MEDRx Co., Ltd

（4586 Mothers） Issued March 17, 2020

Core Fundamentals Improving

Has its own technology in a niche market

MEDRx Co., Ltd. is in the business of developing transdermal absorption formulations based on the active ingredients of existing oral and injection drugs. It collects licensing payments and milestone payments from pharmaceutical companies to whom it has licensed out products and, later, royalties on sales made by the licensee in the market.

Unlike most other companies developing new drugs, MEDRx uses the active ingredients of existing drugs, thus ensuring a higher probability of success. Since this is a niche business there are relatively few competitors, in addition to which the company's proprietary ILTS® and NCTS® technologies give it a distinctive edge. The company has also developed a "vaccine application" technology using microneedles. This technology is now being subjected to feasibility studies.

Product development has been accelerating since autumn 2019

Unfortunately, development of the company's oxycodone tape formulation was suspended in the autumn of 2019. This was because the environment in the opioid market, particularly the bankruptcy of Purdue Pharma, had such a deleterious effect on pharmaceuticals companies. But the development of MEDRx's lidocaine tape formulation continued regardless, such that an application is almost ready for submission to the authorities. At the same time, the company's fentanyl tape formulation, its second major development after oxycodone tape, has seen outstanding progress and will soon start pilot pharmacokinetics evaluation. Likewise, the memantine patch formulation is scheduled to soon begin clinical trials. Product development had been at a halt but has been moving ahead since the second half of 2019.

The four product pipelines are valued at JPY36.7 billion, but...

The development of MEDRx's top product, oxycodone tape, was suspended but the product that emerged to replace it, fentanyl tape, has an anticipated value of JPY20 billion. Meanwhile, lidocaine tape has completed the clinical phase of development and the company is expected to submit an application sometime this year. Altogether the company has four products: fentanyl tape, lidocaine tape, memantine patches and tizanidine tape, which it has licensed out to Cipla USA. We calculate that the total value of these four is JPY36.7 billion (before tax). While no direct comparison can be made, there is a wide gap with the company's market cap of JPY2-3 billion. Following application and approval, the licensing-out and merchandising (possibly in 2021) of lidocaine tape should give MEDRx a stable source of income. If progress is then made on the next major product, fentanyl tape, the market's evaluation of MEDRx could well undergo a change.

Note: This report is the English-language version of the original Japanese-language report issued on March 17, 2020, to which you should refer for precise details

Revised Basic Report

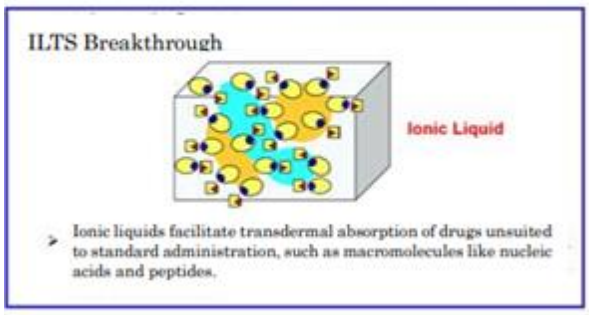
Fair Research Inc.
Tsuyoshi Suzuki

Company Outline	
Location	Kagawa
President	Yonehiro Matsumura
Establishment	January 2002
Capital	JPY6,704 mil.
Listed	Feb. 2013
URL	www.medrx.co.jp
Industry	Pharmaceuticals
Employees	26 (consol)
Key Indicators (Mar. 16 2020)	
Share Price	160
Year High	615
Year Low	160
Shares Outstanding	14,214,100
Trading Unit	100 shares
Market Cap	JPY2,274 mil.
Dividend (est.)	0
EPS (est.)	-86.88JPY
Forecast PER	na
BPS (actual)	136.46JPY
PBR (actual)	1.17X

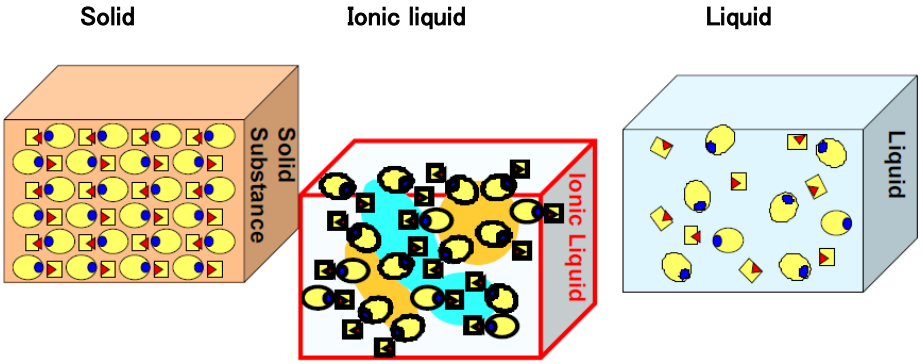
Calculated on the basis of total shares outstanding, excl. treasury shares

Results	Revenues JPY mil	YoY %	OP Income JPYmil	YoY %	RP Income JPYmil	YoY %	Net Income JPYmil	YoY %	EPS JPY	Share Price JPY	
										High	Low
15/12 Actual	37	43.1	-999	na	-990	na	-878	na	-131.2	1,446	500
16/12 Actual	22	-40.6	-1,342	na	-1,301	na	-1,259	na	-155.5	1,455	341
17/12 Actual	198	787.2	-983	na	-988	na	-884	na	-103.2	1,345	453
18/12 Actual	8	-95.8	-1,273	na	-1,285	na	-1,267	na	-126.77	2,060	425
19/12 Actual	169	1922.9	-1,627	na	-1,633	na	-1,616	na	-134.32	698	301
20/12 Forecast	234	37.9	-1,189	na	-1,188	na	-1,191	na	-86.88		

Company outline – management philosophy

A venture company in the business of developing transdermal absorption formulations	In broad terms the company's business is based on developing transdermal absorption formulations using the active ingredients of existing oral and injection drugs. It then licenses out the formulations to pharmaceutical companies from whom it collects milestone payments and, after commercialisation, royalty payments. Transdermal absorption formulations constitute a growing medium to long-term pharmaceutical segment thanks to a number of attributes: maximisation of pharmaceutical effect, reduced side effects and enhanced quality of life for the patient. These attributes are achieved by the following: ① By providing a consistent and sustained release of active ingredients to maintain a constant level of the drug in the bloodstream. ② Little or no first-pass effect: while the efficacy of oral drugs can be reduced by 10-20% as they pass through the liver, this is not an issue with transdermal absorption formulations. ③ Better medication compliance: suitable for patients who find it difficult to take oral drugs due to a problem swallowing, and also reduces the problem of forgetting to medicate. ④ Unlike drug delivery by injection transdermal delivery is painless. ⑤ Transdermal delivery lends itself to a wide range of indications.
The company has a proprietary technology, giving it a higher probability of success than other new drug discovery business	The MEDRx business model is also distinctive in two ways: (a) It is low risk (i.e. has a high probability of success) because it does not involve the discovery or development of new active ingredients. (b) The company has its own transdermal absorption technology using ionic liquids (ILTS: Ionic Liquid Transdermal System) which distinguishes it from other companies. Note: Ionic liquids are salts in liquid form at room temperature composed of ions which are resistant to crystalisation. They are non-volatile, non-flammable and electric conductive. In recent years these properties have led to applications in lithium batteries and elsewhere. With ILTS®, MEDRx was the first in the world to apply the use of ionic liquids to transdermal absorption, allowing drugs which could not normally be delivered through the skin to do so.  Source: MEDRx company briefing The skin is composed of a highly hydrophobic stratum corneum and a highly hydrophilic epidermis/dermis layer. The active ingredient, having a high hydrophilicity, has little distribution and diffusion in the highly hydrophobic stratum corneum. In the ionic liquid, the anion, or negative part (blue circle in the figure), is bonded to the hydrophilic group, and the cation, or positive part (red △ in the figure), is bonded to the hydrophobic group. It has medium properties (both hydrophilic and hydrophobic properties). In addition, molecules do not move randomly as in a normal liquid. When viewed closely, structural

formation can be seen at the nano-level. That is, the molecules that have been converted into ionic liquids are separately assembled (light blue ellipse and orange ellipse in the figure i.e. the alkyl aggregate portion and the clone aggregate portion). This relies on the Nano-structured Fluid Hypothesis. Based on this hypothesis, the active ingredients of a drug dissolve in the ionic liquid and are in a state similar to encapsulation in nanoparticles. By this technique, the transdermal absorbability of nucleic acids and high molecular drugs, which are conventionally difficult to transdermally absorb, can be significantly improved.



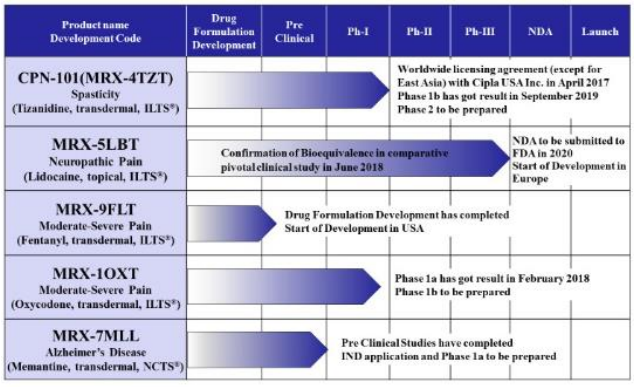
Source: MEDRx company briefing

Another interesting feature of MEDRx is that it has built high barriers to entry. It has a 'library' of several hundred ionic liquids formed from combinations of compounds with a track record of human use as pharmaceuticals and various additives. It also has extensive know-how on selecting optimum ionic liquids for particular drug properties, and formulation expertise to maintain and enhance the transdermal absorbability of ionic liquids.

The company's efforts are directly mainly at the US market for transdermal absorption formulations, the attraction being the potential size of the market for tape-type formulations.

Also, by basing its activities in the US on existing formulations the clinical trials required to acquire FDA approval are simpler than for new drugs or formulations (although not true in all cases, after Phase 1 Phase 2 can be omitted and the process moves straight to Phase 3. Also worth bearing in mind is the fact that patch-type drugs tend to command higher prices in the US than in Japan.

MEDRx's main product pipelines



Source: MEDRx company briefing

MEDRx has used its own ILTS® technology in its four main pipelines

The four main products using the ILTS® technology are the tizanidine tape formulation (CPN-101, MRX-4TZT), successfully licensed out to Cipla USA, the lidocaine tape formulation (MRX-5LBT), the fentanyl tape formulation (MRX-9FLT), and the oxycodone tape formulation (MRX-1OXT).

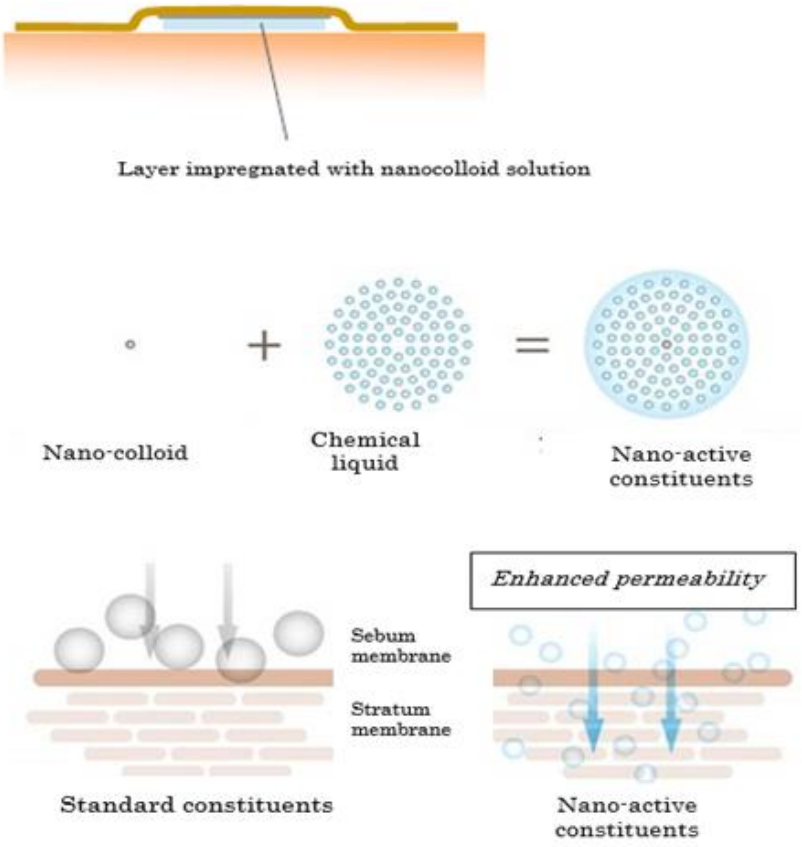
Memantine patches is one product that uses NCTS® and nano-colloids

The company also has a Nano-Sized Colloid Transdermal System (NCTS), a technology used to deliver nano-sized colloids. The ILTS® technology mentioned earlier is used for the transdermal absorption of polymers such as nucleic acids and peptides. The NCTS® technology aims to enhance transdermal absorption by converting relatively low-molecular-weight active pharmaceutical ingredients into nano-sized colloids. Among the products that are in the development stage is MRX-7MLL (a transdermal absorption agent for memantine, indicated for Alzheimer's patients) with the added advantage that it can suppress the skin irritation of memantine.

Note 1: A joint development with Daiichi Sankyo using NCTS® unveiled in February 2018 was terminated in August 2019 when non-clinical tests failed to provide supportive results. We surmise there was a transdermal safety issue involving the pharmaceutical ingredients, and it was not a problem with NCTS® technology itself.

Note 2: The company had a licensing agreement with Takeda Pharmaceutical relating to ILTS® and NCTS® technology development. However, failure to meet the evaluation criteria meant the agreement was terminated in October 2019. Again, the problem was not with the technology itself but with the existence of other competing formulations and a number of other considerations.

NCTS®: Nano-sized Colloid Transdermal System – Image



Source: Fair Research Inc. using company briefing materials

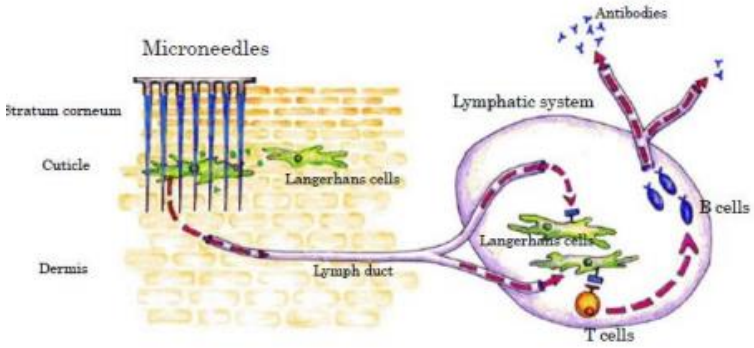
Elsewhere, MEDRx also has technology relating to microneedle arrays used for “attachable vaccinations”. This technology uses super-fine needles to pierce the surface of the skin and deliver the relevant drug into the skin. In addition to providing a physical barrier preventing the intrusion of foreign matter into the body, the skin also has the immunological function of expelling foreign matter. Antigen presenting cells, which are present in the epithelium under the stratum corneum as Langerhans cells, and under the dermis as dermal dendritic cells, play an important role in defensive reactions in the body. A powerful immune response can be elicited by efficiently transferring vaccine to these antigen-presenting cells.

However, even if the vaccine is applied to the skin it cannot penetrate because of he barrier presented by the stratum corneum. Super-fine microneedles, however, puncture the epithelium, allowing the vaccine into the skin. Since the microneedles are less than 1mm in length they pierce the skin without reaching the nerves, making painless vaccinations possible. This technique is therefore a sort of “vaccination attachment”.

This technique has social significance. There is no pain from injections (minimally invasive) and no medical staff are required for administration (self-administration). Furthermore, the application of a solid vaccine antigen to a microneedle represents a promising technique for tackling pandemics in developing countries, where room temperature storage is the norm, transportation is rudimentary, and the medical environment inadequate.

Among the companies now pursuing the development of medical microneedles worldwide are the US companies Zosano Pharma Corp and, in a tie-up with 3M, Radius Health Inc. In Japan, in addition to MEDRx, there is Fuji Film and Nipro Pharma. No products have been authorised as yet but in December 2019 Zosano submitted an application to the FDA for a microneedle to deliver migraine drugs. Zosano and Radius plan to outsource large-scale production of their own product to Patheon, a subsidiary of Thermo Fisher Scientific, the worldwide maker of analytical devices.

Microneedle array technology - image



(source) Fair Research Inc. using various materials

The company was on the way to developing microneedles for vaccine delivery but the entire project is now at a standstill

On April 10 2018, the company announced it was issuing a third-party allotment of options to finance a microneedle production facility, and thereby bring to fruition the research and development it had been working on for 15 years. In May of the same year work was started on a clinical trial plant. However, raising the necessary capital did not go according to plan and in November the project was shelved for the time being. The warrants for new shares were bought back and cancelled. At present the company is carrying out preparations up to the clinical trials stage but as for large-scale output it is conducting various feasibility studies on external options and looking for a business partner to tie up with.

Main product development pipelines

MEDRx's currently has 5 main products: the lidocaine tape formulation (MRX-5LBT), the tizanidine tape formulation (MRX-4TZT), the oxycodone tape formulation (MRX-1OXT) the fentanyl tape formulation (MRX-9FLT) and the memantine patch formulation (MRX-7MLL).

1.The development of the lidocaine tape formulation (MRX-5LBT)

Lidocaine tape is under development as a treatment for post-herpetic neuralgia. It is MEDRX's most developmentally advanced product and is likely to become the company's first product launched in the US market

The tape formulation of lidocaine, a type of local anesthetic, is under development as a treatment for post-herpetic neuralgia. It is MEDRX's most developmentally advanced product and is likely to become the company's first product launched in the US market.

Shingles is a painful disease that occurs when the varicella-zoster virus remaining in the dorsal root ganglion in childhood reactivates and develops. The majority of patients with herpes zoster become free of pain with herpes treatment, but about 10% of patients are reported to have pain for many years after treatment and suffer from post-herpetic neuralgia. Nerve-blocking drugs used to be the main therapy but in March 1993 transdermal Lidoderm® poultices were approved in the US. Lidoderm® became the first therapy choice for post-herpetic neuralgia, at one time recording sales of JPY1.2 billion (there are currently several Lidoderm® generics and the market for lidocaine poultices in the US was valued at JPY50.5 billion in 2018).

Three distinguishing advantages over leading products

MEDRx regards MRX-5LBT as a competitive product because it has a number of distinctive characteristics:

① As a tape and not a poultice, it offers ease of use

② Same effect with 30% of the lidocaine volume as conventionally used

③ Less skin irritation, greater adhesiveness maintained even during physical exertion (= not loosened by perspiration)

First, a brief review of this product's development history. Phase 1 test results in May 2016 suggested that, using the ILTS® methodology, MRX-5LBT could more rapidly and in greater quantity achieve tissue penetration than Lidoderm® (lidocaine patch) (see chart below).

Fig. A Lidocaine concentration in human blood for MRX-5LBT and Lidoderm®

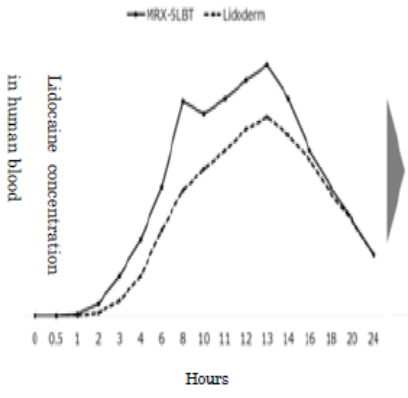
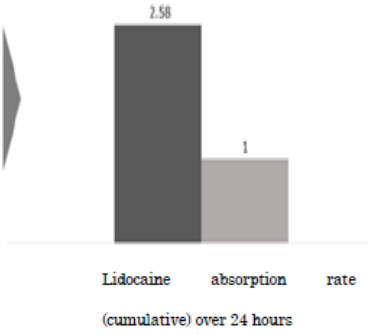


Fig. B Vol. of lidocaine which permeates subcutaneous tissue per unit area for MRX-5LBT and Lidoderm® (inferred from Fig.A data)



Source: Company briefing materials

In June 2018 Lidoderm® test results showed bioequivalence, but in November 2018 the FDA required more tests than originally anticipated for patients with chronic illnesss

However, all tests necessary for making an application were completed in February 2020

No change in 2020 NDA plan

At that point, in the lead-up to an application for approval, the following two avenues suggested themselves:

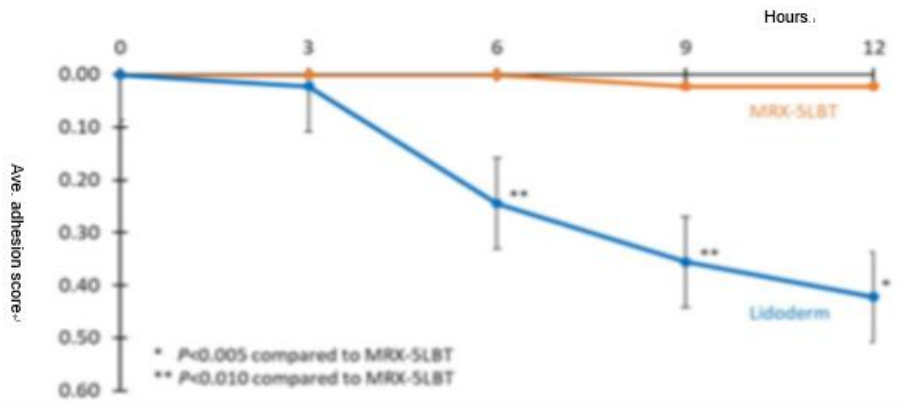
Plan A: Conduct Phase 3 trials showing superior efficacy to Lidoderm®
Plan B: Show bioequivalence with Lidoderm®

After consultations with the FDA, the company gave comprehensive consideration to a number of questions: the level of difficulty involved in acquiring approval; the product competitiveness and level of competition assuming development was successful; and the positioning of the product within MEDRx's overall development portfolio. It was decided as a result to select Plan B, since the time required to win approval was shorter and the probability of proceeding that far was greater. The company then announced in June 2018 that test results had shown bioequivalence (BE) with Lidoderm®. The company indicated that it now plans to carry out clinical trials using the methodology normally associated with the development of transdermal drugs in order to confirm the safety of lidocaine tape on the skin of healthy individuals, and to apply for approval in 2020.

However, in November 2018 as a result of discussions with the FDA concerning the data necessary for the NDA, it had been determined that since the drug was for chronic conditions which could require protracted use, more testing than had originally been anticipated would be necessary. The company was planning to apply for a new drug approval in 2020 and the costs of testing to that end would exceed the original estimate by approximately JPY700-800 million. Mainly in order to secure those funds at an early date the company announced it was going to raise capital (in February 2019) and did so in May.

As a result, in July 2019 it was able to demonstrate in trials a superior level of adhesiveness to that available with Lidoderm®, and in December 2019 a lower incidence of skin irritation.

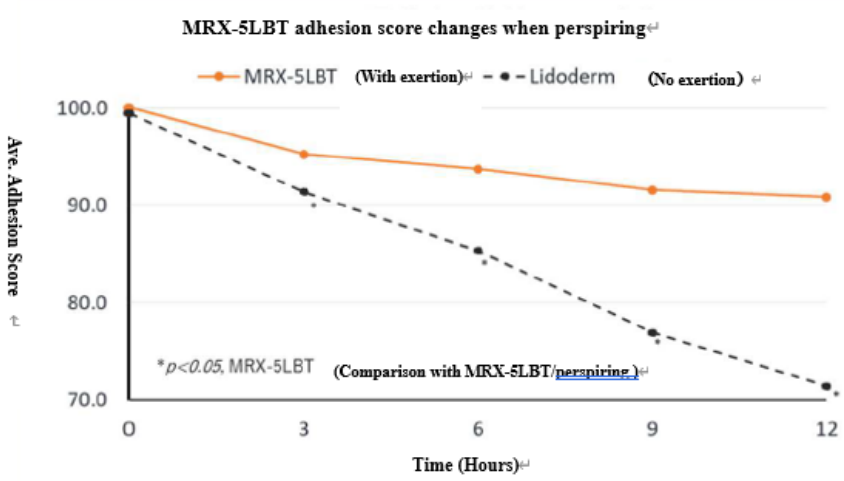
MRX-5LBT : Changes in adhesiveness score during physical exertion



Source: Company briefing materials

Further, in January 2020 in tests to evaluate the effect of physical activity on adhesiveness it was successfully determined that MRX-5LBT retained sufficient adhesiveness at times of perspiration accompanying physical activity. All clinical tests were completed in February of the same year so that the NDA could be submitted as scheduled in 2020. The prospective licensee would study the terms, allowing a decision to be made following application or following approval.

The company is scheduling a decision on licensing out, depending on terms, perhaps following the application or following approval



Source: Company briefing materials

The size of the target market is estimated at 114 million patches, and the price per patch at just less than USD9

The size of the market (US) in 2018 was 114 million patches. There are several Lidoderm® generics on the market selling in the range of USD2-3 per patch. In October 2018 the US company Scilex Pharmaceuticals Inc., a subsidiary of Sorrent Therapeutics Inc., came to the market with a lidocaine tape preparation, ZTlido®, with superior characteristics to Lidoderm®. This sells for USD8.95 per patch and in 2019 recorded annual sales of around USD2.2 - 2.3 billion (Sorrent documentation also mentions a ZTlido generic, SP-103, which it is now selling). MEDRx would be second to the market but we think, depending on how ZTlido does, could sell at around the same price.

The company is also eyeing development and an application in Europe, but depends on progress in raising funds

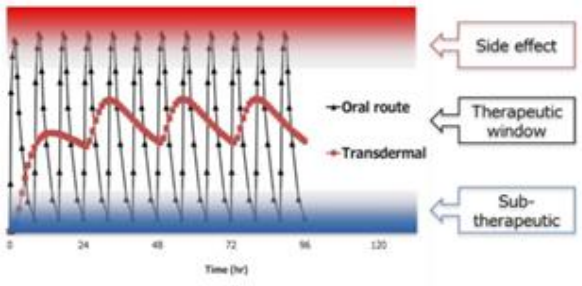
MEDRx is also looking at the US market for its lidocaine tape preparation and has already completed discussions and held interviews and submitted a data package pursuant to an NDA to the European regulator, BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte). In Europe, however, additional tests to those mandated in the US are required and will cost JPY389 million. Hence, if the fund raising planned in November 2019 does not reach a certain amount the plans for Europe may be delayed.

The patch market in the five biggest European countries – Germany, France, UK, Italy and Spain – was estimated in 2018 at JPY23 billion, with the German company, Grunenthal, taking pole position with its product, Versatis®. MEDRx anticipates sales of several billion yen per year.

2. Tizanidine tape: MRX-4TZT (CPN-101)

Tizanidine tape employs tizanidine, a muscle relaxant used also for relieving shoulder stiffness. There are no competing patch products

Tizanidine tape employs tizanidine, a central muscle relaxant used also for relieving shoulder stiffness, rendered transdermal by ILTS®. It acts on the brain/central nervous system, unlike lidocaine, which act locally (on nerve endings and muscles) and relies rather on blood concentration for pharmaceutical effectiveness. The results of US Phase 1a trials (exploration phase of clinical Phase 1) in February 2017, confirmed that the level of sustained concentration in the blood stream is comparable to oral formulations with a reduction in drowsiness and other side effects.



Source: MEDRx company briefing materials

The diagram shows that the transdermal method is superior to the oral method in terms of delivering stable and effective volume of the drug, while making it unlikely that the volume would rise and generate side-effects

Phase 1a trials were completed in February 2017 and licensed out to Cipla in April 2017

At the present time tizanidine is only available in oral form – there are no competing patch or tape-type products. The US market was valued at an estimated USD 800 million in 2016, with around one-third of that expected to be replaced by tape formulations. In April 2017, the company concluded a development and sales licensing agreement with Cipla USA, the wholly owned subsidiary of the major Indian pharmaceutical company Cipla, covering the global market excluding East Asia. (Subsequently, due to restructuring within the Cipla Group, the contractual partner has been changed to Cipla Technologies, LLC., hereafter referred to as Cipla.) Cipla made a lump-sum contract payment of JPY160 million yen in 2017, and appears to have agreed to milestone payments of up to USD30 million and, after launch, royalties in proportion to sales. It was announced in January 2018 that additional Phase 1a' trials had achieved results in line with expectations. The plan was to scale up the investigational drug output and then to conduct additional repeat dose Phase 1b (pharmacokinetic) studies and Phase 2 (pharmacodynamic) studies during 2018 .

Phase 1a' repeat dose trials began in September 2017 and it was expected that Phase 3 would start in the second half of 2018. However, delays in the production scale-up in autumn 2018 led to delays further downstream

Together with this, milestone payments from Cipla slipped to 2019 and after

However, the scaling-up of production took longer than expected and it was not possible to carry out Phase 1b trials during 2018. Rather, they began at the beginning of 2019, and in September pre-set criteria were successfully cleared. Normally, this success at Phase 1b would trigger a milestone payment of USD6 million but, for reasons not entirely clear, the milestone payment for 2019 was reduced to USD1million, with the outstanding USD5 million split up: USD2 million in 2020 and USD3 million in 2021.

After Phase 1b, and assuming a rise in output, the process could move on in two stages to Phase 2 and Phase 3, with an NDA in 2023 After Phase1b, in readiness for any volume increase, test applications for Phase 2 and Phase 3 to be made separately

Looking ahead, the plan is to assume the possibility of an increase in volume and for Cipla to lead Phase 2 tests (from mid-2020 for around 6 months) on a small group of patients to gauge side-effects such as pharmaceutical effect and drowsiness, to then scale up to Phase 3 in late 2021 for a period of around 18 months to 24 months. This would allow an NDA in early 2023 and approval about a year later.

3.Oxycodone tape: MRX-1OXT

It was hoped, until a year ago, that oxycodone tape would become MEDRx's biggest pipeline. MEDRx had used its ILTS® technology to render oxycodone (which had the largest share of the North American opioid pain relief market) transdermally deliverable. It was also developing an oxycodone tape formulation (MRX-1OXT) incorporating AMARTS® to prevent abuse and misuse.

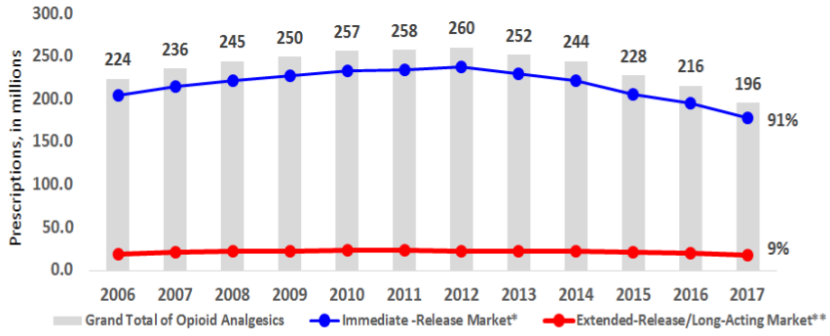
In the US, some 18 million people are reliant on opioid prescriptions for long-term pain relief, so it is thought that the need for opioids will not disappear and, not surprisingly, the authorities have focused on the development of drug preparations which can prevent abuse or misuse. In February 2018, it was announced that, in US Phase 1 clinical trials, it was likely oxycodone tape could achieve the blood concentration necessary for the alleviation of pain. Subsequently, a number of improvements were made to improve absorption, to achieve an effective blood concentration with a smaller patch, and to increase adhesiveness. The company started Phase 1 repeat-dose trials in the second half of 2019 with completion set for the end of 2019.

Note: Opioid is the generic name for opium analogs (no opium) with narcotic properties such as morphine, and is widely used not only in the treatment of moderate to severe pain, but also in anesthesia and cough suppression

Oxycodone tape used to be considered MEDRx's leading product pipeline

However, the drug abuse and misuse problem (the "opioid crisis") surrounding opioid analgesics had become such a problem that all over the country pharmaceutical companies were being sued in court, and the regulators became more careful in their examination of novel analgesic products. In fact, the market rapidly changed, with prescriptions for opioid-like treatments falling 17% compared to 2018, the biggest fall ever.

No. of opioid analgesic prescriptions in the US



Source: FDA Search for Balance: FDA's Approach to the Opioid Crisis 2019 March

In the US, the abuse and misuse of opioid analgesics had become a social problem, such that MEDRx's formulation incorporating its own technology for limiting or preventing abuse and misuse looked set to beat the competition. But finding a licensing-out partner would not be easy

Finally, in September 2019, Purdue Pharma, the manufacturer and distributor of OxyContin® (an oral sustained release form of oxycodone), was forced into bankruptcy by the weight of compensation claims from successive lawsuits. Elsewhere, an NDA for NKTR-181 (developed by Nektar Therapeutics Inc.), which is attracting attention as a newly developed product with reduced side effects that lead to abuse, such as euphoria, was filed with the FDA on July 30, 2018 and accepted. The final examination date (PDUFA date) has been postponed several times, and no determination has yet been delivered.

Because the situation surrounding the development of new drugs is now becoming

more and more opaque, the likelihood of finding a licensee is receding. In the case of oxycodone tape (MRX-1OXT) it seems likely that the emphasis on side-effects will require a Phase 2 and a major Phase 3, the cost of which it will be difficult for MEDRx to cover on its own. For that reason the company has terminated for the time being further progress on MRX-1OXT, the pipeline it had once anticipated becoming its biggest, and has replaced it with a fentanyl tape formulation (MRX-9FLT) which we look at below.

4. Fentanyl tape (MRX-9FLT)

Fentanyl is an opioid used to treat severe-acute, chronic and cancer pain and is usually administered in patch form. In particular, fentanyl patches are in general use for medium-severe cancer pain. As the medicine can be administered transdermally it is used for patients who cannot swallow and, compared to other opioid medicines, it rarely causes drowsiness or constipation, and is used for patients who have evidenced side-effects with other opioids. However, insufficient functional receptors sometimes make it necessary to switch from fentanyl to other preparations.

The first company to develop patches was the US concern, Alza Pharmaceuticals. As a result of its success with patches it was bought up by Janssen Pharmaceuticals (the medical products arm Johnson & Johnson) for USD10.5 billion in 2001. Janssen's sales of fentanyl patches in the US exceeded USD2.4 billion (JPY260 billion) in 2004, immediately before patent expiry. The price at the time was USD10 per patch, but with patent expiry and the entry of generics into the market, the price has since dropped to below USD10. The market in the US is now valued at JPY34 billion, mainly generics.

The company judges that a licensee cannot be found without FDA drug approval and has therefore suspended development

However, with the current fentanyl parches there are cases of children and infants biting or applying those which have been disposed of after use, resulting in death, and this is something which is causing concern among officials. MEDRX's new formulation uses its own technology to control or prevent such accidents. In May 2019, in dialogues with the FDA it was apparent that the prevention of accidents to children involving fentanyl was an important and valuable goal. Shortly after, in November, MEDRx announced its new fentanyl pipeline (MRX-9FLT).

Background to the development of the fentanyl tape formulation

・Fentanyl is an opioid designated as a medical narcotic and indicated, usually in patch form, for the amelioration of severe acute pain, Chronic and cancer pain.
・There have been reports of infants and children dying after mistakenly chewing or applying the existing form of fentanyl patches which have been discarded after use.

Development of fentanyl tape emerges as an alternative to oxycodone tape

The fentanyl patch preparation is widely used for medium to strong cancer pain

The US market is estimated at JPY34 billion

The FDA is of the view that the prevention of accidents involving chidren and infants

・MRX-9FLT:A novel fentanyl parch formulation incorporating MEDRx's own technology to curtail or prevent accidental use.
⇒ In the meeting in May 2019 with the Food and Drug Administration (the US regulator), the view was expressed that the prevention of the accident caused to infants and children by the accidental exposure of fentanyl patches was important and worthwhile goal.

・The US market for fentanyl patches was valued at JPY 34 billion in 2018.
⇒ The company expects to capture and enlarge market share with the value added by incorporating functions to prevent accidents caused by misuse.

is an important and worthwhile goalFentanyl patches are in general use for the alleviation of medium to high cancer pain	Source: MEDRx “Supplementary explanation to raising capital” November 15, 2019 In terms of the development schedule, the company plans, from the spring of 2020, to start pilot PK tests for a preliminary evaluation of bloodstream density and kinetics. After conducting pivotal biological equivalence tests in the second half of 2020, the company will consult with the FDA and then undertake skin safety tests and tests on preventing accidental use. Finally, in late 2021 and early 2022 it plans to submit an application for approval.
	5. Memantine patches (MRX-7MLL) MEDRx has been developing a memantine (trade name: Memary) patch formulation for treating Alzheimer’s. In the past, it had been developing a patch (MRX-5DML) utilizing the NCTS® technology and combining donepezil (brand name Aricept) and memantine, but in the United States, the sales volume of this combination did not grow, while the ratio of oral prescriptions of memantine and donepezil each was high. Hence, a decision was made to switch to developing patches using the memantine monotherapy (MRX-7MLL) and donepezil monotherapy separately. Companies like Corium, Nitto Denko and Hisamitsu Pharmaceutical have advanced the development of donepezil patches, but memantine has been ahead since NCTS® technology is more active. Non-clinical trials began in July 2018. In December 2018, the FDA said, in response to a pre-clinical guidance request, that the content of the current non-clinical trial was sufficient to initiate Phase 1 and that if bioequivalence to oral memantine was demonstrated, Phases 2 and 3 would become unnecessary. The company believes this has made it possible to submit an NDA relatively early.
Plan is to commence PK tests in the spring of 2020, have consultations with the FDA, undertake safety tests and, from the second half of 2021 to 2022, submit an NDA	Non-clinical tests were completed within 2019 and preparations are now underway to submit an application for clinical tests. Once this application is accepted the company plans to carry out two stages of pharmacokinetic tests and a bioequivalence test. Since Phases 2 and 3 are unnecessary, the company is currently selecting manufacturers to whom it will outsource production. Given the above we surmise that an NDA will be submitted in 2022.
	（Reference） US market for Alzheimer drugs: around JPY150 billion of which, oral memantine: around JPY75 billion Donepezil･memantine compound: around JPY14 billion Source: MEDRx Timely Disclosure materials, July 18, 2018
Using NCTS® the company had developed a hybrid tape preparation (MRX-5DML) combining donepezil (trade name:Aricept) and memantine, but has now started non-clinical tests on a memantine-only tape formulation (MRX-7MLL)	
Non-clinical tests were completed in 2019 and preparations are in hand for the submission of an NDA	

2019 annual results and 2020 outlook

Dispersion of Cipla milestone payments and acceleration of R&D means increased loss in 2019

Sales in 2019 were initially forecast to exceed JPY1 billion but actually came in at JPY169 million. This was because of a change in the scheduling of milestone payments from Cipla for completion of Phase 1a development work on tizanidine tape, from an originally scheduled USD6 million to a staggered payment of USD1 million for 2019, followed by USD2 million for 2020 and USD3 million for 2021. Iodocoat ointment sales were JPY23 million. R&D outlays rose more than JYP500 million over the previous year to JPY1,512 million, due to accelerated development of lidocaine tape, the emergence of fentanyl tape, and the successful completion of non-clinical tests for memantine tape. Hence, mainly as a result of more rapid product development, operating revenue posted a loss of just over JPY1.6 billion. At the net level there was a loss of just over JPY1.6 billion.

In 2020, completion of lidocaine tape development means lower R&D costs and reduced losses

However, current company plan does not include lidocaine licensing-out contract fee or European development costs

Sales in 2020 are expected to come in at JPY234 million, including JPY14 million in sales of iodine ointment and about JPY220 million in postponed milestone payments from Cipla. The figures to not reflect the expectation of any licensing revenue for the completed lidocaine tape development. In 2020, despite the start of clinical trials of memantine tape and the accelerated development of fentanyl tape, R&D expenses are expected to decrease to JPY1,145 million, due to the expected completion of development work on lidocaine tape. As a result, the deficit based on net income is expected to shrink from the previous year to JPY1,191 million. This R&D cost does not appear to include the cost of developing lidocaine tape in Europe.

Results for 2018 and outlook for 2019

(million JPY)

	2012/12	2013/12	2014/12	2015/12	2016/12	2017/12	2018/12	2019/12	2020/12 (company est.)
Sales	87	68	26	37	22	198	8	169	234
Product Sales	71	33	26	37	22	28	8	23	14
R&D Revenue	16	36	0	0	0	170	0	146	220
Cost of Goods	33	8	9	12	8	7	2	5	3
SG&A	621	664	1,020	1,025	1,357	1,174	1,279	1,792	1,420
R&D Cost	415	397	718	716	1,074	888	980	1,512	1,145
Others	206	267	302	309	283	286	299	280	274
Operating Profts	-567	-604	-1,003	-999	-1,342	-983	-1,273	-1,627	-1,189
Recurring Profits	-578	-616	-1,012	-990	-1,301	-988	-1,285	-1,633	-1,188
Net Income	-571	-621	-1,016	-878	-1,259	-884	-1,267	-1,616	-1,191

Source: Fair Research Inc. using results meeting materials

The company raised JPY1,310 million in 2019 from the exercise of options. Cash on the balance sheet at the end of 2019 stood at around JPY1,400 million, or around 18 months of net income

Cash and deposits on the balance sheet at the end of December 2019 stood at JPY1,410 million, equivalent to one and a half years of projected net income for 2020. In 2019, MEDRx raised two rounds of financing (issuing and exercising stock options). The first was the 14th issue of stock options (issued in March) with the primary purpose of financing the development of lidocaine tape, which it was expected would raise JPY1,310 million, but actually raised JPY1,027 million by May. The options are fully exercised. The second was in December, when the company issued its 15th stock options (expected to raise JPY1,040 million), mainly for the development of fentanyl tape and lidocaine tape in Europe. Exercise was approximately 30% complete in December. The issuance of shares from the exercise of the 14th and 15th stock options during 2019 raised JPY1,310 million. As a result, the deficit expanded to the JPY1,600 million level in 2019, but the decline in cash and deposits was restrained at about JPY380 million compared to the previous year.

In 2019, the company raised JY1,310 million from the exercise of options. With cash on the balance sheet at the end of December at the JPY1,400 million level, it has 18 nonths of cash

Exercise of the 15th round of stock options made progress in January and February 2020, raising a total of JPY220 million in those two months, and about JPY500 million in cumulative terms since December. About half has been absorbed and

As of February 2020, sufficient funds have been raised to finance clinical tests on fentanyl tape.
It seems likely that plans to expand lidocaine into Europe will be put off

sufficient funds have been secured for promoting the development of fentanyl tape. However, given the current state of the stock market, it may be difficult to raise JPY1 billion as planned, and development of lidocaine tape in Europe (budget just under JPY400 million) is likely to be postponed.

Trend in the balance sheet

(million JPY)

	2010/12	2011/12	2012/12	2013/12 IPO	2014/12	2015/12	2016/12 CB Issue	2017/12 CB conv. Completed	2018/12	2019/12
LiquidAssets	730	649	507	4,008	2,857	2,204	2,736	1,836	1,937	1,501
Cash	691	614	465	3,937	2,780	2,063	2,640	1,737	1,796	1,410
Others	39	35	42	71	77	141	96	98	141	91
Fixed assets	335	304	280	722	831	774	342	296	373	546
Tangibles	265	240	215	256	346	278	264	220	295	471
Intangibles	0	0	0	1	3	2	1	0	0	0
Investments,	89	64	65	465	483	494	76	75	77	75
Total assets	1,085	952	787	4,730	3,685	2,978	3,079	2,133	2,311	2,047
Liabilities	80	106	511	227	171	205	573	99	180	126
Liquid liabiliti	64	79	450	158	79	110	103	88	170	116
Fixed labilitie	16	27	61	69	92	96	469	10	10	10
Net assets	1,005	847	275	4,503	3,514	2,772	2,507	2,037	2,130	1,920

Source: compiled by Fair Research from short-form financial statements

Uses of funds raised in the issue of series 15 stock options (issued Dec. 2019)

Source: MEDRx Supplementary materials for capital raising (Nov. 15 2019)

Pipeline values recalculated taking into account changes in development status

Pipeline current value calculation

We have used the DCF method to recalculate below the current values of the different pipelines.
（Note: the estimates are based on multiple challenging assumptions and are intended only as broadly indicative）

（Preliminary assumptions）

Our view of the schedule assumes that it will take around 4-5 years from market launch to peak sales, that after the peak, sales will decline by approximately 5% per year until 2038 when, due to generics and other factors, sales will start declining by 10% per year. In addition to the ROE of 8% required by the stock market we must factor in the reality that the company has no major drugs market presence and that it is regarded as a bio-venture running consistently at a loss. An appropriate discount rate we therefore think would be 12%. We have assumed that royalties income will be around 10-15% of sales, although this would depend on the product's stage of development at the time of licensing. We are still considering how to value tizanidine, but for the other product pipelines total milestones would be in the range of 20-30% of sales.

（Results of calculation）

On the basis of a number of preconditions we posit the pipeline value for all four main products at around JPY36.7 billion (before tax)

(100 mil JPY)

	Before success prob.	After success prob.
Lidocaine tape (MRX-5 LBT) Prob. Of success 90%	82	74
Fentanyl tape (MRX-9 FLT) Prob of success 80%	263	209
Memantine patches (MRX-7 MLL) Prob. of success 40%	102	33
Tizanidine tape (MRX-4 TZT) Prob. of success 50%	104	52
	551	367

Source: Fair Research Inc.
Note: Changes in any of the preconditions will affect the calculation
Enterprise value is not just pipeline value but also various costs, tax, etc.

①Lidocaine tape is now nearing its NDA stage so we would give it a 90% probability of reaching the market. We posit peak sales of JPY9 billion, given 10% of the market volume and assuming around the same pricing as ZTlido®. We therefore posit a pipeline value of around JPY7.4 billion. On the severe assumption of sales of 3 million patches (the same level as ZTlido's® minimum target) and given a 90% probability of reaching the market, the company could recoup its development outlays of around JPY1.7 billion.

②Our assumptions for fentanyl tape are as follows:

・Given that the product has new functions we are assuming pricing of around 1.5 times that of generics.
・We are targeting a 50% market share in view of the appeal of the product's accident prevention function. This would give it a peak sales value of JPY26

billion.
・Licensing out after FDA approval. Royalties assumption of 15% of sales. Milestones value of JPY5 billion (= one-off licensing-out fee + sales milestones).
・Since there are other fentanyl tape products on the market and since we see it as qualified to apply for BE testing we posit an 80% probability of success.

We would therefore posit a value for fentanyl tape of around JPY20.9 billion.

③We have assumed peak sales of memantine tape at around one-quarter the level of oral memantine and therefore posit a value of JPY22.5 billion. Phases 2 and 3 are not required, and the pre-clinical stage has been completed, so we assume a 40% probability of success. This would give it a pipeline value of JPY3.3 billion. If it replaced half the sales of the oral version, or if progress in development drove up the probability of success, we believe the value could be much higher.

④We are assuming peak sales for tizanidine tape of JPY30 billion, and a 50% probability of successfully reaching the market. We therefore posit a value of around JPY5.2 billion. At a 100% probability of success this would rise to JPY10.4 billion.

The divergence from market cap is likely due to development being delayed until mid-2019, changes in the environment surrounding oxycodone tape, and a series of financings.

The current market evaluation of MEDRx in market cap terms is JPY2-3 billion. Even after taking into account the remainder of the financing announced in November 2019, that is still a long way from the 4-pipeline total current value of approximately JPY3.58 billion (pre-tax). We can suggest four reasons for this difference: ①There were delays in the development of all four pipelines until mid-2001, with consequent delays in the receipt of milestone payments; ②The agreements with Dai-Ichi Sankyo and Takeda were terminated without producing anything for the market; ③The development of oxycodone tape, regarded as the company's most promising product, was suspended; and ④The occurrence of a number of financings, such as the financing for the microneedle project (in April 2018), for the acceleration of lidocaine tape development (February 2019), and for fentanyl tape development (November 2019).

In the second half of 2019, however, there were a series of postive events

We can expect more stable income stream sooner or later

In and after mid-2019, however, there were a number of positive developments. The lidocaine tape formulation completed clinical trials, there was a start to milestone payments related to the tizanidine tape formulation, and fentanyl tape emerged as a replacement for oxycodone tape. Finally, it appeared that a successful licensing-out and launch of lidocaine tape in 2021 would secure MEDRx a stable source of finance and allow the company to pursue independent product development.

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