. Part IV: Clinical aspects

Introduction

All but four clinical studies from all phases of development were conducted according to the ICH GCP guidelines. The four exceptions were early Japanese Phase 1 studies (JP-95-501, JP-95-502, JP-05-503, JP-95-504), which were conducted before 1997 according to Japanese GCP guidelines in force at that time. All studies have been subject to regular monitoring by Pfizer or Contract Research Organizations.

All studies were performed in accordance with the World Medical Association's Declaration of Helsinki and its amendments.

A clinical pharmacology program is presented consisting of 48 phase I studies conducted in healthy volunteers in the US or Europe (Western studies) and 5 phase I studies conducted in Japan. The objective was to determine the pharmacokinetics (PK) of darifenacin in humans, to assess the effects of drug dosing on pharmacodynamic (PD) parameters and to explore the influence of intrinsic and extrinsic factors on darifenacin PK and PD.

Pharmacokinetics

Seven clinical studies explored the absorption, distribution, metabolism and excretion of darifenacin or the intrinsic pharmacokinetic properties of the drug administered as a solution via intravenous (iv)or oral routes (Studies 137-201, 137-202,137-203,137-209,137-214,137-219 and 137-221).One in vitro study was performed to investigate the membrane permeability of darifenacin (DM-03-137-26)while four studies were performed to characterize the pathways by which darifenacin is metabolized (DM-99-137-01,DM-99-137-01A, DM-99-137-01B and DM-00-137-01D).The extent to which darifenacin and its metabolites bind to protein was investigated in five equilibrium dialysis studies (DM-99-137-08,DM-99-137-08A,DM-01-137-08B,DM-01-137-08C and DM-01-137-01F).
Concentrations of darifenacin and the principal metabolite UK-148,993 in human plasma and urine were measured using solid-phase extraction (SPE) followed by reversed phase high-pressure liquid chromato-graphy (HPLC). Validation reports support each bioanalytical method.
A variety of SPE cartridges and reversed phase HPLC columns were used and modifications were made to the LC/MS/MS detection to improve assay sensitivity but the method conditions remained essentially the same. A further method using organic solvant protein precipitation, automated on line SPE column switching and reversed phase HPLC with fluorescence detection was used by a separate laboratory.
The methods used are very sensitive with lower limits of quantification of 0.025 ng/ml for darifenacin and 0.05 ng/ml for UK-148,993, and slightly higher with the fluorescence detection.
Pharmacokinetic parameters were assessed and defined according to standard criteria.

- Absorption – Bioavailability

Darifenacin is a lipophilic and basic molecule that appears to be completely absorbed from the gastrointestinal tract. Following the administration of an oral solution, darifenacin appeared rapidly in the peripheral circulation (Tmax: 1h) with an elimination half-life of around 0.3h. For this reason a

controlled release formulation was developed. Pooled data from studies using repeated controlled release (CR) tablet dosing indicate that Cmax from 7.5mg and 15mg CR tablets at steady state is achieved approximately 7h after dosing.
The oral bioavailability of darifenacin from 7.5 mg and 15 mg CR tablets was estimated to be 15.4% and 18.6% respectively in CYP2D6 extensive metabolisers (EM) subjects at steady state. The most likely explanation for incomplete oral bioavailability is extensive first pass metabolism by CYP3A4 and CYP2D6 in the liver and CYP3A4 in the gut wall. The hepatic extraction ratio is high: $E_H = 0.73$.
Inter- and intra- subject variability in oral bioavailability of darifenacin is significant and caused by a combination of factors, including CYP2D6 genotype, co-administration of CYP3A4 inhibitors, race, gender, age, and hepatic function.
Oral bioavailability of darifenacin is both time-and dose-dependent. Darifenacin exposure from 15mg CR tablets at steady state was 86% higher than after a single dose and doubling of the CR tablet dose increased steady state exposure by approximately 150% (dose proportionality constant 1.33, 95% CI 1.21,1.45).
Co-administration of food with a single 15mg or 30mg CR tablet produced a higher peak darifenacin concentration (Cmax ratio fed/fasted =1.22). However, the total drug exposure (AUC) remained unchanged. Once darifenacin plasma concentrations had reached steady state, ingestion of food had no effect on the pharmacokinetics of darifenacin. Therefore, specific dosing recommendations on the use of darifenacin CR in relation to meals are not required.

- Bioequivalence

Bioequivalence between the CR tablet formulation intended for commercial production and the other 18-h release CR tablet formulations used during clinical development of darifenacin was assessed in five studies. Bioequivalence was established between the proposed commercial formulations of 7.5mg, 15mg and 30mg tablet strengths and the corresponding clinical research tablets.

- Distribution

Darifenacin has a volume of distribution well in excess of total body water. The estimated Vss of darifenacin is 163 L. This is consistent with extensive distribution of the drug into body tissues, although there is limited penetration into brain.
The mean plasma protein binding for darifenacin is 98%, primarily to α1-acid glycoprotein. The plasma protein binding is reduced to 97% in mild hepatic impairment (Child-Pugh A) and to 95.5% in moderate hepatic impairment (Child-Pugh B). The binding is not reduced by renal impairment.

- Elimination

Darifenacin is extensively metabolised with 3% of unchanged drug excreted in either urine or faeces following oral dosing. Metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4. The three main metabolic routes are monohydroxylation into the dihydrobenzofuran, dihydrobenzofuran ring opening, and N-dealkylation of the pyrrolidin nitrogen.
As darifenacin has multiple route of metabolism, the impact of a loss of one of the pathways is lessened by ongoing metabolic activity through the other pathways.
The major circulating metabolites identified were UK-73,689 (N-dealkylation) and UK-148,993 (hydroxylation). The only metabolite of darifenacin that has shown pharmacological activity is UK-148,993 which has shown a similar antimuscarinic M3-Receptor binding selectivity, although at a 3- to 10-fold lower potency than darifenacin. The relative in vivo potency of the metabolite UK-148,993 compared to darifenacin was estimated by population pharmacokinetic/pharmacodynamic modelling of the reduction in salivary flow. UK-148,993 makes a negligible contribution to changes in salivary flow, based on the absence of correlation between salivary flow and plasma metabolite concentrations.
The pharmacokinetics of UK-148,993 follow the pharmacokinetics of darifenacin. The steady state UK-148,993 plasma concentration versus time profile from CR tablet dosing is similar to that of darifenacin and UK-148,993 PK parameters show the same trends as darifenacin PK parameters.

In Phase 1 studies, steady state total exposure was approximately 164% higher in poor metaboliser (PM) subjects compared with extensive metaboliser (EM) following administration of 7.5mg CR tablets, and 99% higher following 15mg od dosing. Estimates of darifenacin exposure based on population analysis of Phase 3 data indicated that steady state AUC was 66% higher among PMs than EMs at each dose. However, there is considerable overlap between the ranges of exposures seen in these two populations. Adequate information on this issue has been included in the SPC.
Darifenacin and its metabolites are eliminated from the body via the urine and faeces; about 60% of the drug dose was excreted in the urine and 40% in the faeces. Most of a dose is excreted within 48h of dosing. The metabolites present in the urine are primarily from hydroxylation and dihydrobenzofuran ring opening. Very little darifenacin was directly excreted via either the urine or faeces (3%).

- Dose proportionality and time dependencies

Darifenacin pharmacokinetics from PR tablets is dose-dependent. Bioavailability increases with increasing dose and was higher at steady state than from single dose data.
Doubling the darifenacin dose resulted in a 150% increase in exposure. This dose-dependency could be due to increasing saturation of CYP3A4-mediated gut wall metabolism at higher doses, combined with a dose-dependent reduction in the contribution of CYP2D6 metabolism to darifenacin oral clearance at steady state.

- Special populations

Among patients with OAB in Phase III studies, the PK of darifenacin was similar to that in healthy volunteers in Phase I studies.
Renal impairment has no clinically relevant effect on the pharmacokinetics of darifenacin. No relationship between darifenacin clearance and renal function was established. Plasma protein binding of darifenacin was also not reduced in subjects with renal impairment.
Mild hepatic impairment does not alter darifenacin PK in a clinically relevant manner. However, moderate hepatic impairment has an effect on darifenacin PK. Both clearance and protein binding were lower among subjects with moderate hepatic impairment. Steady-state unbound darifenacin exposure was estimated to be 300-370 % higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. In accordance with this, the SPC recommends that in patients with moderate hepatic impairment (i.e. Child Pugh B), patients should only be treated if the benefit outweighs the risk, and that the patients should be restricted to 7.5 mg daily. Darifenacin is contraindicated for patients with severe hepatic impairment (Child Pugh C).
Darifenacin exposure is lower in men than in women. Darifenacin CL/F was 30% higher and steady-state AUC 23 % lower among males than females. This variation is not sufficient to demand a change in dose according to gender.
Because the number of non-white subjects in Western studies was low, it was not possible to determine the influence of ethnic background on darifenacin pharmacokinetics. Apart from differences in exposure (steady-state AUC was 34% lower among Japanese subjects compared with Western subjects), the pharmacokinetic behaviour of darifenacin was broadly similar in Japanese and Western subjects.
Children have not been studied. Darifenacin cannot be recommended for use in these patients.

- Interaction studies

Since darifenacin is metabolised via CYP3A4 and CYP2D6 enzyme pathways, the PK is affected when CYP3A4 and CYP2D6 expression or activity are altered. A series of in vitro and in vivo drug interaction studies have been performed to investigate the consequences of concomitant administrations of CYP3A4 and CYP2D6 inhibitors on darifenacin exposure. The impact of cytochrome P450 induction on darifenacin PK has also been explored. Conversely, a series of in vitro and in vivo drug interaction studies have been performed to investigate the impact of darifenacin administration on the PK of other drugs.
The choice of interacting drugs was based on US and European guidelines on the investigation of drug interactions.

- *In vitro*

Darifenacin metabolism in vitro was inhibited by CYP2D6 and CYP3A4 inhibitors in a manner consistent with the known potency of each compound against other substrates. Concomitant use of a potent CYP2D6 inhibitor with darifenacin causes an increase in steady-state darifenacin exposure in EM subjects.
In vitro studies suggest that CYP3A4 is the primary route of metabolism *in vitro*. The effects of a variety of CYP3A4 inhibitors on the metabolism of darifenacin were initially examined *in vitro* using human microsomes. Extrapolation of these data to a clinical situation is not straighforward because the relative contribution of the CYP3A4 and CYP2D6 pathways to darifenacin metabolism in vivo varies with time and dose.

- *In vivo*

CYP3A4 inhibitors
Co-administration of ketoconazole with darifenacin caused the largest increase in steady-state darifenacin exposure: about 10-fold with the 15- and 30-mg doses, and 5-fold with the 7.5-mg dose. The co-administration with potent CYP3A4 inhibitors such as protease inhibitors, ketoconazole and itraconazole is contraindicated, as quoted in the SPC. Potent P-glycoprotein inhibitors such as cyclosporine and verapamil should also be avoided. Co-administration of darifenacin 7.5 mg with the potent CYP3A4 inhibitor ketoconazole 400 mg resulted in a 5-fold increase in steady state darifenacin AUC. In subjects who are poor metabolisers, darifenacin exposure increased by approximately 10-fold. Due to a greater contribution of CYP3A4 after higher darifenacin doses, the magnitude of the effect is expected to be even more pronounced when combining ketoconazole with darifenacin 15 mg.
When co-administered with moderate CYP3A4 inhibitors such as erythromycin, clarithromycin, telitromycin, fluconazole and grapefruit juice, the recommended starting dose of darifenacin should be 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated. Darifenacin AUC_{24} and C_{max} from 30 mg od dosing in subjects who are extensive metabolisers were 95% and 128% higher, when erythromycin (moderate CYP3A inhibitor) was co-administered with darifenacin than when darifenacin was taken alone.
The magnitude of interaction with grapefruit juice will be dependent on the volume and frequency of administration. Since erythromycin is a moderate CYP3A inhibitor and grapefruit juice showed smaller effect relative to erythromycin following daily administration, it is reasonable to conclude that the anticipated effect of grapefruit juice on darifenacin pharmacokinetics will not exceed that of erythromycin.
The possibility of an interaction with darifenacin and CYP3A4 inducers such as rifampicin, rifampin, carbamazepin, barbiturates and St John´s wort (Hypericum perforatum) cannot be excluded, and they are likely to decrease the plasma concentrations of darifenacin

CYP2D6 inhibitors
In patients receiving drugs that are potent CYP2D6 inhibitors (e.g. paroxetine, terbinafine and quinidine) the recommended starting dose should be 7.5 mg daily. The dose may be titrated to 15 mg daily to obtain an improved clinical response provided the dose is well tolerated.
To quantify the effects of CYP2D6 inhibition on steady-state darifenacin pharmacokinetics in vivo, a clinical study was performed in which paroxetine was co-administered with darifenacin 30mg CR tablets. Darifenacin AUC_{24} and Cmax after co-administration of paroxetine were 33% and 36% higher than when darifenacin was taken alone. However, lower strength darifenacin tablets were not tested. Mean darifenacin exposure was similar in EMs receiving paroxetine and PMs receiving darifenacin alone.

Cytochrome P450 inducers
Co-administration of drugs that have the potential to induce cytochrome P450 expression had little apparent effect on the pharmacokinetics of darifenacin among patients in phase III studies. Any effect cytochrome P450 inducers may have on darifenacin pharmacokinetics are small in the context of other sources of variability.

Effects of darifenacin on other medicinal products
Based on the midazolam and oral contraceptives hormones studies, it is concluded that darifenacin does not inhibit the CYP3A4 isoenzyme at clinically relevant concentrations. Darifenacin co-administered with digoxin at steady-state results in a small increase on digoxin levels. Darifenacin had no clinically relevant effect on the exposure of the CYP3A4 substrate midazolam and had no effect on the pharmacokinetics of the oral contraceptives levonogestrel or ethinylestradiol.
The effect of warfarin on prothrombin time was not altered when co-administered with darifenacin.
As with any other antimuscarinic agents, the concomitant medication with medicinal products that possess antimuscarinic properties, such as oxybutynin, tolterodine and flavoxate may result in more pronounced therapeutic and side effects. The potentiation of anticholinergic effects with anti-parkinson drugs and tricyclic antidepressants may also occur if antimuscarinic agents are used concurrently with such medicinal products. However, no studies involving the interaction with anti-parkinson drugs and tricyclic antidepressants have been performed.

Pharmacodynamics

The primary pharmacodynamic effects of darifenacin were investigated in *in vitro* studies to characterize the binding of darifenacin and its metabolites to muscarinic receptors, and to determine the functional effects of darifenacin on in vitro models of M_3-mediated pharmacological responses.
Four exploratory Phase 2 studies were conducted to address the effect of darifenacin on urodynamic parameters indicative of bladder disfunction and detrusor overactivity.
In order to determine the pharmacological effects of darifenacin on body systems other than the bladder, a variety of pharmacodynamic endpoints were measured in a number of Phase 1, Phase 2 and Phase 3 studies during the clinical program. These endpoints were salivary flow, visual nearpoint, pupillometry, heart rate, heart rate variability, GI motility, CNS function and QT interval.

- Mechanism of action

Darifenacin is an antimuscarinic agent that binds to all five subtypes of muscarinic receptors. It is targeted to the M_3 subtype for which it is selective.
Other anti-muscarinic drugs are used for urinary incontinence-related indications. According to the data, the tested alternatives are generally less selective. This is particularly true for the M_1 subtype (where there was little or no selectivity with tolterodine, oxybutinin or propiverin). For the other subtypes, selectivity varies e.g. oxybutinin appears more selective than darifenacin in relation the M_5 subtype. Tolterodine has been used as an active comparator in phase 3 studies.
It can be said that the selectivity profile of darifenacin would be an advantage. However, it has to be considered that selectivity is a matter of concentration, e.g., increasing around 10 times the concentration of darifenacin would result in disappearance of the selectivity against M_1 and M_5 receptors. In addition a 10 times difference in affinity is not foolproof and does not necessarily guarantee full selectivity in vivo. Depending on the slope of the dose-response curve of the agonist and of its relative concentrations at every receptor, it is possible that the concentrations needed to fully block the response in the relevant M_3 receptors are sufficient to produce also an unwanted degree of block in other receptors. Pharmacokinetic considerations also apply (e.g. lack of CNS penetration would offset lack of CNS receptor selectivity). As a consequence, confirmation in phase 3 studies of the theoretical advantages is needed.
In vitro studies in guinea pig bladder and preclinical data in dogs and rats indicated that darifenacin antagonizes bladder contraction.
Darifenacin reduces induced contraction of human bladder tissue in a concentration-dependent manner. Based on the pKb values for effects on carbachol-induced contraction of bladder tissue, the rank order of potency was: darifenacin> atropine> oxybutynin> propiverine. Darifenacin was also

effective in antagonizing contractile responses of human bladder strips induced by electrical field stimulation (EFS); darifenacin pre-treatment (10^{9} M to 10^{-6} M) inhibited the maximum contractile response to EFS by up to 49%.

- Primary pharmacology

The results of four in vitro studies using human biomaterials are presented. The measurements of the affinity of darifenacin for recombinant human muscarinic receptors 1 to 5 cloned in CHO cells showed that the selectivity ratios for M3 over M1, M5, M2 and M4 were around 9, 12, 60 and 60-fold, respectively. The pKi of darifenacin for human M3 receptors was 9.1.
Darifenacin inhibited carbachol-induced contractions in human bladder tissue with a pKb of 9.6, close to its pKi for M3 receptors.
In clinical studies, cystometry and flowmetry were used to obtain quantitative measurements of the effects of darifenacin on bladder outflow. The greatest results were obtained in study JP-95601 that was uncontrolled. In most cases, the included population had previous urodynamic pathology, which does not exactly match the population included in the phase III studies or the target population. The studies showed increased bladder capacity, increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions after darifenacin treatment. These findings are consistent with the later clinical observations of reduced frequency of incontinence, reduced frequency of micturition, reduced frequency of urgency and increased functional bladder capacity observed in patients with overactive bladder
There is a dose-effect relationship for both the primary and secondary pharmacological endpoints.

- Secondary pharmacology

Several "secondary pharmacology" studies and or analyses addressed potential side effects of antimuscarinic drugs. As expected, darifenacin reduces salivary flow and gastrointestinal motility in a dose-dependent manner. Visual accommodation is affected at high doses; CNS effects have only been documented in some of the studies with the highest doses assessed and in a few of the studied parameters (however, the subjects included had always normal cognitive function). Effects on heart rate were scarce although no reference is made to the baseline vagal tone of the studied subjects.
In relation to QT prolongation (*in vitro*, pre-clinical and clinical data), it can be concluded that the overall risk assessment for darifenacin is reassuring. The fact that darifenacin is not associated with QT prolongation is further supported by the available preclinical and clinical QT studies. The clinical trial information is based upon information obtained from over 960 treated patients (i.e. elderly, patients with risk factors for QT prolongation and those with pre-existing cardiac diseases). Overall, there were no statistically or clinically relevant mean differences from placebo for heart rate and QTc.

Clinical efficacy

The clinical program was developed to assess the efficacy and safety of darifenacin in patients with OAB.
Dose selection for the Phase 3 program was based primarily on 2 fixed dose Phase 2 studies, which assessed efficacy of total daily doses of 15mg and 30mg darifenacin on OAB symptoms. One additional Phase 2 studies conducted in Japan was aimed to assess the dose response relationship of different doses of darifenacin CR.
Four pivotal Phase 3 randomized, double blind, placebo controlled, parallel group 12-week studies support the use of darifenacin 7.5mg and 15mg in the treatment of OAB (Studies A1371047, A1371041, A1371002 and A1371001). Data from three of these studies were pooled together for meta-analysis.
In addition a number of supportive efficacy trials were conducted. These included 2 Phase 3 flexible dosing regimen studies; a number of pharmacodynamic and efficacy studies. In addition 4 open label long term studies assessed the long term safety and efficacy of darifenacin and 2 special studies evaluated the efficacy of darifenacin 30mg on urgency and nocturia.

Initially, an immediate release (IR) formulation was used. This formulation was superseded by a prolonged-release (PR) formulation for once daily dosing. All pivotal studies have being conducted with the PR formulation, which is the only formulation for which approval is sought.
In OAB studies with either the IR or CR formulations, 3796 patients were treated, of whom 3306 received the CR formulation and 1069 were treated with darifenacin in fixed dose Phase 3 studies.

- Dose response studies

Study 137-305
A multicenter double blind (12 week), placebo controlled, parallel group dose response study of IR darifenacin (2.5mg tid, 5mg tid, 10mg tid) in women with OAB and detrusor overactivity. A total of 447 patients with objective evidence of unstable detrusor contractions were randomized, of which 369 completed the study.
This study showed a statistically significant improvement at Week 4 (primary evaluation) in the number of incontinence episodes per week, frequency of urgency per day, frequency of micturition per day and volume of urine passed per void for the 10 mg tid dose of darifenacin, when compared with placebo.
Furthermore by 12 weeks, subjects on darifenacin groups had a reduction in the number of incontinent episodes/week compared to placebo (treatment difference of -1.0, -1.0 and –1.5 for darifenacin 2.5 mg tid, 5 mg tid and 10 mg tid, respectively). However, the improvement in incontinence episodes per week on 2.5mg and 5 mg tid IR darifenacin in the study were not significantly different from placebo.

Study 137-666
A double blind, placebo-controlled, four-way crossover study (14 days per period) to compare the safety and efficacy of controlled-release darifenacin and oxybutynin tablets in the treatment of urge incontinence.
A total of 76 subjects with urge urinary incontinence (UUI) due to detrusor instability diagnosed by cystometry were treated with darifenacin 15mg od, darifenacin 30mg od, oxybutynin 5mg tid or placebo for 14 days, with a 10 day washout between treatment periods. Of the 76 subjects enrolled, 16 permanently discontinued from the study. A total of 60 subjects completed the entire study.
Darifenacin 30mg treatment was significantly better than placebo for reducing all of the symptoms of urge incontinence (micturition/day, incontinence/week, significant incontinence/week, urinary urge/day and severity of urge/episode) and significantly better than darifenacin 15mg in reducing micturitions/day, significant incontinence/week and severity of urge/episode. Both darifenacin 15mg and oxybutynin 5mg tid were statistically significantly better than placebo in reducing incontinence per week, urinary urge per day and the severity of urge per episode. There was no statistically significant difference between darifenacin 30mg and oxybutynin 5mg. From the point of view of efficacy, 30 mg od would appear more efficacious than 15 mg od at two weeks.

Study A1371012
A multicenter double blind (6 week), placebo controlled, randomized, parallel group, fixed dose comparison study of controlled release darifenacin (7.5mg, 15mg and 30mg od) in patients with OAB. The primary objective was to study the dose response of darifenacin on symptoms of OAB. In total 389 patients with symptoms of overactive bladder entered the study (96 to placebo, 96 to darifenacin 7.5mg, 96 to darifenacin 15mg and 101 to darifenacin 30mg).
This study had a 2 week washout period for patients on prohibited medication followed by a 2 week placebo run-in period followed by a 6 week double blind randomized period.
At Week 6, subjects treated with darifenacin (7.5mg, 15mg or 30mg) experienced a numerically larger reduction in the frequency of incontinent episodes after six weeks of treatment than subjects who received placebo (median treatment difference compared with placebo were –0.5, -1.1 and –1.8 episodes per week, respectively). The difference from placebo was statistically significant for darifenacin 30mg (p=0.012).
Dose selection was based on adequate balance of efficacy and adverse reactions. Several doses were tested not only in the “dose-finding” phase 2 studies but in many phase 3 studies including “pivotal”. The finally recommended dosage schedule (7.5 mg od with optional up-titration to 15 mg) was assessed, as such, in only one of the pivotal trials (A1371047). Phase 2 and 3 studies (including

pivotal) were consistent in finding a dose-response relationship on most variables, particularly the most often used, incontinence frequency.
It can be concluded that a general finding of the three previous studies is the superiority of the 30 mg od dose over the 15 mg od dose (the highest dose finally recommended), and this one was more effective than 7.5 mg (the lowest of the two finally recommended dose).

- MAIN STUDIES.

The efficacy of darifenacin in the treatment of OAB have been studied in 3 double blind, randomised, placebo controlled parallel group, fixed dose Phase 3 studies of 12-week treatment duration (Studies A1371002, A1371041 and A1371001) and one placebo controlled upward dose titration study (A1371047)
The doses studied in the Phase 3 program included darifenacin 3.75mg, 7.5mg, 15mg and 30mg od. Study A1371001 also included tolterodine 2mg bid as an active comparator, which is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.
A 2-week washout period (pre-screening visit) for patients on prohibited medication was followed by a 2-week placebo run-in period (except Study A1371001 where a medication free run-in was used), which was then followed by a 12-week double blind treatment.
The subject's eligibility was assessed based on symptoms of OAB, willingness to complete an electronic patient diary, medical history and the subject's self-report of childbearing potential.
Efficacy data were collected using electronic patient diaries. Electronic diary was developed together with Araccel according to strict sponsor specifications and it was tested and validated.
The study protocols of the 3 pivotal studies (A137 1002, A137 1041, A137 1001) were similar and allowed a pooled analysis.

Study Participants

The following inclusion criteria applied to patients enrolled in the pivotal studies:

a) Patients were male or female (non-childbearing potential or using effective contraception) and 18 years of age or older.
b) Patients were expected to have all 3 cardinal symptoms of OAB (urgency, urge incontinence and micturition frequency) for at least 6 months and were expected to exhibit these symptoms at specified levels during the run-in period:
   • Incontinence: 5-50 episodes of urinary incontinence per week, average.
   • Micturition frequency: at least 8 micturitions per 24 hours on average.
   • Urgency: at least once per 24 hours on average.
c) They had to be in good health and capable of taking study medication on an outpatient basis, as well as capable of independent toileting and of independently completing the electronic patient diary

Patients were excluded if they experienced clinically significant stress incontinence (i.e. greater than 1 episode of stress incontinence per week), significant bladder outlet obstruction and/or a post void residual (PVR) volume of greater than 200 mls (as measured by pelvic ultrasound or catheterisation). Likewise, patients with significant urogenital disease, such as recurrent urinary tract infection (UTI) or interstitial cystitis and patients who had undergone hysterectomy or prostatectomy in the past 6 months were excluded.
Patients with both idiopathic and neurogenic OAB were included, but by far the majority of patients were found to have idiopathic OAB.
Prohibited medication included drugs with significant anticholinergic or antispasmodic effects, potent inhibitors of CYP3A4 enzyme systems (ketoconazole, itraconazole, miconazole, troleandomycin and nefazodone), estrogens if taken for less than 2 months as well as opioids and other drugs that could cause significant constipation. Bulking agents and stool softeners were allowed for the treatment of constipation.
Patients in whom antimuscarinic drugs were contraindicated were excluded (e.g. those with uncontrolled narrow-angle glaucoma, urinary retention or gastric retention). In studies with tolterodine, drugs contraindicated by the tolterodine label were also excluded.

The intentional randomization of patients known to be responsive to, or tolerant of, anticholinergic therapy was avoided. In Studies A1371041 and A1371047, patients who had participated in previous controlled, double blind darifenacin studies of 16 weeks or less were allowed to participate if they discontinued medication as required by these protocols. Patients who had participated in an open long-term (greater than 16 weeks) darifenacin study, such as study A1371014 or 137-311 were excluded. The minimum period for any subject between completion of a previous darifenacin study and the start of Studies A1371041 or A1371047 was 4 months.

Treatments

The OAB Phase 3 program was designed to study the dose range from 7.5mg to 30mg.
The 3.75 mg dose was studied in Study A1371041. A significant number of the Phase 3 patients received the 30mg dose as fixed doses (A1371001, A1371002).
The active comparator used in this development program was tolterodine IR 2mg bid. At the time of the start of the Phase 3 OAB clinical program, the long acting (LA) formulation of tolterodine was not available. In terms of the efficacy and safety profile, however, there it is not expected to be any difference between both formulations of tolterodine, as has been reported in the published literature.
Dosing in all Phase 3 studies was performed on an outpatient administered as a CR tablet od with or without food. In the active comparator, 2 tablets and a capsule were taken in the morning and another capsule was taken at night.

Objectives

For study A137 1002 and study A137 1041, the primary objective was to assess the clinical efficacy of 3 doses of darifenacin on symptoms of OAB. Secondary was to evaluate the safety and toleration of darifenacin, to evaluate the population pharmacokinetics of darifenacin and to evaluate the effect of darifenacin on quality of life in subjects with overactive bladder.
Study A137 1001 aimed to compare the clinical efficacy of controlled release darifenacin (15mg od and 30mg od) with tolterodine (2mg bid) and placebo in patients with OAB. For study A137 1047, the primary objective was to assess the efficacy of darifenacin 7.5mg, with the option of up-titration to 15mg at Week 2, on the symptoms of OAB.
The secondary objective was similar to that for studies A137 1002 and A137 1041.

Outcomes/endpoints

The analysis of efficacy relied on patient recorded symptoms. All Phase 3 studies assessed the same efficacy evaluations.
The primary efficacy outcome was the frequency of incontinence episodes per week as measured after 12 weeks of treatment. The primary efficacy evaluation was the difference from placebo for the number of incontinence episodes per week. Studies were not powered individually to show statistical superiority over placebo on any of the secondary evaluations.
Secondary evaluations measured effects on frequency of micturition, volume of urine voided, frequency and severity of urgency, other symptoms related to OAB and measures of quality of life and patient perceived quality of treatment (PPQT). These evaluations were also recorded in the bladder diary.

- number of incontinence episodes per week resulting in a change of clothing or pad
- number of micturitions per day
- volume of urine passed per void
- maximum volume voided (studies A1371001 and A1371002). It was omitted from Studies A1371041 and A1371047, because the data from earlier Phase 3 studies suggested that this evaluation may not provide the best representation of bladder capacity.
- number of episodes of urgency per day
- severity of urgency per day: There is no widely accepted method for the assessment of severity of urgency. A 100mm visual analog scale, which ranged from mild (scored 0) to severe (scored 100) was used in the Phase 3 studies. Patients were asked to complete the visual analog scale at the end of each day if they recorded an episode of urgency at any time during the day.
- number of nocturnal awakenings due to OAB per week.

•Responder rates were calculated for a few parameters to obtain information about the efficacy rates in patients who were noted to have clinically significant improvements in these parameters.
•Incontinence responders: These were defined as patients who achieved a 50% or greater reduction from baseline in the number of incontinence episodes per week. This response rate was chosen because it exceeds the expected placebo response rate in clinical trials, which is 30-50%.
•Frequency of micturition responders: These were defined as patients who achieved a normal frequency of micturition (<8 micturitions per day) using the International Continence Society (ISC) definition at the time of the studies. Studies A1371041 and A1371047 had response defined as achieving at least three dry days per week (of those subjects with zero dry days at baseline) as an additional response evaluation.
An assessment of patient reported outcomes (PRO) was made using the King's Health Questionnaire (KHQ) and a new instrument, the patient perceived quality of treatment (PPQT) questions.
The KHQ is a disease-specific health-related QoL questionnaire.
Patient Perceived Quality of Treatment (PPQT) has been developed as a method for assessing patient satisfaction in conjunction with the disease-specific quality o life measures used in clinical trials.
The PPQT instrument was validated using data from Study A1371002.

Sample size

A total of 2078 subjects were enrolled in the four pivotal studies. Of these patients, 64.2% were randomised to darifenacin (3.75 mg, 7.5 mg, 15 mg, 30 mg), 10.7% to active (tolterodine) group and 24.9% to placebo arm. The mean age of the study population was between 53 and 65 years and patient were predominantly female (79-90%). The majority of patients were Caucasian.
In study A137 1002, a total of 439 patients were randomized (109 to placebo, 108 to darifenacin 7.5mg, 107 to darifenacin 15mg and 115 to darifenacin 30mg).
For study A137 1041, 561 patients were randomized (164 to placebo, 53 to darifenacin 3.75mg, 229 to darifenacin 7.5mg and 115 to darifenacin 30mg).
For study A137 1001, 680 patients were randomized (115 to placebo, 112 to darifenacin 15mg, 230 to darifenacin 30mg and 223 to tolterodine).
For study A137 1047, 398 patients were randomised (129 to placebo, 269 to darifenacin).

Randomisation

A randomisation list was produced with an equal (1002) /unequal (1041, 1001, 1047) allocation randomisation ratio using a block size of six-eight-ten. The randomisation was not stratified by any factor, although complete blocks of subject numbers and medication packs were issued to each recruiting centre.

Blinding

These were double blind studies with (two or four) treatment groups. The different dosages of darifenacin (7.5 mg, 15 mg, 30 mg) were distinguishable by the colour and shape of the tablets. Tolterodine was supplied as white capsules. Blinding was maintained by inclusion of matching placebos for the non-active dosage forms (double dummy design).

Statistical methods

The primary time point for analysis was Week 12.
Two efficacy populations were defined in the individual studies. These were the full analysis set (FAS), including all subjects who were randomised, took at least 1 dose of medication and had some bladder diary data a baseline and postbaseline efficacy assessment and the per-protocol set (PPS), defined as those subjects from the FAS who adhered to the major aspects of the protocol. The FAS is not a true ITT population, as one would expect. Even if due to the small number of discontinuations it is likely that there are no much differences between both analyses, a true ITT analysis was requested. The analysis provided evidenced that the ITT results were essentially identical to those obtained from the FAS.

In the individual studies, for tests that relate to the assessment of superiority, the FAS was the primary population and the PPS was a secondary population. Both the per-protocol and the FAS analyses used the last-observation-carried-forward (LOCF) algorithm where efficacy data were missing.

Studies A1371041 and A1371047: An additional population, the intent-to-treat population, was defined as all randomised subjects, regardless of whether treatment was received or whether data were collected. Primary and secondary endpoints were also analysed using the all randomised subjects population to assess the robustness of results from the full analysis set.

The comparability of the treatment groups at baseline was assessed using descriptive statistics. No significance testing between the treatment groups was performed. Wherever possible, efficacy analyses were adjusted for baseline severity. Baseline severity of OAB was categorized using the baseline data of the primary efficacy variable as Mild to Moderate (<21 episodes of incontinence per week) and Severe (≥21 episodes per week). Age was examined split by both (<65 and ≥65) and (18-44, 45-64, 65-74 and ≥75). This second split by age was done for the meta-analysis only, because the number of subjects was insufficient in the individual studies for a useful comparison.

Statistical tests for the drug treatment groups against placebo were generally assessed at the 5% significance level, except for Study A1371001 in which the tests were assessed at the 2.5% significance level to manage multiple comparisons against placebo and the active comparator, tolterodine.
The assessment of non-inferiority of darifenacin compared with tolterodine was made only if superiority of darifenacin against tolterodine had not been first established.
Using the confidence interval for the darifenacin versus tolterodine contrast, non-inferiority was assessed by comparing the upper limit of the confidence interval to the pre-defined limit of non-inferiority, which was defined as 3 episodes of incontinence per week. If the upper limit was 3 or less then a conclusion of non-inferiority of darifenacin against tolterodine was made.

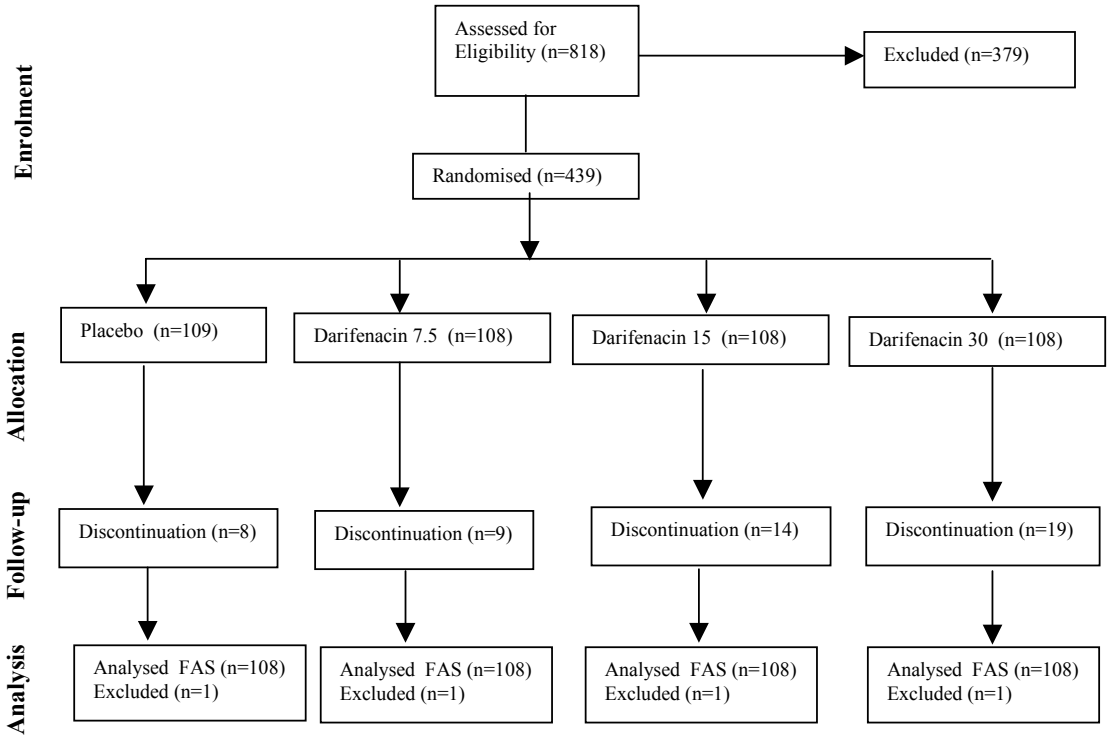
In Studies A1371002 and A1371041, a step down testing procedure was used for the efficacy data, where the testing of a lower dose was dependent upon significance (at 5%) being first found for the previous dose. A similar stepped testing strategy was applied where darifenacin 30mg and 15mg were compared with placebo and tolterodine in Study A1371001. In this study all tests were done at the (two sided) 2.5% significance level. Darifenacin 15mg and 30mg were first tested against placebo. Each dose that was found to be significantly better than placebo was then tested against tolterodine. Non-inferiority testing was to be performed for the primary efficacy endpoint if the dose was found not superior to tolterodine.
In addition analyses at Week 2 were also performed for the primary variable and all secondary variables, except the incontinence and frequency of micturition responders, in order to examine the efficacy at this early time point.
These were secondary efficacy analyses to the Week 12 analyses
Data from only the fixed dose, placebo controlled, 12 week studies with similar design (A1371002, A1371041 and A1371001) were pooled. The pooled analyses did not include data from the double blind, 12 week dosing regimen Study A1371047.
No statistical analysis of long-term data was performed, and only descriptive statistics of the data are presented in the summary.

RESULTS

Study A137 1002

A multicenter double blind (12 week), placebo controlled, randomized, parallel group, fixed dose comparison study of controlled release darifenacin (7.5mg, 15mg and 30mg od) in patients with OAB.

Participant flow



Recruitment

Males and females (using adequate contraception if of child bearing potential), aged 18 years and older (actual ages 21 to 88 years) with symptoms of overactive bladder (UUI) for at least six months prior to entry in the study.

Numbers analysed

In total 439 patients were randomised (109 to placebo, 108 to darifenacin 7.5mg, 107 to darifenacin 15mg and 115 to darifenacin 30mg). Of the 439 patients, 50 (11.4%) were discontinued. Insufficient therapeutic effect led to a premature discontinuation in one (0.9%) darifenacin 7.5mg, two (1.9%) in 15mg group and one (0.9%) in darifenacin 30mg, and 2 (1.8%) placebo subjects. Adverse events led to a premature discontinuation in 2.8% of the placebo group and 1.9%, 5.6% and 11.3% in 7.5 mg, 15 mg and 30 mg groups, respectively.

The full analysis set for efficacy analyses included 436 subjects (99.3% of subjects who took medication). The per protocol set for efficacy excluded 9, 11, 16, 8 subjects in the placebo, 7.5mg, 15mg and 30mg groups, respectively.

Outcomes and estimation

At Week 12, statistically significant improvements in the number of incontinence episodes per week were seen, for patients on all 3 doses of darifenacin compared with placebo.

Relative to placebo there was a dose related reduction: darifenacin 7.5mg subjects improved by an average (median) of 2.8 episodes per week, darifenacin 15mg subjects improved by an average of 4.3 episodes per week and darifenacin 30mg subjects improved by an average of 6.3 episodes per week, representing 68.7, 76.5 and 77.3% reductions from baseline, respectively, compared with a reduction of 46.0% for subjects on placebo. The median reductions seen from baseline for the per protocol assessment, were similar to those observed for the full analysis set.

A large part of the reduction in the number of incontinent episodes per week seen at Week 12 was also evident by Week 2.

Average number of incontinent episodes per week - Week 2	*Double Blind Placebo N = 108*	*Darifenacin 7.5mg od N = 107*	*Darifenacin 15mg od N = 106*	*Darifenacin 30mg od N = 114*
Baseline median (median change)	16.1 (-3.8)	14.0 (-5.4)	17.3 (-7.6)	19.1 (-9.5)
Median percent change from baseline	-31.5%	-43.1%	-48.7%	-59.0%
Median treatment difference (95% CIs) *	-	-2.1 (-3.8,-0.3)	-3.8 (-5.6,-2.0)	-6.1 (-8.2,-4.1)
p-value for treatment difference ~	-	0.016	<0.001	<0.001

Source: Table 5.7.1
* CI - Confidence interval produced for Hodges-Lehmann estimate of treatment difference against placebo
~ Using Wilcoxon test of active group against placebo

Statistically significant benefits over placebo were seen in 7/9 secondary efficacy evaluations (number of micturitions per day, volume of urine passed per voiding, number and severity of episodes of urgency per day, number of nocturnal awakenings for OAB per week, number of incontinent episodes per week resulting in a change of clothing or pad and incontinence responders) for both darifenacin 30mg and 15mg and in 3/9 secondary efficacy evaluations for darifenacin 7.5mg (number of nocturnal awakenings due to OAB per week, number of incontinence episodes resulting in a change of clothing or pad and incontinence responders).

The analysis of incontinence responder rates at Week 12 showed that 67% of darifenacin 7.5mg subjects, 72% of darifenacin 15mg subjects and 75% of darifenacin 30mg subjects demonstrated at least a 50% improvement in the number of incontinent episodes compared with 49% on placebo ($p = 0.007$, 0.001 and $p<0.001$, respectively).

A similar examination of the proportion of responders defined by normalisation of micturition at Week 12 indicated 36% of darifenacin 7.5mg subjects, 39% of darifenacin 15mg subjects and 42% of darifenacin 30mg subjects demonstrated frequencies of micturition of less than eight per day compared with 31% on placebo. None of the comparisons of darifenacin with placebo was statistically significant.

For the Kings Health Questionnaire, darifenacin 30mg showed statistical difference from placebo in 6/9 domains (all except general health perceptions, physical limitations and personal relationships) and darifenacin 7.5mg and 15mg showed statistically significant benefits over placebo in 5/9 domains (social limitations, role limitations, sleep/energy, emotions and severity measures) and 2/9 domains (social limitations and severity measures) respectively.

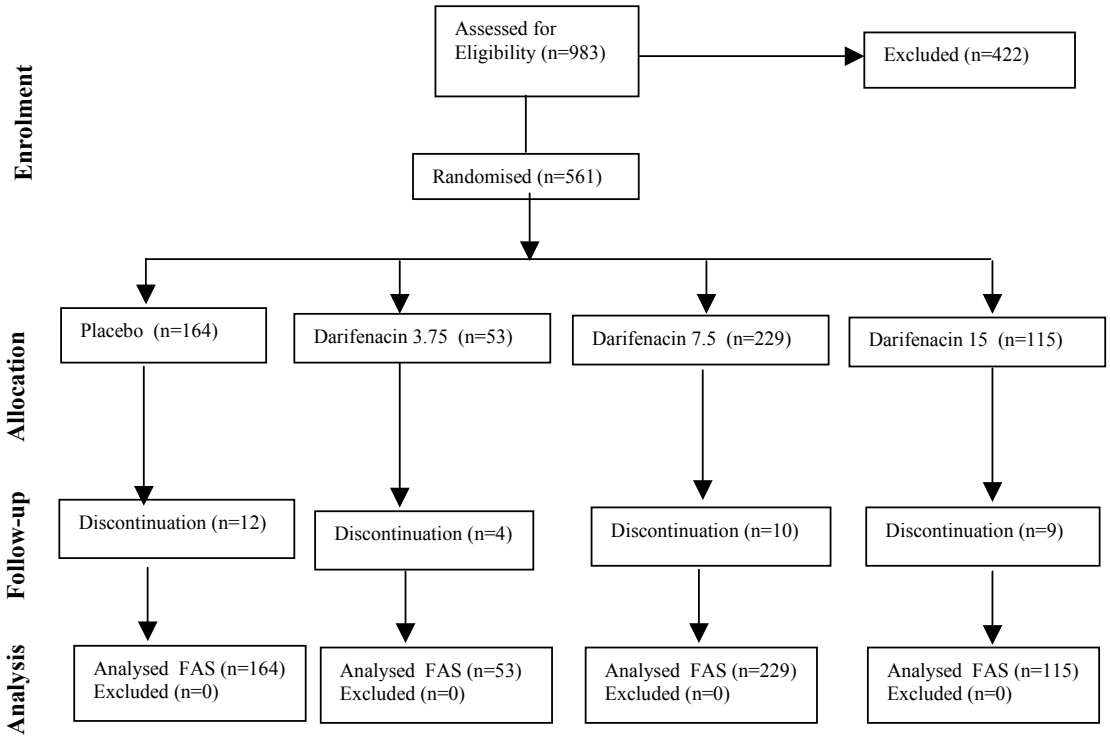
For the PPQT, all doses of darifenacin showed statistically significant benefits over placebo in patient satisfaction with treatment and patient preference for treatment. In addition darifenacin 30mg and 7.5mg showed statistically significant benefits over placebo in patient willingness to use medication again.

In conclusion, there was a consistent significant response for 15 and 30 mg doses in the majority of variables including the primary variable number of incontinence episodes per week. The effect of 7.5 mg was smaller and significant only in a few variables including the primary one. The effect was considerably less clear in the two patient reported outcomes measures.

Study A137 1041

A multicenter phase 3b double blind (12 week), placebo controlled, randomized, parallel group, fixed dose comparison study of controlled release darifenacin (3.75mg, 7.5mg and 15mg) in patients with OAB.

Participant flow



Numbers analysed

A total of 561 subjects were randomised to treatment, of which 35 (6.2%) discontinued. Six subjects (one placebo, one darifenacin 3.75mg, two darifenacin 7.5mg and two darifenacin 15mg) discontinued due to insufficient clinical response. Ten subjects (three placebo, one darifenacin 3.75mg, three darifenacin 7.5mg and three darifenacin 15mg) discontinued due to adverse events.

A total of 561 subjects were included in the full analysis set. In total, 62 (11.1%) subjects were excluded from the per protocol set (10.4%, 15.1%, 11.4% and 9.6% of subjects in the placebo, darifenacin 3.75mg, 7.5mg and 15mg groups, respectively).

Outcomes and estimation

At Week 12 both darifenacin 7.5mg and 15mg showed a statistically significant reduction in the number of incontinence episodes per week. Darifenacin 7.5mg subjects achieved an average (median) reduction of 9.0 incontinent episodes per week and darifenacin 15mg subjects a reduction of 10.4 episodes per week compared with an average reduction of 7.6 episodes in the placebo group. Subjects in the darifenacin 3.75mg group improved by an average of 8.6 episodes per week.

For all treatment groups, the median reductions from baseline for the per protocol population were similar to those observed for the full analysis set.

At Week 2, subjects treated with darifenacin 7.5mg and 15mg experienced statistically significantly greater reductions in the frequency of incontinent episodes per week than subjects treated with placebo (–2.0, p=0.003 for darifenacin 7.5mg and –4.0, p<0.001 for darifenacin 15mg). There was a dose

dependent reduction in the number of incontinent episodes per week in the darifenacin groups compared with placebo at Weeks 2 and 12. The dose response was not statistically significant (p=0.049).

In addition, at Weeks 12 and 2, patients treated with darifenacin 7.5mg and 15mg had statistically greater improvements in the average number of micturitions per day, average volume of urine passed per void, average number of episodes and average severity of urgency per day compared with patients treated with placebo. In addition, at Weeks 12 and 2, statistically significant improvements in number of incontinent episodes per week resulting in a change of clothing or pad (all patients and patients with more than 1 episode per week at baseline) and normalised micturition frequency (average number of micturitions required to void 1000ml, only Week 2 for darifenacin 7.5mg) were experienced by patients treated with darifenacin 7.5mg and 15mg compared with patients treated with placebo.

The results of the per protocol analysis were very similar to the results obtained using the full analysis set

Table 2. Study A1371041, LOCF, FAS

Week 12

Dose	N	Median base-line	Median change from baseline	Median differen-ce from placebo	95% CI	P value
Number of incontinence episodes per week						
Placebo	163	16.6	-7.6	--	--	--
Darifenacin 3.75mg *od*	53	16.0	-8.6	-0.7	(-3.0, 1.2)	--
Darifenacin 7.5mg *od*	228	16.3	-9.0	-1.5*	(-3.0, -0.4)	0.010
Darifenacin 15mg *od*	115	17.0	-10.4	-2.1*	(-3.5, -0.3)	0.017
Number of micturitions per day						
Placebo	163	10.1	-0.8	--	--	--
Darifenacin 3.75mg *od*	53	10.4	-1.7	-0.6	(-1.2, 0.0)	--
Darifenacin 7.5mg *od*	228	10.1	-1.6	-0.8*	(-1.2, -0.4)	<0.001
Darifenacin 15mg *od*	115	10.1	-1.7	-0.9*	(-1.4, -0.4)	<0.001
Number of episodes of urgency per day						
Placebo	163	8.3	-0.9	--	--	--
Darifenacin 3.75mg *od*	53	7.5	-1.8	-0.5	(-1.3, 0.5)	--
Darifenacin 7.5mg *od*	228	7.7	-2.0	-0.9*	(-1.5, -0.4)	0.001
Darifenacin 15mg *od*	115	8.0	-2.0	-0.9*	(-1.5, -0.3)	0.005
Average volume of urine passed per void (ml)						
Placebo	153	162.4	7.6	--	--	--
Darifenacin 3.75mg *od*	52	162.1	5.4	-0.8	(-12.6, 10.3)	--
Darifenacin 7.5mg *od*	220	160.2	14.9	9.1*	(0.4, 17.8)	0.040
Darifenacin 15mg *od*	110	151.8	30.9	20.7*	(9.6, 32.6)	<0.001

Source: Study report: A1371041 Tables 5.1.3 & 5.2.3.

* The difference between darifenacin and placebo was statistically significant (p<0.05), Wilcoxon test.

There was a non significant higher percentage of incontinence responders in the darifenacin groups than in the placebo group; 57% of darifenacin 3.75mg subjects, 65% of darifenacin 7.5mg subjects and 65% of darifenacin 15mg subjects responded at Week 12 compared with 54% of subjects on placebo.

There was a non significant higher percentage of responders defined by normalisation of micturition in the darifenacin groups than in the placebo group; 30% of darifenacin 3.75mg subjects, 33% of darifenacin 7.5mg subjects and 31% of darifenacin 15mg subjects responded at Week 12 compared with 24% of subjects on placebo.

There was a non significant higher percentage of responders defined by at least three dry days per week (for subjects with no dry days at baseline) in the darifenacin groups than in the placebo group; 53% of darifenacin 3.75mg subjects, 43% of darifenacin 7.5mg subjects and 49% of darifenacin 15mg subjects responded to treatment at Week 12 compared with 38% of subjects on placebo.

None of the comparisons of darifenacin with placebo reached statistical significance.

Analyses of the change from baseline in responses to the Kings Health Questionnaire showed that subjects treated with darifenacin 7.5mg and 15mg had statistically significant improvements in the incontinence impact, role limitations, social limitations and severity measures domains compared with placebo. Subjects treated with darifenacin 15mg also had a statistically significant improvement in the emotions domain compared with subjects treated with placebo.

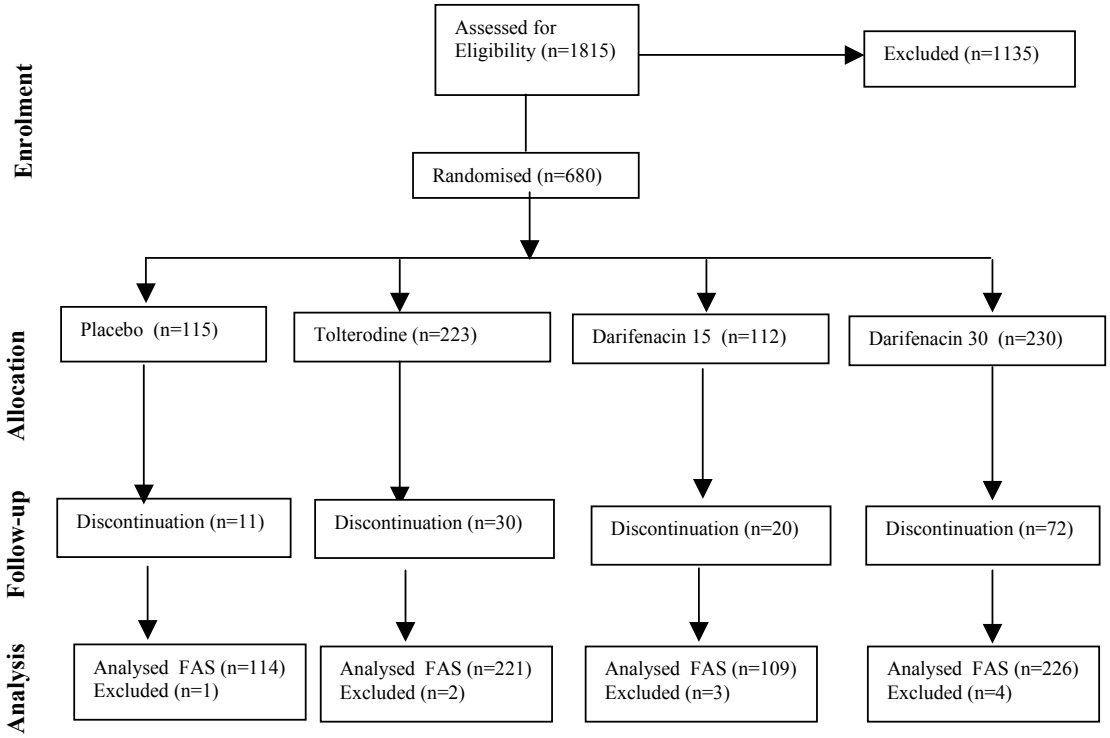
Statistically significantly more subjects treated with darifenacin 7.5mg and 15mg were satisfied with study treatment and more willing to re-use study treatment than subjects treated with placebo. In addition, a higher proportion of subjects in these groups preferred study treatment to their previous treatment compared with subjects in the placebo group (71% of subjects in both darifenacin groups compared with 63% of subjects in the placebo group).

In conclusion, the study shows a consistent response on many of the symptom effects, compared to placebo.

Study A137 1001

A multicenter, double blind (12 week), placebo controlled, parallel group study to compare the clinical efficacy of controlled release darifenacin (15mg od and 30mg od) with tolterodine (2mg bid) and placebo in patients with OAB.

Participant flow



Recruitment

Males and females (using adequate contraception if of child bearing potential), aged 18 years and older (actual ages 21 to 93 years) with symptoms of overactive bladder for at least six months prior to entry in the study.

Numbers analysed

A total of 680 subjects were randomised to treatment. Of them, 133 (19.6%) discontinued treatment. Overall, a greater percentage of subjects discontinued in the darifenacin 30mg group (31.3%) than in the darifenacin 15mg (17.8%), tolterodine (13.5%) and placebo groups (9.6%).One (0.9%) darifenacin 15mg od, one (0.4%) darifenacin 30mg od, one (0.4%) tolterodine 2mg bid and two (1.7%) placebo subjects withdrew because of insufficient clinical response. Ninety-three subjects discontinued due to adverse events: 8 (7.1%) darifenacin 15mg od, 64 (27.8%) darifenacin 30mg od, 17 (7.6%) tolterodine 2mg bid and 4 (3.5%) placebo subjects.

The full analysis set for efficacy analyses included 670 subjects (98.5% of subjects who took medication). There were a total of 572 subjects in the per protocol set: 98, 180, 188 and 106 subjects in the darifenacin 15 and 30mg, tolterodine and placebo groups, respectively.

Outcomes and estimation

The median reductions observed from baseline to Week 12 were 11.4 (83.3%) and 12.6 (81.7%) episodes per week for darifenacin 15 and 30mg subjects, respectively, compared with 10.3 (73.7%) episodes per week for tolterodine and 9.0 (70.9%) for placebo subjects. There was a statistically significant reduction in the number of incontinent episodes per week for darifenacin 30mg subjects compared with placebo ($p<0.001$) at Week 12 but not for darifenacin 15mg compared with placebo (p

Table 3. Study A1371001, LOCF, FAS

Week 12

Dose	N	Median base-line	Median change from baseline	Median differen-ce from placebo	97.5% CI	P value
Number of incontinence episodes per week						
Placebo	113	15.5	-9.0	--	--	--
Darifenacin 15mg *od*	109	16.2	-11.4	-2.4	(-5.2, 0.3)	0.049
Darifenacin 30mg *od*	225	18.5	-12.6	-4.2*	(-6.7, -1.9)	<0.001
Tolterodine 2mg *bid*	221	17.0	-10.3	-1.5	(-3.6, 0.8)	ND
Comparison with tolterodine						
Darifenacin 15mg *od*				-0.9	(-3.4, 1.4)	ND
Darifenacin 30mg *od*				-2.7	(-4.8, -0.8)	0.002*
Number of micturitions per day						
Placebo	114	10.4	-1.2	--	--	--
Darifenacin 15mg *od*	109	10.5	-1.9	-0.5	(-1.1, 0.1)	0.076
Darifenacin 30mg *od*	225	10.4	-1.9	-0.5	(-1.1, 0.1)	0.047
Tolterodine 2mg *bid*	221	10.4	-2.0	-0.5	(-1.0, 0.1)	ND
Comparison with tolterodine						
Darifenacin 15mg *od*				0.0	(-0.6, 0.5)	ND
Darifenacin 30mg *od*				0.0	(-0.5, 0.4)	ND
Number of episodes of urgency per day						
Placebo	113	8.5	-1.9	--	--	--
Darifenacin 15mg *od*	109	8.6	-2.6	-0.7	(-1.6, 0.1)	0.061
Darifenacin 30mg *od*	225	8.7	-2.7	-0.9*	(-1.7, -0.1)	0.014
Tolterodine 2mg *bid*	221	8.6	-2.3	-0.5	(-1.3, 0.3)	ND
Comparison with tolterodine						
Darifenacin 15mg *od*				-0.3	(-1.1, 0.6)	ND
Darifenacin 30mg *od*				-0.4	(-1.0, 0.3)	0.198
Volume of urine passed per void						
Placebo	111	147.1	4.6	--	--	--
Darifenacin 15mg *od*	107	155.0	26.7	20.1*	(5.6, 34.4)	0.002
Darifenacin 30mg *od*	219	171.5	40.0	34.6*	(22.8, 46.6)	<0.001
Tolterodine 2mg *bid*	219	164.6	21.6	15.0	(4.0, 25.9)	ND
Comparison with tolterodine						
Darifenacin 15mg *od*				5.3	(-8.3, 18.8)	0.379
Darifenacin 30mg *od*				19.9*	(9.4, 30.4)	<0.001

Source: Study report: A1371001 Tables 5.1.3 & 5.2.3.
* The difference between darifenacin and placebo/tolterodine was statistically significant ($p<0.025$).
ND: Not done due to step down testing procedure.

= 0.049) [0.025 was the pre-established significance level due to multiple comparisons].

The comparison of darifenacin 30mg with tolterodine also reached statistical significance ($p = 0.002$). In accordance with the step down strategy darifenacin 15mg, was not tested against tolterodine. The median reductions seen from baseline were similar to those observed for the full analysis set discussed above.

Efficacy was also observed by Week 2, particularly for subjects on darifenacin 30mg, for which the reduction in the number of incontinent episodes per week seen at Week 12 was also evident by Week 2. The median reductions observed from baseline to Week 2 were 8.9 and 10.5 episodes per week for darifenacin 15 and 30mg subjects, respectively, compared with 7.3 episodes per week for tolterodine and 5.9 for placebo subjects. There was a statistically significant reduction in the number of incontinent episodes per week for both darifenacin 15mg and darifenacin 30mg subjects compared with placebo at Week 2, however only the subsequent comparison of darifenacin 30mg with tolterodine reached statistical significance.

In seven out of ten secondary endpoints, darifenacin 30mg showed statistically significant efficacy over placebo. In particular, darifenacin 30mg was statistically more effective than placebo in the average volume of urine passed per voiding and the average number of episodes of urgency per day. The endpoints that did not show statistical significance were the average number of micturitions per day, the average number of nocturnal awakenings for OAB per week and responders defined by normalisation of micturition. Also, for two secondary endpoints (the average volume of urine passed per voiding and the maximum volume voided), darifenacin 30mg was statistically significantly better than tolterodine. Darifenacin 15mg was statistically significantly more effective than placebo for two secondary endpoints (the average volume of urine passed per voiding and the severity of urgency) although in both cases the comparison with tolterodine was not statistically significant.

Examination of the proportion of responders defined by relative improvement in incontinent episodes at Week 12 indicated that, despite a high placebo response, statistically significantly more subjects improved on darifenacin 30mg than on placebo (73% and 81% of darifenacin 15 and 30mg subjects, respectively, and 72% of tolterodine subjects demonstrated at least a 50% improvement in the number of incontinent episodes, compared with 66% for placebo subjects). The comparison of darifenacin 30mg with tolterodine was not statistically significant. The comparisons of darifenacin 15mg with placebo were not statistically significant.

A similar examination of the proportion of responders defined by normalisation of micturition at Week 12 indicated 35% of darifenacin 15mg subjects, 39% of darifenacin 30mg subjects and 38% of tolterodine subjects demonstrated frequencies of micturition of less than eight per day. Neither of the comparisons of darifenacin with placebo reached statistical significance.

Responders defined by relative improvement in incontinent episodes (≥50%) - Week 12	*Darifenacin 15mg od N = 109*	*Darifenacin 30mg od N = 225*	*Tolterodine 2mg bid N = 221*	*Double Blind Placebo N = 113*
Number of Responders (%)	80 (73%)	182 (81%)	160 (72%)	75 (66%)
Odds Ratio (97.5% CIs*) vs placebo	1.4 (0.7,2.7)	2.1 (1.2,3.9)	1.3 (0.8,2.3)	-
p-value vs placebo	0.255	0.004	0.255	-
Odds Ratio (97.5% CIs*) vs tolterodine	1.1 (0.6,1.9)	1.6 (1.0,2.7)	-	-
p-value vs tolterodine	-	0.035	-	-
Responders defined by normalisation of micturition (<8 per day) - Week 12	***Darifenacin 15mg od N = 109***	***Darifenacin 30mg od N = 225***	***Tolterodine 2mg bid N = 221***	***Double Blind Placebo N = 114***
Number of Responders (%)	38 (35%)	87 (39%)	85 (38%)	35 (31%)
Odds Ratio (97.5% CIs*) vs placebo	1.2 (0.6,2.3)	1.4 (0.8,2.5)	1.4 (0.8,2.4)	-
p-value vs placebo	0.508	0.150	0.161	-
Odds Ratio (97.5% CIs*) vs tolterodine	0.9 (0.5,1.5)	1.0 (0.7,1.6)	-	-
p-value vs tolterodine	-	-	-	-

Source: Table 5.5
* CI - Confidence interval

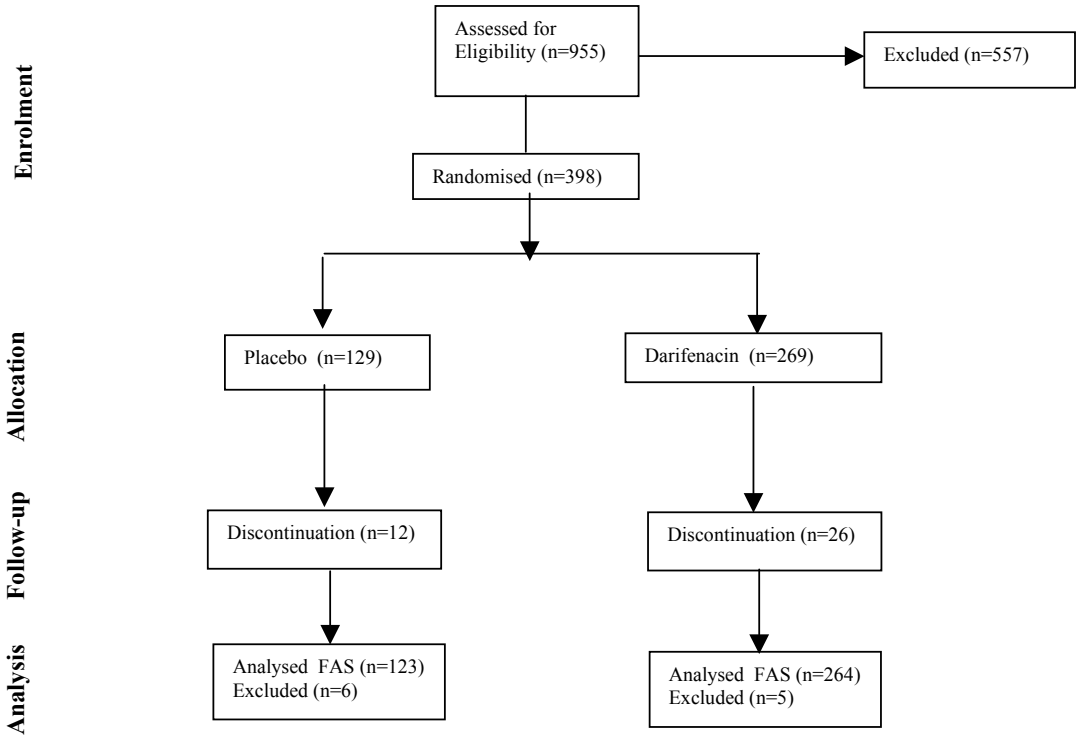
Darifenacin 15mg showed statistically significant efficacy over placebo in three out of nine domains of the Kings Health Questionnaire (incontinence impact, role limitations and severity measures). Darifenacin 30mg showed statistically significant benefits over placebo in two out of nine endpoints (incontinence impact and role limitations). None of the subsequent comparisons of darifenacin with tolterodine reached statistical significance.

Both darifenacin doses were statistically better than placebo in the patient satisfaction with treatment and patient willingness to use treatment again evaluations.

Study A137 1047

A multicenter, phase 3b double blind (12 week), upward dose titration, placebo controlled, parallel group study of darifenacin 7.5mg and 15mg in patients with OAB.

Participant flow



Recruitment

Male and female (using adequate contraception if of child bearing potential), aged 18 years and older (actual ages 22 to 89)with symptoms of OAB for at least six months prior to entry in the study.

Numbers analysed

A total of 398 patients were randomised to receive 7.5mg darifenacin or placebo on a once daily basis for 12 weeks. After two weeks of treatment, the investigator and the subject assessed the efficacy and tolerability achieved. Upward dose adjustment to 15mg od darifenacin (for subjects randomised to darifenacin), or placebo (for subjects randomised to placebo), was allowed at this time.

Of the 395 subjects randomised and who received treatment, 38 (9.6%) were discontinued. Two (0.7%) darifenacin and one (0.8%) placebo subjects withdrew because of insufficient clinical response. In addition, 22 discontinued due to adverse events, 18 (6.7%) darifenacin and 4 (3.1%) placebo subjects.

A total of 158 (59.0%) darifenacin and 86 (67.7%) placebo subjects dose escalated.

The full analysis set included 387 subjects (97.2% of randomised subjects), of which 264 were in the darifenacin group and 123 in the placebo group. Eleven additional subjects were included in the all randomised subjects population compared to the full analysis set. The results for the primary endpoint, all randomised subjects, are very similar to that seen for the full analysis. In total, 73 (18.9%) subjects included in the full analysis set were excluded from the per protocol set (17.8% in the darifenacin group and 21.1%in the placebo group).

Outcomes and estimation

Subjects treated with darifenacin experienced statistically significantly greater reductions in the frequency of incontinent episodes per week than subjects treated with placebo (-1.4; p = 0.035). The median reductions from baseline to Week 12 were 8.2 episodes per week for darifenacin subjects compared with 6.0 episodes per week for subjects on placebo representing a 62.9% reduction from baseline for darifenacin subjects compared with a reduction of 48.1% for placebo subjects.

Average number of incontinent episodes per week - Week 12	*Darifenacin N = 261*	*Placebo N = 123*
Baseline median (median change)	16.0 (-8.2)	14.0 (-6.0)
Median percent change from baseline	-62.9%	-48.1%
Median treatment difference (95% CIs) *	-1.4 (-2.9, -0.0)	-
p-value for treatment difference ~	0.035	-

Source: Table 5.1.3
* CI - Confidence interval produced for Hodges-Lehmann estimate of treatment difference against placebo
~ Using stratified Wilcoxon test of active group against placebo

At the same time the upper limit of the 95% confidence interval is very close to 0, this is because of a large number of tied observations between the two treatment groups.

At Week 2, statistically significant improvements were seen in the primary efficacy evaluation. Subjects treated with darifenacin experienced statistically significantly greater reductions in the frequency of incontinent episodes per week than subjects treated with placebo (-1.4; p = 0.042).

For both treatment groups, the median reductions from baseline for subjects on a per protocol basis were similar to those observed for the full analysis set discussed above.

At Week 12, subjects treated with darifenacin had statistically significant greater improvements in the average number of micturitions per day, the average volume of urine passed per voiding, the average number of episodes of urgency per day, the average severity of urgency per day, the number of incontinent episodes per week resulting in a change of clothing or pad (all subjects and those with a baseline >0) and normalised micturition frequency (average number of micturitions required to void 1000 ml)

There was a higher percentage of responders defined by a relative improvement in incontinent episodes in the darifenacin group than in the placebo group at Week 12: 62% of darifenacin subjects compared with 49% of placebo subjects.

There was a higher percentage of responders defined by normalisation of micturition in the darifenacin group than in the placebo group: 39%of darifenacin subjects responded at Week 12 compared with 23%of placebo subjects.

There was a higher percentage of responders defined by at least three dry days per week in the darifenacin group than in the placebo group:30%of darifenacin subjects responded to treatment at Week 12 compared with 23% of placebo subjects.

For the KHQ, darifenacin was statistically significantly better than placebo in 3/9 domains (role limitations, physical limitations and social limitations).

Darifenacin showed statistically significant benefits over placebo in patient satisfaction with treatment and patient willingness to use medication again [PPQT 2/3 positive results].

- Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis has been performed for the main pivotal clinical studies.

Dose	N	Median baseline	Median change from baseline	Median difference from placebo	95% CI	P value
Placebo (1002 &1041)	271	16.6	-7.0	--	--	--
Darifenacin 7.5mg *od*	335	16.0	-8.8	-2.0*	(-3.6, -0.7)	0.004
Placebo (1002, 1001 &1041)	384	16.6	-7.5	--	--	--
Darifenacin 15mg *od*	330	16.9	-10.6	-3.2*	(-4.5, -2.0)	<0.001
Placebo (1002 &1001)	221	15.6	-7.5	--	--	--
Darifenacin 30mg *od*	339	18.5	-12.5	-5.0*	(-6.6, -3.3)	<0.001
Placebo (1047)	123	14.0	- 6.0	--	--	--
Darifenacin 7.5mg→15mg	261	16.0	- 8.2	- 1.4*	(- 2.9, -0.0)	0.035

SCE-Tables 2.1, Study A1371047: table 5.1.3.
*The difference between darifenacin and placebo was statistically significant ($p<0.05$).
FAS: Full Analysis Set. LOCF: Last observation carried forward.

This pooled analysis clearly showed superiority of darifenacin 7.5 and 15 mg (and 30 mg which is not included in this application) *od* over placebo.

- Supportive studies

A number of supportive efficacy trials were conducted. These included 2 Phase 3 flexible dosing regimen studies (Studies A1371011 and A1371013) and a number of efficacy studies (Studies 137-312, 137-315 and 137-308). In addition 2 special studies evaluated the efficacy of darifenacin 30mg on urgency (Study A1371019) and nocturia (Study A1371027). The two showed significant differences for the high dose of 30 mg.
Two long-term studies (A137 311 and A137 1014) have been conducted for 52 and 40 weeks duration. Both showed maintained efficacy over time.

- Discussion on clinical efficacy

The Applicant has demonstrated an effect on the primary variable used for the pivotal studies (number of incontinence episodes per week). However, at the recommended doses, as with other antimuscarinic drugs, the size of the effect in relation to placebo is rather small, and casts doubts on its clinical significance. Also, with some definitions of "responder" based on the primary variable, the number needed to treat can appear high for a symptomatic treatment.

This is, however, a general concern on antimuscarinic drugs for the treatment of overactive bladder as further reflected in a systematic review published by Herbison et al. (BMJ; 326:841–7, 2003) where it is concluded that the "differences between anticholinergics and placebo may be of questionable clinical significance". Several products have been recently approved both via the centralised and mutual recognition procedures. It was considered, therefore, important to know whether the effect of darifenacin, at its proposed dosage, reaches, at least, the small level of effectiveness that is to be expected from anticholinergics and whether this is done with a safety profile sufficiently reassuring so as to justify a near marginal therapeutic effect.

The Applicant has addressed the issue of clinical relevance, mainly by reanalysing the data on the King's Health Questionnaire (KHQ) that was a secondary variable in the pivotal trials. The issue of the validity of the KHQ can now be considered sufficiently addressed in relation to the parallelism observed between the improvements observed with it and those seen in the main variable. This would confirm that the improvements in the questionnaire are, indeed, related to the effect of the drug on incontinence

The dose of 30 mg (not to be marketed) is now excluded from the analysis. There is a dose response relationship as the 30 mg results confirmed: (it was considerably more effective but rejected for tolerability reasons). But it would appear that 7.5 and 15 mg are still in the low slope part of the dose response curve while 30 mg would be in the steep part and would have greater efficacy.

It is however accepted that it is possible to increase on an individual basis 7.5 mg up to 15 mg in case of non-response, as it is proposed by the Applicant.

Little comparative data has been obtained during the development of darifenacin, and upon CHMP request, new analyses on the relative effects of darifenacin and other anticholinergics were provided.

There is only a pivotal trial (A1371001) where an active comparator (tolterodine 2 mg bid) was included, but in this study, only darifenacin 30 mg od was significantly better both than tolterodine and placebo and neither darifenacin 15 mg nor tolterodine were significantly better than placebo. Tolterodine itself was, also, apparently noneffective which casts doubts on the validity of the study. The inconsistency with previous studies (where 15 mg were significantly better than placebo) is claimed to be due to the fact that a substantial part of the effect can be achieved with placebo

A further Poisson analysis of study A137001 has now been submitted. Although there are some uncertainties on the statistical plan for significance, the differences between darifenacin and placebo appear to be statistically significant. However, it is difficult to give more weight to a study after reanalysis.

In order to further explore this issue, the Applicant has performed a comparison of Darifenacin with the Herbison meta-analysis (Herbison et al., 2003) an independently conducted and published meta-analysis on anticholinergics as treatment for OAB, where trials comparing mean daily reduction in incontinence episodes over placebo were reviewed. Some indication of whether the effect of darifenacin falls within what is expected from an anticholinergic drug is found in this comparison. It provides some evidence that the effect of darifenacin (at the 15 mg dose) is likely similar to that of other marketed anticholinergic substances, however questionable the latter may be in the opinion of the authors of the meta- analysis.

The analysis in relation to perceived cure or improvement of symptoms in the case of darifenacin is of limited value given the use of the PPQT, a scale which has not been validated with drugs other than darifenacin. The results calculated by the Applicant from the published meta-analysis and for darifenacin are both close to six as the number of patients needed to be treated for one patient reporting perceived cure or improvement in symptoms over placebo. This appears rather high, but not only for darifenacin.

Scores in the KHQ or different definitions of responder based on improvement in symptoms were considered as the basis for further analyses; the usefulness of comparing published results is limited because of the different definitions of responders and ways of assessing used in several of the trials. Darifenacin data, however appear to fit within those extremely variable profiles of other drugs.

As a conclusion, although demonstrative face-to-face comparisons are still lacking, the recent availability of an independently conducted and published meta-analysis on anticholinergics as treatment for OAB has made it simpler to put in context the, obtained results with darifenacin.

From the three main darifenacin studies, it appears that darifenacin fits sufficiently with what is expected from anticholinergics in general for OAB.

The use of darifenacin in the elderly population was further discussed by the CHMP. Response in the elderly in terms of incontinence episodes seems similar to that in the other age groups, although it appears to be somewhat lower with 7.5 mg (making it likely that more patients in this age group will require up-titration to 15 mg) and it appears to translate less into a measurable improvement in quality of life. No specific cause for concern has been identified in relation to safety (see safety section).

Clinical safety

The clinical development program for darifenacin in OAB began in 1991 using the immediate release (IR) formulation. The IR formulation was superseded by early development of a prolonged release

(PR) formulation for once daily (od) dosing. The OAB Phase 3 program started in 1999 using only the PR formulation. Both formulations of darifenacin were also evaluated in the irritable bowel syndrome (IBS).

The cut-off data for studies to be included in the integrated darifenacin database was 31 January 2003. The cut-off data for deaths and other serious adverse events (SAEs) was 09 February 2003.

- Patient exposure

The integrated darifenacin database includes a total of 7257 subjects treated with darifenacin derived from 95 clinical studies completed prior to the cut-off date of January 2003.

Several safety data sets were defined:
a) OAB fixed dose Phase 3 studies: This has been considered as the primary dataset. It includes data from the fixed dose placebo controlled Phase 3 studies, A1371001, A1371002 and A1371041.b) OAB placebo controlled studies.

c) Phase 2/3 OAB/IBS studies: it contains a variety of formulations (IR, CR and iv) and indications (IBS, OAB, BPH and UUI).

d) Long term studies: it uses data from the uncontrolled OAB studies 137-311 and A1371014, and Study 137-359, a six month study in IBS subjects.

A number of studies were not included in the integrated presentation of safety data. It should be clarified that no unexpected and/or serious adverse events were reported in them

- Adverse events

The incidence and severity of the common treatment-emergent (all causality) adverse events were assessed at the recommended therapeutic doses (7.5mg and 15mg) as well as the higher 30mg dose in three placebo controlled fixed dose OAB studies (A1371001, A1371002 and A1371041).

Approximately 60% of the patients treated with the doses of either 7.5mg or 15mg of darifenacin experienced adverse drug reactions during Phase 3 clinical development. Most of these were mild or moderate and transient, and only a few of them resulted in discontinuation.

In darifenacin treated subjects, the most common adverse events which occurred more frequently than placebo were dry mouth, constipation and dyspepsia. This finding was consistent throughout the development program. A dose relationship was seen with these common adverse events.

The majority of darifenacin treated subjects who reported dry mouth and constipation did so within the first two weeks of starting treatment.

<u>Dry mouth</u>
Dry mouth is the adverse event most commonly reported as a consequence of antimuscarinic therapy. It was the most commonly reported adverse event in the darifenacin clinical program. It appeared in 20.2% and 35% for the 7.5 and 15 mg dose, respectively vs. 8% in the placebo group.

Most of the patients required no treatment or other actions, and of those who did, half had a cleared outcome. Of the 7.5mg treated subjects, no patients discontinued due to dry mouth and of the 15mg treated subjects, only three patients (0.9%) discontinued due to dry mouth. Dry mouth is an annoying but no severe adverse reaction, and if patients are informed, this adverse reaction can be bore, either with or without treatment.

Constipation

Constipation was the second most commonly reported adverse event in the darifenacin clinical program.

There is an apparent relationship between the dose of darifenacin and the incidence of constipation with frequencies of 14.8%, 21.3%, 38.8% for 7.5mg, 15mg and 30mg, respectively, compared to 5.4% in the placebo group.

The majority of darifenacin treated subjects who reported constipation did so within the first two weeks of starting treatment.

No serious complications have been caused by this adverse event, however possible problems cannot be excluded when the product is given to a larger population, which is not as closely followed as the study population.

Only 2 patients (0.6%) discontinued due to constipation in the 7.5mg treatment group, and only 4 patients (1.2%) in the 15mg treated subjects 3 (0.9%)

Dyspepsia

Dyspepsia was the third most commonly reported adverse event in the darifenacin clinical program.

The majority of darifenacin treated subjects who reported dyspepsia did so within the first two weeks of starting treatment. Dyspepsia in 2.7%, 8.4%, 15.7% for 7.5mg, 15mg and 30mg, respectively, compared to 2.6% in the placebo group.

The most frequent action for subjects who experienced mild dyspepsia was 'no action'.

Dyspepsia was considered an important adverse event, leading to a considerable amount of treatments (mostly antacid treatment) and discontinuations. Dyspepsia is not life threatening and most of the time treatment resulted in relief of this adverse effect.

No patients discontinued due to dyspepsia in the 7.5mg treatment group, and only 3 (0.9%) of the 15mg treated subjects discontinued due to dyspepsia

Others adverse events

In the fixed dose OAB Phase 3 studies, occurrence of central nervous system adverse events was low for darifenacin and similar to placebo. A total of five cognitive function studies have been performed and similarly did not show changes vs placebo.

The incidence of cardiovascular adverse events in the darifenacin group was low and similar to that in the placebo group

Data on QT interval on 1225 patients was examined. In 964 darifenacin treated patients, there was no evidence that darifenacin caused a change in heart rate (mean difference from placebo = 0.1bpm) or a prolongation of the QTcF interval (mean difference from placebo = 0.3msec). Four out of 964 patients (0.4%) on darifenacin had a >60msec increase in QTcF from baseline compared with one out of 261 patients (0.4%) on placebo. Four male patients had maximum on treatment QTcF values of >450msec, although an underlying conduction defect was identified at baseline for all cases. No association was found between the change in QTcF from baseline and darifenacin free plasma concentrations up to 26-fold the mean exposure seen with 15 mg.

An additional cardiac safety study (DAR328 2302) was performed. This was a single centre, double blind, randomised, parallel group, placebo- and active-controlled (moxifloxacin), multiple-dose study in poor and extensive CYP2D6 substrate metabolisers. The objective of the study was to evaluate the effects of darifenacin on QTcF interval at steady-state concentrations (day 6 of treatment). A total of 179 patients were included in the study. The study results demonstrated a reassuring cardiovascular safety profile for darifenacin, with no concerns regarding QT/QTc prolongation at doses up to 75 mg/day (5 times the maximum therapeutic dose). The trend profiles for change in QT/QTc interval with increasing drug plasma concentration showed no increase with darifenacin. The mean change from baseline in QT interval and QTcF interval was not significantly different from placebo either overall or at Tmax.

- Serious adverse event/deaths/other significant events

Although the overall number of adverse events is rather high, the number of serious adverse events is low. There were two cases of atrioventricular block which should be followed in the future. Acute urinary retention is an adverse reaction of which most physicians could expect when treating patients with anti-muscarinic agents, and this does not seem to form a major problem for darifenacin. Nevertheless, it is important to keep this possible and potentially serious adverse reaction in mind. As rare adverse events may only be detected in a large population, they should be followed in the post-marketing phase as well, although so far no events of this type were considered darifenacin-related.

Four deaths were recorded during the darifenacin clinical program: liver and pancreatic cancer, hepatic failure, urinary bladder carcinoma and suicide by hanging. None of the four deaths were considered causally related to darifenacin treatment.

- Laboratory findings

There were no detectable patterns in the nature or incidence of observed laboratory test abnormalities, which would indicate a specific effect of darifenacin on any particular organ system or laboratory test parameter. These data do not indicate a concern with respect to the effect of administration of darifenacin on laboratory test parameters.

- Safety in special populations

Age: There were 207 patients aged ≥65 years compared with 464 patients aged <65 years treated with darifenacin 7.5mg or 15mg in the fixed dose Phase 3 OAB studies population. There was little difference between patients aged <65 years and ≥ 65 years in either the incidence (59% cf. 62%) or the severity (11% severe cf. 6% severe) of overall adverse events in the 7.5mg/15mg group. This is similar to the difference seen in the placebo group (48% cf. 51%). In addition, the discontinuation rate due to adverse events was higher in the older age group (2% cf. 5%).

Gender: There were 569 female patients compared with 102 male patients treated with darifenacin 7.5mg or 15mg in the fixed dose Phase 3 OAB studies population. The incidence of overall adverse events was a little higher in women compared with men (61% cf. 53%), although there was little difference in the severity of adverse events (10% severe cf. 7% severe) in the 7.5mg/15mg group. There was no difference in the discontinuation rate due to adverse events between the groups (3% cf. 4%).

Race: The vast majority of patients in the darifenacin development program were Caucasian. There were 644 Caucasian patients compared with 27 non-Caucasian patients treated with darifenacin 7.5mg or 15mg in the fixed dose Phase 3 OAB studies population. The adverse event and discontinuation data were examined according to the following racial groups: Caucasian, Black, Asian and Other. The incidence of adverse events was similar between the Caucasian and non-Caucasian populations, although the number of subjects in the non-Caucasian population is small.

CYP2D6 genotype: All patients participating in Phase 3 studies were assessed with respect to their CYP2D6 genotype, although not all samples were processed appropriately. There were 106 PM patients compared with 466 EM patients treated with darifenacin 7.5mg or 15mg in the fixed dose Phase 3 OAB studies population.

The incidence of overall adverse events was a little higher in EMs compared with PMs (61% cf. 52%), although there was little difference in the severity (8% severe cf. 9% severe). However, the discontinuation rate due to adverse events was a little higher in PMs compared with EMs (3% cf. 1%).

Renal and hepatic impairment: Darifenacin has been administered to patients with either renal or hepatic impairment in two Phase 1 studies designed to assess the effect of these impairments on the pharmacokinetic behavior of darifenacin. No difference in the adverse events was seen between patients with normal renal function and mild, moderate or severe renal impairment. Similarly, patients

with normal hepatic function and mild or moderate hepatic impairment did not show any difference in the adverse event profile.

- Safety related to drug-drug interactions and other interactions

Darifenacin is mainly cleared by hepatic metabolism, with only a small percentage excreted unchanged in the urine following oral and iv administration. Darifenacin is metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4.
The incidence and severity of adverse events was higher in both placebo and darifenacin patients that took either a CYP3A4 or CYP2D6 inhibitor at any time during the study compared with the whole population, although the results are difficult to interpret. Due to pharmacokinetic considerations, the concomitant use of strong CYP3A4 interactants and CYP2D6 interactants with narrow therapeutic window is to be used with caution.

- Discontinuation due to adverse events

In OAB fixed dose Phase 3 studies, 1.2%, 5.1% and 21.7% of the subjects discontinued due to treatment related adverse events in the 7.5mg, 15mg and 30mg dose group, respectively. In the comparator and placebo group, 7.6% and 2.6% of the subjects discontinued due to treatment related adverse events, respectively. The most common adverse events leading to discontinuation were dry mouth, constipation and dyspepsia.

The rates of discontinuation for all treatment related reasons were similar for subjects in long term studies and subjects treated with 30mg *od* darifenacin in fixed dose Phase 3 studies. The majority of subjects who discontinued did so in the first three months. Thereafter, the rates of discontinuation due to adverse events were low. There appeared to be no influence of age, race, gender or genotype on discontinuations from long-term studies.

- Long term safety

Additional safety data was provided from an interim analysis of study A1371042 and from study DAR328 2302. Study 1042 is 2-year open-label with patients from two feeder studies, A1371041 and A1371047, starting treatment at a dose of 7.5 mg with the option to dose-escalate to 15 mg after 2 weeks and or to up- or down escalate at every follow-up visit. The adverse events profile during long-term treatment with darifenacin was evaluated by time of first onset in 3-month intervals in both populations, and the event rates were shown to decrease over time. The apparent adverse event rates decline in the long term was somewhat to be expected when the results are adjusted in relation of years of exposure and even more when the adverse events reported are chronic (patients tend to report them mainly at the beginning). There were no increased risk associated with long-term exposure to the 7.5 mg and 15 mg doses of darifenacin in patients who have reached different timepoints along the treatment period up to >15 months.

Due to the low numbers of patients from 1 year, we can only conclude that darifenacin appears well tolerated in the long term only up to 12 months. No new adverse events were reported and the adverse events profile observed during long-term treatment was generally similar to what was previously seen in the OAB fixed dose phase 3 studies and all phase 2/3 OAB/IBS studies suggesting no increased risk associated with long-term darifenacin treatment.

- Discussion on clinical safety

Dry mouth, constipation, dyspepsia and headache were the four most common all causality adverse events reported in the pivotal clinical trials. In study A1371042, the incidence of the four most common adverse events was comparable that observed in the placebo group of the pooled OAB fixed dose phase 3 studies.

With regard to the central nervous and cardiovascular system the safety profile is maintained in study 1042

No new types of adverse events were seen in the new interim analysis, and the overall all causality adverse events rates were comparable to the observed in phase 3 studies. No deaths were reported during this new analyzed period. However, given that the efficacy of darifenacin at the proposed doses seems comparable to current marketed antimuscarinics, a fully reassuring safety profile is requested. In this sense, the additional cardiac safety study (DAR328 2302) has been considered very relevant.

The CHMP believes that the study population is rather extensive and representative of the target patient population. In summary, the safety profile appears comparable to that of other anti-muscarinic drugs. However, it is not known whether the selectivity for the M3 receptor translates into any clinical advantage when treating symptoms of overactive bladder syndrome**.**

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The active substance and product are defined and characterised in an acceptable way, typical for a modified release tablet. There are no unresolved quality issues, which may have an impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

The preclinical part of the dossier demonstrates that darifenacin is a selective antagonist of M3 receptors of acetylcholine, and that it inhibits human bladder contraction at concentrations consistent with the human exposure during treatment at recommended doses

Both the primary and secondary pharmacology of darifenacin have been well characterised, and adequate pharmacological studies have been performed to elucidate the antimuscarinic effects of darifenacin both *in vitro* and *in vivo* test.

The general pharmacology studies are appropriate to support the non-clinical pharmacology profile of darifenacin. Safety pharmacology studies have not given rise to any serious safety concern. Studies on cardiac repolarization, as well as in others systems and organs have been performed, and support the use of darifenacin in humans

From the pharmacokinetic point of view mice, rats, rabbits and dogs were the most relevant species for non-clinical efficacy and safety studies, and were exposed to darifenacin in relation to the highest exposure expected in the clinical situation. The non-clinical pharmacokinetics properties for darifenacin have been appropriately described. A number of studies concerning the absorption, distribution, metabolism, and excretion of darifenacin have been performed. Darifenacin showed extensive absorption by oral route, important first-pass effect, and extensive distribution. Metabolism occurs namely in the liver, involving CYP3A4 and CYP2D6.

Overall, the toxicology programme did not raise special concern. Dog was chosen as non-rodent species for use in toxicology programme. The observed toxicity is in part consequence of its pharmacological activity on M3 receptors. Adequate genotoxicity and carcinogenicity studies did not anticipate any potential hazard for the use of darifenacin in humans. Although darifenacin had no effect on fertility and no teratogenic action, and peri and post natal toxicity were observed at systemic exposure levels up to 11 times higher than the expected clinical exposure, the CHMP considered that darifenacin should not be recommended during pregnancy.

Efficacy

The efficacy of darifenacin in the treatment of overactive bladder (OAB) have been studied in 3 double blind, randomised, placebo controlled parallel group, fixed dose Phase 3 studies of 12-week treatment duration (Studies A1371002, A1371041 and A1371001) and one placebo controlled upward dose titration study (A1371047) The study protocols of the 3 pivotal studies were similar and allowed a pooled analysis.

The finally recommended dosage schedule is 7.5 mg once daily with optional up-titration to 15 mg. Dose selection was based on tolerability rather than on efficacy. Several doses were tested not only in the dose-finding phase 2 studies but also in phase 3 studies including "pivotal". Phase 2 and 3 studies (including pivotal) were consistent in finding a dose-response relationship on most variables, particularly on incontinence frequency.

The primary objective in the pivotal studies was to assess the clinical efficacy of 3 doses of darifenacin on symptoms of OAB. The secondary objective was to evaluate the safety and tolerability of darifenacin, to evaluate the population pharmacokinetics of darifenacin and to evaluate the effect of darifenacin on quality of life in subjects with overactive bladder. Additionally one of the studies compared the efficacy of darifenacin with tolterodine.

The analysis of efficacy relied on patient daries electronic diaries completion. The primary efficacy outcome was the frequency of incontinence episodes per week as measured after 12 weeks of treatment.

A statistical effect on the primary variable used for the pivotal studies was shown. However, at the recommended doses, the size of the effect in relation to placebo is rather small, and the clinical significance of the effect was thoroughly discussed at the CHMP. The lack of adequate results in the comparative study with tolterodine created also concern. The issue was discussed in written with the Applicant, and new post-hoc analyses on the relative effects of darifenacin and other anticholinergics were provided. The main data comes from a comparison of darifenacin with the published (Herbison) meta-analysis, an independently conducted meta-analysis on anticholinergics for treatment of OAB.Darifenacin appears to fit sufficiently with what is expected from anticholinergics in general for OAB. However, the clinical relevance of the demonstrated effect remains weak, even with this comparison, where the independent authors, question the marginal efficacy of anticholinergics for the treatment of this condition

Safety

The primary database for the evaluation of safety includes data from the three main placebo controlled studies. The incidence and severity of the common treatment-emergent (all causality) adverse events were assessed at the recommended therapeutic doses (7.5mg and 15mg) as well as the higher 30mg dose in three placebo controlled fixed dose OAB studies. The most common adverse events that occurred more frequently than placebo were dry mouth, constipation and dyspepsia.

Approximately 44% of the patients treated with the doses of either 7.5mg or 15mg of darifenacin experienced adverse drug reactions during Phase 3 clinical development. Most of these were mild or moderate and transient, and only a few of them resulted in discontinuation.

Contrary to the rather high number of adverse events, , the number of serious adverse events is low. No detectable patterns in the nature or incidence of observed laboratory test abnormalities, which would indicate a specific effect of darifenacin on any particular organ system or laboratory test parameter was found in the studies performed.

Additional long term safety data were provided by the Applicant, and no new types of adverse events were seen, and all-causality adverse events rates were comparable to that observed in phase 3 studies. Reassurance on lack of QT prolongation susceptibility has been provided by a recent specific study involving an active control (moxiflocacin)

In conclusion, the study population analysed for safety is rather extensive and representative of the target patient population. The safety profile appears similar to that of other anti-muscarinic drugs.

Although it was expected, it is not known whether this selectivity for the M3 receptor translates into any clinical advantage when treating symptoms of overactive bladder syndrome.

Benefit/risk assessment

Following evaluation of the documentation submitted it is concluded that data on pharmaceutical quality of the medicinal product is considered acceptable.

The nonclinical toxicology and safety pharmacology studies have not given rise to any serious safety concerns.

The pharmacokinetics of darifenacin was rather extensively studied and is judged to be sufficiently characterised.

Overall, the clinical programme of darifenacin in the treatment of OAB showed statistically significant effect in the pivotal studies. Although the clinical relevance of the effect of darifenacin at the recommended dosage was questioned by the CHMP and although no unequivocal face to face comparisons are available, based on published evidence, it now appears likely that effect is not very different from that of other anticholinergic drugs (also questionable according to the literature) Although the response corresponding to the 15 mg dose appears very close to that of the proposed as initial 7.5 mg dose on some relevant variables, there is some difference on the primary variable and it may be useful for some patients to uptitrate to 15 mg depending on the response to 7.5 mg.

The safety of darifenacin treatment in the intended population has been sufficiently documented in a fairly large number of patients, and the tolerability profile of darifenacin seems acceptable Therefore, taking all these considerations into account the CHMP was of the opinion that a positive benefit/risk can be concluded.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of EMSELEX in the treatment of symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome, was favourable and therefore recommended the granting of the marketing authorisation.