Trinity Delta

Futura Medical

Elegant and effective treatment for Erectile Dysfunction

Initiation of Coverage

25 November 2019

Futura Medical is rapidly approaching a major inflection point as the results of a pivotal Phase III study (FM57) for its lead compound, MED2005, are due to read out in December. MED2005 is a fast-acting glyceryl trinitrate gel that addresses erectile dysfunction (ED). The FM57 data is expected to be positive and will influence the design of the remaining Phase III trial (FM59) required for US approval (and possibly Europe too). This data will also fuel licensing discussions with potential partners. The commercial opportunity in ED is sizeable, although addressing the various elements of the market segments and different geographies optimally will, in our view, be critical. Our DCF-based model employs conservative assumptions and currently values Futura Medical at £127m, equivalent to 62p a share.

Year-end: December 31	2017	2018	2019E	2020E
Sales (£m)	0.4	0.0	0.0	0.0
Adj. PBT (£m)	(4.8)	(7.2)	(10.4)	(10.1)
Net Income (£m)	(3.9)	(5.9)	(8.6)	(8.2)
EPS (p)	(3.2)	(4.5)	(4.2)	(4.0)
Cash (£m)	8.4	9.2	1.5	8.4
EBITDA (£m)	(4.8)	(7.2)	(10.4)	(10.1)

Source: Trinity Delta Note: Adjusted PBT excludes exceptionals, Cash includes short-term investments, and 2020E cash figure includes £15m injection of funds.

- **Key Phase III read out in December** Top-line results from the pivotal FM57 Phase III study for MED2005 in erectile dysfunction (ED) are expected in December. The nature and structure of the trial, placebo and three active doses (0.2%, 0.4%, and 0.6%) and three patient groups (Mild-, Moderate-, and Severe-ED) means that a conclusive headline result is, in our view, unlikely. We do expect significantly positive outcomes, especially at the higher doses, in the Mild- and Moderate-ED groups; Severe-ED tends to be associated with more complicated health issues.
- **Groundwork for regulatory filings in place** FDA requires a smaller confirmatory Phase III study (FM59) to be performed for US approval. In Europe, a filing may be potentially acceptable if FM57 results are highly compelling; however, we model conservatively on the basis that supportive FM59 data will be needed for approval. FM59 preparations are underway, with clinical sites identified including in the US, although it requires funding to be in place ahead of recruitment starting in 2020.
- **Partnering needs careful targeting** Partnering discussions are ongoing and are expected to expand and advance once FM57 data is known. We believe the ED market is evolving, especially in the US, and a single, global partner is unlikely to be able to optimise MED2005's potential income. We would expect European, and possibly select Asian, regions to be partnered first (markets that are relatively conventional), with a US deal later.
- **Under-valued and relatively low-risk** We value Futura Medical using a risk-adjusted DCF model and use conservative assumptions throughout. We expect to revisit these assumptions as Phase III data becomes available and visibility of the commercialisation strategies improves. Our current valuation is £127m (62p/share).

Price	31.2p
Market Cap	£63.8m
Enterprise Value	£58.2m
Shares in issue	205m
12 month range	5.65-49.2p
Free float	70.4%
Primary exchange	AIM
Other exchanges	N/A
Sector	Healthcare
Company Code	FUM
Corporate client	Yes

Company description

Futura Medical is an R&D driven small pharma company, with a novel DermaSys transdermal delivery platform. The lead programme, MED2005, is a topically applied gel that is in Phase III trials for erectile dysfunction (ED). A pain relief gel, TPR100, is awaiting UK approval.

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Investment case

Renewed vigour as focussed commercial strategy progresses

Futura Medical has developed a proprietary transdermal delivery platform known as DermaSys. This drives an active drug rapidly through the skin, achieving high concentrations with minimal residual effects. An erectogenic GTN-based condom (CSD500) was developed and commercialised, although the larger marketing partners did not launch their branded offering. A number of potential applications have been explored, but a strategic review in 2018 decided to focus resources on two key programmes: MED2005, a topical gel for treating erectile dysfunction; and TPR100, a topical diclofenac pain relief gel. Both are in late-stage clinical development with pivotal news flow expected over the coming 12 months.

Investor interest will focus on the MED2005 Phase III study results expected in December 2019, which although commercially critical are not likely to be a binary go/no go. The data will help guide the next Phase III clinical trial, required for FDA approval, and possibly European approval. Futura Medical will seek partners for MED2005 commercialisation, initially as a prescription-only medicine before an expected transition into an OTC product (particularly in Europe). Futura Medical was founded in 1997, listed on AIM in 2003, and is based in Guildford, Surrey. It has 15 full time employees.

Valuation

A string of value inflection points expected over the next 24 months

We view Futura Medical as a classic R&D play and so believe that a DCF-based model is particularly suitable. We calculate a risk-adjusted net present value (rNPV) of the clinical projects, adjust them for success probabilities, sum them, and net this against costs. We always seek to adopt conservative assumptions throughout, and this can be notably seen in the adoption curves and penetrations employed within the market potential for MED2005. Despite this, our model results in a current valuation of £127m, or 62p per share on a fully diluted basis. We would expect to revisit our assumptions as the MED2005 clinical programme is further de-risked and the visibility of the commercialisation strategy improves.

Financials

Tight cost control but funding needs are well flagged

Futura Medical had net cash of £5.63m at June 2019, with a further £1.36m R&D tax credit received in August. The lean nature of the company structure means that central costs are low, c £2.5m pa, with the majority of the spend being the funding of clinical trials. The next key trial, FM59, will require additional funding.

Sensitivities

Main risks centre on MED2005 but these are relatively contained

As a small loss-making pharmaceutical company, the typical industry risks apply. Here the later clinical stages, coupled with the non-binary nature of the key Phase III trial, means Futura Medical's risk profile tends to be lower. Nonetheless, the sensitivities associated with trial results, successfully navigating regulatory hurdles, ensuring sufficient financing is in place, concluding partnering discussions and, eventually, obtaining suitable pricing and gaining commercial traction, have to be recognised. Our main sensitivities are detailed later (in the body of the note), with particular emphasis on the main elements of the MED2005 programme.

Futura Medical: Rising to the challenges

Futura Medical is approaching a defining point in its long journey as results from a key Phase III trial (FM57) are expected in December 2019. The trial design and evidence from earlier studies suggest the data should confirm MED2005's efficacy and safety in treating erectile dysfunction (ED). The next stage requires a confirmatory Phase III study to support an FDA filing, however a European submission may be initiated based on FM57 results alone. The FM57 data should also encourage discussions with potential commercialisation partners. We believe that more complex, targeted partnerships are required in order to maximise MED2005's value. Whilst not without risks, we believe the current valuation fails to reflect the material progress achieved and the prospects ahead.

MED2005 will shape the future, and the FM57 results are crucial

MED2005's outlook will determine Futura Medical's fate as management seeks to leverage its proprietary DermaSys topical delivery platform. The widely anticipated results of a pivotal Phase III study (FM57) for erectile dysfunction (ED) will be known in December 2019. The variety and nature of the possible permutations mean a conclusive positive result on all metrics is unlikely. Nonetheless, the well-planned trial design, coupled with encouraging results from earlier studies, suggest the data will be compelling, and therefore positive, supporting filing either on this study alone in Europe, or following a confirmatory trial. We believe FM57 data will facilitate licensing discussions with potential partners for European and Asian markets.

Funding required for the next step, followed by out-licensing

Regulatory submission for the commercially important US market will require an additional Phase III trial (FM59). Clearly this would only happen following positive FM57 results, and so should be easily funded. The simpler nature of this confirmatory study suggests an injection of funds of c £10-15m is required for its completion and FDA filing, most likely in 2021. We expect licensing discussions for North America will not necessarily follow a similar path to those for other regions given the evolving market dynamics in the region. We believe Futura Medical may seek to partner with smaller, more nimble players who are prepared to share MED2005 income in more innovative structures than typical sales royalties and commercial milestones.

An attractive profile in a large and growing market segment

The market opportunity for ED treatments is large, now worth c $5.6bn (IQVIA) despite falling from its peak as genericisation of the leading PDE5 products takes hold. The number of men expected to seek treatment for mild- and moderate-dysfunction is forecast to rise. We believe this is not simply because of increasing incidences due to demographics and the consequences of chronic diseases (such as diabetes), but also greater awareness and, importantly, expectations (from both partners) that healthy sexual activity can be restored. MED2005's profile, particularly ease of use and rapid onset of action, suggests that it offers material benefits that would enable a significant share of the market to be captured.

Commercial potential and inherent value under-appreciated

Futura Medical has undergone a subtle, yet important, transformation of late, with a greater focus on the commercial strategy once MED2005 is approved. It is the multi-faceted elements of these medium-term plans to optimise MED2005's income streams and expand the DermaSys portfolio that will increasingly shape the investment case. We believe the current valuation fails to reflect the progress that has been made and the inherent value of the business.

Erectile Dysfunction (ED) is no laughing matter

A common complaint with a long history and multiple repercussions

The erect penis has always been a symbol of a man's virility, masculinity, and sexual prowess[1]. All men will have experienced occasional episodes of loss of libido; however, the incidence and frequency tend to rise with age and the onset of certain diseases (most notably diabetes and obesity). Importantly, it is not simply a modern "first-world" problem and nor is it a trivial inconvenience:

- Impotence (deemed a pejorative term from the Latin for loss of power), and its treatment, was described in the oldest known medical texts. The Yellow Emperor's Classic of Internal Medicine of c 2,600BC identifies it and defines a number of Traditional Chinese Medicine (TCM) remedies, and it is similarly described in the later Egyptian Papyrus Ebers, an Ancient Egyptian medical document of c 1,550BC.
- An active sex life is associated with improvement in mortality and quality of life measures. The Caerphilly Cohort Study (BMJ 1997) showed that sexual activity seems to have a significant protective effect on men's (aged 55-69) health. Similar positive findings were seen in a Swedish study[2] examining 70-year-old men and in the Duke Longitudinal Study of Ageing[3], with regular sexual activity improving multiple health parameters.

Women are the same as men, but different…

A similar benefit is seen in women, with sexual activity a significant predictor of longevity, resulting in a mean of an extra 4.28 years of life. Tellingly, whilst the quantity of intercourse is the largest determinant of improvement in men, in women it appears correlated to the rating of the quality of the sexual experience. And, whilst it may discomfort their children to know this, most "middle aged" (45-65 years old) couples report having sexual intercourse one or more times a week (men 57%, women 51%). The importance of this, other than the known health benefits, is that relationships often suffer when one or other partner cannot sustain what are deemed, until then, "normal" sexual activities.

ED is widespread and has far-reaching consequences

Psychological consequences of ED tend to be more immediate than the physical ones

Erectile dysfunction (ED), defined as the prolonged inability to attain and maintain an erection sufficient to permit satisfactory sexual performance, is associated with sizeable near-term issues as well as the longer-term consequences described above. The main one is the loss of self-esteem and confidence, which in turn can lead to doubts about the partner and even fuel suspicions of infidelity. Long term relationships can break down surprisingly easily as communication reduces and there is less physical intimacy. The psychological effects can rapidly spread to other family relationships and even work can suffer, with many men progressing into depressive states (with an incidence 2.92x higher in ED patients than not).

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[1] Erectile dysfunction Nat Rev Dis Primers. 2:16003 10.1038 2016.3

[2] Persson, G. Five-Year Mortality in a 70-Year-Old Population in Gothenburg Acta Psychiatr. Scand. (1981) 64:244.

[3] Duke University Longitudinal Studies of Aging Gerontol. 1993 May-Jun; 26(3):123-8.

ED is widespread, with Mild and Moderate cases most common

The landmark Massachusetts Male Aging Study[4] (MMAS) found that 52% of men between 40 and 70 years old had some form of ED. The reality is that ED is a natural part of ageing and that the prevalence increases with age. In MMAS, they found that roughly 50% of men at 50 years old, 60% of men at 60 years old and 70% of men at 70 years old had ED. Hence, with an increasingly ageing population, nearly all men who live long enough are likely to develop ED. Of the men, aged 40 to 70 (n=1290), 48% had no erectile dysfunction, 17% had minimal ED, 25% had moderate ED, and 10% had complete ED. The more serious cases were often associated with metabolic conditions, such as diabetes, or cardiovascular conditions, such as atherosclerosis.

Causes of ED are manifold, with demographics driving incidence

ED has many possible causes and can be the first symptom of an undiagnosed condition. Essentially, erections are caused by the balance of blood flow into and out of the penis. Conditions that result in changes in the penis' blood flow are common causes of ED. As mentioned above, the most common medical problems linked to ED are diabetes and atherosclerosis (hardening of the arteries). Obesity is also associated with both blood vessel changes and hormone changes that can negatively affect erections. Another cause of ED is damage to the nerves involved in getting erections. This can happen with diseases of the nervous system (eg multiple sclerosis, Parkinson's disease) or with surgery (eg for prostate cancer). Hormone problems, eg low testosterone; the side effects of medications, eg some used to treat high blood pressure; and psychogenic causes, can also result in ED.

Treatment options were revolutionised 20 years ago

PDE5 inhibitors transformed the outlook for treatment…

The first step is always to examine lifestyles and reduce factors, such as smoking, excessive alcohol, and obesity, that have an impact on ED. Often these measures have a material impact on not only the physical causes of the ED but, importantly, on the psychological aspects too. A better self-image will aid any therapeutic intervention.

Approval of Pfizer's Viagra (sildenafil) in 1998 transformed the ED therapeutic landscape and brought it into the mainstream. Previously, treatments had centred on rather esoteric formulations of prostaglandin E1 (alprostadil) such as MUSE (Medical Urethral System for Erection), intra-urethral pellets (IUS), and Caverject, an intra-cavernosal injection (ICI), that increased blood flow into the penis. The pellet form results in a successful erection in 30%-40% of cases, while the injectable can achieve results in >80% of cases; although neither are easy to use.

…but older, and less discreet, options still remain popular

Other popular treatments included Vacuum Constriction Devices (VCD), essentially a clear plastic chamber that is placed over the penis and then a vacuum is created. If this results in a successful erection, a small constriction band is placed over the base of the penis to maintain an erection for around 30 minutes. The success rates of VCDs range from 50% to 80%. The cumbersome nature of these formulations and devices does mean a degree of planning is required, with a consequent loss of spontaneity and intimacy. Other options included surgery, with implantation of a penile prosthetic device, which have good long-term outcomes.

[4] Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. Feldman HA, Goldstein I, Hatzichristou DG, et al J Urol 1994;151:54–61

Viagra was the first of a new class of PDE5 inhibitor therapies

It was against this eclectic background that Viagra (sildenafil) burst into the clinical and public consciousness. Normal erectile function depends on the release of NO (nitric oxide) and endothelial-dependent vasodilation of the penile arteries. Viagra (sildenafil) belongs to a class known as the PDE5 inhibitors, which act on the L-arginine–nitric oxide–guanylyl cyclase–cyclic guanosine monophosphate (cGMP) pathway to generate both penile arterial dilatation and venous constriction to stimulate and maintain an erection.

Differences between PDE5s are marginal, so patient choice is key

Viagra was followed by the analogues Levitra (vardenafil) from Bayer and Cialis (tadalafil) from Eli Lilly in 2003. These differ mainly in their onset of action and duration of effect which, in the absence of properly conducted comparison studies, in reality means patient preference has become a primary determinant of choice. A fourth PDE5 inhibitor, Spedra/Stendra (avanafil), was launched in 2012 by Mitsubishi Tanabe, which claims to be a second-generation PDE5 and to have the fastest onset of action (within 15 minutes). Other, mainly regional, "me-too" PDE5s are also available.

Exhibit 1: Top PDE5 inhibitors and key properties

	Generic (Brand)	Company	Median tmax (min)	Half-life (hours)	Absorption affected by food	Dosed
First generation	Sildenafil (Viagra)	Pfizer	60	3-5	Yes (high fat food)	As needed
	Tadalafil (Cialis)	Eli Lilly	120	17.5	No	Daily or weekender
	Vardenafil (Levitra)	Bayer	60	4-5	Yes (high fat food)	As needed
Second generation	Udenafil* (Zydena)	Dong-A Pharmaceutical	60-90	11-13	No	Daily or as needed
	Avanafil (Spedra/Stendra)	Menarini / Metuchen Pharma	30-45	5-10	No	As needed
	Mirodenafil* (Mvix)	SK Chemicals Life Science	75	2.5	Limited data	As needed

Source: Trinity Delta, Cleveland Clinic, FDA Note: * = not FDA approved

PDE5 inhibitors have become first-line choices

PDE5s are convenient, effective, safe and well-established

The arrival of the PDE5 class transformed the ED marketplace. The availability of a simple oral medication resulted in a ground swell of patient awareness that was unheard of in pre-internet days. Viagra became a household name and doctors were soon asked for the product by brand name. The results were seen in the sales charts, with two of the original PDE5 products achieving blockbuster status (defined as annual sales over $1bn).

Viagra achieved peak sales of $2.1bn in 2012 (just ahead of patent expiries ex-US) and Cialis had peak sales of $2.3bn in 2017, whilst Levitra always ranked a poor third as its marketing campaigns failed to resonate with either users or clinicians, and no clear differentiation vs Viagra/Cialis. The newer "me-too" prescription PDE5s are not expected to achieve meaningful revenues as the market is effectively now genericised. However, the Viagra switch to OTC (over the counter) status in several geographies means that established brand names have a renewed and longer lifecycle, albeit at a lower price point.

PDE5s have proven efficacy but still some notable limitations

Their commercial success reflects their clinical efficacy, with over two-thirds of men finding they provide sufficient improvement in their erections to achieve the desired intercourse. But, despite their undoubted benefits, PDE5s are not without their limitations[5]. Because of their mode of action, PDE5s are contraindicated in patients taking certain medications, notably nitrates and alpha-blockers, and between 11% and 18% of the mild and moderate ED population is excluded due to possibility of blood pressure interactions. A similar proportion, 12% to 16%, discontinue treatment due to side-effects (headaches, flushing, gastro-intestinal, and visual disturbances), despite these typically being transient and mild in nature.

Treatment discontinuations highlight the various issues

A larger proportion of ED patients, between 14% and 31%, discontinue treatment after an initial trial period, despite a satisfactory pharmacological effect. A recent meta-analysis suggests discontinuations over one year reach almost 50%[6]. The reasons vary by geography and age-group, ranging from a lack of desire and/or opportunity to a partner's loss of libido, and is probably related to individual cultural and psycho-social factors. However, a common theme (arising from both partners) is that the oral administration and need to "time it" means that there is a loss of spontaneity, and that intimacy and "naturalness" is reduced as a result.

MED2005 is a fast-acting erectogenic gel

An easy to use and effective transdermal gel that delivers GTN directly to the penis

MED2005 is an elegant clear gel formulation of the vasodilator glyceryl trinitrate (GTN) that is applied topically to the head of the penis (the glans). It employs a DermaSys formulation, Futura Medical's proprietary transdermal drug delivery platform, that can rapidly achieve therapeutic drug levels in the target tissues of the corpus cavernosum. The quick absorption results in a therapeutic effect within 5-10 minutes, faster than on-demand PDE5s, with a predictable clearance.

GTN is an established and effective vasodilator that is widely used in the treatment of angina and other related cardiovascular conditions. Its long history means that its safety profile is well-documented and understood, resulting in several dosage forms (notably sublingual tablets and sprays) being available without prescription in some markets. Medically the greatest concern is severe hypotension when used in conjunction with certain other cardiovascular drugs (hence the interaction warning with PDE5s); however, from a patient's perspective, it is the incidence of headaches that is noteworthy. These effects are closely linked to the GTN levels circulating in the body.

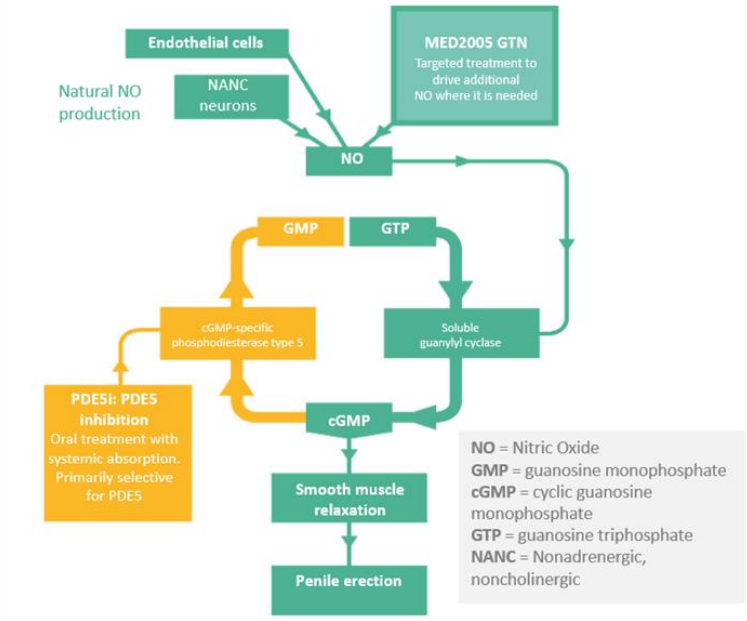
GTN works on a related pathway to the PDE5 inhibitors

Pharmacologically, it is the NO-cGMP axis[7] that plays a pivotal role in promoting and maintaining an erection. When applied topically to the glans or head of the penis MED2005 works by delivering the necessary NO to the soluble guanylyl cyclase side of the pathway (Exhibit 2), resulting in an increase in cGMP production and so smooth muscle relaxation. The PDE5 inhibitors effectively work on the same pathways but raise the levels of cGMP available by inhibiting activity

[5] Phosphodiesterase-5 (PDE5) Inhibitors in the management of erectile dysfunction. Huang S et al Pharmacy & Therapeutics 2013 July 38(7):407, 414-419
[6] First generation phosphodiesterase type 5 inhibitors dropout: a comprehensive review and meta-analysis. Corona G et al. Andrology 2016, 4: 1002-1009
[7] Erectile dysfunction: from biochemical pharmacology to advances in medical therapy. Maggi M et al European Journal of Endocrinology (2000) 143 143-154

of a specific phosphodiesterase. Although arguably capable of working in a synergistic manner, MED2005 is unlikely to be approved for use in combination with PDE5s inhibitors.

Exhibit 2: MED2005 mechanism of action

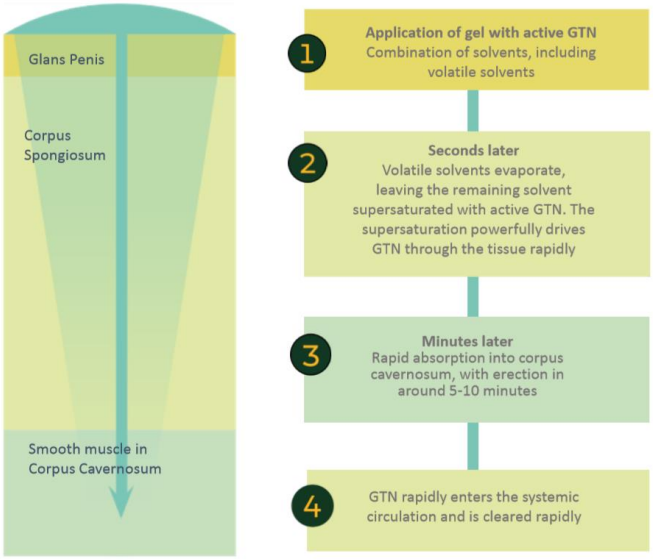


Source: Futura Medical Note: PDE5 = phosphodiesterase type 5

Rapid absorption means a quick result, with clean elimination too

The way MED2005 is delivered transdermally is shown in Exhibit 3. The formulation allows a rapid delivery to the corpus cavernosum and typically results in onset of erection within 5-10 minutes. The active concentration is achieved locally, with the systemic effects limited, and elimination from the body generally within an hour. The benefits of such a delivery and elimination are summarised in Exhibit 4. The clear message being that MED2005 would offer an attractive, clearly differentiated (not 'me too'), and competitive clinical profile compared to the market leading class of PDE5 inhibitors.

Exhibit 3: Transdermal delivery of MED2005



Source: Futura Medical

Exhibit 4: Benefits of MED2005

Benefit	Key enabling feature
Well tolerated	Lower systemic side-effect potential than PDE5 inhibitors
Works rapidly	Potential to have the fastest speed of onset (5-10 minutes) for any ED treatment
Enables spontaneity	Removes the need for planning of sex associated with some oral PDE5i medications
Restores intimacy	Direct mode of application (by the male or his sexual partner) can form part of foreplay, which combined with speed of onset can help restore intimacy

Source: Trinity Delta, Futura Medical

Clinical profile demonstrated in earlier studies

An extensive development programme that has guided the pivotal FM57 Phase III study

The clinical study programme has been extensive and well executed. MED2005 has undergone c 15 clinical trials; with the majority being the early stage studies to explore the best formulation, the pharmacokinetic profile, and dosage optimisation. A summary of the more relevant trials is shown in Exhibit 5.

Exhibit 5: MED2005 clinical study programme

Study code	Phase (no. of subjects)	Test article	Study status
FM33	**Phase I** PK (16)	0.025%, 0.033%, 0.083% and 0.166% MED2003, 0.25% MED2004, and 0.4% MED2005	Complete
FM35	**Phase I** PD (15)	0.003%, 0.025%, 0.083% MED2003, and 0.2% MED2005	Complete
FM53	**Phase IIa** (231)	0.2% MED2005 vs placebo	Complete: headline data Sept 2016; peer reviewed journal publication early 2018
FM58	**Phase I** PK (40)	0.2%, 0.4%, 0.6%, and 0.8% MED2005 and Nitrostat	Complete
FM57	**Phase III** (1,000): safety and efficacy dose ranging	0.2%, 0.4%, and 0.6% MED2005 and placebo	Ongoing: topline results Dec 2019
FM59	**Phase III** (690): safety and efficacy confirmatory study	0.2%, 0.4%, and 0.6% MED2005 and placebo (likely choosing two of three doses from FM57)	H219 start*, study completion by end-2020, data read-out 2021

Source: Futura Medical Note: PK = pharmacokinetic; PD = pharmacodynamic; placebo = identical gel to MED2005 but without the active pharmaceutical ingredient glyceryl trinitrate; * regulatory and ethics submissions expected in H219 to allow patient enrolment to commence H120. Studies FM02 to FM07, FM22, FM23, and FM27 were early phase exploratory studies using previous MED formulations and are not presented above.

FM33 and FM35 Phase I studies confirmed the pharmacodynamic properties were promising

FM33 was a Phase I pharmacokinetic study exploring dose levels, six ranging from 0.025% to 0.4%, in 16 healthy patients. FM35 employed Doppler ultrasound to measure penile blood flow in 15 healthy patients at four doses (from 0.0033% to 0.2%). The data showed a dose response curve, with the higher dose 0.25% achieving the desired haemodynamic effects. These studies and FM58 showed that MED2005 was rapidly absorbed, achieving a peak plasma concentration within 10-12 minutes, with this peak subsiding within 45 minutes and blood levels normalising after a few hours.

FM53 Phase IIa proof-of-concept trial produced encouraging results

FM53 was a Phase IIa trial involving evaluable 231 patients in a double-blind, cross-over design over eight weeks. Patients were selected if they had a

confirmed diagnosis of ED for over three months and scored less than 25 on the International Index of Erectile Function (IIEF) criteria. The IIEF format is robust and validated, with good correlations across cultures, races, and ages. Broadly, a score of 26-30 represents normal erectile function, 18-25 is viewed as "mild" dysfunction, 11-17 is seen as "moderate", and 10 and below as "severe". Four recruitment sites, one in the UK and three in Poland, were used. The mean age was 43 years (range 19-70), and the mean IIEF-EF score was 17.1 (SD 5.7).

Treatment duration was four weeks

The study employed a four week "run in" during which no treatments were allowed and at least four intercourse events were tried. This was then followed by either four weeks on active treatment or placebo, and then (after a wash-out period of a week) switched over to placebo or active treatment. Again, in each four-week period at least four intercourse attempts were to be made. There were no restrictions on who applied the gel to the male, it could be applied by either partner, but this had to be logged. Only one dose, 0.2% (0.6mg of GTN), was evaluated.

Trial endpoints based on established and validated scales

The primary endpoint was based improvements of the IIEF scale, with secondary endpoints employing other domains of the IIEF, the Sexual Encounter Profile (SEP) and the Global Assessment Questionnaire (GAQ). A comprehensive review of the standards and methods employed in sexual dysfunction clinical trials was published in The Journal of Sexual Medicine in 2017[8] and, for those interested in the details, is worth reading. Speed of onset, safety and patient acceptability were also evaluated. The results and discussion of FM53 were published in the Journal of Sexual Medicine in 2018[9].

Results were encouraging but dosage was probably too low

The data showed mean IIEF-EF scores after treatment with MED2005 or placebo were 19.6 (SD 7.5) and 18.5 (SD 6.7), respectively, compared with a mean score during the run-in period of 17.1 (SD 5.7). Although encouraging, and statistically significant, an increase of four or more points is typically viewed as being clinically relevant; 23.1% of MED2005 and 14.0% of placebo patients saw this four-point improvement. MED2005 also showed significant improvements in scores for the other IIEF domains, SEP, and GAQ, compared with placebo. It is worth noting that the greatest effect was, unsurprisingly, seen in the mild and moderate patient groups. A major finding of the study was that, after assessing side effects, the 0.2% dose could be considered a minimally effective dose.

Attractive onset of action and clean side-effect profile seen

The other measures, such as onset of action and safety, were positive. Onset of an erection was seen in 44% of intercourse attempts within five minutes and 70% of attempts within 10 minutes. This was despite no restrictions on food or alcohol intake (although alcoholism was an exclusion criterion). MED2005 was also well tolerated, with no severe adverse events. The most common problem was headache, a known side-effect of GTN therapy, but this occurred in only 14 incidents during 1,003 intercourse attempts. The speed of onset and adverse event profiles compare favourably with those seen in PDE5 inhibitors and other topically applied products (eg alprostadil).

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[8] Standards for Clinical Trials in Male and Female Sexual Dysfunction:III. Unique Aspects of Clinical Trials in Male Sexual Dysfunction Fisher WA et al J Sex Med 2017;14:3-18.
[9] Efficacy and Safety of MED2005, a Topical Glyceryl Trinitrate Formulation, in the Treatment of Erectile Dysfunction Ralph D et al J Sex Med 2018;15:167-175

Interestingly, the side-effect profile in the female partners was very low (two mild headaches in 1,003 intercourse attempts), which suggests the transference of GTN to the partner was low even when the gel was applied by the partner (more than 300 times in the study). Specific transference studies have been performed for regulatory compliance, with corroborating results.

Post-FM53 discussions confirm two Phase III trials for FDA but European approval could be one

The FM53 outcomes were used as a basis for discussions with the regulatory agencies, with the resulting conclusions on the data required and study designs forming the basis for the pivotal Phase III programme. The FDA requires two Phase III studies for approval. For Europe, should the first Phase III study (FM57) data meet criteria that would class it as 'extremely compelling', there is a regulatory pathway which would facilitate filing on this study alone; otherwise a confirmatory study would be required, which is usually the case. Regulatory discussions requested that higher doses should be explored in the pivotal trial, with a Phase I PK study (FM58) carried out to identify these. The US regulatory pathway for MED2005 employs the abbreviated 505(b)2 route, which allows for existing safety and efficacy data on the active ingredient to be included in the filing: in this case the GTN-based angina medication Nitrostat is the reference product. Both the FDA and EMA will require a period of prescription-only (Rx) use of MED2005 before considering an OTC switch.

FM58 Phase I trial used to provide supporting evidence for pivotal Phase III study

The FM58 Phase I pharmacokinetic study explored higher doses of MED2005 (0.2%, 0.4%, 0.6% and 0.8%) and compared them with Nitrostat. The study involved 40 healthy patients and was split into two parts. The first part, with 30 patients, showed all doses performed as expected: the absorption profile was rapid, with first appearance in plasma/bloodstream within 4-5 minutes and peak levels seen at 10-12 minutes; the plasma concentration showed a clear dose-related response; the absorption through the topical route was excellent (73% of the dose within 5 minutes); and the incidence of adverse events remained acceptably low at all dose levels tested.

The importance of FM58 was to determine the suitability of higher doses for the pivotal FM57 Phase III trial, with 0.2%, 0.4% and 0.6% selected, and to ensure that MED2005 does meet the requirements for the preferred regulatory pathways in Europe (Article 8(3) of Directive 2001/83/EC2) and in the US (505(b)2).

FM57 is the defining Phase III trial for MED2005

Previous studies helped guide format and nature of FM57

The previous studies served to determine the nature and scope of the pivotal FM57 Phase III trial. The proof of concept was demonstrated by the data from the FM53 Phase IIa study, with the indications that a higher MED2005 dose was likely to perform better (yet still have an acceptable adverse event profile) confirmed by the FM58 study.

12-week study duration should ensure a smaller placebo effect

FM57 consists of three active arms, with gel doses of 0.2%, 0.4%, and 0.6%, and a placebo arm run in parallel. The study involves a total of 1,000 males aged 18-70, 250 in each arm, who have confirmed clinical diagnosis of erectile dysfunction (defined as an IIEF score of less than 25) for at least three months. They will undertake a four-week run-in period followed by 12 weeks of treatment (in contrast FM53 was a four-week treatment period). The longer study period should help create better differentiation between treatment and placebo arms.

Primary endpoints broadened and more relevant

The primary efficacy endpoint is based on the erectile function domains of the IIEF questionnaire (the same as FM53), but with additional questions from the SEP2 to SEP3 survey (assessing the satisfaction with the erection hardness and the ability to complete sexual intercourse). Secondary endpoints include the SEAR (Self-Esteem And Relationship) questionnaire for men and women, the Global Assessment Questionnaire (GAQ), the additional domains of the IIEF as well as subjective measures of the time of onset and duration of action (erection) and additional questions on usage and application.

Top-line data due in Q419, which if positive could mean a European submission as soon as mid-2020

The initial results of the double-blind part of FM57 are expected in December 2019, with full results in H220. Around 450 patients are continuing in a six-month open label extension long-term safety study, with a further 100 of these will be followed for a total of 12 months from the end of the study period. Depending on the strength of the initial data, Futura Medical may be able to opt for a single Phase III approval pathway with the European regulatory agencies, in which case submission could be as early as mid-2020. A second Phase III efficacy study (FM59) is required for FDA approval; if the data from FM57 is not sufficiently compelling then European approval would include results from this study too. We highlight that two pivotal studies for Europe is the usual requirement for a filing.

FM57's complexity means a simple binary outcome is unlikely

The three treatment arms, coupled with the number of primary and secondary evaluation criteria, means that the trial data are not going to produce a simple efficacy outcome. There are literally hundreds of potential permutations of results and very few of these would be expected to produce an unequivocal conclusion on all measures; however, regulatory bodies are aware of such study structures. For a filing based on a single study, the EMA requires this data to be 'extremely compelling'.

To aid understanding we stratify patients into nine groups

We believe a means to get a better picture of the likely outcomes is to consider the three dosage regimens and the fact that ED is classified as Mild, Moderate, and Severe. This gives a total of nine possible scenarios that will generate data. Realistically, the nature of Severe ED means, in our view, it is unlikely that any dosage of MED2005 will produce meaningfully positive results. Severe ED is usually associated with material co-morbidities, such as testosterone insufficiencies or the sequelae of prostate cancer surgery, and treatment with a NO-cGMP acting agent (eg PDE5s and MED2005) alone is unlikely to generate the required effect.

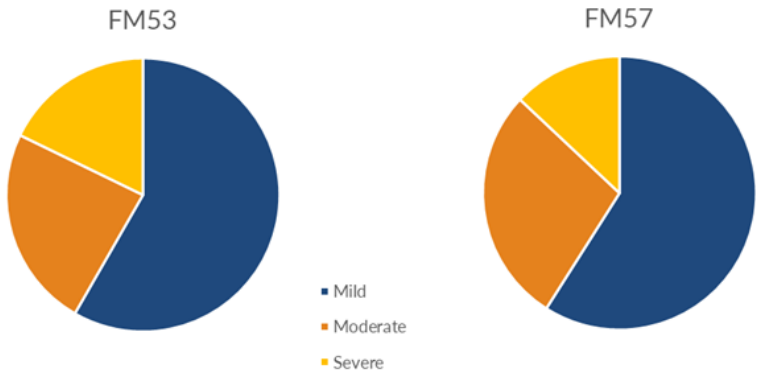
The difficult to treat Severe patient groups is relatively small

The patient segmentation in terms of ED severity for the FM53 and FM57 studies are shown in Exhibit 6. The profile of the FM53 population was 58% were classed as Mild, 24% were Moderate, and 18% were Severe. The equivalent profile in the FM57 show 59% as Mild, 28% as Moderate, and 13% as Severe. The patient splits are comparable and suggest that a population bias is unlikely to skew the FM57 efficacy results.

The Mild and Moderate groups at the higher doses will be key

The Severe ED patients have to be included within the study (safety and tolerability data is required), but we expect the real evidence of MED2005's efficacy should be found within the Mild and Moderate patient groups. The addition of the higher 0.4% and 0.6% dosages suggests that the efficacy should be materially improved, with the only question being by how much? Unfortunately, despite a good dose response curve (see the FM58 study), the subjective variabilities seen in the treatment of ED mean that we cannot predict the likely outcomes.

Exhibit 6: Patient segmentation by ED severity for FM53 and FM57 studies



Source: Trinity Delta, Futura Medical

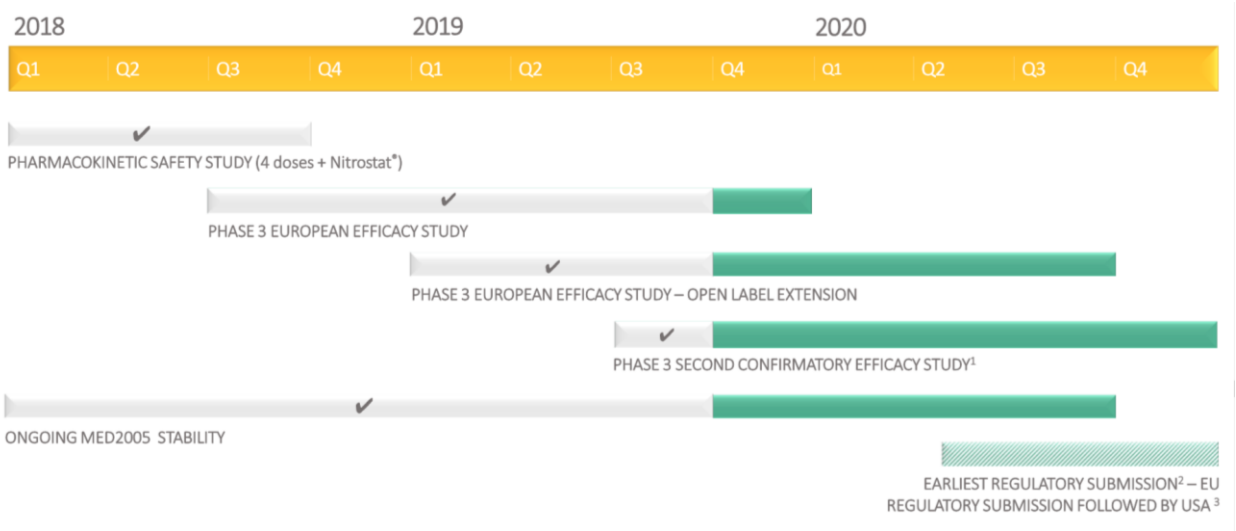
Longer treatment duration should create more divergence between active and placebo

Nonetheless, the lessons learned from performing FM53, and the subsequent changes to the study's structure and measurements, suggest that the results generated by FM57 should be better than those seen before. Of particular note is the longer treatment duration (12 weeks against four) and the two higher dosage strengths. These, coupled with tighter definitions of primary endpoints and tight patient selection, should produce more meaningful results. As the safety and acceptance of the MED2005 gel have never been material concerns (the regulators have substantial experience of GTN and GTN-containing products), we would argue that the likelihood of data being sufficiently robust to support a regulatory submission is above that typically seen in such Phase III studies.

Second confirmatory Phase III study required by FDA but European filing could be earlier

The European regulator has indicated that if the result of FM57 is "extremely compelling" then a second Phase III study would not be necessary for approval. Nonetheless, the data from the second study, FM59, would be available for review after the initial submission. The FDA are very clear and the data from FM59 would have to be available ahead of a regulatory submission. Despite our belief that the data from FM57 is likely to be positive, we have not factored an early European approval in our base scenario. We would view such an outcome as upside rather than a core expectation.

Exhibit 7: MED2005 indicative development path timelines



Source: Futura Medical Note: 1. Regulatory and ethics submissions expected H219 to allow patient enrolment to commence H120; 2. If data meets qualifying criteria for EU single study pathway then in some circumstances Futura may file an EU submission prior to completion of the second Phase III otherwise at same time as FDA submission; 3. FDA submission as soon as practicable after completion of second Phase III.

FM59 study planning complete, awaiting FM57 data and funding

The second Phase III study design (FM59) will be similar to FM57 but for two doses (selected after the initial results of FM57 are known) and placebo. A total of around 700 patients will be studied, including a cohort from USA. The planning is underway, and the two dosage levels will be selected once the headline results of FM57 are known. Enrolment is expected to start in H120, with study completion around 12 months later. We view FM59 largely as a confirmatory study and so carries a lower risk profile than FM57 (and FM53). Importantly, the initiation of FM59 is conditional on sufficient funding being in place (see later).

Timing of Rx to OTC switch remains uncertain, with large regional variations likely

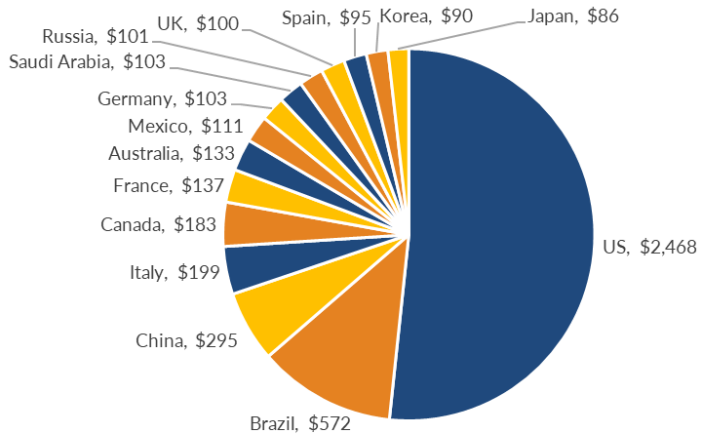
The opportunity for a switch to OTC remains attractive. The proven safety profile of GTN as an angina medication means that an OTC label has a precedent in some countries. The regulatory issues then centre more simply on demonstrating that there are no unintended consequences from usage outside of the tightly controlled settings of Rx use. This suggests that a suitable period to build a suitable experience base will be required and, we believe, that an OTC switch could happen within five years of approval as an Rx indication. An OTC indication for MED2005 would be commercially important as PDE5s usage is increasingly demonstrating sales volume growth is driven by the greater ease of access.

A sizeable and dynamic market opportunity

ED market is large and growing

The genericisation of the leading PDE5 brands has resulted in the monetary value of the ED treatment segment falling. The total sales for the ED category[10] in 2018 was $4.8bn, down from the 2017 peak of $5.8bn as the patent expiries of the PDE5 class took their toll. The US, the largest value geography, saw the biggest decline with 2018 sales of $2.4bn, down from the 2017 result of $3.5bn. In contrast, volumes remain solid. In 2015 the global volumes[11] were 856m doses, growing by 4% CAGR to 958m in 2018.

Exhibit 8: The ED market sales by country 2018 ($m)



Source: IQIVA

Surprising difference in ED prevalence in US vs Europe

The reported estimates of the prevalence of ED varies according to the ages, health status, and emotional well-being of the study subjects; what emerges is that North America and areas in South East Asia have a higher prevalence than

[10] IQVIA Midas Top 15 markets (formerly known as IMS Heath) data
[11] idem

Europe and South America. For instance, MMAS showed the average prevalence in the 40-70 age group in the US is 52%, whereas in Europe[12] it is c 30%. Similarly, the incidence (the number of new cases) ranges from 19 to 66 per 1,000 men per annum, such that the current estimate of over 200m cases worldwide is forecast to rise to 322m cases by 2025[13].

The size of the ED population is not the addressable market

However, we caution that this should not be considered as the addressable market for any ED treatment. Using the more comprehensive US sales data as a reality check, the 2018 ED volumes were 146.2m doses; which, using an average of 71 sexual episodes per annum in this age group, suggests c 2m men were routinely using a form of ED therapy. Clearly the result is highly dependent on the assumptions of the number of sexual episodes per annum, and this frequency will vary across ED severity, but even a conservative 12 per annum results in a population of c 12m. This compares with the c 30m US men which epidemiology studies predict as having ED.

Around a third of ED men will seek and continue treatment

This is borne out by the clinical experience since Viagra was first launched twenty years ago, which, despite extensive and creative marketing campaigns, resulted in only around a third of men with mild-to-moderate ED wishing to seek treatment. The reality is that for a variety of factors the majority of men will not seek treatment; these probably reflect similar traits to those men mentioned earlier who discontinue PDE5 therapy and include decreased libido, absence of an interested sexual partner, medical contraindications, as well as embarrassment at admitting a need.

Our modelling is very cautious, both in markets and adoption

For our modelling purposes we have based our estimates on penetration into the established Western markets only, using the PDE5 volumes as the best proxy for the realistically addressable patient population. Initially we have modelled the European markets and North America as prescription-only usage, with any potential sales from the Asian regions ignored until the visibility of a possible partnering deal improves. The period as a prescription-only product is chosen as five years but we acknowledge that this may be overly cautious, as both the active ingredient (GTN) and the indication of ED is approved for OTC products in some European markets.

Rx peak sales are $235m in US and $185m in Europe

Despite our conservative approach, we arrive at peak sales for MED2005 Rx of $185m in Europe and $235m in North America five years post initial launch, with an incremental sales potential of $225m in Europe and $250m in the US following the OTC switch. More aggressive assumptions, notably on the earlier availability of OTC approvals and on pertinent and commercially shrewd partners, could result in materially higher peak sales. Attempting to forecast likely Asian sales is thwarted by the number of variables; hence these remain as pure upside to our modelling. Our estimates support the revenue expectations of $660m to $1bn that Futura Medical has collated from third-party agencies.

[12] Age-related changes in general and sexual health in middle-aged and older men: European Male Ageing Study (EMAS). Corona G, et al. J Sex Med. 2010; 7:1362–1380.
[13] The worldwide prevalence and epidemiology of erectile dysfunction. McKinlay JB. Int J Impot Res. 2000;12 (suppl 4):S6-S11

Selecting the right partners for the right job is key

Licensing MED2005 should not be straightforward or easy

Typically, the most challenging part of developing a new pharmaceutical product is the development phase; it is the navigation of the clinical trials and subsequent regulatory approvals that is associated with the greatest proportion of programme failures. In contrast, the commercialisation of a new product is relatively straight-forward with the positioning, pricing, distribution, and myriad other factors being issues that are material but seldom seem to grab as much investor attention. Arguably we are being overly simplistic, but it is usually only the extremes, unexpected successes or disappointing revenues, that truly influence share prices.

We believe a conventional deal will not optimise value

Futura Medical should, assuming MED2005 generates positive data with FM57, be engaging meaningfully with potential partners for its global commercialisation. The conventional route would be to identify a global player with a sizeable sales franchise in the therapeutic area, negotiate reasonable royalties on net sales, add some commercial milestones to capture further value, sign a deal, then sit back and watch the income stream in. Unfortunately, products such as MED2005 do not, in our view, fit such a simple structure.

History shows the perils of a global deal with a leading player

We believe that there are no suitable global players that operate in the ED space, which are well positioned for both Rx (prescription only) and OTC, for whom MED2005 would be a strategically important product. Futura Medical has in the past experienced this very situation, notably with the erectogenic condom CSD500, where an acknowledged market leader was signed up to market it within its own branded range. In both cases, firstly Durex (SSL International, now Reckitt Benckiser) and then Trojan (Church & Dwight), a change in circumstances at the commercial partner saw CSD500 de-prioritised and the rights returned. In our view, Futura Medical should resist the temptation to seek a single partner, irrespective of the operational and organisation appeal that would embody.

Smaller, more nimble, regional specialists have great appeal in less conventional markets

In contrast, we feel that the partners targeted should be smaller, more nimble, players for whom MED2005, and its success, would be a major element of their future growth. Partnership(s) with such players may also lend themselves to less traditional deal types, such as a profit share or other novel deal structure. Greater risk-sharing would enable a deal to be structured to maximise income potential (especially in the key US market) at the expense of smaller upfronts. Additionally, we believe there are clear regional difference in how ED is perceived, and treatment sought. There are notable differences not only across major geographies such as Asia, Europe, and North America but also subtle, yet significant, variations between, for instance, Northern and Southern Europe.

Rx and OTC markets require different approaches

A further factor is that MED2005 is initially expected be approved as a Rx product and then, in most regions, become available OTC. Differences in the approach required for marketing ethical pharmaceuticals compared to consumer products are marked, and few companies have the resources and capabilities to address both segments fully. Admittedly, a number of Rx products have benefitted from extensive DTC (direct to consumer) campaigns in the US that effectively straddle the two segments, but we believe MED2005's positioning would be best achieved by judicious selection of specialist players in each target segment.

Addressing the emerging consumer health needs requires new skills

A recent White Paper by IQVIA, Consumer Health Innovation for the Future, details a number of the developments that are already underway. Importantly for

us, it also highlights how the "simple" Rx to OTC switches have happened and how the next wave will require greater interaction between company, regulator, and patient in order to address the more "complex" issues. These developments are driven by an increasingly aware consumer, who literally has previously unimaginable access to healthcare information. To call these seismic shifts in the marketplace is not an exaggeration, and such disruption inevitably means that the current "winners" may not (probably will not) remain the leaders in their fields.

Our view would be to appoint European (and Asian) partners then wait for the US

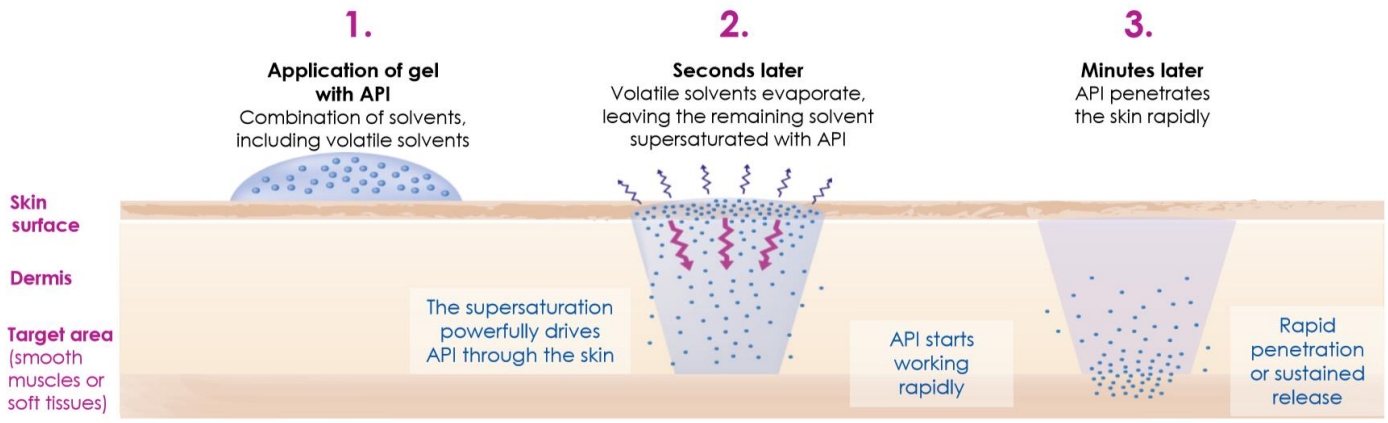
Our preferred option would see European partners chosen ahead of a first Rx approval, with additional partners brought on board ahead of the OTC switch. In many Asian markets the distinction between Rx and OTC is more blurred and so one partner per discrete geography would, we believe, suffice. The commercially important US market would, in our view, require a more creative approach. Unlike much of Europe, the US is seeing a faster and more marked transition in how patients are becoming aware of, selecting, and then sourcing "lifestyle" products (testosterone replacement therapies are a pertinent example). Here, we could envision an opportunity in addressing the unmet need seen in psychogenic ED, where sufferers tend to have Mild- or Moderate-ED caused by, for example, performance anxiety, peer pressure, or perception of partner expectations. Hence, we would prefer Futura Medical to adopt a "wait and see" approach to partnering for the US and, in the meantime, build up experience and learnings from the other markets.

Pain relief gel showcases DermaSys potential

DermaSys technology drives absorption through the skin

Futura Medical's pipeline is based on the DermaSys transdermal delivery system. This proprietary technology is designed to be dynamically unstable when exposed to the air; the formulation consists of a gel or cream that contains volatile and non-volatile solvents. When applied topically the volatile elements evaporate quickly and leave the remaining solvent supersaturated with active drug. This creates a high, and sustained, concentration gradient that drives the active drug through the various layers of the skin to the site of action.

Exhibit 9: DermaSys transdermal technology



Source: Futura Medical Note: API = Active Pharmaceutical Ingredient

Versatile formulations tailored to specific needs and no permeation enhancers

The inherent versatility of the formulations means the dose, onset time and duration of action can be individualised to each therapeutic application. For instance, MED2005 is designed to achieve a rapid absorption but with little residual activity to avoid potential transference to a partner. Importantly, considering the primary indication being developed, this high level of drug delivery is achieved without the need for harsh skin permeation enhancers.

TPR100 diclofenac gel is the most advanced…

Futura Medical has formulated a number of pain relief products, with TPR100 being the most advanced. This contains diclofenac, a non-steroidal anti-inflammatory (NSAID) widely used in the treatment of muscular and joint pain. Topical NSAID preparations aim to overcome the gastric side-effects seen with oral products but are dogged by poor efficacy, slow onset of action and the need for frequent re-application.

…with potential benefits over the market leader…

TPR100 is a 1.86% diclofenac formulation aimed at OTC use in most markets; this excludes the US, where topical NSAIDs remain prescription only for the time being. The DermaSys formulation has shown itself to be superior to Voltarol Emulgel, the clear market leader, with *in vitro* studies showing improved skin permeation and *in vivo* trials showing higher bioavailability. These results suggest that TPR100 could achieve pain and inflammation relief comparable to lower doses of oral presentations and is faster and longer lasting than current topical formulations.

…and UK approval expected in the near-term

The UK rights for TPR100 were licensed to Thornton & Ross (part of STADA), which has a respected portfolio of topical analgesics, in 2017. The regulatory submission was completed in July 2018, with the UK regulator (MHRA) requesting

additional information in April 2019. The required responses are expected be submitted in Q120, which should result in the first European approval being granted in mid-2021. Partnering discussions for other European regions are likely to be progressed following approval. For the US, the FDA has confirmed that a clinical study will be required, and management has stated that it will only commit to the clinical programme with a partner in place.

TIB200, an ibuprofen gel, is available for partnering

A related programme is TIB200, where the active ingredient is ibuprofen as a 10% gel that has shown 8x higher skin penetration than market leading brands. This should translate into a product that only requires twice-daily application, compared to the current three to four times daily. Regulatory filing in Europe would need a large placebo-controlled efficacy study, with the US expected to follow a similar pathway to TPR100. Again, management has stated that this programme will only proceed if the required clinical trials are funded by a partner.

CBD100 is a topical cannabinoid project with CBDerma Technology

CBD100 is the recently announced joint venture with CBDerma Technology. This involves Futura Medical applying its DermaSys expertise to develop a range of cannabis-based topical formulations. The initial focus will be on optimising a formulation, that could be applied to cosmetic dermatological products although medical indications (such as pain relief) could also be explored. The venture is expected to cost initially around $1m and last about 15 months, with Futura Medical contributing its existing internal resources, knowhow and skills. All the intellectual property generated will be jointly owned by Futura Medical and CBDerma Technology.

Sensitivities

Key sensitivities are common to all small R&D driven companies

In common with most innovative healthcare companies the three main sensitivities relate to the clinical and regulatory aspects, the execution of the commercialisation plans, and the financial resources required to accomplish these. More specifically, the key near- and medium-term sensitivities are directed to the clinical and partnering progress of the two clinical programmes.

- MED2005 is, understandably, the main sensitivity as it represents the largest commercial opportunity and is set to deliver pivotal Phase III results. However, the risks are contained compared to similar industry standard probabilities; firstly, the trial has been designed to maximise the chances of success and, secondly, the results are unlikely to be binary and most of the expected scenarios would result in an approval.
- Currently TPR100 does not feature highly as a sensitivity and there is little attributed to it in many investors' minds. Yet it appears to be progressing well and a UK approval is likely during 2021. Although its commercial importance is less than MED2005, it does provide useful reminder of the DermaSys platform's broader potential.

It has been a rollercoaster ride for investors and management

Delving into Futura Medical's past shows a rollercoaster ride. Expectations were first raised when an erectogenic condom, CSD500, was licensed in the early 2000s to SSL International, the makers of the Durex brand condoms. Following the takeover by Reckitt Benckiser, the rights to CSD500 were returned in 2012. CSD500 was licensed to Church & Dwight, makers of the Trojan brand, but again, following a portfolio review in 2017, the rights were returned. Such ups and downs were endured by investors and management, with re-positioning, tight cost control and fund raises ensuring Futura Medical's survival. In September 2018, as part of a strategic review, the nettle was grasped and CSD500 de-emphasised.

Remaining patent life may be an issue if new 2017 applications are not granted

MED2005's long development period has resulted in a material erosion of the patent life, with the original formulation patent expected to expire in Europe in 2025 and for the US in 2028. The data exclusivity in Europe (10 years from first European approval) would effectively mean commercial protection through to c 2031. In the US the data protection is only five years hence would offer little benefit. However, further patent protection was filed for in 2017 which, if successful, would extend the intellectual rights through to 2037. We await future disclosures regarding this, and note that at H119 interims the company confirmed PCT filing would be moving into the National Filing phase in Q120.

Funding required to complete MED2005 registration studies

Funding is an ever-present issue for pre-revenue healthcare companies and Futura Medical is no exception. The tight focus on cost control has meant that the R&D spend has been modest and the clinical programmes to date achieved with commendable thrift. In part this reflects the "virtual" company structure, with only 15 employees and the remainder of the workflows outsourced as necessary. Looking ahead, funding is in place for the current trials to be completed. However, further funds will be required to initiate the second Phase III MED2005 study.

When, where, and what is the best out-licensing strategy?

The key question remains as to what the best value-creating out-licensing strategy for MED2005 is? We believe that an early and wide-ranging deal is unlikely to achieve the optimal outcome. We cover the various options we envisage earlier in the body of this note.

Valuation

Classic risk-adjusted DCF model is the best valuation tool

We believe a DCF model to be the most appropriate way to value Futura Medical. The rNPV of each clinical programme is assessed, with MED2005 split into prescription-only (Rx) and over-the-counter (OTC) scenarios; however, we have excluded any contribution from potential Asian market sales until the commercialisation pathway is more visible. The success probabilities are adjusted for the inherent clinical, commercial, and execution risks each carries. These are summed and netted against the costs of running the operation and net cash.

MED2005 success probability is higher than industry norm

The success probabilities are based on standard industry criteria for the respective stage of the clinical development process but, importantly, are flexed to reflect the inherent risks of the individual programme, the indication targeted, and the trial design. It is worth noting that we view the clinical development risk for MED2005 as below industry standards although that is not fully reflected in the model. We have also factored an element for the execution and commercial risks, notably on MED2005.

Current valuation is £127m, equivalent to 62p a share

As always, we employ conservative assumptions throughout our modelling, particularly regarding market sizes and growth rates, net pricing, adoption curves, and peak market penetration. Our model results (see Exhibit 10 below) in a current valuation of £127m, or 62p per share on a fully diluted basis, for Futura Medical.

Exhibit 10: Futura Medical risk-adjusted DCF model

	Total NPV ($m)	Total NPV (£m)	Likelihood of approval/ switch	rNPV ($m)	rNPV (£m)	rNPV/ share (p)	Notes
MED2005 Rx (Europe)	106.8	82.1	65%	42.4	32.6	16.0	Peak sales: $185m; Launch year: 2021
MED2005 Rx (US)	117.1	90.1	65%	45.9	35.3	17.2	Peak sales: $236m; Launch year: 2022
MED2005 OTC (Europe)	100.1	77.0	60%	38.8	29.9	14.6	Incremental sales: $225m; Switch year: 2024
MED2005 OTC (US)	92.5	71.1	60%	35.8	27.5	13.4	Incremental sales: $250m; Switch year: 2025
TPR100	2.1	1.6	40%	0.9	0.7	0.3	Peak sales: $6.2m; Launch year: 2022
Non-R&D operating costs	(5.1)	(3.9)		(5.1)	(3.9)	(1.9)	
Net cash	7.3	5.6		7.3	5.6	2.7	At June 2019
Total	**420.8**	**323.7**		**166.0**	**127.5**	**62.4**	

Source: Trinity Delta Note: Assumptions include a 12.5% discount rate; a 1.3 $/£ FX rate, and 10% tax rate from 2026 with the benefit of the UK patent box

Clearly the majority of the value arises from MED2005, mainly from the nearer term Rx revenues in Europe and US, although our model suggests that the OTC switch could generate significant additional sales. As mentioned previously, no value is yet ascribed to Asian markets.

MED2005 will likely be launched first in Europe…

For Europe, we have assumed that the first Rx launch is in 2021, with peak sales of $185m occurring around five years post-launch. The first OTC launch is modelled as being in 2024, but we acknowledge this could happen sooner as

some regulator(s) appear comfortable with both the availability of GTN and the DermaSys formulation. We model additional sales of $225m for OTC Europe, peaking five years post switch. We highlight that at present there is some uncertainty in the precise split of Rx and OTC sales, and the potential size of the latter market. This is due to various factors including, but not limited to: how many European markets switch to OTC, their size, and timing; the magnitude of sales retained by the Rx segment; and the commercial strategies of future partners.

In both cases we have been conservative with the patient numbers, addressable market, speed of reimbursement, and adoption curves. We prefer to be cautious in our approach and will review our models once the likely partners for commercialisation are known.

The rNPV for Europe Rx is £32.6m ($42.4m at $1.3/£) and for Europe OTC it is £29.9m ($38.8m), equivalent to 16.0p and 14.6p per share respectively. The total rNPV for Europe is £62.5m ($81.2m) and 30.6p per share.

...but US has the potential to be more sizeable in the longer term

Similarly, for the US market we have assumed the earliest Rx launch in 2022, with peak sales of $236m, and OTC availability in 2025, with additional sales of $250m. It is here that the greatest sensitivity in our valuation lies. If the US market does continue to evolve towards there being less of a distinction between Rx and OTC in the commercialisation of "lifestyle" drugs, then not only will the differences between Rx and OTC status diminish but access to (and in turn, adoption of) such drugs would improve too. Clearly there remains a deal of uncertainty over likely developments and it is this that makes us suggest that a pause before entering US partnering discussions may be warranted. Nonetheless, we maintain our view that the optimisation of MED2005's potential is better served with smaller, innovative, and more nimble companies.

Currently our rNPV for the US Rx segment is £35.3m ($45.9m) and for the OTC segment it is £27.5m ($35.8m), equivalent to 17.2p and 13.4p a share respectively. The total rNPV for the US is £62.8m ($81.7m) and 30.6p per share. Again, this is an important element in our modelling that we will revisit as there is more clarity around future market developments.

TRP100 adds a relatively minor £0.6m, or 0.3p a share

Our valuation for TPR100 is based on first approval and launch in 2022 in the UK only. We will include the contributions from additional regions once they are partnered. We have assumed peak sales of £6.2m, with an rNPV of £0.7m ($0.9m) and 0.3p a share.

Summing these and netting out the costs of the running the business and cash gives our risk-adjusted valuation of £127.5m, equivalent to 62.4p a share.

Financials

Net loss is contained as emphasis is on cost control…

Over the last 18 months Futura Medical has made solid headway in progressing its clinical pipeline, notably with MED2005. The reported six-month results to June 2019 showed tight control had limited the net loss for the period to £4.46m (vs £1.95m in H118). The cash resources at June 2019 were £5.63m (£6.01m H118), with a further R&D tax credit of £1.36m (£0.94m H118) received in August.

…and maximising focus on clinical development

R&D costs were the major expenditure, rising from £1.65m to £4.74m, with the increase due to the costs of the FM57 study (which remains on time and on budget). Administrative costs dropped from £0.85m to £0.53m and reflects the small central team (only 15 staff are employed directly, the remaining workload is largely outsourced and varies as programmes progress).

FY19 R&D spend largely connected to FM57 study

For FY19 we expect R&D spend of £9.35m (associated with the FM57 study and preparatory work for FM59) with G&A for the full year of £1.08m. On this basis we forecast an EBITDA of £10.4m and net loss of 8.6m (4.2p per share).

Regulatory filings set to become the biggest cost item

Looking ahead, we expect R&D investment to reduce once the costs connected with FM59 are dealt with. Expenditure in the disclosed other development programmes is small and essentially financed by partners, with similar funding arrangements expected for any future projects. Costs associated with the filings for approvals of MED2005 in the various regulatory regions is expected to become the largest single element of spend. Administrative expenses should remain contained as the small central team is highly cost effective. We estimate that Futura Medical's low-cost strategy means that recurring underlying costs will remain around £2.5m a year.

Near-term funding for FM59 likely to be an equity raise…

The funding needs are well documented; the resources to undertake the second pivotal Phase III trial (required for FDA approval and most likely for Europe too, in our view) are the first requirement. Although the actual cost is likely to be c £7m, less than the FM57 study as it has fewer patients and is simpler in nature, we would expect Futura Medical to target a c £10-15m injection of funds. A potential equity raise following positive data from the FM57 study could benefit from a higher share price, limiting dilution. Despite the difficult market conditions for equity raises, it should be noted that Futura Medical is well positioned; it has clearly defined near-term strategic targets, a variety of licensing options, and better commercial prospects than at any point in its recent past.

…but longer-term funding may be from a variety of sources

In the longer term, it could be argued that sufficient funding would arise from the upfront payments of any out-licensing and partnering deals. Whilst this is possible, we would expect such deals to be structured to maximise the income potential (especially in the important US market), which suggests greater risk-sharing and smaller (if any) upfronts. An appeal of the risk-sharing route is that Futura Medical is well placed to find funding from a variety of possible sources, including debt instruments, equity, or a hybrid combination.

Exhibit 11: Summary of financials

Year-end: December 31 £'000s	2017	2018	2019E	2020E	2021E
INCOME STATEMENT					
Revenues	**363**	**0**	**0**	**0**	**0**
Cost of goods sold	0	0	0	0	0
Gross Profit	**363**	**0**	**0**	**0**	**0**
R&D expenses	(4,100)	(6,039)	(9,346)	(8,556)	(4,962)
General and administrative expenses	(1,118)	(1,228)	(1,084)	(1,583)	(1,706)
Underlying operating profit	**(4,856)**	**(7,266)**	**(10,430)**	**(10,139)**	**(6,669)**
Other revenue/expenses	0	0	0	0	0
EBITDA	**(4,843)**	**(7,247)**	**(10,411)**	**(10,115)**	**(6,643)**
Operating Profit	**(4,856)**	**(7,266)**	**(10,430)**	**(10,139)**	**(6,669)**
Interest expense	19	28	19	(1)	17
Profit Before Taxes	**(4,837)**	**(7,239)**	**(10,411)**	**(10,140)**	**(6,652)**
Adj. PBT	**(4,837)**	**(7,239)**	**(10,411)**	**(10,140)**	**(6,652)**
Current tax income	936	1,358	1,836	1,925	1,117
Cumulative preferred stock dividend	0	0	0	0	0
Net Income	**(3,900)**	**(5,881)**	**(8,574)**	**(8,215)**	**(5,535)**
EPS (p)	**(3.2)**	**(4.5)**	**(4.2)**	**(4.0)**	**(2.7)**
Adj. EPS (p)	**(3.2)**	**(4.5)**	**(4.2)**	**(4.0)**	**(2.7)**
DPS (p)	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Average no. of shares (m)	120.6	131.9	204.7	204.7	204.7
Gross margin	*100%*	*N/A*	*N/A*	*N/A*	*N/A*
BALANCE SHEET					
Current assets	**9,541**	**10,830**	**3,856**	**10,711**	**5,247**
Cash and cash equivalents	8,363	9,158	1,473	8,390	3,129
Accounts receivable	181	306	98	98	98
Inventories	70	8	8	8	8
Other current assets	927	1,358	2,276	2,214	2,012
Non-current assets	**64**	**47**	**64**	**86**	**111**
Property, plant & equipment	64	47	64	86	111
Other non-current assets	0	0	0	0	0
Current liabilities	**(499)**	**(2,026)**	**(3,535)**	**(18,535)**	**(18,535)**
Short-term debt	0	0	0	(15,000)	(15,000)
Accounts payable	(499)	(2,026)	(3,535)	(3,535)	(3,535)
Other current liabilities	0	0	0	0	0
Non-current liabilities	**0**	**0**	**0**	**0**	**0**
Long-term debt	0	0	0	0	0
Other non-current liabilities	0	0	0	0	0
Equity	**9,106**	**8,852**	**385**	**(7,739)**	**(13,178)**
Share capital	44,913	50,393	50,412	50,412	50,412
Other	(35,807)	(41,541)	(50,028)	(58,151)	(63,590)
CASH FLOW STATEMENTS					
Operating cash flow	**(4,155)**	**(4,680)**	**(7,669)**	**(8,037)**	**(5,211)**
Profit before tax	(4,837)	(7,239)	(10,411)	(10,140)	(6,652)
Non-cash adjustments	195	140	87	117	105
Change in working capital	(385)	1,464	1,718	0	0
Interest paid	19	28	19	(1)	17
Taxes paid	851	927	918	1,987	1,319
Investing cash flow	**(56)**	**(5)**	**(35)**	**(46)**	**(51)**
CAPEX on tangible assets	(56)	(5)	(35)	(46)	(51)
Other investing cash flows	0	0	0	0	0
Financing cash flow	**221**	**5,480**	**19**	**15,000**	**0**
Proceeds from equity	221	5,480	19	0	0
Increase in loans	0	0	0	15,000	0
Other financing cash flow	0	0	0	0	0
Net increase in cash	**(3,990)**	**795**	**(7,685)**	**6,917**	**(5,262)**
Cash at start of year	12,353	8,363	9,158	1,473	8,390
Cash at end of year	**8,363**	**9,158**	**1,473**	**8,390**	**3,129**
Net cash at end of year	**8,363**	**9,158**	**1,473**	**(6,610)**	**(11,871)**

Source: Company, Trinity Delta Note: Adjusted numbers exclude exceptionals. The funding requirement is shown as short-term debt in FY20e, until transaction type, source and size are confirmed.

Company information

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Key personnel

Person	Position	Biography
John Clarke	Non-Executive Chairman	Chairman since 2012, following a 35-yr career at GlaxoSmithKline latterly as President of GSK Consumer Healthcare (2006 to retirement, 2011). Non-Exec Chairman of Science in Sport, Kind Consumer and, pre-acquisition, Quantum Pharma. A senior adviser to Helios Investment Partners LLP.
James Barder	CEO	CEO since 2001. Previously Managing Director of Aon Capital Markets and Non-Exec Director of Lorega Ltd. Extensive experience in striking and managing partnerships and licensing agreements.
Angela Hildreth	FD and COO	Joined in 2018, adding further financial, operational, and strategic experience to the executive team. Previously six years as UK Finance Director at Shield Therapeutics Plc.
Ken James	Head of R&D	Joined in 2016. Previously SVP of R&D for GSK Consumer Healthcare, having spent over 40 years in a variety of roles there and bringing over 200 consumer products to market.

Top shareholders

	% holding
Lombard Odier Asset Management (Europe) Ltd	12.96
T Adams	6.98
WT Lamb Investments Ltd	5.00
RA Lamb	4.68
Disclosable shareholdings (>3%)	**29.62**
Other shareholders	70.38
Total shareholders	**100.00**

Source: Futura Medical

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Disclaimer

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