MEDRx Co., Ltd.

(4586 Mothers) Issued: Sept. 28, 2021

Next Major Product Has Blockbuster Potential

2H/2021: Development work restarts

R&D outlays in the first half of 2021stood at JPY331 million, below the level of the same period of the previous year. This was due to a number of factors including a delay in the start of clinical trials for memantine patches due to lack of capacity on the part of the contractor manufacturing the clinical trial product, the effect of the COVID-19 pandemic, and a delay in the transfer of technology to the manufacturer of fentanyl tape. Phase-2 trials for tizanidine tape have not started yet due to a change in strategy at the company's partner. In the second half, however, the company thinks these projects will be ready to re-start. Pivotal BE trials on fentanyl tape will start within the year and are scheduled for completion in the Spring of 2022. As for memantine patches, as soon as production of the investigational drug is completed an application for clinical trials will be submitted, with pilot PK tests (Phase-1a) starting during 2021. For tizanidine tape the plan is to re-start Phase-2 when a decision is made on the sub-licensee.

Next major product has blockbuster market potential

MEDRx's next major product is diclofenac-lidocaine tape (MRX-6LDT), from which the supplementary or synergistic effects of diclofenac and lidocaine, which have different pain mechanisms, can be expected. Pre-clinical studies are expected to start soon. Its development will probably be directed initially at osteoarthritis of the knee. In the US there are an estimated 9 million patients receiving treatment for this condition. The annual cost of non-steroidal analgesics for such patients comes to USD442, which makes for a total value of USD4 billion (JPY436.4 billion). Even one-quarter of this is worth JPY100 billion, making MRX-6LDT a blockbuster prospect in the market. Hisamitsu Pharmaceuticals is at the same time developing a diclofenac tape, HP-5000, for the treatment of knee osteoarthritis. It seems likely that, just as HP-5000 is launched and the market begins to appreciate the benefits of diclofenac tape, MEDRx's diclofenac-lidocaine tape should be completing Phase-2 and heading for a licensing-out.

New developments in microneedles project

Research and development is currently going on worldwide into the preparation of vaccines using microneedles, and there are several studies into the administration of COVID-19 vaccines using microneedle patches. MEDRx's microneedle test facility was completed in April 2020 and upgraded in January 2021 to allow the handling of pathogenic bacteria, viruses and genetically modified organisms used in vaccines, etc. The company is now seeking to confirm the effectiveness and safety of vaccine microneedles, and is also looking at feasibility, with a view to tying up with a pharmaceutical company or vaccine venture. In this connection, in August 2021, the company disclosed it had undertaken a feasibility study in which FunPep's antibody-inducing peptide (AJP001) was applied to MEDRx microneedles. It is hoped that in 2022 the results of animal testing will allow the company to move to the next stage.

Follow-up Report

Fair Research Inc.
Tsuyoshi Suzuki

Company Outline	
Location	Kagawa Pref.
President	Yonehiro Matsumura
Established	January 2002
Capital	JPY7,679 mil.
Listed	Feb. 2013
URL	www.medrx.co.jp
Industry	Pharma
Employees	22 (consol.)
Key Indicators (Sept. 27, 2021)	
Share Price	175
52-Week Low	167
52-Week High	327
Shares Issued	22,695,100
Trading Unit	100 shares
Market Cap	JPY3,972 mil.
Forecast div.	0
EPS (est)	JPY-53.3
PER (est)	na
BPS (actual)	JPY91.98
PBR (actual)	1.90X

Note: On basis of shares outstanding, excl, treasury shares

Results	Revenue JPY mil	YOY %	Op. income JPYmil	YoY %	R.P. Income JPYmil	YoY %	Net Income JPYmil	YoY %	EPS JPY	Share Price (JPY) High	Share Price (JPY) Low
18/12 Actual	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	697	301
20/12 Actual	115	-32.2	-1,130	na	-1,152	na	-1,114	na	-68.6	426	425
21/12 Forecast	327	184.2	-1,111	na	-1,115	na	-1,117	na	-53.3	698	160
20/6 1H Actual	15	-47.7	-706	na	-713	na	-713	na	-23.9	433	158
21/6 1H Actual	7	-50.4	-471	na	-483	na	-473	na	-47.1	327	199

Company Outline – management philosophy

A venture company engaged in developing transdermal absorption formulations

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 orally administered 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 drugs orally 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.

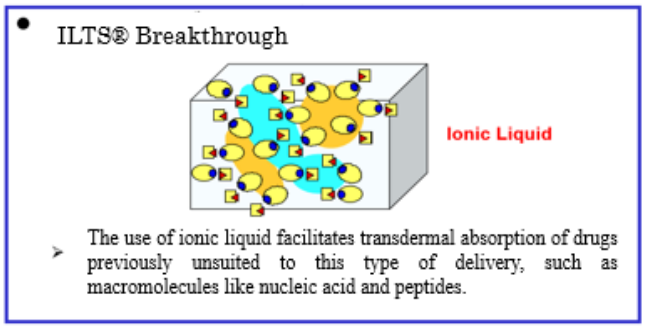
The company has proprietary technologies, giving its products a higher probability of success than for other new drug discovery businesses

The MEDRx business model is also distinctive in two ways:

(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.



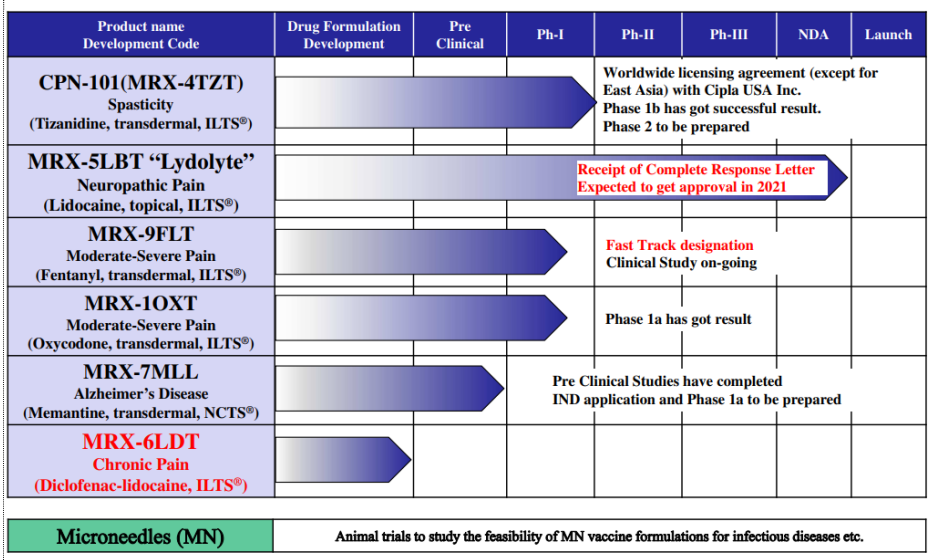
（Source）MEDRx company briefing materials

Another notable 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. The company 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 primacy 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 clinical trials, 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) Company briefing materials, August 2021

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

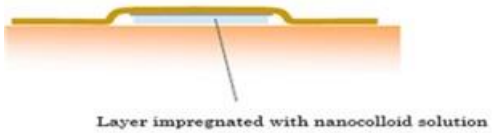
The main products to which the ILTS® technology is applied are tizanidine tape (CPN-101, MRX-4TZT), which has been successfully licensed out to Cipla Corp. lidocaine tape (MRX-5LBT), fentanyl tape (MRX-9FLT), oxycodone tape (MRX-1OXT) and the newest product, diclofenac-lidocaine tape (MRX-6LDT).

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 reducing pharmacologically active components to 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 microneedle technology to provide “vaccination patches”

NCTS®: Nano-sized Colloid Transdermal System - Image



(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 an “attachable vaccination”.

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

MEDRx’s microneedle array

(Source) MEDRx company briefing materials

1. Development progress in the first half of 2021

In the first half of the year some delays were seen in development

The company explained the development status of each of its pipelines in a briefing in August 2021, and it appears there are pipelines where development has fallen behind because of the effects of COVID-19. However, the company also explained that its next big product, MRX-6LDT, would very soon be starting pre-clinical tests, and that, in the microneedle business, another product expected to grow in size, they would be starting a feasibility study with FunPep Co. on the formulation of antibody-inducing peptide microneedle products.

(1) MRX-5LBT “Lydolyte”

CRL received with respect to the completed lidocaine tape submission

MEDRx submitted a new drug application for the lidocaine tape formulation MRX-5LBT (Lydolyte) to the FDA in August 2020, and this was accepted in October of the same year. On July 5 of 2021, MEDRx announced that the company had received the Complete Response Letter from the FDA, and further that it was required to deal with some questions posed by the FDA. According to MEDRx, there was no need for further trials. Having dealt appropriately with the FDA’s questions, the company posits no change in the schedule for receiving approval within 2021.

Since additional tests were not required and the company’s responses to the FDA’s questions were accepted, there has been no change in the outlook for approval within this year

The US market for lidocaine tape continues to grow, in terms of the number of tapes, at a rate of around 5% per year to a current size of 95-100 million tapes. Sales of ZTlido®, which was launched ahead of MRX-5LBT (Lydolyte) in the fourth quarter of 2018, total in excess of 6 million tapes annually with a target of 10 million for a market share of 10%. MRX-5LBT (Lydolyte) is expected to achieve sales of JPY2-3 billion within 2-3 years of launch. MEDRx is now looking for a sales tie-up partner.

Lidocaine tape market now growing at 5% per year, with sales expected to reach JPY2-3 billion in 2-3 years after launch

Sales of ZTlido®

USD-mil

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

(Source) Fair Research Inc. from Sorrento Therapeutics’ securities reports

(2) MRX-4TZT（CPN-101）

Preparations for tizanidine tape Phase-2 have been at the preparatory stage for some two years

Preparations are now underway for Phase-2 clinical trials for tizanidine tape, MRX-4TZT (CPN-101), which was licensed out to Cipla Limited in 2017. Phase-2 was initially scheduled to start some time in 2020 but testing delays due to COVID-19, and a change in strategy on the part of Cipla (sub-licensing in the CNS area) meant that Phase-2 could never really get underway. MEDRx is now pursuing Phase-2 preparations and at the same time discussing with Cipla the way forward. It is thought that MEDRx will be responsible for Phase-2 preparations and that Cipla will sub-license a third party to undertake the actual trials.

Phase-2 to start once a sub-licensee has been identified

(3) MRX-9FLT

Fentanyl tape received fast track designation from the FDA in July 2021

MRX-9FLT, a fentanyl tape under development for the treatment of cancer pain, is a novel fentanyl patch which incorporates MEDRx’s own technology for reducing and preventing misuse. An application for authorisation to conduct trials was submitted in March 2020 and in September of that year it was ascertained that the patch provided the same bloodstream concentration as the reference drug, Duragsic®, and preliminary confirmation was made of the product’s usefulness in preventing accidents arising from misuse. Regarding this as an important function of the fentanyl patch the FDA gave it fast track status in July 2021. Development is currently proceeding with comparative trials (Pivotal BE trials) to demonstrate bio-equivalence with reference products, and to verify the misuse prevention function. Insufficient capacity at the company (Tapemark) delegated to produce the tape led to a shortage of clinical trial materials in the first half

Delays in the supply of clincial trial materials in the first half led to delays in

development but Pivotal BE tests are scheduled to begin within the year

of 2021, but Pivotal BE studies will begin within the year for completion in the Spring of 2022. Subsequently, after consultations with the FDA on trial design, the company intends to move on to misuse prevention tests and, in the first half of 2023, to submit a new drug application. It also seems possible that the company could license out after finalising the design of tests for misuse prevention.

(4) MRX-7MLL

For memantine patches, technology transfer needed for manufacturing investigational products has been delayed due to the effects of COVID-19

Once the manufacture of investigational materials is complete the company plans to submit an application to conduct tests and, during 2021, to start pilot PK tests (Phase-1a)

MRX-7MLL is a memantine treatment for Alzheimer's rendered into patch form using MEDRx's NCTS® technology. This confers several advantages: drug administrations can be visually confirmed, and administration frequency can be reduced from once a day using the oral preparation to once every three or seven days. The entry of generics has reduced the value of the US oral memantine market from JPY75 billion to around JPY12 billion. However, MEDRx believes that the advantages of the patch form will be recognised, that there is no competition from generics, and that the market will accept a relatively high price. MRX-7MLL completed pre-clinical studies in 2019 and preparations are now ongoing for submitting an IND (application to conduct clinical trials). Since Phases 2 and 3 are not required the company is now involved in selecting a manufacturer to whom it could delegate production from the outset through to commercial production. However, technology transfer has been delayed by the COVID-19 pandemic and restrictions on travel between the US and Japan. The plan now is to submit an application for authorisation to conduct trials once trial drugs have been manufactured and, during 2021, to make a start on pilot PK tests (Phase-1a).

Elsewhere, progress has been made in the development of diclofenac-lidocaine tape (MRX-6LDT) and microneedle arrays. Both of these have the potential to become major pipelines. We look at them in the next section.

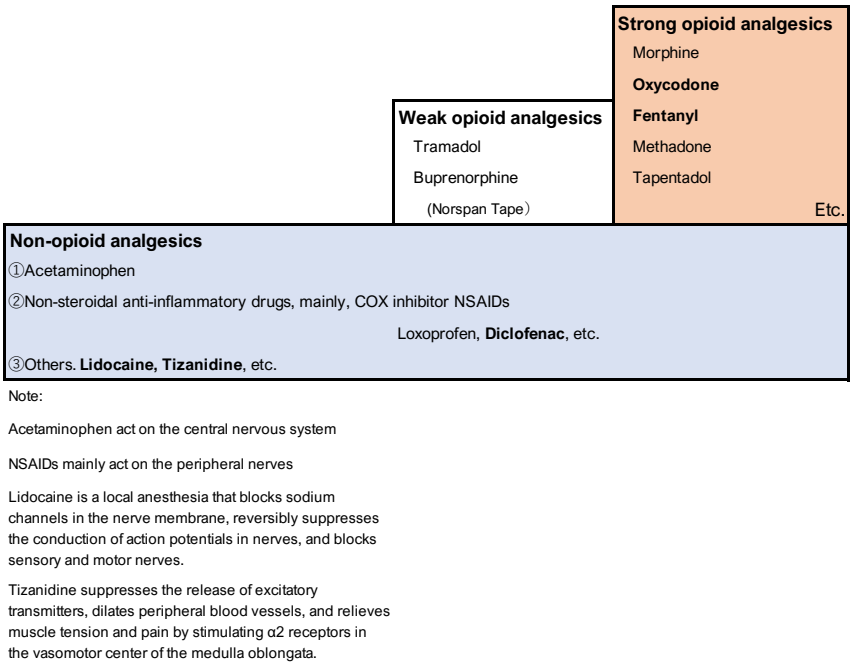
2. Market potential for MRX-6LDT, the company's next major development

Plans for a major development candidate, diclofenac-lidocaine tape (MRX-6LDT), emerged in May 2021

On May 18 2021, MEDRx announced plans to develop a new pipeline, MRX-6LDT. This is a tape product using MEDRx's own transdermal drug technology, ILTS®. The tape allows simultaneous transdermal absorption of both the anti-inflammatory analgesic diclofenac, and the local anesthetic, lidocaine. At present there are no tapes or patches providing both diclofenac and lidocaine, and no-one else is developing one. At its briefing in August 2021 the company announced that pre-clinical studies were about to begin.

At a briefing in August it was revealed that pre-clinical studies would begin soon

＜Ref: Types of analgesic＞

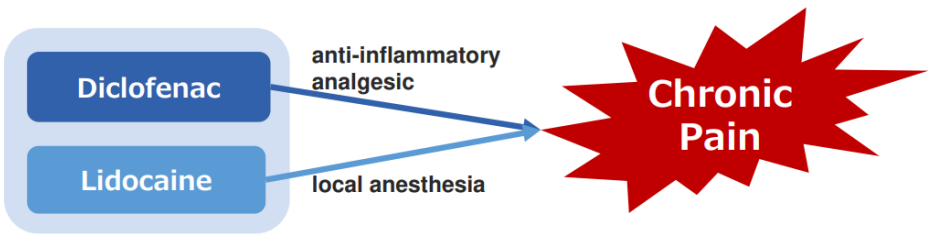


(Source) Fair Research Inc. using various materials

＜Characteristics of MRX-6LDT＞

MRX-6LDT contains diclofenac and lidocaine, which work on pain in different ways, and the expectation is that they will have a supplementary or synergistic therapeutic effect (see illustration below).

MRX-6LDT contains diclofenac and lidocaine, which work on pain in different ways, and the expectation is that they will have a supplementary or synergistic therapeutic effect. And there are no analogous predecessors



(Source) Company briefing materials, August 2021

Hisamitsu Pharmaceutical is developing in the United States the HP-5000 diclofenac patch, which provides a high

By using ILTS® technology, MRX-6LDT aims to achieve a concentration of diclofenac dermal penetration that is several times higher than that of conventional diclofenac patches widely used in Japan and other countries. Hisamitsu Pharmaceutical is developing the HP-5000 diclofenac patch in the US to treat the pain of knee

level of diclofenac in the bloodstream

The aim is for MRX-6LDT to provide an elevated blood concentration of diclofenac and for the amount of lidocaine to be several times that of Lydolyte

osteoarthritis. Hisamitsu announced in November 2019 that in Phase-2 trials covering knee osteoarthritis, high levels of the drug were delivered to the affected part, with results pointing to efficacy and safety. Additionally, in March 2021, Hisamitsu received approval in Japan for its diclofenac patch (ZICTHORU® tape for cancer pain). This tape contains 75mg of diclofenac, about 5 times the concentration found in commercially available OTC patches. The diclofenac content of HP-5000 has not been released but we assume it might be about the same as ZICTHORU® tape. MEDRx has begun to develop MRX-6LDT with the aim of delivering a high concentration of diclofenac to the affected area.

On the other hand, regarding lidocaine, it seems that MEDRx is considering a formulation with a transdermal penetration amount that is several times higher than that of Lydolyte (lidocaine tape), which is currently under NDA application. Even at several times the level of Lydolyte, it will not reach the blood concentration at which side effects occur with administration by injection, so it is expected that sufficient tolerability will be ensured.

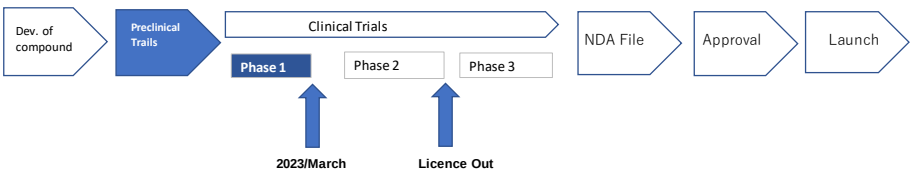
＜Development schedule＞

Formulation development completed

The plan now is to undertake pre-clinical Phase-1 for completion in March 2023

Phase-2 will then be undertaken and MRX-6LDT will be ready for licensing out, just as HP-5000 has pioneered the market

Formulation development for MRX-6LDT has now been completed. Pre-clinicals will commence shortly and it is planned to carry out Phase-1 clinical trials in 2022. At Phase-1, safety and tolerability will be ascertained, as well as confirmation of drug absorption (blood concentration, etc.). We see Phase-1 trials being finalized in around March 2023, following which, in Phase-2, three or so clinical indications will be selected to ascertain responses by administering the drug to several dozen cases per indication for 2-3 months. We assume the company is intending to license out after Phase-2 results have been confirmed (2024 or after). Since Phase-3 trials for HP-5000 are scheduled for completion in December 2022 we imagine its sales in, probably 2024-2025. That may provide a tail wind for the diclofenac patch market for the treatment of osteoarthritis of the knee and just the right timing for a licensing-out of MRX-6LDT.



(Source) MEDRx, from supplementary explanation for capital raising, May 2021

＜Clinical indications＞

While there has as yet been no announcement it seems likely that the first indication will be osteoarthritis of the knee

With that in mind the first indication to be targeted will probably be osteoarthritis of the knee. The difficulty of developing analgesics was highlighted in the case of the Etoreat® tape, which failed because of reliance on how individuals feel as the endpoint measuring drug effectiveness. Individuals feel pain differently and allowing for that can be the difference between success or failure in drug development. The level of pain from osteoarthritis of the knee is said to be easier in this respect. It seems very likely that development will start with this and, if successful, will expand to lower back pain, for which major demand is now served by Oxycodone, and other indications.

With osteoarthritis of the knee the last line of therapy is surgery, but before that point is reached, pain relief is the main treatment using mainly opioids and NSAIDs

The last line of treatment for knee osteoarthritis is currently surgery for replacement with artificial joints (regenerative medicine with autologous cell culture is also available but is more expensive). Before reaching the surgery stage the main line of treatment is pain relief. In the last ten years opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have played a major role and are used by most patients. Opioids, however, are addictive and can lead to abuse. Likewise, long term use of NSAIDs can give rise to side-effects related to the digestive system and cardiovascular system. There is thus a need for the development of drugs with a new action mechanism.

Development of new drugs is underway, but the development of the anti-NGF antibody, which has received the most attention, has experienced setbacks

At present, development of a number of new drugs is underway. The development of anti-NGF antibodies is attracting the most attention, but with a chequered history Astra-Zeneca 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 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.)

For the time being opioids and NSAIDs will continue to be the key therapy

In addition, studies have been done into a radical treatment by directly administering m-RNA of the cartilage-inducing transcription factor RUNX1 which induces the regeneration of knee cartilage into the knee joint. However, research is still in the early stages.

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.

＜Estimating the size of the US market＞

There is data showing that around 4% of the US adult population is receiving treatment for osteoarthritis of the knee

There are 54 million patients with arthritis in the US, of whom an estimated 32.5 million have osteoarthritis (CDC: Osteoarthritis Prevalence and Burden, 2015). The most prevalent form of osteoarthritis is osteoarthritis of the knee, with an estimated 14 million individuals having symptoms (2016). However, those with mild symptoms do not necessarily seek treatment. In fact, the proportion receiving treatment is an estimated 4% of the US adult population. （「Real-world Healthcare Resource Utilization and Costs among US patients with Knee Osteoarthritis Compared with Control 」ClinicoEconomics and Outcomes Research, May 2021）.

The US adult population stands at 255 million (2019), of whom we assume 88% have some form of health insurance. We can therefore say that an estimated 9 million patients receiving treatment are insured.

Therefore, an estimated 9 million patients are receiving treatment

Number of Patients with treatment of Knee OA	9.0	million
<Prepositions>		
US population	328	million
of which Adults	255	million
Healthcare insurance coverage	88%	
Prevalance of Knee OA with treatment	4% (/Adluts)	

(Source) Fair Research Inc. using various materials

On the other hand, average annual medical costs per person are estimated at USD4,674. Drug costs come to USD3,255, non-selective NSAIDs such as diclofenac to USD442, and opioids to USD727.

Annual drug costs per patient are USD3,255, of which USD442 is for non-selective, non-steroidal agents like diclofenac

Knee OA-related Costs per patient per year

		(USD)
Total Medical Cost	Mean	4,674
Total Pharmacotherapies of Interest	Mean	3,255
of which		
Nonselective NSAID	Mean	442
COX-2 inhibitors	Mean	150
Intra-articular(IA) Corticosterois	Mean	616
Non-IA Corticosteroid	Mean	309
IA Hyaluronic Acid	Mean	1,012
Non-Acute opioids	Mean	727

(source) Fair Research compiled based on Bedenbaugh et al. "Real-world Healthcare Resource Utilization and Costs among US Patients with Knee Osteoarthritis Compared with Controls" ClinicoEcomomics and Outcomes Research 2021 May

Multiplied by the number of patients the value of the market for non-selective non-steroidal agents comes to USD4 billion

Modeling the market by multiplying the annual cost per patient by the number of patients receiving treatment yields an overall value for drugs of USD29.2 billion (JPY3,214 billion). Of that total, USD4 billion (JPY4,364 billion) is for non-selective, non-steroidal agents, and USD6.5 billion (JPY718 billion) for opioids. If the MRX-6LDT target is one quarter of the non-selective NSAIDs market, then it equates to a market with a value in excess of JPY100 billion. Postulating a price per MRX-6LDT patch of USD10, and assuming usage of one patch per day per patient brings annual expenditure to USD3,650. If 3% of the 9 million patients being treated for osteoarthritis of the knee used MRX-6LDT daily the total outlay would come to USD980 million, equating to a JPY100 billon market.

The market being targeted by MRX-6LDT could have blockbuster potential

Knee OA related Costs (US)

		(billion USD)	(billionJPY)
Total Medical Cost	Mean	42.0	4,615
Total Pharmacotherapies of Interest	Mean	29.2	3,214
of which			
Nonselective NSAID	Mean	4.0	436
COX-2 inhibitors	Mean	1.3	148
Intra-articular(IA) Corticosterois	Mean	5.5	608
Non-IA Corticosteroid	Mean	2.8	305
IA Hyaluronic Acid	Mean	9.1	999
Non-Acute opioids	Mean	6.5	718

1USD=110JPY

(Source) Compiled by Fair Research

3. New developments in the microneedle business

MEDRx has continued to develop microneedles for the last 16 years with the aim of providing a means of drug administration which is both easy and secure. This necessitates painless vertical insertion of the needle as far as the dermis, the key to which is the shape of the needle tip and the provision of an applicator. The company has patented the applicator in Japan and China, and aims to secure rights in the US, Europe, Brazil and India.

MEDRx envisages using the microneedle mainly for vaccinations, since an effective vaccine load is as small as tens of micrograms, and therefore suitable for microneedle administration. In addition, microneedle administration provides slow release, thereby enhancing antigen presentation capability which is important for vaccines.

R&D is being carried out across the world into vaccines using microneedles

R&D is currently being carried out around the world into vaccines using microneedles, including a number of research projects on the use of microneedles for vaccinating against COVID-19.

Companies developing microneedle vaccines

Company	Type of Micro Needle	Vaccine
Micron Biomedical	Dissolving MN	Inactivated rotavirus
3M(Kindeva)	Hollow MN	Cancer vaccines
BD technologies (BS Soluvia)	Stainless steel MN	Influenza
Flugen	Metal MN	Influenza
Debiothech	Hollow MN	COVID-19
Verndari(Vaxipatch)	Stainless steel MN	Influenza, COVID-19
Nanopass(MicroJet)	Silicon MN	Influenza, Polio, Cancers, Hepatitis B, COVID-19, Varicella-Zonster
BioSerenTach Inc.	Dissolving MN	Vaccine
Sorrento therapeutics(Sofusa)	Nanotopographical imprinted MN (coated)	Immuno-oncology
Vaxxas (Nanopatch)	Coated MN array patch	Influenza, COVID-19
Quadmedicine	Dissolving MN	Influenza, Canine Influenza
Vaxess	Dissolving MN	Influenza, COVID-19, skin cancer
Raphas	Dissolving MN	HPV, Polio, Tdap, HBV, IPV, Hepatitis B

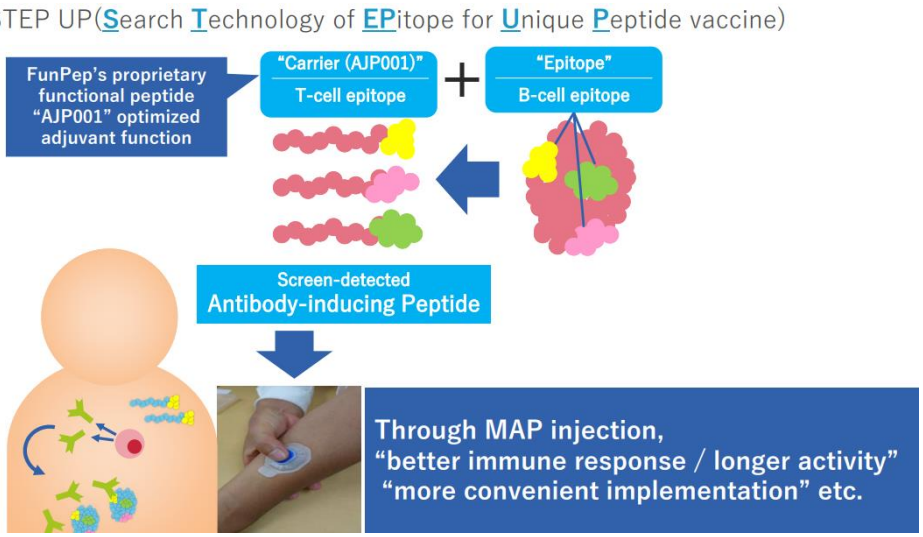
（source）Menon, I. et al, "Microneedles: A new Generation Vaccine Delivery System" Micromachines 2021 Apr.

However, few of these have reached the clinical trial stage

The problem is that a structure and system is needed to ensure high volume and stable supply

The source for the above table, “Microneedles: A New Generation Vaccine Delivery System” (Micromachines 2021, Apr.), notes that 236 papers published since 2017 were found in a PubMed search using the keywords “microneedle vaccine”. However, there were very few papers dealing with clinical trials. The reason for this is that in the vaccine business high volumes and stable supplies are necessary and, in order to enter clinical trials, it is necessary to consider large-scale manufacturing in anticipation of commercial production.

The mega-pharmas themselves have little interest in developing medical instruments and, although their subsidiaries may get involved in vaccine development, are unlikely to develop or produce microneedles.

MEDRx was planning its own volume production plant but this was put on hold and instead the company completed a testing facility	MEDRx drew up a detailed plan for mass production and, in order to expedite discussions with some of the major pharmaceutical companies, decided to build a high-volume plant. In April 2018, it announced a capital raising plan for this purpose. However, the capital raising failed to make headway and, in November 2018, the company put the full project on hold, opting instead in 2019 for the provision of a testing facility as an interim objective. This facility was up and running in April 2020, manufacturing the product to GMP standards for administration to human subjects in clinical trials. The company then, in July 2020, decided to upgrade the facility to handle pathological bacteria and viruses used in vaccines, along with genetically modified organisms. On January 28, 2021, the upgrade was completed with an emphasis centering on "diffusion prevention and other biosafety measures".
Now undertaking feasibility studies with several Japanese and overseas pharmaceutical companies and vaccine ventures	The company is now looking for an operational tie-up by conducting feasibility studies (animal experiments) with 5-10 Japanese and overseas pharmaceutical companies and vaccine ventures. In August 2021 it revealed that it had conducted a feasibility study on a formulation in which FunPep's antibody-inducing peptide (AJP001) was applied to MEDRx microneedles. **The FunPep antibody-inducing peptide and microneedle formulation**  (Source) MEDRx company briefing, August 2021
Progress from the experimental stage to the next stage could be made in 2022	Further progress from the experimental stage could be made in 2022, so a continued watch is warranted.

4. Status of fund raising

In August 2021, the exercise of No. 20 new share acquisition rights was completed

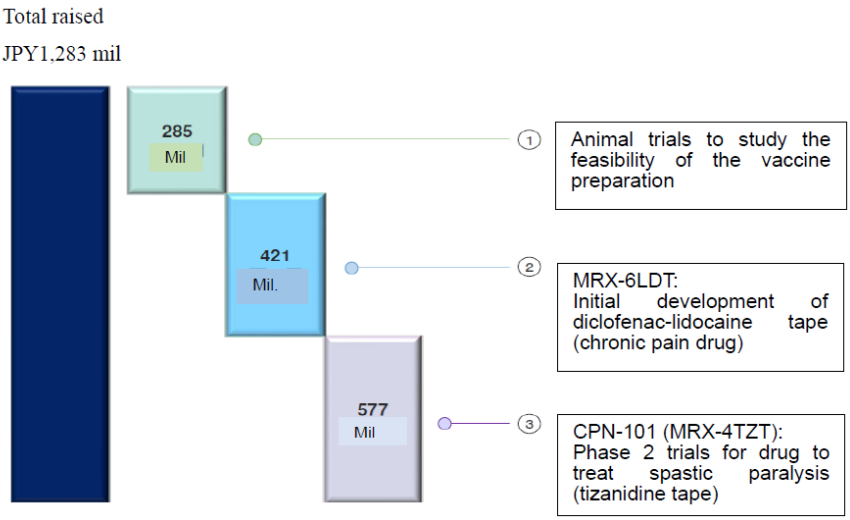
In September 2021, the No. 21 new stock acquisition rights were converted to MS warrants

On May 18 2021, alongside the emergence of MRX-6LDT, MEDRx announced a new fund raising plan with a planned total procurement of JPY1,283 million. Under the original plan, the company would raise JPY550 million from the issue of corporate bonds and subsequently preferentially redeem the bonds using moving strike (MS) warrants (No. 20 new stock acquisition rights). It would then raise a further JPY120 million (total: JPY670 million). In addition, the plan was to raise JPY627 million from the issue of new stock acquisition rights (No. 21). Further, if the amount raised by the MS warrants (No. 20 stock acquisition rights) was less than JPY 550 million due to exercise price adjustment, then the scheme called for the conversion of the No. 21 new stock acquisition rights to MS warrants and the preferential allocation to the redemption of unredeemed corporate bonds.

By August 25 2021, the exercise of the No. 20 new stock acquisition rights was completed and JPY555 million thereby raised. The amount raised was only about level with the redemption of the previously issued corporate bonds (JPY550 million), below the scheduled procurement amount. On September 10, 2021, therefore, the No. 21 new stock acquisition rights were converted to MS warrants.

The initial plan for the use of funds raised is depicted in the chart below, in the order of fund allocation preference: ① Animal experiments to determine the viability of microneedle vaccine preparations; ② Early development of MRX-6LDT (pre-clinical and Phase-1); ③ CPN-101 (MRX-4TZT) tizanidine tape: Phase-2.

Uses of funds raised under the fund raising plan announced in May 2021



(Source) MEDRx supplementary explanation for fund raising

MEDRx plans to cover the costs of the microneedle infection vaccine preparation, and outlays on early development of MRX-6LDT, but cannot cover the costs of tizanidine Phase-2

A successful sub-licensing of tizanidine tape could resolve this fund shortage because MEDRX should cover only the preparation stage of Phase-2

Looking ahead, if the No. 21 new share acquisition rights were exercised at around the current share price level (JPY167) we assume this would raise an estimated JPY310 million. Together with the exercise of No. 20 rights, the total would come to JPY860 million. This being the case, there would be sufficient funds to cover primary uses: ①The animal experiments to look into the feasibility of a microneedle vaccine preparation for infectious diseases, and ② Initial development of MRX-6LDT (pre-clinical Phase-1) However, it would not cover the costs of CPN-101 Phase-2. The amount available for allocation to ③ would be around JPY150 million. However, with a successful sub-licensing of CPN-101, while Phase-2 preparation costs (around JPY100 million for preparation of the investigational drug, etc.) would be borne by MEDRx, subsequent trial costs would probably be borne by the sub-licensee. Hence, the company is not at present under pressure of another fund raising.

There is no change to the sales forecast but costs are expected to swell on account of putative new product developments and advances in microneedle development

Supplement: 1H2021 corporate results and outlook for 2021

While the only sales in the first half of 2021 were recorded by Iodine Coat ointment (JPY7 million) the sales forecast for 2021 stands at JPY327 million. This includes the JPY7 million for Iodine Coat, the deferred milestone payment of around JPY220 million from Cipla, and the Lydolyte authorisation milestone of JPY100 million from DWTI. The figures do not reflect Lydolyte licensing-out income.

The R&D disbursements for the first half came to JPY331 million, a decline from the same period of the previous year. This reflects delays in the start of clinical tests for memantine tape and in fentanyl tape development. For the full 2021 year, expenditures in line with the previous year's JPY945 million were initially expected. However, development of the chronic pain treatment MRX-6LDT (diclofenac-lidocaine tape) and animal experiments to look into the feasibility of a microneedle vaccine preparation for infectious diseases generated costs of JPY225 million, pushing up actual disbursements to JPY1,170 million.

As noted above, sales in 2021 are expected to be JPY212 million higher than the previous year but, with R&D and other SG&A components expanding to JPY185 million, operating losses will total JPY1,111 million, on a par with last year's losses of JPY1,113 million.

1H 2021 results and full year expectations

(JPY-mil)

	1H2020	1H2021	2020	2021(comp. forecast)
Sales	15	7	115	327
Product sales	15	7	15	7
R&D income			100	320
SG&A	717	477	1,241	1,436
R&D,etc.	574	331	967	1,170
Others	142	145	274	266
Operating losses	-706	-471	-1,130	-1,111
Recurring losses	-713	-483	-1,152	-1,115
Net loss	-713	-473	-1,114	-1,117

(Source) MEDRx company briefing, August 2021

As of the end of June 2021, cash on the balance sheet stood at JPY2,252 million. JPY864 million was raised in the first half of 2021. This consisted of JPY49 million from the exercise in January of the No.17 new stock rights, the JPY550 million from the issue of corporate bonds, and that portion of the No. 20 new stock rights exercised in the first half. The completion of exercise of the No. 20 new stock rights was in August 2021, with JPY324 million being raised through the exercise of rights by June and JPY303 million in July-August.

Balance sheet at the end of June 2021

(JPY-mil)

		End Dec. 2020	End June 2021	Change	Note
Liquid assets		1,886	2,309	422	
	Cash	1,812	2,252	440	Raised 864 Acquisition of tangible fixed assets△1 Costs of clincal trials, etc.△424
	Others	74	56	△18	
Fixed asssets		410	381	△19	
	Tangibles	328	299	△28	
	Investments, etc.	82	81	△0	
Total asssets		2,297	2,690	392	
Liabilities		149	700	550	
	Liquid liabs	122	673	550	Bond issue 550
	Fixed liabs	27	27	0	
Net assets		2,147	1,989	△158	

(Source) MEDRx company briefing

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