MEDRx Co., Ltd.

（4586 Mothers） Issued: May 31, 2021

Prospective Major Products Emerging

Emergence of major next-generation products

Since suspending the development of what had been its major product, oxycodone tape (MRX-1OXT), in November 2019, MEDRx has started the development of fentanyl tape (MRX-9FLT) and has reached the application stage for the lidocaine tape preparation, Lydolyte. However, both products faced severe competition from generics, and since fentanyl tape's main target is the cancer pain market it had little possibility of being used in the broader area of severe pain. The emergence in May 2021 of diclofenac-lidocaine tape (MRX-6LDT) changed the equation. It has no predecessors in the market, and has became MEDRx's next major product, replacing the terminated oxycodone tape. At the same time, there has been steady progress in the development of microneedles for the application of vaccines to prevent infections. Both products will take some time to develop but have the potential to become extremely significant.

Big demand for treatments for osteoarthritis

The distinctive characteristic of diclofenac-lidocaine tape (MRX-6LDT) is that diclofenac and lidocaine work differently and thereby promise to provide additive or synergistic pain relief. There are at present no analogous predecessors or candidates being developed. The final aim is to use it as an anti-inflammatory analgesic to treat a wide variety of acute pain, but initially it will probably be developed to treat osteoarthritis of the knee. The difficulty of developing analgesics is that the endpoint by which clinical trials are evaluated lies in how pain is felt by different individuals. With osteoarthritis patients this is said to be relatively straightforward. In the US there are an estimated 63 million osteoarthritis patients. Hisamitsu Pharmaceuticals is currently developing diclofenac sodium patches (HP-5000) for the treatment of osteoarthritis. MEDRx's diclofenac-lidocaine tape has just completed Phase 2 and has a high probability of being licensed out. The timing is perfect, with the HP-5000 launch stimulating interest in diclofenac patches for osteoarthritis indications.

Promising progress also in microneedle development

Microneedles can have important social implications. Their use in "vaccination patches" is painless, because minimally invasive, and administration does not require medical staff, because self-administered. In addition, room temperature is all that is necessary when solid vaccine antigens are applied to the superfine needles, and for ease of transportation and storage. We see a big market for microneedles, especially in tackling pandemics in poorer countries, where the medical environment may be rudimentary. MEDRx estimates the potential value of the market for vaccine microneedles at JPY47-940 billion. A clinical testing facility has already been completed and has been remodeled to enable handling of the pathogenic bacteria, viruses and genetically modified organisms used in vaccines. Looking ahead, the company plans to conduct animal tests to confirm the efficacy and safety of vaccines and microneedle formulations for infectious diseases, and to examine their feasibility. MEDRx hopes to accelerate business alliances with pharmaceutical companies and vaccine ventures.

Follow-up Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Information	
Location	Kagawa Pref.
President	Yonehiro Matsumura
Established	January 2002
Capital	JPY7,401 mil.
Listed	February 2013
URL	www.medrx.co.jp
Industry	Pharma
Employees	24 (consol. basis)
Key Indicators as of May 28 2021	
Share Price	218
Year Low	192
Year High	426
Shares outstanding	19,695,100
Trading Unit	100 shares
Market Cap	JPY4,294 mil.
Dividend (est)	0
EPS (est)	-56.8JPY
Forecast PER	na
BPS (actual)	95.76 JPY
PBR (actual)	2.28X

Calculated on the basis of shares outstanding (excl. treasury shares)

Results	Revenue JPY mil	YoY %	Op. Income JPY mil	YoY %	RP Income JPY mil	YoY %	Net Income JPY mil	YoY %	EPS JPY	Share Price High	Share Price Low
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
18/12Actual	8	-95.8	-1,273	na	-1,285	na	-1,267	na	-126.7	2,060	425
19/12 Actual	169	1922.9	-1,627	na	-1,633	na	-1,616	na	-134.3	698	301
20/12 Actual	115	-32.2	-1,130	na	-1,152	na	-1,114	na	-68.6	426	160
21/12 Forecast	327	184.2	-1,111	na	-1,115	na	-1,117	na	-56.8		

Company Outline – management philosophy

A venture company engaged in developing transdermal absorption formulations

Business Model

In broad terms, the company is involved in developing transdermal absorption formulations using the active ingredients of existing oral and injectable drugs. In terms of business model, it licenses out these formulations to pharmaceutical companies, collecting milestone payments and, after launching in the market, royalties on sales.

Transdermal absorption formulations make up a growing medium to long-term segment of the pharmaceutical market. Among their attributes are maximisation of pharmaceutical effect, reduced side-effects and better quality of life for the patient. These attributes are achieved by the following:

① Providing a consistent and sustained release of active ingredients: enabling the maintenance of a constant volume of the drug in the bloodstream.

② Little or no first-pass effect: while the efficacy of oral drugs can be reduced to 10-20% as they pass through the liver, this is not an issue in the case of transdermal absorption formulations.

③ Better medication compliance: suitable for patients who find it difficult to take oral drugs due to problems 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 conditions.

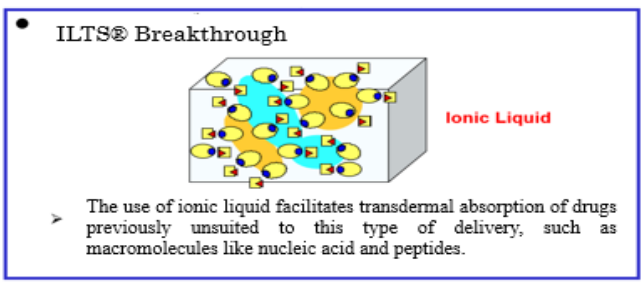
The MEDRx business model is also distinctive in two ways:

The company has proprietary technologies, giving its products a higher probability of success than for other new drug discovery businesses

(a) It is low risk (i.e. 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 crystalization. They are non-volatile, non-flammable and electricity conductive. In recent years these properties have led to applications in lithium battery electrolysis and elsewhere. With ILTS®, MEDRx was the first to develop the technology for the transdermal absorption of ionic liquids, thus facilitating the administration of drugs which are normally difficult to administer transdermally. With existing technology, transdermal absorption was difficult in the case of nucleic acid or macromolecular formulations, but ILTS® has made it much easier.



Source: MEDRx company briefing

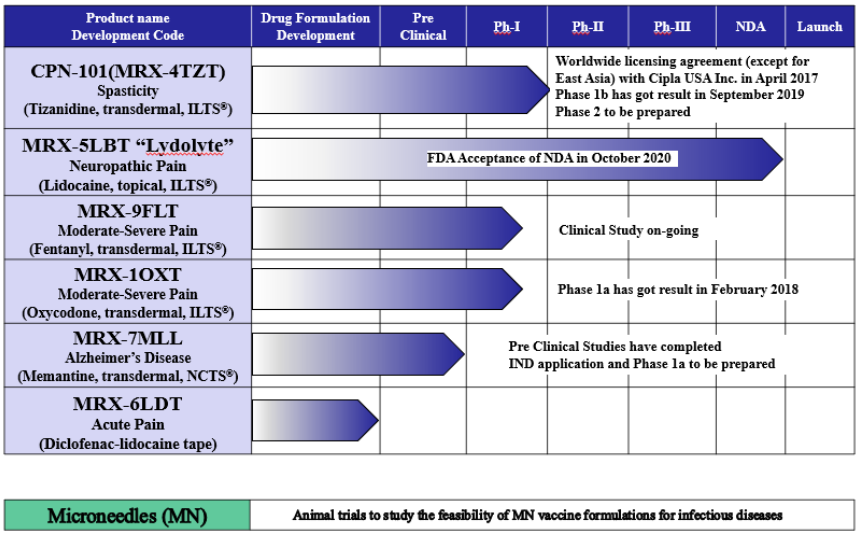
Another interesting feature of MEDRx's ILTS® is that it has built high barriers to entry. The company has a library of several hundred ionic liquids formed from combinations

of compounds with a track record of use on human subjects as pharmaceuticals and additives. It also has extensive know-how on selecting optimum ionic liquids for particular drug properties, and formulation expertise on maintaining and improving the transdermal properties of ionic liquids.

The company's primary target is the US market for transdermal absorption formulations. This preference is based mainly on the potential of the US market for tape-type formulations.

In addition, by basing its activities in the US on existing formulations, the clinical trials required to win FDA approval are simpler than for new drugs (i.e. 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 and tape-type drugs tend to command higher prices in the US than in Japan.

Key product pipelines



Source: MEDRx company briefing, May 2021

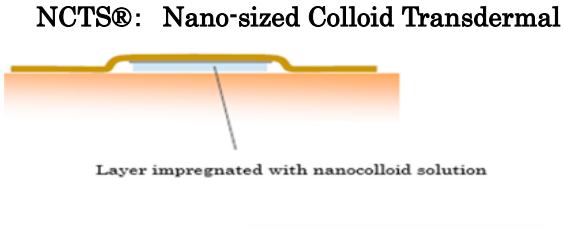
There are five product pipelines to which MEDRx has applied its proprietary ILTS® technology

The main products to which the ILTS® technology is applied are tizanidine tape (CPN-101, MRX-4TZT), which has been successfully out-licensed to Cipla Corp., lidocaine tape (MRX-5LBT), fentanyl tape (MRX-9FLT), oxycodone tape (MRX-1OXT) and the newest product, diclofenac + lidocaine tape (MRX-6LDT).

A memantine patch using NCTS® technology has been developed

The company also has a transdermal absorption technology using nanocolloids (NCTS®: Nano-Sized Colloid Transdermal System). As mentioned earlier, the ILTS® technology is used in the transdermal absorption of macromolecular agents such as peptides and nucleic acids. The NCTS® technology, however, aims to enhance transdermal absorption of relatively low molecular mass agents by rendering pharmacologically active components into nano-sized colloids. Among products now at the development stage for which information has already been disclosed is MRX-7MLL, a transdermal absorption formulation using memantine (for the treatment of Alzheimer's), which can suppress the skin irritation which memantine usually causes.

The company has developed microneedles to provide “vaccination patches”

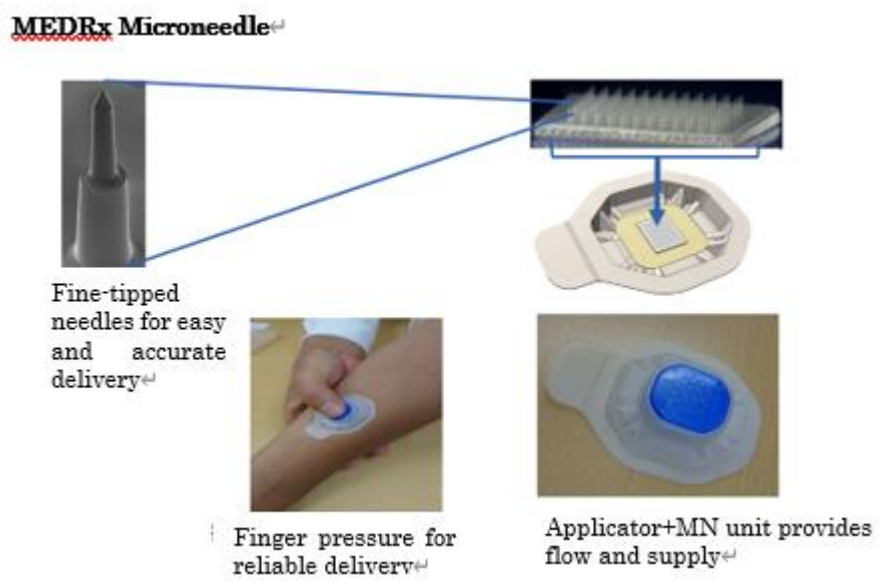


Source: Fair Research Inc. using MEDRx company briefing materials

The company has also developed a technology using microneedle arrays as a sort of “vaccination patch”. The microneedle technique works by using super-fine needles to open apertures in the surface of the skin, thereby allowing access to the vaccine. The skin not only acts as a physical barrier to foreign substances but also acts immunologically to expel such substances. Langerhans cells in the epidermis below the stratum corneum and dermis dendritic cells in the dermis below, are antigen-presenting cells which play an important role in biological defense. A strong immune response can be elicited by efficiently transmitting the vaccine antigen to these antigen-presenting cells.

However, the stratum corneum presents a barrier, so that vaccine applied to the skin does not penetrate. Microneedles transmit drugs into the skin by opening apertures in the epidermis with superfine needles. They are less than 1mm in length and do not reach the nerve, hence providing vaccination without pain. In other words, this method can be seen as a “ vaccination patch”.

MEDRx microneedles come complete with an applicator, allowing drug administration with the press of a finger



Source: Fair Research Inc. using various materials

1. Major next-generation products

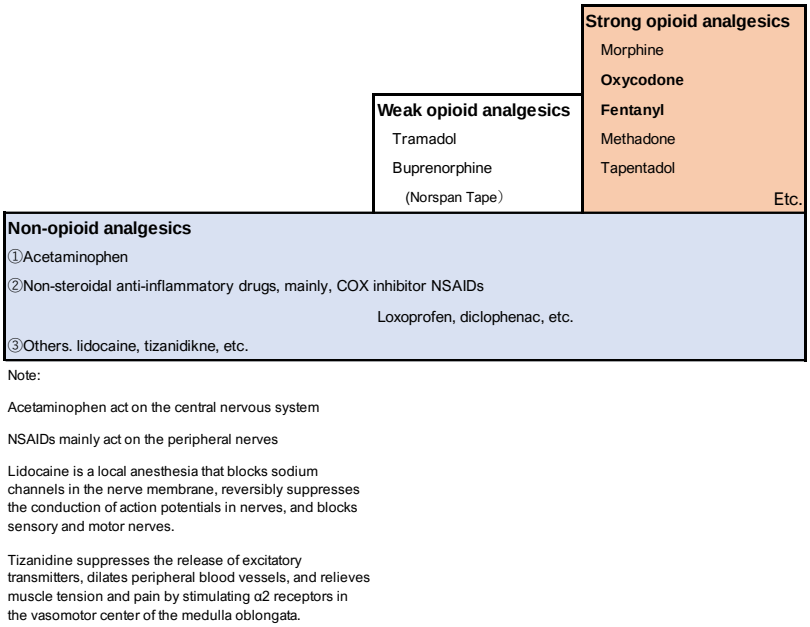
New major development candidate: diclofenac-lidocaine tape (MRX-6LDT)

On May 18 2021 MEDRx announced it was planning to develop a new product pipeline, MRX-6LDT. This is a medical patch that uses MEDRx's unique transdermal technology, ILTS®, to simultaneously infuse both the anti-inflammatory analgesic diclofenac and the local anesthetic lidocaine. There is no other patch which can do this, and no other makers are developing one.

It used to be that oxycodone tape was looked upon as a major development prospect

There has been increasing regulation of opioids in the US

Reference: Types of analgesic



Note:

Acetaminophen act on the central nervous system

NSAIDs mainly act on the peripheral nerves

Lidocaine is a local anesthesia that blocks sodium channels in the nerve membrane, reversibly suppresses the conduction of action potentials in nerves, and blocks sensory and motor nerves.

Tizanidine suppresses the release of excitatory transmitters, dilates peripheral blood vessels, and relieves muscle tension and pain by stimulating α2 receptors in the vasomotor center of the medulla oblongata.

Source: Fair Research Inc. using various materials

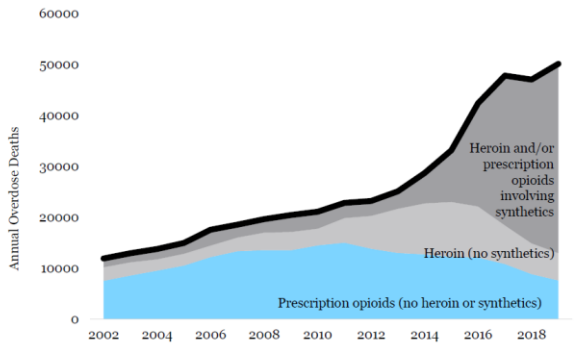
<History of Developments>

Until two years ago, MEDRx's most promising pipeline under development was oxycodone tape (MRX-1OXT). This was based on oxycodone, which had the biggest share in North America's market for analgesic opioids, and which MEDRx had rendered transdermal using its ILTS® technology.

Abuse and misuse of opioid analgesics (the "opioid emergency") had grown so serious in the US that on October 26 2017, the federal government declared a national public health emergency. It was in this context that MEDRx promoted development of its abuse and misuse-deterrent (AMARTS) oxycodone tape (MRX-1OXT).

Deaths in the US from overdosing on opioids

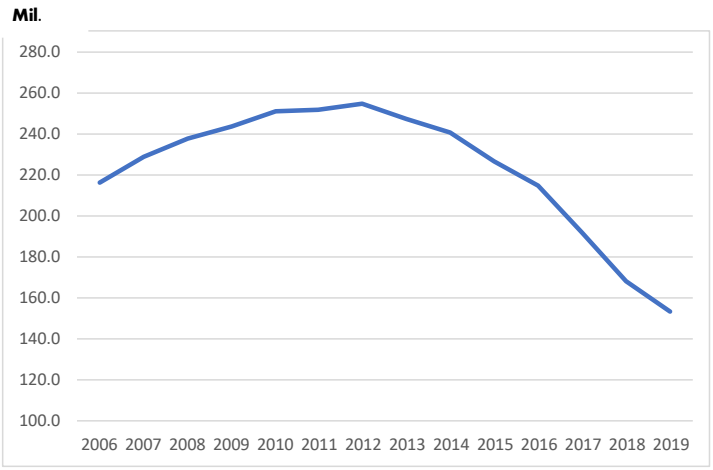
Sharp deterioration in the market



Source: FDA Introduction to Opioid Systems Model White Paper

However, with drug companies being sued in court around the country the authorities became more cautious in vetting new analgesics. And there was a sharp change in market sentiment, with a rapid decline in the number of opioid prescriptions written. Finally, in September 2019, Purdue Pharma, which produced and sold Oxycontin® (a slow-release oral oxycodone formulation), was forced into bankruptcy protection under the weight of a barrage of damages claims.

Prescriptions written in the US for opioid analgesics



Source: Using data in the CDC's US Opioid Dispensing Rate Map

There were more hurdles to development than initially anticipated

Oxycodone tape developmnet was suspended in November 2019

Fentnyl tape subsequently emerged as a development proposition

An application to conduct tests was submitted in March 2020, with the first results becoming available in September. An application for approval will be submitted after tests for bio-equivalence, safety and reliability of misuse prevention

However, fentanyl tape is also subject to opiod regulations, and it is only indicated for cancer pain

With this increasing lack of certainty around the development of new opioids it became apparent that a successful licensing-out relied firstly on getting FDA drug approval. Also apparent was the likelihood that not only Phase 2, but the much more extensive Phase 3 trials would concentrate on the side-effects of MRX-1OXT. MEDRx was not financially equipped to go it alone, and for that reason in November 2019 the company suspended development of what had been its most promising pipeline.

What presented itself next was fentanyl tape (MRX-9FLT). Fentanyl is a form of opioid indicated, usually in patch form, for the alleviation of severe acute pain, chronic pain and cancer pain. Since it can be administered transdermally it is often used in patch form for medium-severe cancer pain for patients who are unable to swallow, and since it is less likely to cause drowsiness or constipation it is indicated for patients who have had an adverse reaction to other opioid analgesics. However, there are occasions when fentanyl is replaced with a different drug because of a limited number of receptors in the body.

With conventional fentanyl patches, each year there are a number of deaths caused by infants and children swallowing or applying used and discarded patches. However, MEDRx's new fentanyl tape is designed to deter and prevent misuse and abuse. In an interview in May 2019 the FDA clearly stated that this was an important and worthwhile goal in fentanyl tape development. In November 2019 MEDRx announced that fentanyl tape (MRX-9FLT) was the company's new product pipeline. An application was submitted to commence clinical trials in March 2020. These began in July and in September the first results were obtained. These included pilot pharmacokinetic (PK) tests to provide preliminary confirmation of blood concentration and dynamics. It was ascertained that the patch provided the same blood concentration as the reference drug, Duragesic®, and preliminary confirmation was made of the product's usefulness in deterring and preventing misuse and abuse. Looking ahead, following Duragesic® pivotal biological equivalence tests and after discussions with the FDA, the company will conduct skin safety tests and will test the product's reliability in preventing

More recently, diclofenac-lidocaine tape (MRX-6LDT) has emerged as a major drug candidate for a broader range of chronic pain indications

Given that diclofenac and lidocaine have different pain relief mechanisms, it is expected that MRX-6LDT will offer additive or synergistic therapy. There are no analogous predecessor products

Hisamitsu Pharmaceuticals is developing in the United States the HP-5000 diclofenac patch, which produces a high blood concentration of the active ingredient

For MRX-6LDT also, a high blood concentration of diclofenac is targeted, and the lidocaine amount will be several times that of Lydolyte

The development of the preparation being finalised, the company will now move on to pre-clinical and Phase 1, scheduled for completion in March 2023

Phase 2 will then follow and a licensing out will be just in time to benefit from the market pioneered by HP-5000

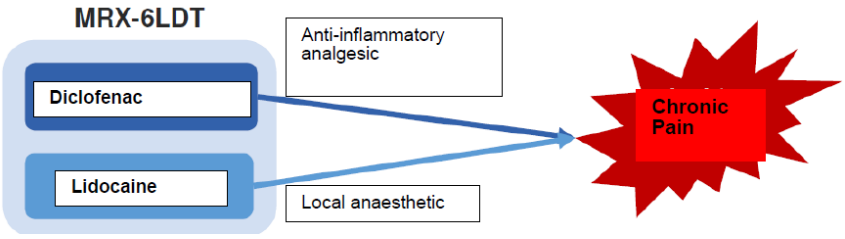
accidental use. The plan is to submit an application for approval in late 2022 or early 2023.

However, in 2019 the US market for the fentanyl tape formulation was valued at around JPY26 billion (mostly generics) and, since 2017, the opioid crisis has led to a more stringent regulatory regime and, consequently, a shrinking of the market for fentanyl tape (at an annual rate of around 20%). Nevertheless, cancer pain is not about to disappear and fentanyl tape will continue to command a certain market position as an essential drug.

Then, in May 2021, MEDRx announced it was developing diclofenac-lidocaine tape (MRX-6LDT) to cover a broader chronic pain area than cancer pain. The diclofenac-lidocaine combination tape is a new drug candidate and there are no similar products.

<Characteristics of MRX-6LDT>

Given that diclofenac and lidocaine have different pain relief mechanisms, it is expected that MRX-6LDT will offer additive or synergistic therapy (see illustration below).



Source: MEDRx supplementary information for financing, May 2021

The intention is to use ILTS® to endow MRX-6LDT with a transdermal level of diclofenac several times more concentrated than the conventional diclofenac patches widely used in Japan and elsewhere. Hisamitsu Pharmaceuticals is currently developing a diclofenac patch (HP-500) in the US for the treatment of pain in osteoarthritis of the knee (PH3; NCT04683627). The company announced in November 2019 that Phase 2 trials, in which a high concentration of the drug was delivered to the affected location, produced beneficial results in terms of effectiveness and safety. MEDRx has also chosen high concentration delivery in its development of MRX-6LDT.

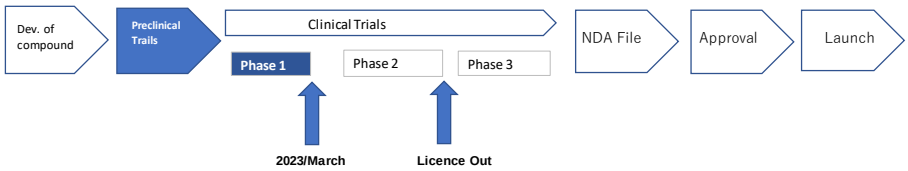
Similarly, regarding lidocaine, it seems that MEDRx is considering a formulation with a transdermal penetration amount several times higher than that of Lydolyte (lidocaine tape), which is currently the subject of an NDA. Even at several times that of Lydolyte, the concentration in the blood is still not high enough to cause the side effects which occur with injection delivery, so it is expected that sufficient tolerability will be ensured.

<Development schedule>

With the finalisation of MRX-6LDT formulation development it was time for pre-clinical tests and Phase 1 clinical tests. At Phase 1 the objective is to ascertain safety, tolerability, and absorbability of the drug in the human body (concentration in the blood, etc.). Phase 1 will be completed in just less than 2 years, in March 2023. Following which, Phase 2 will be undertaken in which, to ascertain applicable indications and effectiveness, tens of cases of some three or so indications will receive administrations for 2-3 months. We assume that the company intends to license out when results are confirmed (in 2024 or later). Meanwhile, HP-5000 Phase 3 trials completion is scheduled for December 2022. If that happens, we imagine that it will take until 2024-

2025 to develop an osteoarthritis market for this drug, this means that MRX-6LDT will be approaching a licensing-out just as the market is primed for an expansion in diclofenac patches.

Although not yet formally announced, the first applicable indication will probably be osteoarthritis



Source: MEDRx supplementary explanation for financing, May 2021

<Applicable indications>

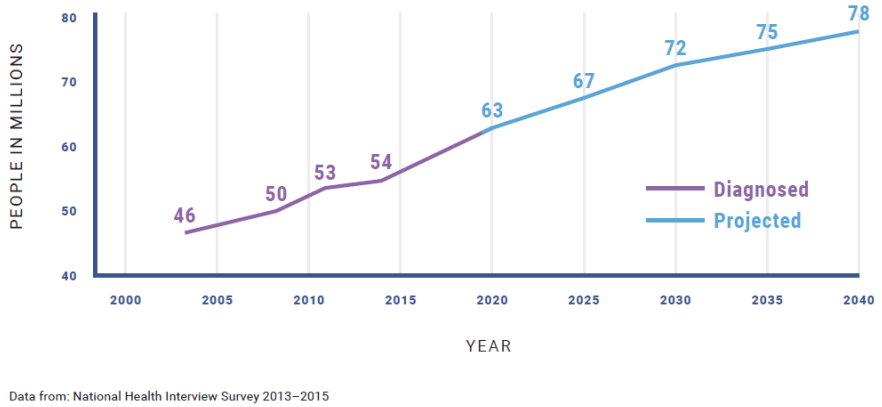
It is estimated that, in the US alone, there are 63 million osteoarthritis patients

Although the company's final objective is the patch's use as an anti-inflammatory analgesic treatment for a broad spectrum of chronic pain, it seems likely that the first indication will be osteoarthritis. The difficulty in developing analgesics stems from the fact that the endpoints measuring effectiveness in clinical trials depend on how individuals feel pain. This difficulty was experienced in the failure of the Etoreat® tape development. Measuring as precisely as possible how different individuals feel different levels of pain can make the difference between success and failure in drug development, and the view is that this can be more easily achieved in the case of osteoarthritis patients. The likelihood, then, is that after pursuing and successfully developing an osteoarthritis treatment, attention will turn to the much bigger market of lower back pain and other areas in which oxycodone has traditionally been indicated.

Note: The osteoarthritis (OA) market

It has been estimated that, as of 2019, 7% of the global population, or 500 million people, suffer from osteoarthritis (source: David J. Hunter et al., the Lancet, November 2020). In the US as of 2015, it was estimated that 54.4 million people have some form of OA, and that this will rise to 78 million in 2040 (CDC data). The expectation is that the value of the market will rise to several billion dollars. In Japan, it is estimated that there are 10 million patients, and more than 80 thousand a year require surgical intervention (Ministry of Health, Labor and Welfare: Summary of Patient Surveys)

US：number of patients diagnosed with osteoarthritis



Source: CDC：OA prevalence and burden

The final therapy for OA is surgery, but before turning to surgery the main therapy is

The final treatment for OA at present is surgical replacement with an artificial joint, but before resorting to surgery the main therapy is treatment of OA pain. In the last ten years opioids and NSAIDs (non-steroidal anti-inflammatory drugs) have played a central role, and the majority of patients have used them. However, opioids are addictive and there is

treatment of the pain from OA, and this is where a central role is played by steroids and NSAIDs (non-steroidal anti-inflammatory drugs)	a risk of abuse. In addition, long-term use of NSAIDs can cause disorders of the digestive system and cardiovascular system. Hence, the search for drugs with novel action mechanisms.
The development of new drugs is proceeding but there have been setbacks in the case of the much watched anti-NGF antibodies.	At present, development of a number of new drugs is underway, but the development of anti-NGF antibodies is attracting the most attention, but with a chequered history. AstraZeneca suspended the development of MEDI-578 at Phase 1 (2012), AbbVie terminated ABT-110 at Phase 1 (2013), J&J abandoned Fulranumab at Phase 3 (2016), Astellas Pharma suspended ASP6294 at Phase 2 (2020), and Regeneron/Teva (Mitsubishi-Tanabe) proceeded as far as Pivotal trials but suspended Fasinumab at drug administration trials (2020) and is now considering how to proceed. In addition, Pfizer-Lilly's very promising Tanezumab received a negative rating from the FDA's Drug Safety and Risk Management Advisory Committee at Phase 3 in May 2021 (In the case of anti-NGF antibodies an increase in joint inflammation and bone infarction have been a not uncommon cause of suspension on safety grounds).
Opioids and NSAIDs will continue to be important for the time being.	The development of OA progression-inhibitors, which would reduce the need for analgesics, is still in the early stages. It seems therefore that opioids and NSAIDs will continue to play a central role in OA treatment.

2. Release of financing plan

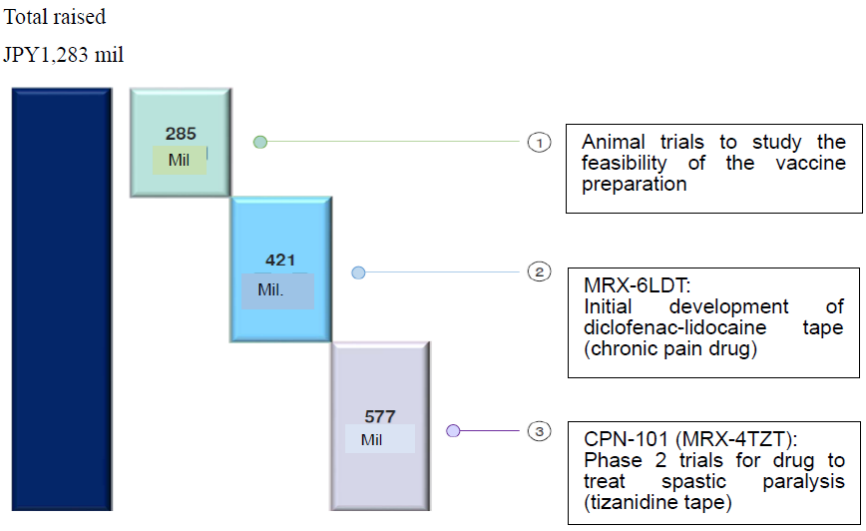
Releases a new plan to raise finance (JPY1,283 million) along with emergence of MRX-6LDT

On May 18 2021, around the same time as the emergence of MRX-6LDT, MEDRx issued a plan to raise fresh finance to the value of JPY1,283 million. On this occasion, the mechanism is designed to secure cash on hand and raise additional funds. The financing calls for, first, the procurement of JPY550 million from the issue of corporate bonds, and then the use of the proceeds from the issue of MS warrants (No. 20 stock options) to preferentially redeem corporate bonds, on top of which to raise a further JPY120 million and, additionally, JPY627 million procured from the issue of new share options (No. 21) If the amount raised by the MS warrants is less than JPY550 million due to exercise price adjustments, the No. 21 new share options will be changed to the MS warrants and will be preferentially allocated to the redemption of unredeemed corporate bonds.

Funds raised will be used for microneedle formulations for infectious diseases, initial development of MRX-6LDT, and Phase 2 trials of tizanidine tape

As shown in the chart below the funds raised will be allocated in the following order: ① To fund animal trias to study the feasibility of microneedle formulations for infectious disease vaccines; ② To fund preliminary development of MRX-6LDT (pre-clinical and Phase 1); ③ To fund tizanidine tape (CPN-101/MRX-4TZT) Phase 2 trials.

Uses of funds raised in the financing plan announced in May 2021



Source: MEDRx supplementary information on financing

① **Animal trials to study the feasibility of microneedle vaccine formulations for infectious diseases** (expected disbursement period: June 2021-May 2022)

Plans to spend JPY285 million on microneedles by May 2022

MEDRx has been developing microneedles as a simple and sure way of administering drugs for the past 16 years. This means the needle must reach the dermis directly and painlessly, which is best achieved by the shape of the needle point and the provision of an applicator. MEDRx holds a patent on the configuration of its needles, has registered the patent on its applicator in Japan and China, and intends to acquire rights in the US, Europe,Brazil and India.

MEDRx intends to use microneedles mainly for vaccines, but the vaccine business requires high volumes and stable supply. The major pharmaceutical companies have little interest in themselves developing medical instruments, and while they might develop vaccines at a subsidiary they are unlikely to develop or manufacture microneedles. MEDRx therefore came up with a concrete plan to produce in volume and, in order to pursue the possibility of collaboration with a major company, in April 2018 announced a plan to raise capital to provide funding for the construction of a high

After various twists and turns microneedle development arrived at operation of a test manufacturing facility in April 2020

In January 2021 an upgrade was completed allowing the facility to handle the pathogenic bacteria, viruses and genetically modified organisms used in vaccine production

The plan now is to use animal studies to test the effectiveness and safety of microneedle vaccines for infectious diseases, and to confirm feasibility

Important social significance and big potential market

Prliminary development of MRX-6LDT to require disbursements of JPY421 million

JPY550 million of the total financing will first be raised from corporate bonds, and the unused portions of previous financing will be appropriated

volume factory. However, the company shelved this idea in November 2018 when the fund-raising stalled.

In April 2020 MEDRx started operation of a test facility that was built in 2019 and intended as the first stage in volume production. It is able to handle GMP manufacture of products which can be administered to humans in, for example, clinical trials. Later, in July 2020, it was decided to upgrade the facility to handle the pathogenic bacteria, viruses and genetically modified organisms often associated with vaccine production. The upgrade, featuring prevention of dissemination and other biosafety measures, was completed on January 28, 2021.

Currently, MEDRx is conducting or discussing feasibility studies with a number of domestic and overseas pharmaceutical companies and vaccine ventures. It is seeking to solidify and accelerate business alliances with these companies prior to moving, in 2022, to the development stage (pre-clinical tests). For this purpose it plans to conduct tests on animals to confirm the effectiveness, safety and viability of microneedle vaccinations against contagious diseases. One of the purposes of the recent JPY285 million financing is to fund these tests.

Microneedles could have important social implications. Their use in “vaccination patches” is painless, because minimally invasive, and administration does not require medical staff, because self-administered. In addition, room temperature is all that is necessary when solid vaccine antigens are applied to the superfine needles, and for ease of transportation and storage. We see a big market for microneedles, especially in tackling pandemics in poorer countries, where the medical environment may be rudimentary. MEDRx estimates the potential value of the market for vaccine microneedles at JPY47-940 billion.

● Vaccine microneedle market: JPY47 billion – 940 billion

(2019 world vaccine market USD42.7bn*) x (Microneedle usage 10% -100%) x (Supplier price to vaccine makers vs final vaccine price 10%-20%)

Estimate according to Reportocean.com

Source: MEDRx supplementary information on financing

② **Preliminary development of MRX-6LDT:** disbursement period: June 2021-March 2023

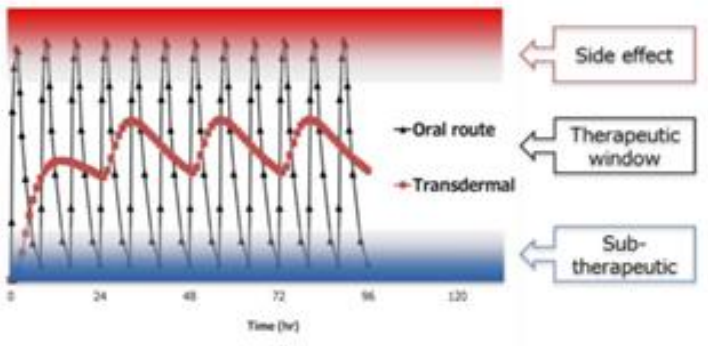
As noted earlier, MRX-6LDT has the potential to take the place of oxycodone tape (MRX-1OXT), whose development was suspended, as the company’s major development candidate. The company is now planning to raise JPY421 million to finance its pre-clinical and Phase 1 trials. The total for ① and ② is around JPY700 million, with the amount from corporate bonds (JPY550 million) being mostly raised at an early date. In addition, if the exercise price is low, we surmise the exercise of two previously issued new share options will be sufficient to make up any shortfall. Development is therefore not seriously threatened with suspension for financial reasons (As note earlier. MEDRx appears to be thinking of itself developing up to Phase 2, and then licensing out. Judging from the inferred scale of Phase 2, we would assume costs of around JPY1 billion, with the trials commencing in or after April 2023).

③ **CPN-101 (MRX-4TZT) Phase 2** (disbursement period: September 2021 –April 2022)

Tizanidine tape, CPN-101 (MRX-4TZT) employs tizanidine, a central muscle relaxant used also for relieving shoulder stiffness, rendered transdermal by ILTS®. It works on the brain/central nervous system, unlike lidocaine or ETOREAT® which work at the local level (peripheral nerves and muscle), where blood concentration produces

MEDRx and Cipla are now in discussions on tizanidine tape Phase 2 development

medicinal effects. Judging from the results of Phase 1a tests (Phase 1 clinical trials exploration phase) conducted in the US in February 2017, tizanidine tape provides the same level of sustained tizanidine in the bloodstream as the oral preparation with less drowsiness or other side-effects.



Source: MEDRx company briefing materials

The above chart shows that transdermal delivery provides a concentration which has a more stable and sustained efficacy than oral delivery but is unlikely to be so high as to produce side-effects

At the present time, tizanidine is only available in oral form – there are no competing patch or tape-type products. The US market for muscle relaxants in 2020 was valued at around USD 961 million. After successful Phase 1a tests, in April 2017, the company concluded a development and sales licensing agreement with Cipla USA, the wholly owned subsidiary of the major Indian pharmaceuticals company Cipla, covering the global market excluding the US and 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 in 2017 and appears to have agreed to milestone payments of up to USD30 million and, after launch, stepped royalties in proportion to sales. In January 2018, it was announced that supplementary Phase 1a' tests were in line with expectations. In addition, in September 2019 the company announced that Phase 1b (PK) tests on animals had successfully cleared all standards.

The plan was then for Cipla to lead Phase 2 trials for about 6 months from mid-2020 to investigate the pharmacological effect and drowsiness or other side-effects of dose increases on a small number of patients. However, due to the effects of Covid-19 infections the transfer of technology to produce the test drug was delayed, and additionally Cipla changed its CNS development strategy during 2020 to put more stress on licensing out. As a result, while going ahead with the preparations for Phase 2 the company is in discussions with Cipla on how to proceed.

Appearances suggest that MEDRx is looking for a sub-licensee, but it is possible the company is seeking to secure the funds necessary to itself finance all or part of Phase 2

No determination has been made between MEDRx and Cipla on how to proceed. We assume that the original agreement with Cipla stipulates that they are wholly responsible for financing of all development and commercialisation from Phase 2 onwards. Appearances suggest that Ciplais looking for a sub-licensee, but it is possible the company is seeking to secure the funds necessary to itself finance all or part of Phase 2.

<Changes to use of funds – selective concentration>

The last two financings were unable to raise sufficient funds for the development of lidocaine tape in Europe

In the past two years MEDRx has gone to the markets twice for financing (see table below). It sought around JPY2,067 million and was able too raise JPY1,663 million. This was enough to cover the urgent development of fentanyl tape and the completion of a microneedle test facility, but was insufficient to fund lidocaine tape in Europe.

The last two financing programs

Issue date	No. 15 new share options 2019/12/9	New share issue and No. 17 options 2020/8/13
Amount targeted	JPY938 mil.	JPY1,129 mil.
Initial uses	①Fentanyl tape pre-clincial (JPY40 mil.)	①MN test facility upgrade - bio-safety, etc. (JPY480 mil.)
	②Fentanyl tape clincial trials (JPY625 mil.)	②Tests to acquire "accident prevention" label for fentanyl tape (JPY418 mil.)
	③Dev. Of lidocaine tape for Europe (JPY273 mil.)	③Dev. Of lidocaine tape for Europe (JPY220 mil.)
Amount raised	JPY736 mil.	JPY927 mil.
Actual uses	①above, JPY40 mil. And ②above, JPY696 mil. ③Not disbursed	① Completed at JPY132 mil. ② To JPY164 mil. ③ Not disbursed Plans to use the remaining JPY631 mil. For tests on fentanyl to acquire accident prevention label

Source: Compiled from MEDRx IR documents

Selective concentration

Development of the lidocaine tape market in Europe has been suspended

Elsewhere, MEDRx had been looking to sell its lidocaine tape formulation in Europe. It has already had meetings with a European regulator (BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte) and has discussed and confirmed a data package required for a new drug application. The five major European countries (Germany, France, the UK, Italy and Spain) were estimated in 2018 to have a potential lidocaine adhesives market of approximately JPY23 billion. Central to this market is Versatis®, produced by Grunenthal. We infer that MEDRx was hoping for sales of several billion yen. However, the off-label use of lidocaine tape has recently been banned in Europe and it seems the market is shrinking. In addition, Europe requires a different set of tests to the US and further finance is needed to fund this. MEDRx has now suspended the development of lidocaine tape in Europe and has decided to channel the funds raised to pipelines ①-③ which were recently announced.

3. Revisions to forecast results

While there is no change to forecast sales revenue, costs are likely to rise due to new product developments and progress in the miconeedle project

On May 18 2021, the company released revisions to its forecast results for 2021 along with its financing plan. There is no change to its sales projection of JPY327 million. Within this total, sales of Iodocoat ointment come to JPY7 million, a deferred milestone payment from Cipla comes to JPY220 million and a milestone payment from DWTI for the Lydolyte approval comes to JPY100 million. Lydolyte licensing-out revenue is not quantified. Initially, R & D expenses in 2021 were expected to remain at the 2020 level of JPY945 million to fund the start of clinical trials of memantine tape and the development of fentanyl tape. In fact, however, the cost of developing the chronic pain treatment MRX-6LDT (diclofenac-lidocaine tape), and the cost of animal tests to study the feasibility of microneedle vaccine preparations for infectious diseases, added a prospective JPY225 million for the year. That was enough to create further forecast losses at the operating level, the recurring profit level, and the net profit level.

Revised results forecasts

(JPY mil.) (JPY)

	Sales	Op. profit	Rec. profit	Net profit	EPS
Initial forecast (Feb. 10)	327	-886	-890	-892	-45.33
Current forecast (May 18)	327	-1,111	-1,115	-1,117	-56.75
Change		-225	-225	-225	
Last period actual	115	-1,130	-1,152	-1,114	-68.61

Source: MEDRx: Notice of revisions to results forecast, May 18, 2021

Following completion of application, Lydolyte licensing-out now under discussion

The pipelines for which progress was not mentioned above are lidocaine tape (Lydolyte) and memantine patch (MRX-7MLL). For Lydolyte、which is now the subject of an NDA, the company is still energetically seeking a licensee, although the negative effects of Covid-19, and increased price competition, have put something of a damper on the sales growth of its rival predecessor, ZTlido®

Sales trend of ZTlido®

(million USD)

2018	2019				2020				2021
4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q
2.6	2.9	4.7	3.8	9.7	5.2	5.8	7.8	7.5	7.0
				2019annual				2020annual	
				21.0				26.3	

Source: Compiled from Sorrento securities report filings

Preparations now in hand for memantine tape (MRX-7MLL) clinical trials application within the year

With the arrival of diclofenac-lidocaine tape (MRX-6LDT) and the further development of microneedle vaccines to treat conagiious diseases, MEDRx has made enoromous strides to move to the next stage

The company completed MRX-7MLL pre-clinical tests during 2019, and is currently preparing to submit an IND (clinical trials application). Since Phase 2 and Phase 3 are not required, the company is now looking for a subcontractor to take on production through to commercial manufacturing. Discussions to that end have been interrupted by the imposition of controls on travel between the US and Japan due to COVID-19. As soon as the test drug has been produced the company will submit a clinical trial application, possibly by the end of 2021. Once the IND has been accepted, two-stage pharmacokinetic studies and bio-equivalence tests will be undertaken, with submission of a new drug application scheduled for 2023 or after.

4. Conclusions

Since terminating its most promising product, oxycodone tape (MRX-1OXT), in November 2019, MEDRx has started to develop fentanyl tape (MRX-9FLT) and has submitted an application for the lidocaine tape, Lydolyte. However, both products face considerable competition from generics, and fentanyl tape is targeted at cancer pain and thought unlikely to be more widely indicated.

However, in May 2021, a product emerged that could finally be widely used in the chronic pain market and which had no analogous predecessor. This is diclofenac-lidocaine tape (MRX-6LDT), a major development drug to replace oxycodone tape. In addition, steady progress has been made in the development of microneedle vaccines for contagious diseases. These two products will take time to develop but have the potential to become major.

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