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Pharmaceutical development and clinical effectiveness of a novel gel technology for transdermal drug delivery

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Transdermal gels are designed to deliver sustained drug amounts, resulting in systemically consistent levels. They represent an improvement compared with transdermal delivery by patches because they offer more dosage flexibility, less irritation potential and a better cosmetic appearance. Advanced Transdermal Delivery™ (ATD™) gel technology was developed in order to provide enhanced passive skin permeation of various active drugs for the treatment of many conditions, including hypogonadism, female sexual dysfunction, postmenopausal symptoms, overactive bladder and anxiety. The technology consists of a combination of solvent systems and permeation enhancers enabling systemic drug delivery, and is covered by many patents. Pharmaceutical development of formulations based on the technology allowed optimisation of physicochemical parameters (rheological profile, pH) as well as skin permeation properties (type and concentration of permeation enhancers, thermodynamic activity of the drug). This gel technology has demonstrated to be efficient for many drugs, as shown in the preclinical and clinical pharmacokinetic studies presented in this technology evaluation.

Keywords: alprazolam, anxiety, hormone replacement therapy, hydroalcoholic gels, hypogonadism, menopause, norethindrone, norethisterone, oestradiol, overactive bladder, oxybutynin, testosterone, transdermal drug delivery

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1. Overview of the market

Pharmaceutical and biotechnology companies view drug delivery as a way of gaining a competitive advantage. Alternative drug delivery technologies avoiding first-pass metabolism are often sought by pharmaceutical and biotechnological companies to extend the period of market exclusivity for a branded drug and thus postpone competition from generic drugs.

Transdermal gel systems for delivering systemic drugs are attractive to developers and formulators as they address some of the shortcomings associated with transdermal patch products. Growth in this sector will be driven by the pressure to extend market protection for numerous drugs with soon-to-expire patents, as well as prescription to over-the-counter switching.

The transdermal gel market is at present not crowded, although the sector is constantly growing. A limited number of transdermal gel prescription products have been approved: Androgel® (testosterone, Unimed), Testim® (testosterone, Auxilium), Oestrogel® (oestradiol, Besins-Iscovesco) and Sandrena® (oestradiol, Organon). Another dozen products are in various stages of the clinical review process. Most of these formulations utilise proprietary technology platforms, but only a few pharmaceutical companies are developing this technology. Table 1 reports the companies developing their own proprietary transdermal gel technologies: Antares Pharma, Bentley Pharmaceuticals, Besins-Iscovesco, Cellegy Pharmaceuticals,

Table 1. Pharmaceutical companies developing proprietary transdermal gel technology.

Company name	Technology description
Antares Pharma	Proprietary patented ATD™ technology consisting of a combination of solvent systems and permeation enhancers enabling local or systemic drug delivery. The first gel technology enabling the delivery of more than one drug at a time. Cosmetically elegant and nonirritating. Bio-E-Gel™ and Libigel® are examples of products in development based on ATD™ technology (sub-licensed to BioSante).
Bentley Pharmaceuticals	Proprietary patented CPE-215 (cyclopentadecanolide) permeation enhancer with a record of safety in humans as a food additive and fragrance. First approved by the FDA in October 2002 as a delivery system in Testim® (testosterone replacement gel).
Besins-Iscovesco	Hydroalcoholic transdermal oestradiol gel (Oestrogel®). Addition of proprietary penetration-enhancing systems (isopropyl myristate and C1-C4 alcohol) for systemic delivery of topically applied testosterone. Androgel® is the first testosterone gel approved and marketed for the treatment of male hypogonadism, licensed to Unimed Pharmaceuticals Inc. (Solvay Pharmaceuticals group). They have also developed a tamoxifen gel, Tamogel™, licensed to Ascend Therapeutics.
Cellegy Pharmaceuticals, Inc.	Addition of proprietary penetration-enhancing systems (oleic acid, C1-C4 alcohol, glycol in the case of testosterone) to formulations for systemic delivery of topically applied drugs.
Macrochem Corporation	Proprietary patented SEPA® (1,3-dioxolanes) permeation enhancers that enhance absorption of drugs through the skin by transiently fluidising lipids in the outermost skin layer (stratum corneum).
NexMed, Inc.	Proprietary patented biodegradable NexACT® ingredients (alkyl-2-[substituted amino]-alkanoate ester, alkanol alkanoate, or a mixture thereof) that enables the rapid and efficient absorption of drugs through the skin and other membranes (nail plate, mucosa).

ATD: Advanced transdermal delivery.

Macrochem Corp. and NexMed. Antares Pharma's ATD™ (advanced transdermal delivery) technology is based on hydroalcoholic gels containing a combination of permeation enhancers. The gel is designed to be absorbed rapidly through the skin after application on arms, shoulders, abdomen or internal parts of the thighs. The formulation causes neither irritation nor occlusion of the skin after the application. Clinical trials involving several hundreds of patients and using different drugs have demonstrated excellent skin tolerability.

2. How the technology works

Pharmaceutical semisolid preparations are defined as topical products intended for the application on the skin or accessible mucous membranes (cornea, rectal mucosa, nasal mucosa, vagina, buccal tissue, urethral membrane, external ear lining) in order to provide localised and sometimes systemic effects at the site of application [1]. Semisolids are characterised by a three-dimensional network that imparts solid-like character to liquid phases. Because of their peculiar rheological behaviour, semisolids are advantageous in terms of ease of preparation, ease of application, adhesion to the application surface and ability to deliver a wide variety of drugs. Semisolids may be classified as ointments, pastes, creams and gels. Ointments are composed mostly of fluid low melting point hydrocarbons entangled in a matrix of higher melting point solid hydrocarbons, imparting a greasy feeling. Ointments soften but do not melt following application onto the skin. Pastes are defined as ointments incorporating a high fraction of insoluble particulate solids. Creams are semisolid, oil-in-water or water-in-oil emulsion systems. Gels are an intermediate state of matter, containing both liquid and solid components in which the solid component (small inorganic particles or large organic molecules) comprises a three-dimensional matrix of interconnected molecules (or aggregates) that immobilises the solution (or the suspension) in the continuous phase. Thickening solutions or suspensions might be responsible for an increase of the therapeutic effect, as demonstrated on topical lidocaine-adrenaline-tetracaine formulations [2]. Gels may be classified into two primary types depending on whether they present an aqueous continuous phase (hydrogels) or an organic solvent as the continuous liquid medium (organogels). Gels can also be further classified based on the nature of the gelling polymer: synthetic macromolecules (e.g., polyacrylic acid, cellulose derivatives and poloxamers), semisynthetic macromolecules (xanthan gum) or natural macromolecules (e.g., alginates, gelatin, pectin, tragacanth gum and guar gum).

The stability of gels is improved due to the presence of these thickening polymers, preventing phase separation (sedimentation, creaming) and subsequent phenomena (flocculation, phase inversion, Ostwald ripening) [3]. Hydrogels or organogels are easy to spread, do not leave greasy feeling on application and vanish rapidly after application contrary to ointments, pastes and creams.

The preparation of gels does not require any heating step, which makes it compatible with thermolabile drugs. Absence of heating and high-shear, high-speed mixing (by means of turboemulsifiers), necessary in preparation of

emulsified systems, is also responsible for lower manufacturing costs.

The preparation of gels always involves the thickening of a solution or suspension. Some polymers are simply dispersed in the continuous phase and let under gentle mixing until they have totally swollen (e.g., xanthan gum, cellulose derivatives); some polymers require a further step, such as the addition of neutralising agents (polyacrylic acids) or ions (alginates).

Generally, addition of polymers is a two-step process. Polymers are first added under vigorous stirring in order to avoid the formation of agglomerates, which would require longer mixing times and would result in heterogeneous gels. Ideally, polymers are first pumped under vacuum into the mixing vessel through a turbine. Subsequently, mixing speed is decreased in order to prevent entrapment of air bubbles. This step is ideally ensured by planetary scrapers. Preferred gelling agents are acrylic acid polymers or cellulose polymers and derivatives thereof. Selection of the gelling agent is dictated by numerous parameters such as the organic solvent/water ratio, the active drug form and the targeted viscosity.

The combination of permeation enhancers not only allows the effective delivery of individual actives, but also the concomitant delivery of two actives in the same gel. Examples for these combination gels include oestradiol/testosterone, oestradiol/norethisterone acetate, oestradiol/levonorgestrel and lidocaine/tetracaine. With the ATD technology it is possible to alter the permeation profile of one compound but not the other, and to adjust the concentration of one active without influencing the permeation of the other.

ATD technology relies on a unique combination of volatile/nonvolatile solvents and additional permeation enhancers that temporarily disturb the skin permeability and speed up the passage of the dissolved drug(s) through the skin. Preferred solvents in use in ATD technology are alcohols, glycols and glycol ethers. Depending on the qualitative/quantitative compositions, gels based on the ATD technology may be self preserved [4-6].

The synergistic combination of nonvolatile solvents used in ATD technology enables the delay of drug crystallisation (Figure 1), thus maintaining the drug(s) in the molecular form for permeation into the skin or the mucosa. The overall effect of ATD technology is to increase thermodynamic activity of the drug. For lipophilic drugs, partitioning to the stratum corneum is favoured, thereby allowing the build-up of a reservoir, which maintains a high diffusional driving force [7].

To summarise, volatile solvents (C2-C4 alcohols) fluidise intercellular skin lipids thus enabling a fast and massive penetration of part of the permeation enhancer(s) and active drug(s). Following evaporation of the solvents, thermodynamic activity in the residual vehicle (glycols, glycol ethers and water) is increased, creating favourable conditions for extended skin permeation of active drug(s) and permeation enhancer(s).

ATD technology is protected by one core patent [101], in which it is disclosed that skin penetration of norethindrone acetate/oestradiol is enhanced by a combination of lauryl alcohol and diethylene glycol monoethyl ether, the latter taking over the early permeation enhancement effect of the former. Although the effect of the individual enhancers is well known, their combined effect is a novelty.

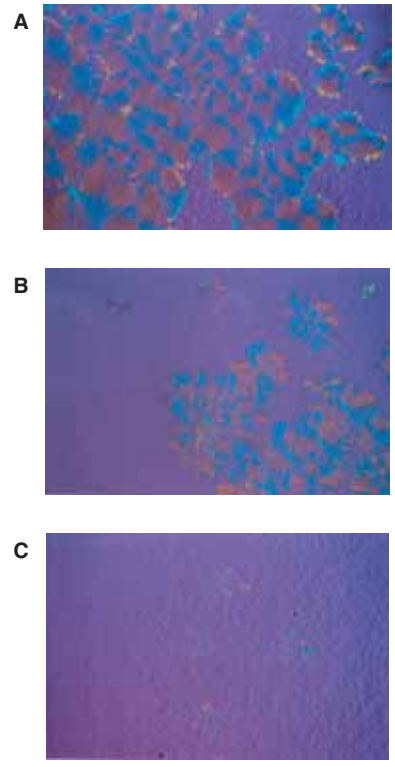

Figure 1. Synergistic effect of nonvolatile solvents on crystallisation using ATD™ technology. Polarised light microscopy pictures of a 1% testosterone hydroalcoholic gel 30 min after application on a glass plate. Magnification: × 1.3. Testosterone crystallisation occurs in presence of 5% diethylene glycol monoethyl ether **(A)** or 6% propylene glycol **(B)**, but not when both solvents are combined **(C)**.
ATD: Advanced transdermal delivery.

The scope of protection of ATD technology has been further extended towards a wide range of active pharmaceutical ingredients administered topically or transdermally through the skin or the mucosa, including sexual hormones [102], anticholinergic agents [103], analgesics, anesthetics, antihypertensives, hypnotics and neuroleptics. ATD technology advantageously addresses the need for transdermal formulations that adequately deliver active agents to patients while avoiding skin tolerability issues such as local irritation, itching or burning: only 4 of the 161 women enrolled in a Phase II trial (clinical study on the safety and efficacy of topical oestradiol gel versus placebo for the treatment of vasomotor symptoms in postmenopausal women) experienced a brief episode of mild application site reaction [201].

Formulations based on ATD technology are optimised for pH. This parameter is optimised so as to offer the best compromise between skin permeability on one hand, and skin tolerability on the other hand. A formulation displaying a pH range of 4 – 10 is generally considered as being well tolerated by the skin [8,9]; however, lipophilic species permeate more easily through the stratum corneum, and the net permeability coefficients of acidic and basic drugs are dictated by the balance between the ionised and the unionised drug fraction in direct contact with the stratum corneum surface [10]. Thus, unionised species permeate more easily through the stratum corneum than ionised species (unless ion pairing occurs). This obviously depends on the $-\log_{10}$ dissociation constant for an acid (pK_a) of the drug, and the pH of the formulation; the fraction of unionised species being readily obtained from the pK_a of the drug and the pH of the formulation, as demonstrated in Henderson–Hasselbach equation:

$$pH = pKa + \log\left\langle \frac{unionised}{ionised} \right\rangle$$

Formulations based on ATD technology are also optimised for rheology profile. Critical parameters such as yield value and spreadability are assessed through viscosity measurements. Viscosity is known to affect the permeation rate of drugs through the skin to some extent [11]. Yield value is defined in viscosity measurements as the force that must be applied to a semisolid layer to induce a movement. The yield value is a valuable parameter that dictates the ease at which the semisolid can be transferred through pipes from the manufacturing tank into the packaging equipment. It also gives an idea of the force required to squeeze a semisolid out of a tube or a sachet. From Figure 2, it clearly appears that the yield value is significantly lower for Androgel (200 Dyn/cm^2) than for the three other gels; that is to say, Androgel would be prone to flow more easily. Associated with its low viscosity, this might be a larger drawback when applying the gel on the skin. The higher yield value of ATD testosterone gel (~ 900 Dyn/cm^2) prevents such dripping or leaking of the formulation when applied on the skin surface area (shoulders, abdomen, upper arms and inner thighs).

Although the yield value indicates how easy it is to dispense the formulation and to apply it on the skin, spreadability indicates what happens when distributing the semisolid over the skin surface application area. As shown in Figure 3, all semisolid formulations are rheofluidifiant (viscosity decreases on spreading). However, ATD testosterone gel is characterised by a higher viscosity than Androgel, at a shear rate close to zero (representing in a way the 'hardness' of the formulations at rest), but viscosity dramatically decreases on spreading and becomes as low as for Androgel. Thus, ATD testosterone gel combines the advantages of a high viscosity at rest (the dose can be accurately dispensed on the skin surface application) with a good spreadability.

ATD gel products are dispensed either in unidose sachets or in metered-dose pumps, providing a highly accurate dosing in a convenient way for the patient. Metered-dose pumps allow the flexibility to titrate the active drug(s) level(s) within the approved doses, converse to transdermal patch systems, which present only fixed dosages. This is all the more important for very potent active drug(s) with a narrow therapeutic window, such as opioids or cytotoxic drugs, requiring patient-by-patient individual adjustments. Delivery of ATD by the means of metered-dose pumps is possible within a range of 0.1 – 5.0 g.

ATD technology is very versatile; its feasibility to deliver actives for many different indications has been proven with drugs used in the following treatments: hormone replacement therapy, contraception, overactive bladder, anxiety, depression, breakthrough pain and osteoarthritis.

3. Clinical profile

3.1 Transdermal gel delivery of testosterone for male hypogonadism

Endogenous androgens, particularly testosterone, are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sexual characteristics. The adult testicles produce 7 – 10 mg/day of testosterone [12], only a fraction of which is bioactive (not bound to sex hormone binding globulin; SHBG). Physiological mean serum levels of young adult men follow a circadian pattern, ranging between 400 ng/dl (15 nmol/l) in the evening and 700 ng/dl (25 nmol/l) in the morning [13]. Total testosterone levels decline with age by ~ 100 ng/dl (3.5 nmol/l) per decade after 50 years, but bioavailable testosterone declines far more dramatically because SHBG increases with age.

Serum testosterone levels < 300 ng/dl (< 11.3 nmol/l) are diagnostic of male hypogonadism [14]. Lower testosterone levels result in clinical symptoms including diminished muscle mass, impotence and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis (hypogonadism is a risk factor for osteoporosis in men).

Hypogonadism affects an estimated 4 – 5 million men in the US, and, although it may occur in men at any age, low testosterone levels are especially common in older males. More than 60% of men > 65 years have testosterone levels below the normal values of men aged 30 – 35. Most have secondary, rather than primary, gonadal deficiency. Alterations in gonadotropin-releasing hormone appear to play a key role in the hormonal changes.

Normalisation of serum testosterone levels may be achieved by replacement therapy. Ideally, this should provide physiological serum testosterone, dihydrotestosterone and oestradiol levels, which would allow optimal virilisation and normal sexual function.

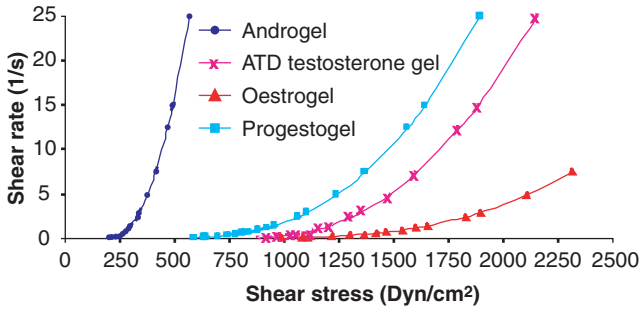

Figure 2. Determination of yield values of ATD™ testosterone gel and other marketed hormonal transdermal gels. ATD™ testosterone gel: ~ 900 Dyn/cm^2; Androgel®: ~ 200 Dyn/cm^2; Oestrogel®: ~ 600 Dyn/cm^2; Progestogel®: ~ 1000 Dyn/cm^2. ATD™ testosterone gel presents an average yield value.
ATD: Advanced transdermal delivery.

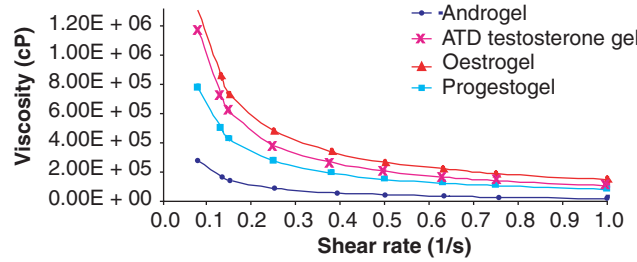

Figure 3. Determination of spreadability of ATD™ testosterone gel and other marketed hormonal transdermal gels. The four gels exhibit a similar viscosity on spreading.
ATD: Advanced transdermal delivery.

Although benefits of testosterone replacement therapy have been well demonstrated in many studies [15], delivery resulting in physiological testosterone pattern (circadian rhythm) and physiological levels of metabolites (dihydrotestosterone and oestradiol) highly depends on the route of administration. The oral and intramuscular routes produce wide fluctuations in the plasma testosterone level, whereas transdermal route provides more physiological levels, due to the constant and sustained delivery pattern typical of that route of administration.

The first testosterone transdermal system was introduced in the late 1980s as scrotal patch (Testoderm®, Alza Corp., CA, USA) [16]. Non-scrotal patches appeared in the late 1990s (Androderm™, Watson Laboratory, CA, USA; and Testoderm TTS), which allowed more physiological dihydrotestosterone serum levels, due to the lower metabolisation of testosterone by 5-α reductase (this enzyme is present in scrotal skin at higher concentration than in non-scrotal skin) [17]. However, testosterone patches have some drawbacks related to the technology: skin irritation [18], adhesion problems, limited dosing flexibility and elevated manufacturing cost.

Transdermal testosterone gel formulations appeared on the market in order to circumvent these issues; two products are currently available and others are in development (Table 2). The feasibility of transdermal delivery of testosterone from gels has been demonstrated in many studies for Androgel [19-21], Testim [22,23], Tostrex™ [24] and Bio-T-Gel™ (development stage not disclosed).

ATD gel testosterone is in clinical development. This new product is based on Antares Pharma's proprietary technology, described in Section 1. It has shown promising results both in preclinical and clinical pharmacokinetic studies.

Preliminary *in vitro* studies using excised skin have first shown feasibility of testosterone systemic delivery using ATD gel. A pilot pharmacokinetic study confirmed attainment of testosterone levels in the physiological range. This single-centre, open-label, multiple-dose pharmacokinetic study was conducted in eight hypogonadal male volunteers, of which seven finished the study (the eighth retired for reasons not related to the study). The study protocol was approved by a local institutional review board. The main inclusion criterion was morning (08.00) testosterone level < 3 ng/ml. The objective of the pharmacokinetic study was to evaluate the serum levels of testosterone after a once-daily application of ATD gel during 12 days of treatment. The investigators wore surgical gloves during the application procedure. Five grams of the tested gel formulation was applied onto both shoulders of the volunteer, treating an area of ~ 600 cm^2. Venous blood samples were removed before the first gel application, and throughout the whole study period, after 1, 7, 8, 11 and 12 days. In addition, on day 12 (after steady-state conditions were reached), intensive blood sampling was performed at 0, 1, 2, 3, 6, 12 and 18 h. Testosterone serum levels were assessed by radioimmunoassay. Area under the concentration/time curve from 0 – 24 h (AUC_{0-24}) was assessed during the intensive sampling day, using the linear trapezoidal method. Steady-state was evaluated by ANOVA-Tukey, performed within the time points that significantly differ from basal time values.

Figure 4 shows the testosterone serum concentration versus time curve during the study period, and Table 3 reports the pharmacokinetic parameters. Physiological testosterone levels are reached after the first day of gel application and then maintained throughout the whole study period. Figure 5 depicts testosterone serum levels during the last day of study (intensive sampling). The kinetic profile of the gel confirms ATD gel capability to deliver sustained and consistent testosterone amounts in a physiological way.

The bioavailability of this novel testosterone gel has been further improved. A new prototype was developed in order to reduce the amount of gel to apply over the skin. It was recently tested in an *in vitro* study against the marketed Androgel as reference, and showed promising outcomes. The study was performed using pig ear skin as the model, which was mounted on vertical diffusion cells (Franz type). The formulations (both containing 1% testosterone) were applied over the skin at the same gel dose (10 mg/cell), and

Table 2. Transdermal testosterone gels for the treatment of hypogonadism available or under development at present.

Brand name	Testosterone strength	Gel daily amount	Testosterone daily dose	Company	Development status
Androgel®	1%	5, 7.5 or 10 g	50, 75 or 100 mg	Unimed	Approved 2000 in US
Testim™	1%	5 or 10 g	50 or 100 mg	Auxilium	Approved 2002 in US
Tostrex™	2%	3 g	60 mg	Cellegy	Approved 2004 in EU
ATD™ gel	1%	Not disclosed	Not disclosed	Antares	Clinical
Bio-T-Gel™	Not disclosed	Not disclosed	Not disclosed	BioSante	Clinical

ATD: Advanced transdermal delivery.

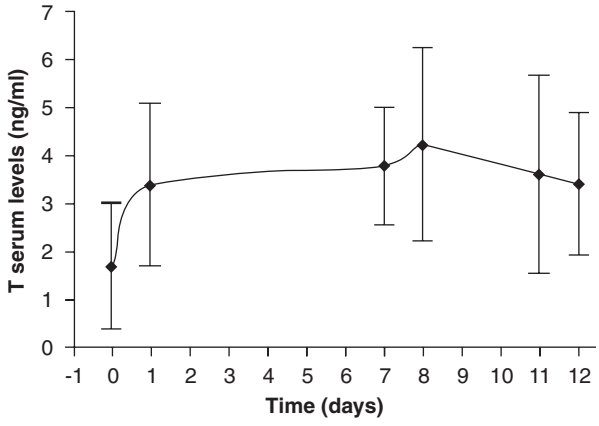

Figure 4. Testosterone serum levels following daily application of 5-g gel formulation (ATD™ gel testosterone) on the shoulders (600 cm^2) of male hypogonadal volunteers during 12 days (mean values ± SD; n = 7).
ATD: Advanced transdermal delivery; SD: Standard deviation: T: Testosterone.

diffusion was allowed for 24 h. Samples of the receptor compartment were removed at defined interval times for testosterone assay. Figure 6 depicts the *in vitro* kinetic profile of absorbed testosterone as a function of time. Levels reached by ATD gel after 24 h permeation are more than twofold higher than those attained by Androgel. This suggests that, theoretically, only 50% of the gel dose (2.5 instead of 5 g) applied over half skin surface would systemically deliver the same drug amount as Androgel.

In order to confirm this interesting outcome, a dose titration study will be performed on hypogonadal volunteers with the newest prototype. In case that this finding is confirmed, dose reduction will represent a relevant progress in the delivery of testosterone to hypogonadal men, as efficacy will be increased and potential interpersonal contamination reduced.

Table 3. Serum testosterone pharmacokinetic parameters after repeated topical application of 5-g ATD™ gel testosterone during 12 days.

Parameter	ATD™ gel testosterone 5 g
AUC (ngh/ml)	82.0 ± 36.3
C_{av} (ng/ml)	4.9 ± 2.3
T_{max} (h)	1
Daily dose (mg)	4.5

Mean values ± SD; n = 7.
ATD: Advanced transdermal delivery.; AUC: Area under the curve; C_{av}: Average plasma level; SD: Standard deviation; T_{max}: Time to maximum drug concentration.

In conclusion, data presented demonstrate that ATD gel is capable of delivering consistent amounts of testosterone across the skin. Antares Pharma have also successfully developed a testosterone gel for the treatment of female sexual dysfunction in surgically menopausal women, based on the ATD technology. The rights of this product (Libigel™) for North America have been licensed to BioSante Pharmaceuticals, Inc. (IL, USA), which has recently publicly disclosed clinical data from a placebo-controlled Phase II study. The trial was performed on 46 surgically menopausal women and showed that treatment with LibiGel significantly increased satisfying sexual events. The effective dose of LibiGel produced testosterone blood levels within the normal physiological range for premenopausal women and the safety profile was similar to that of the placebo product.

3.2 Transdermal gel delivery of oestradiol alone or in combination with norethisterone for menopause

Oestrogen production gradually declines in ageing women, and the number of ovarian follicles decreases until menopause. Early signs and symptoms of menopause include irregular menstrual cycles, hot flushes, changes in mood and cognition, sleep disorders, headache, dry skin, genital atrophy, urinary disorders and osteoporosis.

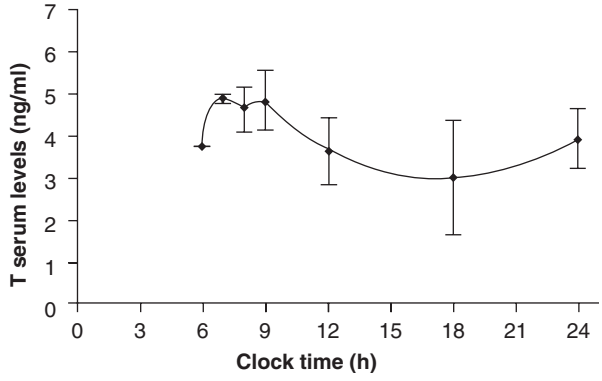

Figure 5. Testosterone serum levels following application of 5-g gel formulation (ATD™ gel testosterone) on the shoulders (600 cm^2) of male hypogonadal volunteers. Intensive blood sampling during the last 12 days treatment (mean values ± SD; n = 7).
ATD: Advanced transdermal delivery, SD: Standard deviation; T: Testosterone.

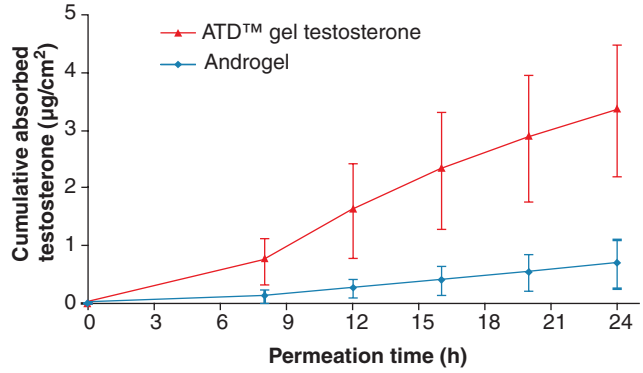

Figure 6. *In vitro* delivery profile of transdermally absorbed testosterone from gel formulations (Androgel® and ATD™ gel) applied over excised pig skin (mean values ± SD; n = 3 – 4).
ATD: Advanced transdermal delivery, SD: Standard deviation.

A number of therapies are available for postmenopausal symptoms, but the most popular is hormone replacement therapy (HRT). The indications for menopause HRT are primarily to correct vasomotor symptoms, vaginal atrophy, the decrease in accelerated bone loss and the risk of osteoporosis.

HRT monotherapy with oestradiol alone ('unopposed oestrogen') is addressed to hysterectomised women, whereas combined therapy with oestrogen plus progestin is intended for women with intact uterus, because unopposed oestrogen increases the risk of endometrial hyperplasia.

The oestrogens used at present include micronised oestradiol and conjugated oestrogens. Progestins include natural progesterone and its synthetic derivatives. Progesterone has a very irregular oral absorption and extensive hepatic metabolism. For this reason, synthetic progestins are preferred; the most frequently used are medroxyprogesterone (derived from progesterone) and norethisterone (derived from testosterone).

There is some controversy about oral HRT, as reported by the Women's Health Initiative (WHI) trial, which included > 16,000 healthy, postmenopausal women aged 50 – 79 years [25]. The combination HRT arm of the study showed a small but significantly higher risk of breast cancer, stroke, heart disease and blood clots at 5.2 years compared with placebo.

The oral administration of oestradiol results in massive bioconversion to oestrone by the liver, leading to higher serum levels of oestrone (E1) and its conjugates than oestradiol (E2). In order to avoid the first-pass effect, a most suitable oestradiol replacement therapy can be achieved by the transdermal route, which more closely mimics production and delivery by the ovaries, and requires lower doses compared with the oral route. A patch delivering oestradiol 50 µg/day is as effective as an oral dose 20 – 40-fold higher, with less metabolic fallout, which results in lower levels of E1, and consequently a more physiological E2/E1 ratio [26]. Another advantage of transdermal HRT is that transdermally administered oestradiol does not have the same impact on hepatic protein synthesis as orally administered doses [27]. Finally, transdermal oestrogen was shown to decrease triglycerides, a cardiovascular disease risk factor, whereas oral oestrogen increases them [28].

Results of the WHI study do not necessarily apply to the transdermal route. Lower doses of HRT, such as provided by transdermal treatment, are likely to have fewer short- and long-term side effects, thereby allowing an increase of the duration of treatment. Transdermal combined HRT using oestradiol plus norethisterone has proven its beneficial effect on climacteric disorders: relief of vasomotor symptoms [29] and reduction of bone loss [30]. It has also shown a protective effect on endometrial hyperplasia [31,32].

The first developed transdermal systems for HRT were patches containing oestradiol alone (e.g., Estraderm®, Alora®, Climara®, Vivelle™, FemPatch®) or combined with a progestin (e.g., Combipatch™, Estracombi®, Evorel™, Sequi™). Transdermal gels for HRT appeared later, and have demonstrated equal efficacy as patches [33] but with less irritation potential to the skin than patches [33,34].

Only transdermal gels for unopposed HRT are available or under development (Table 4) at present, and include Oestrogel [35] and Sandrena [36]. ATD technology is suitable not only for the delivery of oestradiol alone, but also in combination with norethisterone, as confirmed by the following pharmacokinetic studies.

The study concerning oestradiol alone was a single-centre, multiple-dose, randomised, controlled, crossover, open-label pharmacokinetic study. It was conducted in eight healthy postmenopausal female volunteers during 7 days, comparing the ATD gel oestradiol formulation against a commercially available gel formulation (Oestrogel 0.06% oestradiol, Besins-Iscovesco). All volunteers received a daily application

Table 4. Transdermal unopposed oestradiol gels for the treatment of HRT available or under development at present.

Brand name	Oestradiol strength	Gel daily amount	Oestradiol daily dose	Company	Development status
Oestrogel™	0.06%	2.5 g	1.5 mg	Besins-Iscovesco	Approved 1980 in France
Sandrena®	0.1%	0.5 or 1 g	0.5 or 1 mg	Organon	Approved 1996 in UK
Bio-E-Gel™*	0.06%	Not disclosed	Not disclosed	BioSante	Phase III completed

*Licensed from Antares Pharma.
HRT: Hormone replacement therapy.

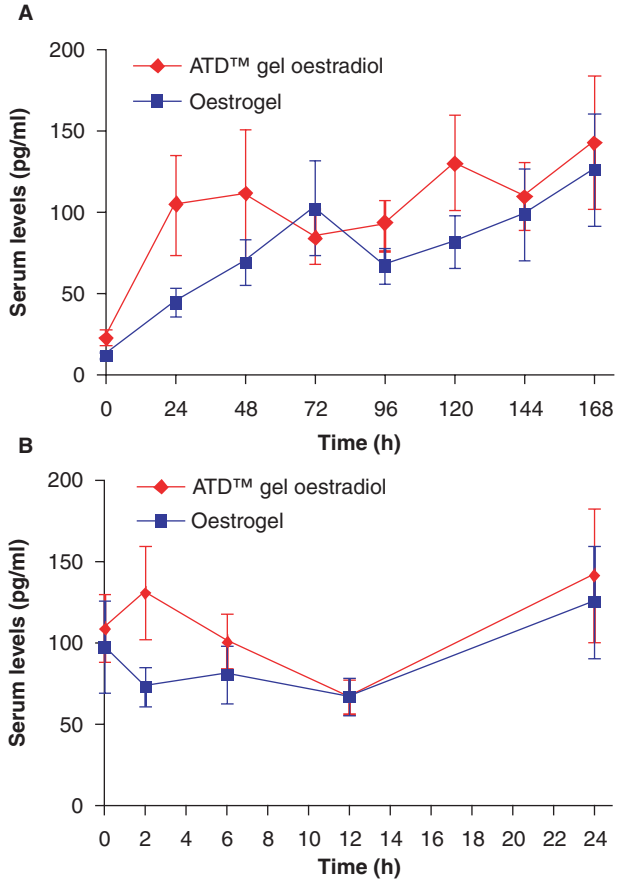

Figure 7. Serum levels of transdermally absorbed oestradiol following 7 days application of ATD™ gel oestradiol 0.06%, and Oestrogel™ (mean values ± SD; n = 8). A. Daily sampling, every day in the morning. **B.** Intensive sampling on day 7.
ATD: Advanced transdermal delivery; SD: Standard deviation.

of ATD gel oestradiol during the first 7 days of treatment and Oestrogel during the second 7 days of treatment; both periods were separated by a 2-week washout period. The investigator wore surgical gloves during the gel application procedures, in which 2.5 g of the tested formulation was applied onto an area of ~ 600 cm^2 of one shoulder and arm. One shoulder was used for the first period, and the other shoulder was used in the second period. All volunteers concluded the study and were submitted to analysis.

The AUC was calculated by the trapezoidal rule. Maximum drug concentration (C_{max}) and time to maximum drug concentration (T_{max}) were obtained directly from the data of each volunteer without interpolation (PKCAL software). Oestradiol serum levels lower than the quantification limit (25 pg/ml) were not considered. Steady state was evaluated by ANOVA-Tukey, performed within the time points, which significantly differ from basal time values.

The average oestradiol serum levels are illustrated in Figure 7. Oestradiol steady state was maintained 24 – 168 h for ATD gel oestradiol, and 48 – 168 h for Oestrogel. Mean oestradiol serum levels within the steady state were 107.3 and 85.0 pg/ml, respectively. Pharmacokinetic parameters derived from the individual values are depicted in Table 5. AUC and daily dose were calculated between 144 and 168 h (extensively sampling day), when the steady state had been reached. Results show that the plasma concentrations of oestradiol are similar for both formulations. This study demonstrates, therefore, that ATD gel oestradiol delivers sufficient quantities of the drug transdermally to achieve serum concentrations within the therapeutic levels.

The rights of this product (Bio-E-Gel™) for North America and certain other territories have been licensed to BioSante Pharmaceuticals, Inc., whereas Europe, Japan and other important markets remain under control of Antares Pharma.

Bio-E-Gel successfully completed a pivotal Phase II clinical trial, and is currently in pivotal Phase III, clinical trial demonstrating safety and efficacy for the treatment of moderate-to-severe hot flushes in menopausal women. The Phase III trial was a 12-week, randomised, double-blind, placebo-controlled study of 484 symptomatic menopausal women. Following FDA recommendations, the Phase III trial tested three doses of Bio-E-Gel in order to establish the lowest effective dose and maximise the safety profile. The four co-primary endpoints, as defined by the FDA, were a significant decrease over placebo in both the number and severity of hot flushes at week 4 and week 12 of treatment. Across the low, mid and high Bio-E-Gel doses tested in the Phase III trial, there was a clear dose response in the reduction in the number and severity of hot flushes [202].

Table 5. Serum oestradiol pharmacokinetic parameters after repeated topical application of 2.5-g ATD™ gel oestradiol 0.06% and Oestrogel™ during 7 days.

Parameter	ATD™ gel oestradiol 0.06%	Oestrogel™ gel oestradiol 0.06%
$AUC_{144-168\ h}$ (pgh/ml)	1924.4 ± 1124.7	1797.9 ± 926.4
C_{max} (pg/ml)	119.9 ± 99.5	114.1 ± 76.7
C_{ss} (pg/ml)	107.3 ± 66.4	85.0 ± 52.4
T_{max} (h)	7.5 ± 10.2	21.0 ± 8.5
Daily dose (µg)	108.3 ± 63.3	101.2 ± 52.2

Mean values ± SD; n = 8.

ATD: Advanced transdermal delivery; AUC: Area under the curve; C_{max}: Maximum concentration; C_{ss}: Concentration at steady-state; SD: Standard deviation; T_{max}: Time to maximum concentration.

For combined HRT, ATD gel technology has also shown to allow simultaneous skin permeation of two actives: oestradiol 0.06% plus norethisterone acetate 1.2% (NETA). Again, *in vitro* studies first showed feasibility of simultaneous penetration without significant interference between the two drugs. Furthermore, a pilot pharmacokinetic study was performed in order to confirm the *in vitro* data. Because no gel was commercially available, a marketed patch also containing oestradiol plus NETA (Estragest® patch, delivering oestradiol 50 µg/day and NETA 250 µg/day) was used as reference. This single-centre, randomised, open-label, controlled, two-way crossover pharmacokinetic study included eight healthy postmenopausal female volunteers, treated during 14 days. The gel (2.5 g unit dose) was applied once daily during 14 days of treatment by the investigator (wearing gloves) on shoulders, arms and upper back each morning. The patches were applied to the buttock and changed twice weekly (every 4 and 3 days). The two treatment periods of 14 days each were separated by a washout period of 4 weeks. Venous blood samples were collected over the whole treatment period. Analysis of the two actives was performed using a radioimmunoassay method.

Figure 8 illustrates the kinetic profile for both formulations, and Table 6 reports the pharmacokinetic parameters. Steady state for both oestradiol and NETA was reached at the latest after application of the first two Estragest patches, whereas for the gel, steady state was reached after 2 days for oestradiol and after 4 days for NETA. Oestradiol serum levels measured in the interval between days 8 and 11 averaged 72 pg/ml for the patch and 47 pg/ml for the gel. NETA serum levels were ~ threefold higher for the gel compared with the patch.

As the daily dose of NETA for ATD gel is 30 mg, whereas for Estragest patch it is 30 mg for 3 – 4 days, it can be anticipated that reduction of NETA strength in the gel to one third or less of the concentration could lead to the same plasma levels as obtained for Estragest. A further internal study has confirmed this hypothesis.

Table 6. Serum oestradiol and NETA pharmacokinetic parameters after 14 days of repeated topical application of 2.5-g ATD™ gel oestradiol plus NETA (once daily) and Estragest® patch (twice weekly), delivering oestradiol 50 µg/day and NETA 250 µg/day.

	ATD™ gel		*Estragest™ patch*	
Parameter	Oestradiol	NETA	Oestradiol	NETA
AUC (pgh/ml)	171	10426	202	3195
C_{max} (pg/ml)	65	3829	75	1397
C_{min} (pg/ml)	33	2055	41	544
C_{ss} (pg/ml)	49	3005	58	933
T_{max} (h)	9	9.5	10	7.5

Mean values; n = 8.

ATD: Advanced transdermal delivery; AUC: Area under the curve; C_{max}: Maximum concentration; C_{min}: Minimum concentration; C_{ss}: Concentration at steady state; NETA: Norethisterone acetate; T_{max}: Time to maximum concentration.

The rights of this product for Europa, Latin America and Asia (except Japan and Korea) have been licensed to Solvay Pharmaceuticals (Brussels, Belgium), whereas rights for North America and Canada have been licensed to BioSante Pharmaceuticals, Inc. (IL, USA).

3.3 Transdermal gel delivery of oxybutynin for overactive bladder

Overactive bladder (OAB) is a lower urinary tract disorder resulting in a symptom syndrome including urgency with (OAB wet) or without (OAB dry) urge incontinence, usually with frequency and/or nocturia [37]. The most frequent origin of these symptoms is detrusor overactivity (involuntary bladder contractions), but other forms of urethrovesical dysfunctions may be involved.

OAB is estimated to affect > 22 million people in Europe [38], and > 33 million in the US [39]. Therefore, growing interest is being devoted to this clinical problem, and pharmacological treatments with optimised efficacy/tolerance profile are still needed.

Although oral administration of oxybutynin is the gold standard in the treatment of OAB (Ditropan®, or Ditropan XL®, Ortho-McNeil), it is often associated with significant anticholinergic side effects, especially dry mouth, requiring patients to discontinue treatment. The high plasma levels (5 – 11-fold higher than that of the parent compound) of the primary active metabolite of oxybutynin, *N*-desethyloxybutynin (DEO), and the higher affinity for the parotid gland, are believed to be responsible for those adverse events [40].

Transdermal patch administration of oxybutynin (Oxytrol™, Watson Laboratories) circumvents its extensive hepatic metabolism, resulting in DEO levels only 1.4-fold higher than the parent compound, and in an efficacy comparable with oral formulations [41]; however, oxybutynin patch

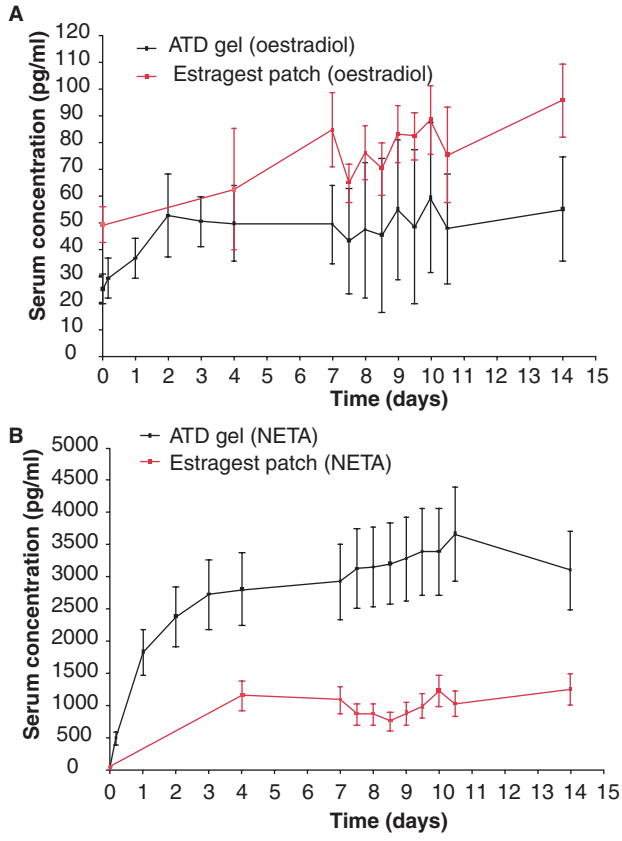

Figure 8. Serum levels of transdermally absorbed oestradiol (A) and NETA (B) following 14 days application of 2.5-g ATD™ gel oestradiol plus NETA (once daily) and Estragest® patch (twice weekly) delivering oestradiol 50 µg/day and NETA 250 µg/day (mean values; n = 8).

ATD: Advanced transdermal delivery, NETA: Norethisterone acetate.

treatment was associated with a relatively high incidence of local skin reactions, which varied from study to study: 27 [42], 38 [43], 48 – 56 [44] and 73% [45] of the subjects. Furthermore, the limited area of the patch does not allow optimal dose adjustments for subpopulations prone to under- or overdosage with the standard treatment regimen. For these reasons, feasibility of a transdermal gel based on ATD technology was carried out. The composition was tailored to oxybutynin so as to maximise its absorption across the skin.

In vitro studies on excised human skin, using vertical diffusion cells (Franz type), were performed in order to evaluate the absorption performance of the optimised prototype. As the ATD gel is the first in its kind to be designed for the treatment of OAB, no similar reference was available on the market; however, Oxytrol patch was used as reference. The studies revealed encouraging results for ATD gel oxybutynin 3%.

Based on the *in vitro* preclinical development, a pilot pharmacokinetic study was performed with the gel, in order to determine the appropriate daily dose of oxybutynin. This single-centre, randomised, open-label, uncontrolled, two-way crossover, multiple dose, titration pilot pharmacokinetic study was performed in eight healthy female subjects (90% of patients treated with oxybutynin are women), aged 27 – 47 years (mean 38). All subjects fulfilled all inclusion criteria and none of the exclusion criteria of the study protocol. The study was conducted in compliance with good clinical practice, and approved by the local institutional ethics committee. Two different doses of the gel (1 and 2 g) were administered topically once/day during two sequential periods of 7 consecutive days, separated by a 1-week washout period. The gel was applied onto the lower abdominal region over an area of 250 cm² (1-g gel) and 500 cm² (2-g gel). Venous blood samples for analysis of plasma oxybutynin and DEO levels were collected before the first gel application, then once daily, and the last day intensively (five samples). Plasma concentrations were analysed by a validated liquid chromatography–mass spectroscopy/mass spectroscopy (LC–MS/MS) method.

All calculations of pharmacokinetic variables were carried out using validated software modules (BABE 8.2) based on SAS language and procedures (SAS software 8.2, SAS-Institute, Cary, NC). Bioavailability was used as surrogate parameter for efficacy. The area under the curve within the last dosage interval (AUC_{SS}) was calculated by linear trapezoidal integration. ANOVA was performed after logarithmic transformation on all parameters except T_{max}, primarily in order to estimate the residual error that was used to construct the 90% confidence intervals.

Figure 9 shows the plasma profile of oxybutynin and DEO after application of 1 and 2 g ATD gel. From those profiles it can be easily observed that DEO levels are very close to oxybutynin levels. Table 7 reports the pharmacokinetic parameters obtained after multiple-dose application of the formulation. The average DEO level is 0.8-fold lower than the parent compound for 1-g gel, and 0.9-fold lower for 2-g gel. In comparison, the average DEO plasma level after multiple doses of Oxytrol patch (average plasma level [C_{av}] = 5.8 ± 3.3 ng/ml) was ~ 1.4-fold higher than that of the parent drug [42]. The metabolite levels of the gel are therefore the lowest compared with the patch and the oral treatment, as shown on Figure 10. The reason for the discrepancy may be a true difference of the oxybutynin metabolism and/or distribution between gel and patch application.

From Table 7 it can be observed that approximately linear pharmacokinetics appears to apply within the investigated dose range for oxybutynin, because C_{av} for 2-g gel (6.8 ± 2.3 ng/ml) is about twofold that for 1-g gel (3.2 ± 1.3 ng/ml). These plasma levels seem to fall within the range of those obtained by Zobrist *et al.* [44]. These authors have shown that multiple doses of Oxytrol patch deliver an average of oxybutynin 3.9 mg/day, leading to a C_{av} of 4.2 ± 1.1 ng/ml. This concentration was shown to be effective for the treatment of OAB. It should therefore be possible to estimate the gel dose that maintains an average oxybutynin concentration bioequivalent to that after repeated doses of Oxytrol patch. Using simple linear interpolation, it was

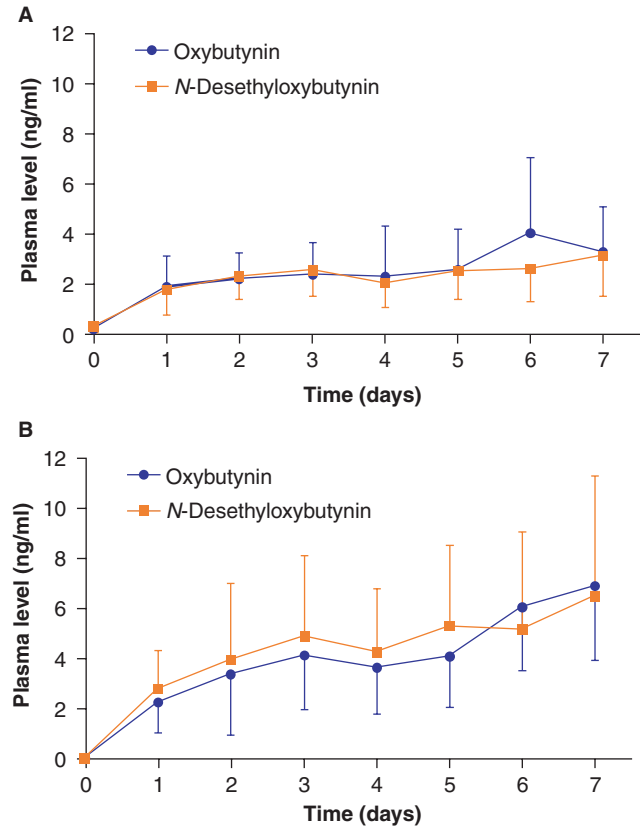

Figure 9. Plasma levels of oxybutynin and *N*-desethyloxybutynin following transdermal ATD™ gel oxybutynin administration once daily during 7 days (mean values ± SD; n = 8). A. 1-g gel. **B.** 2-g gel.
ATD: Advanced transdermal delivery; SD: Standard deviation

estimated that multiple doses ATD gel 1.3 g should be sufficient to maintain an C_{av} of 4.2 ng/ml.

Adverse effects monitoring during both dose regimens showed that the treatment was well tolerated, as dry mouth was observed in only one subject, and only after administration of 2-g gel. Furthermore, no skin reactions at all were observed.

In conclusion, this pharmacokinetic study showed that topical daily administration of ATD gel can deliver sufficient oxybutynin amounts leading to comparable plasma levels with respect to the marketed Oxytrol patch.

Based on the promising outcomes of this study, Antares Pharma filed, in March 2005, an Investigational New Drug application on oxybutynin ATD gel for overactive bladder syndrome (OAB). The Company was granted the right to proceed directly into a Phase II dose-ranging study following concurrence with the protocol submitted, as well as conduct only a single Phase III study.

Table 7. Plasma pharmacokinetic parameters of OXY and DEO after topical administration of 1- or 2-g ATD™ gel during 7 days (mean ± SD; n = 8).

	1-g ATD™ gel		*2-g ATD™ gel*	
Parameter	**OXY**	**DEO**	**OXY**	**DEO**
C_{max} (ng/ml)	4.7 ± 2.6	3.3 ± 1.7	9.3 ± 3.4	7.5 ± 5.3
C_{av} (ng/ml)	3.2 ± 1.3	2.7 ± 1.3	6.8 ± 2.3	6.2 ± 4.2
T_{max}(h)	152.7 ± 9.4	159.0 ± 10.6	155.8 ± 8.0	157.0 ± 7.3
AUC (ngh/ml)	75.5 ± 30.1	64.1 ± 30.7	164.0 ± 55.3	149.0 ± 101.3
Ratio DEO/ OXY (C_{av})	0.8		0.9	

AUC: Area under the curve; C_{av}: Average plasma level; C_{max}: Maximum concentration; DEO: *N*-desethyloxybutynin; OXY: Oxybutynin; SD: Standard deviation; T_{max}: Time to maximum concetration.

3.4 Transdermal gel delivery of alprazolam for anxiety disorders

Different benzodiazepines are used for the treatment of anxiety disorders; for example, chlordiazepoxide, diazepam, oxazepam, clorazepate, lorazepam, alprazolam and prazepam. Alprazolam is a triazolobenzodiazepine, and its receptor binding characteristics are qualitatively similar to those of the other benzodiazepines [46]. It is extensively used in treatment of anxiety disorders, at doses of 0.25 – 0.5 mg t.i.d. p.o., and increased where necessary up to a total dose of 3 or 4 mg/day. Doses of ≤ 10 mg/day of alprazolam have been used in the treatment of anxiety with depression.

The drug is metabolised primarily by hepatic microsomal oxidation to at least 29 different metabolites, including two minor active metabolites, 4-hydroxyalprazolam and α-hydroxyalprazolam, which, combined, are usually < 15% of the concentration of the parent drug in human plasma. The α-hydroxyalprazolam is reported to be ~ 50% as active as the parent compound [47].

As with other benzodiazepines, high doses of alprazolam must be given for long periods of time and then abruptly withdrawn before marked withdrawn symptoms appear. In addition, precipitated abstinence syndrome has been described as a consequence of a chronic administration of high doses of alprazolam and after the intravenous injection of a specific benzodiazepine antagonist in dogs; however, it has been suggested that this physical dependence produced by alprazolam is related to the accumulation of α–hydroxyalprazolam [48]. On the other hand, some observations show that benzodiazepines of intermediate half-life, such as alprazolam and lorazepam, might be associated with the emergence of symptoms of anxiety between doses [49]. Therefore, a transdermal delivery system, which suppress first-pass metabolism and avoids the decrease in plasma levels of alprazolam between doses, would provide sustained plasmatic levels of the drug.

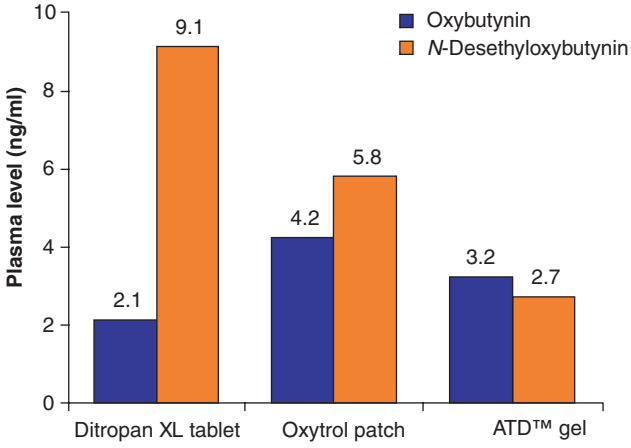

Figure 10. Average plasma oxybutynin and *N*-desethyloxybutynin levels at steady-state comparing Ditropan® XL extended-release tablet (10 mg/day [40]), Oxytrol™ patch (3.9 mg/day [42]) and ATD™ gel oxybutynin (1-g gel/day). Data are only indicative and were obtained from independent studies.
ATD: Advanced transdermal delivery.

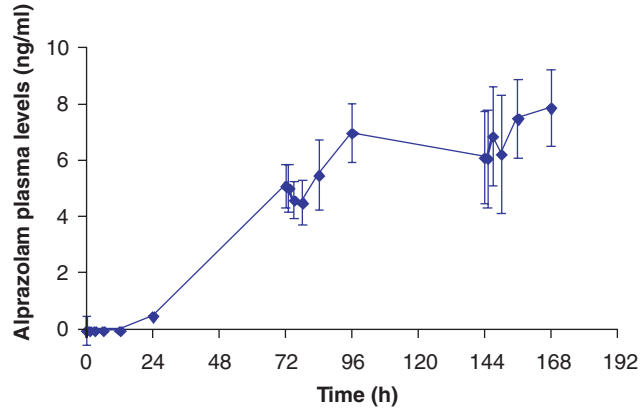

Figure 11. Average alprazolam plasma levels versus treatment time, following 7 days topical application of 2 g of ATD™ gel alprazolam (mean ± SD; n = 4).
ATD: Advanced transdermal delivery; SD: Standard deviation.

Transdermal administration of alprazolam by the means of ATD gel was therefore evaluated. The development of the gel was based on following criteria: i) to deliver consistent therapeutic levels of alprazolam; ii) to achieve suitable plasma concentrations of the active agent, comparable with those obtained by oral treatment; iii) to deliver the drug by a once-daily gel application; and iv) to offer a transdermal dosage form with good cosmetic properties and low irritation potential.

Taking into account that the recommended dose of alprazolam for the management of anxiety disorders vary from 0.25 to 0.5 mg t.i.d. p.o., the objective of the gel was to deliver these amounts following a daily application. *In vitro* studies on excised guinea-pig skin have shown feasibility of transdermal alprazolam delivery. A further *in vivo* study on rabbits comparing transdermal (ATD gel) and oral (Xanax® 0.5 mg b.i.d.) alprazolam confirmed *in vitro* results (data not shown).

Finally, a single-centre, open-label, multiple-dose pilot pharmacokinetic study was performed on four adult healthy volunteers (all of which satisfied the inclusion criteria), during 7 days of treatment. ATD gel alprazolam 1% 2 g was applied onto the shoulders and arms of the volunteers. Venous blood samples were collected at different time points during the seven days of treatment period, and were analysed by HPLC.

Figure 11 shows alprazolam plasma concentration versus time curve during the whole study period. Alprazolam steady state is maintained between 84 and 168 h. The average alprazolam plasma level within this period is 6.6 ng/ml. The pharmacokinetic parameters derived are depicted on Table 8. The results presented herein show that alprazolam gel based on the ATD technology is capable of delivering across the skin enough quantities of the benzodiazepine drug to reach therapeutic doses. A plasma concentration of 6.6 ng/ml of alprazolam in the steady state is reached after ~ 3.5 days of treatment. The dose to plasma level ratio is very close to that mentioned in the literature, where for each additional milligram per day dose of alprazolam, there is a corresponding increase of approximately 10 ng/ml in the plasma.

4. Conclusion

ATD proprietary technology platform consists of a hydroalcoholic gel containing a combination of permeation enhancers such as propylene glycol, ethoxydiglycol, fatty alcohols and the alcoholic solvent itself. The penetration enhancers, along with the alcoholic solvent, alter the permeability of the stratum corneum in order to allow the active drugs to diffuse rapidly across the skin. The concentration of the enhancers is optimised so as to exert the maximum effect and minimise skin irritation. Although the individual effect of these enhancers has been previously well described, their combined effect achieved with this technology has demonstrated to be a novelty.

Furthermore, formulation of the active drug as a gel allows better skin penetration compared with creams, because the drug molecule, unlike in creams, is freely available for diffusion and is not entrapped in dispersed micelles or particles. This allows the active to exert a high thermodynamic activity, and, therefore, to be readily transferred from the formulation into the skin. Following evaporation of the volatile phase, the thermodynamic activity of the drug increases again but the active remains in the molecular form without crystallising, due to the presence of nonvolatile cosolvents.

Table 8. Plasma alprazolam pharmacokinetic parameters after repeated topical application of 2-g ATD™ gel alprazolam.

Parameter	ATD™ gel alprazolam 2 g
AUC_{ss} (ngh/ml)	590 ± 226
C_{max} (ng/ml)	8.2 ± 2.7
C_{ss} (ng/ml)	6.6 ± 2.8
T_{max} (h)	156 ± 24
Daily dose (mg)	0.7 ± 0.3

AUC and C_{ss} were calculated between 84 and 168 h. Alprazolam daily dose delivered from the formulation into the bloodstream was calculated using C_{ss} and clearance (1.02 ml/min/kg) [47]. Mean values ± SD.
ATD: Advanced transdermal delivery; AUC_{ss}: Area under the curve at steady state; C_{max}: Maximum concentration; C_{ss}: Concentration at steady state; SD: Standard deviation; T_{max}: Time to peak concentration.

The pH of the gel is optimised in order to maintain the drug predominantly in the unionised form (which diffuses better through the lipidic stratum corneum) but also avoiding potential irritation of the skin.

All of these optimisation steps have been designed so as to allow use of the formulation on a once daily basis, ensuring sustained systemic delivery of the drug. A range of active agents have been successfully formulated with the gel technology, and have resulted in clinically consistent levels compared with similar marketed products. Application of a gel for treating menopause symptoms, OAB, or anxiety seems rather odd but patches have also been considered a curiosity in the past decade, until the use for HRT and tobacco cessation made them very popular and accepted by the patients.

Several projects of transdermal gels are in early phase of preclinical development but were not presented for evident reasons of confidentiality. This demonstrates the number of potential therapeutic fields where a transdermal gel could provide elegant and innovative alternative to existing conventional dosage forms.

5. Expert opinion

Transdermal gels are clearly designed for long-term therapy, as they represent an alternative to patches. Acceptability of this treatment option will depend on many parameters: ease of use, no skin reactions, appealing cosmetic aspect and dose flexibility.

Ease of use is an important parameter, as it is directly related to patient compliance, and, therefore, success of the treatment and gain of popularity. Once-daily application is a prerequisite for ease of use but requires development of efficient formulations that allow penetration of the active drug into the skin at a high and sustained rate, and provide consistent systemic levels of the medication during a whole day.

Absence or low incidence of skin reactions is the second major parameter for transdermal gel acceptance. As transdermal gels are designed to treat chronic conditions for extended periods of time, and must be applied over large skin surfaces, they must not trigger dermal reactions.

Known causes of skin sensitisation are occlusion, excipients and the active drug itself (type of drug and concentration). The individual impact of these parameters is difficult to evaluate in a clinical trial, unless a placebo formulation is used as reference. However, the irritation potential of transdermal gels is more often compared with that of patches. Many studies reported less skin irritation for the former than the latter; for example, skin irritation was observed in 6% of subjects in a testosterone gel study [50], compared with 66% in the patch group. In an oestradiol gel trial, local skin reactions occurred in 3% of patients in the gel group, and 46% in the patch group [33]. Local lower drug dose per unit skin area in gels than in patches certainly contributes in limiting the irritation potential.

The cosmetic aspect is the third parameter. Even if probably not medically relevant, it is certainly a significant factor that should not be ignored for a formulation that is displayed on the skin. Gels are generally applied onto the same skin area, so that the underlying stratum corneum layer becomes saturated with the active, and acts as an internal drug reservoir. It is therefore possible, by this way, to avoid an externally visible reservoir; thus improving the cosmetic appearance of the treatment, provided the gel has been formulated with non-greasy, fully transparent excipients that do not leave residues.

Finally, the dose flexibility is the fourth parameter. Provided the drug is relatively potent and does not need high plasma levels to achieve therapeutic efficacy, transdermal gels are designed to be applied over no more than 1000 cm^2 of skin (~ 30 × 30 cm). This allows excellent dosage flexibility, particularly for dose titration in patient populations requiring dose adjustments. Patches also allow dosage flexibility, as, they can be cut at the desired size or added in duplicate, except reservoir type systems. Gels offer greater flexibility of dosing regimen; once-daily application of a gel enables a more rapid reaction than a patch in case of sub- or supra-therapeutic levels. A patch has by nature an intrinsic inertia.

Besides previous arguments in favour of transdermal gels, some limitations may be identified: lack of drug candidates and permeation enhancers, limited surface area control and risk of cross-contamination.

The first limitation is that transdermal drug administration is feasible for a limited number of drugs compared with the oral route. The ideal transdermal candidate should need low doses to achieve efficacy (< 10 mg), with a short half-life (< 10 h), a small molecular weight (< 1000 Da), and an intermediate octanol/water partitioning coefficient (logP 1 – 3) [51]. As a consequence, transdermal drug delivery market will probably remain relatively limited. However, it is currently driven by the gels, which are in constant growth and boosted by the success generated by Androgel and other hormone replacement therapies.

The second limitation is that the number of permeation enhancers approved for human use is limited to compendial or

generally recognised as safe compounds. Any new chemical displaying permeation-enhancing properties must first undergo extensive toxicological testing, which remains extremely expensive and does not guarantee efficacy for all kind of drugs.

The third limitation is that application surface area can be controlled only to a certain extent with gels. The size of the application area may have an impact on the absorbed dose. However, the stratum corneum acts as a reservoir and can, to a certain extent, compensate fluctuations in the application area. This issue was specifically addressed in a clinical study comparing the pharmacokinetics of an oestradiol gel applied at the same dose (1 mg oestradiol) over skin areas of 200 and 400 cm^2 [52].

Even if higher absorption was achieved from a smaller application area, no marked differences were observed in the pharmacokinetics between 200 and 400 cm^2 application areas, which are those recommended for the studies of oestradiol gel preparation.

The fourth limitation is that cross-contamination could occur between the patient and partner after gel application. This could be an issue for hypogonadal men under testosterone gel treatment, considering the potential virilising action on females. Interpersonal testosterone transfer was evaluated in two clinical randomised, open, single-centre studies on 40 healthy male volunteers [53]. The endogenous testosterone production in the receiving subjects was suppressed by injecting 400 mg norethisterone enanthate. After intense skin contact with a volunteer who had applied testosterone gel on his forearm, no increase in testosterone levels could be found in the norethisterone enanthate-suppressed men.

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