MEDRx Co. Ltd.

（4586 Growth） Issued: Sept. 14 2022

Major problems overcome by “selective concentration”

Product development stagnates in 1H/2022

MEDRx explained the status of each of its pipeline products at a company briefing in August 2022. While there have been no product failures neither has there yet been great progress. Phase-2 clinical trials for tizanidine tape (MRX-4TZT, CPN-101) are now at the preparatory stage and details of supplementary tests for the lidocaine tape Lydolyte (MRX-5LBT) have not yet been finalised. The next trials for fentanyl tape (MRX-9FLT) and the memantine patch (MRX-7MLL) are due to begin. Going forward, in the context of limited product development funds, the company intends to reduce the number of products it develops at any one time. Instead, it will concentrate on products whose development promises an early payoff. Once a product starts to produce a certain level of returns it will move on to the next product.

“Selective concentration”

Within its “selective concentration” strategy the company’s top priority is the Lydolyte lidocaine tape, which is the closest to approval and market launch. The cost of supplementary tests will depend on the reply from the FDA but the tests proposed by MEDRx will cost just under JPY200 million, an amount which is already factored into its 2022 budget. The company’s next priority, given its advanced development and marketability, is tizanidine tape. The company has already decided to raise the necessary funds for further development by issuing new share subscription rights (the 24th such issue). The third priority will then be fentanyl tape or memantine patches. While commercial considerations would favour the latter, which uses the company’s NCTS®, in development risk terms, the former, which uses ILTS® would be preferred. About JPY200 million is likely to be spent this term on Pivotal BE tests for fentanyl tape, and this amount also has been budgeted.

Two major products after overcoming recent problems

As a result of the company’s policy of concentrating on selective goals, the next twelve months should see the approval and launch of the Lydolyte lidocaine tape, the receipt of milestone income of JPY100 million from DWTI, and possibly a licensing-out opportunity. A stabilisation of the company’s finances will thereby have been achieved. Subsequently, once funds have been secured to conduct verification tests on fentanyl tape’s accident prevention mechanism, and if those tests are successful, a licensing-out becomes a possibility. Tizanidine tape Phase-2 development will be funded by a new round of fund raising and, if successful, could lead to a further licensing-out in or around 2024 at the earliest, with the licensee conducting Phase-3 development. Fair Research believes MEDRx will overcome the “valley of death” syndrome faced by many ventures through “selective concentration” and will continue to see new out-licensing opportunities. Development of two major next-generation development products (Diclofenac Lidocaine tape MRX-6LDT and microneedles) is progressing, which we expect will lead to a further increase in corporate value.

Follow-up report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Kagawa Pref.
President	Yonehiro Matsumura
Established	Jan. 2002
Capital	JPY50 million
Listed	Feb. 2013
URL	www.medrx.co.jp
Industry	Pharma
Employees	21 (non-consol)
Key Indicators (Sept. 13, 2022)	
Stock price	JPY114
52-week low	JPY94
52-week high	JPY189
Shares outstanding	24,595,100
Trading unit	100 shares
Market cap	JPY2,779 mil
Dividend	0
Forecast EPS	-40.9
Forecast PER	na
Actual BPS	JPY61.72
Actual PBR	1.85X

Based on shares outstanding excl. treasury shares

Results	Revenue JPY mil	YoY %	Op. Profit JPY mil	YoY %	Rec.Profit JPY mil	YoY %	Net Profit JPY mil	YoY %	EPS JPY	Stock Price (JPY) High	Stock Price (JPY) Low
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 Actual	8	-92.7	-1,061	na	-1,066	na	-1,059	na	-49.6	327	126
22/12 Plan	289	nm	-1,002	na	-1,003	na	-1,006	na	-40.9		
21/6 H1 Actual	7	-50.4	-471	na	-475	na	-473	na	-23.9	327	199
22/6 H1 Actual	9	26.7	-374	na	-382	na	-381	na	-15.5	134	94

Company Outline & Philosophy

A venture company engaged in developing transdermal absorption drugs

In broad terms, the company is engaged in developing transdermal absorption formulations using the active ingredients of existing oral and injectable drugs. 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 are achieved by the following:

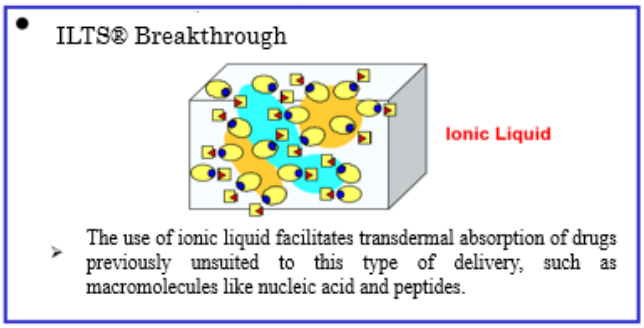
① Providing a consistent and sustained release of active ingredients: enabling the maintenance of a constant volume of the drug in the bloodstream.
② Little or no first-pass effect: while the efficacy of orally administered drugs can be reduced to 10-20% on passage through the liver, this is not an issue with transdermal absorption formulations.
③ Better medication compliance: suitable for patients who find it difficult to take 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 is the case in other new drug discovery businesses

The MEDRx business model is 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.



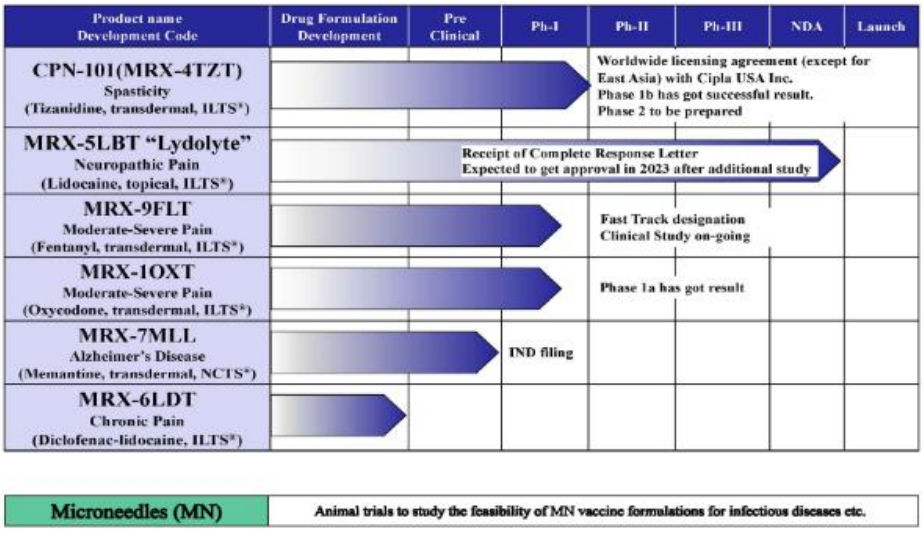
Source: MEDRx company briefing

A notable feature of MEDRx's ILTS® is that it has high built-in 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 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, mainly because of the size of the potential market.

In addition, winning approval in the US for formulations using existing drugs does not require the pre-clinical testing necessary to submit an application for a new drug (while not true in all cases, after Phase-1 clinical trials, Phase-2 can be omitted and the process moves directly to Phase-3). Also worth bearing in mind is that patch and tape-type drugs tend to command higher prices in the US than in Japan.

Main product pipelines



Source: Company briefing, August 2022

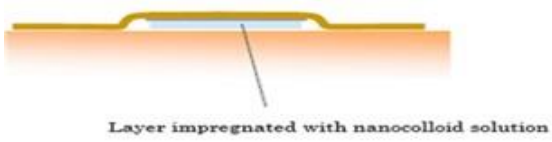
There are five product pipelines to which MEDRx has applied its proprietary ILTS® technology

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 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, enhances 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.

NCTS®: Nano-sized Colloid Transdermal System (image)



Source: Fair Research Inc, using company briefing

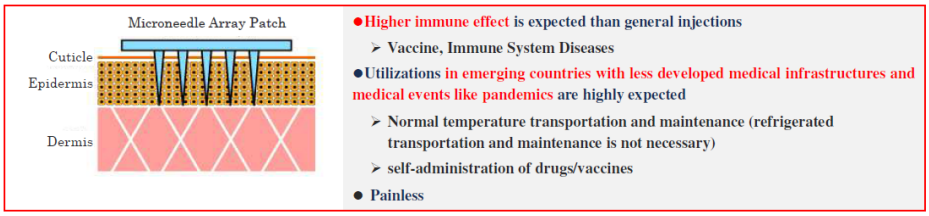
The company has developed microneedle technology to provide “vaccination patches”

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 drug. 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, preventing vaccine applied to the skin from penetrating. 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 with an applicator, allowing easy administration with finger pressure alone

Microneedle characteristics



Source; MEDRx company briefing

1. Status of each pipeline

Sluggish progess in product development

MEDRx explained the status of each of its pipeline products at a company briefing in August 2022. While there have been no product failures neither has there yet been great progress. Phase-2 clinical trials for tizanidine tape (MRX-4TZT, CPN-101) are now at the preparatory stage and details of supplementary tests for the lidocaine tape Lydolyte (MRX-5LBT) have not yet been finalised. The next trials for fentanyl tape (MRX-9FLT) and the memantine patch (MRX-7MLL) are due to begin. Meanwhile, much more time is needed for the realisation of such promising major projects as the MRX-6LDT lidocaine-diclofenac tape and microneedles.

Going forward, in the context of limited product development funds, the company intends to more efficiently deploy its financial and other resources by reducing the number of products it develops at any one time. Instead, it will concentrate on products whose development promises an early payoff. Once a product starts to produce a certain level of returns the company will move on to the next major development. Before considering the order in which selection and concentration are carried out, let's take a look at the current state of the pipelines. (Please refer to our Basic Report released on March 23 2022 for details of each pipeline.)

(1) Current status of MRX-4TZT (CPN-101)

Tizanidine tape (MRX-4TZT, CPN-101) was out-licensed to Cipla in 2017, and is currently being prepared for Phase-2 trials. The original idea was that Phase-2 trials would start in mid-2020 but delays caused by the COVID-19 pandemic and Cipla's decision to sub-license in the area of CNS meant that Phase-2 could not get underway.

Tizanidine tape has been stalled at the Phase-2 preparatory stage for more than two years

MEDRx then changed its policy to conduct Phase-2 trials partially or entirely at its own expense and is now in discussions with Cipla on how to proceed. MEDRx is of a mind to start Phase-2 by the end of the year and is considering paying the entire cost itself. If it does cover the entire amount itself, it is highly likely that the number of Phase-2 cases will be whittled down and that Phase-3 will be required before applying for approval. In this case, the probability is that there will be a licensing-out after successfully completing Phase-2. Phase-2 expenditures, after reducing the number of cases, would probably total JPY500-600 million. On August 22, 2022 MEDRx announced it was raising funds through the 24th issue of new stock subscription rights. The amount raised would be JPY737 million, with JPY557 million of that being allocated to Phase-2.

MEDRx planning to start Phase-2 under its own steam

Announced financing to cover Phase-2

Undertaking Phase-2 at its own expense raises the possibility of a buy-back of rights that were licensed out and it appears that this is part of the discussion with Cipla. Under the present agreement, with the commencement of Phase-2 Cipla is to pay MEDRx a milestone fee of USD2 million. However, it is possible that milestone payments could be partially offset by a rights buyback.

(2) MRX-5LBT "Lydolyte"

In August 2020 an NDA was submitted to the FDA for the Lydolyte lidocaine tape (MRX-5LBT), and in October of the same year the application was accepted. However, on July 5 2021 MEDRx received a Complete Response Letter from the FDA in which a number of questions were posed. MEDRx initially thought it could reply to these questions without the need for supplementary tests, and that approval would be granted in 2021. However, it became apparent in discussions with the FDA that a number of supplementary tests would be required in order to secure regulatory approval.

Supplementary testing required

Reference: In July 2021 the FDA issued a new "Draft guidance for transdermal adhesion systems." It describes the level of adhesiveness required and makes a number of points related to the tests, such as adhesive properties when exercising, sweating, or taking a shower, and resistance to peeling off when rubbed against clothes or bedding.

MEDRx now waiting for FDA response to plan for supplementary tests

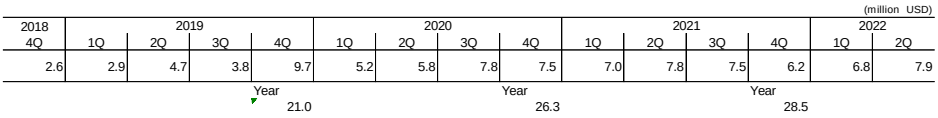
MEDRx has already submitted to the FDA a proposed design for the supplementary tests and is awaiting a response. The outlook now is that, if all proceeds smoothly, a response will be in hand by October 2022, that supplementary tests will commence within the year, ready for a re-submission in the first half of 2023, which would suggest receipt of approval in the same year and launch in the market in 2024.

If all goes well, application in first half of 2023

Lidocaine tape already exists in the US. In October 2018, the US company Scilex Pharmaceuticals Inc., a subsidiary of Sorrento Therapeutics Inc., launched ZTlido®, a lidocaine tape with superior features to Lidoderm®. ZTlido® has sales in excess of 6 million tapes a year and is aiming for 10 million tapes to give it a 10% market share. It is thought that Lydolyte (MRX-5LBT) could achieve sales of JPY2-3 billion 2-3 years after launch. MEDRx plans to re-start negotiations on a sales tie-up after re-submission to the FDA.

After re-submission, re-start of sales tie-up negotiations

ZTlido® sales



Source: Fair Research Inc. using Sorrento Therapeutics securities report filings

Note 1: The above are net sales figures after the deduction of promotional and other costs. Gross sales in Q1 2022 came to USD18.4 million, up 26% on the same period of the previous year. Gross sales are growing but we can infer that so are promotional costs.

Note 2: Scilex is also developing a tape (SP-103, for lower back pain) with 3 times the lidocaine level. In Phase-2 since May 2022.

(3) MRX-9FLT: Fentanyl tape

Fentanyl tape was accorded fast track status in July 2021

The fentanyl tape MRX-9FLT, which is under development for cancer pain, is a new fentanyl patch that applies MEDRx's proprietary technology to control and prevent misuse and accidents. An application for clinical trials was submitted in March 2020, and in September 2020 preliminary confirmation of utility in human subjects was obtained in terms of blood concentration relative to the reference product, Duragsic®, and in terms of safety. In July 2021, the fentanyl patch received fast-track designation from the FDA, which thereby emphasized its ability to reduce misuse and prevent accidents. Comparative clinical tests (Pivotal and BE tests) demonstrating bioequivalence with the reference product would be completed in 2022, after which there would be discussions with the FDA on test design before moving on to tests for skin safety and tests validating the safety mechanism, prior to submission of an application in the first half of 2024. However, comparative clinical tests (Pivotal BE tests) are presently in train and will take an expected USD2 million to complete. It is thought possible that the company will move to license out once the misuse and accident prevention design is finalized.

Now undergoing Pivotal BE tests

Memantine patches have a big market potential

(4) MRX-7MLL memantine patches

MRX-7MLL is the Alzheimer's drug memantine which MEDRx has rendered into patch form using NCTS®. Memantine is a skin irritant and is difficult to formulate in patch form. However, it is believed that NCTS® can solve both problems. In addition, the patch formulation allows administration to be confirmed visually, and administration is only necessary once every three or seven days, compared to daily in the case of oral administration. In the US, the oral memantine market has, because of generics, shrunk from JPY75 billion to around JPY12 billion. MEDRx believes that the functions of its patch will be highly evaluated, that it will not need to compete with generics, and that it will be accepted by the market at a relatively high price. Assuming it gets about 25% of the market and assuming a price level in line with previous products we posit a market size of close to JPY20 billion.

While an application to conduct clinical trials on MRX-7MLL was completed in November 2021, the trials have not yet begun. The original schedule was for pharmacokinetic tests to take place in two stages in 2022, for bioequivalence tests to start in 2023 and, following skin safety tests and long-term stability tests, for an application for approval to be submitted in 2024. There is at present a lag of about 6 months.

Manufacture of the investigational drug has already been completed and a clinical trial application has been submitted, but a pilot PK study (Ph1a) has not started

Reference: Donepezil patch (Aricept®) once-weekly application; launch scheduled for Autumn 2022
In March 2022, Corium Inc's donepezil patch ADLARITY® received regulatory approval: scheduled for launch in the Autumn. Sales price not released

(5) Next major development candidate: MRX-6LDT: Diclofenac-lidocaine tape

On May 18, 2021 MEDRx announced the development of a new pipeline, MRX-6LDT. It is a tape formulation using MEDRx's proprietary ILTS® technology allowing the simultaneous subcutaneous administration of the diclofenac inflammation analgesic and the local anaesthetic, lidocaine. There are at present no other patches containing this combination and no companies other than MEDRx developing one (but see note below).

Diclofenac-lidocaine tape (MRX-6LDT) emerged as a major development candidate in May 2021

Note: In 2017-2018, the German company, Grünenthal GmbH, tried but failed to develop a patch combining lidocaine and diclofenac-epolamine (development code: GRT7019). Both components were at the same volumes as patches now on the market and tests showed no significant advantage over the comparative group.

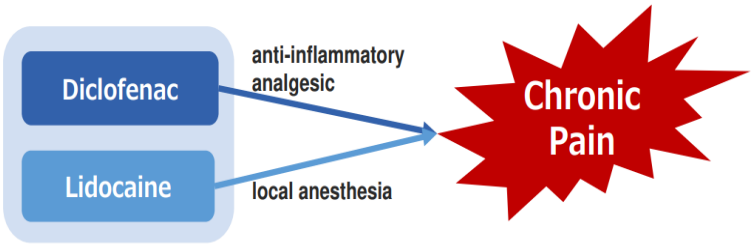
The company posits a broad spectrum of chronic pain ailments, but the primary indication at the early development stage will probably be knee osteoarthritis (Knee OA). Research in the US estimates 4% of the adult population, or 9 million people, are receiving treatment for Knee OA. The annual drug cost per patient comes to USD3,255. Of this, the cost of diclofenac and other non-selective non-steroidal agents comes to USD442 which, simply multiplied by the number of patients, makes for a total of USD4 billion. In this market it is possible that demand could make MRX-6LDT a blockbuster.

The idea is that MRX-6LDT should have a wide spectrum of indications and could have blockbuster potential. While not yet confirmed, the initial pain targeted will probably be Knee OA

By using the ILTS® technology, MRX-6LDT could increase the transdermal penetration of diclofenac several times beyond than that of conventional diclofenac patches widely used in Japan.

Reference: Special 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).



Source: MEDRx, materials supplementary to financing, May 2021

In the US, Hisamitsu Pharmaceutical is developing HP-5000, a diclofenac patch, capable of delivering a high volume of diclofenac to the blood

MRX-6LDT should also achieve a high blood concentration of diclofenac, and the amount of lidocaine is also intended to be several times that of Lydolyte

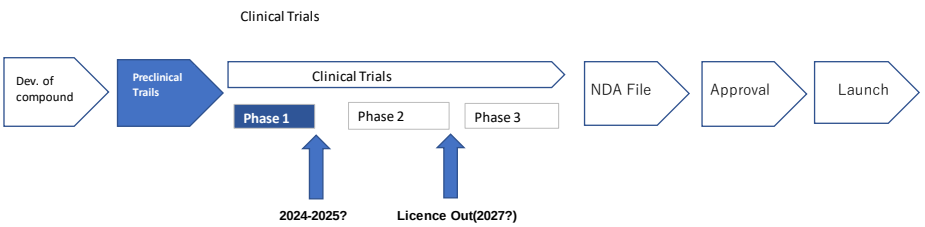
Currently, Hisamitsu Pharmaceutical in the US is developing a diclofenac patch (HP-5000) for the pain caused by osteoarthritis of the knee (knee OA), and it is now at Phase-3 (NCT04683627). Hisamitsu has disclosed (November 2019) that in Phase-2 trials in which a high concentration was delivered to the affected part, results pointed to effectiveness and safety. Also, in March 2021, Hisamitsu's diclofenac patch (Dictor® for the alleviation of cancer pain) was authorised in Japan. Further, in June 2022, indications were expanded to include lower back pain and others. The concentration of diclofenac in this tape is, at 75mg per tape, about 5 times that of commercially available OTC diclofenac patches. Since 2 or 3 patches can be attached at the same time it could provide 10-15 times the conventional volume. While the volume of diclofenac in HP-5000 has not been disclosed, we assume it might be around the same level as Dictor® tape. MEDRx is probably intending for MRX-6LDT to deliver a high volume of diclofenac to the affected part.

Returning to lidocaine, MEDRx is probably thinking that its Lydolyte lidocaine tape, now the subject of an NDA submission, will have a transdermal absorption ability several times higher. It is expected that sufficient tolerability will be ensured because the blood concentration does not reach the level at which side effects occur with injections.

Formulation development completed
Preclinical trials have not yet begun

Planning to license out afer Phase-2

As of August 2021, development of MRX-6LDT has been completed and the plan is now to start pre-clinical trials. However, Lydolyte requires additional tests and this has delayed development and the start of those trials. When they have been completed the process will move on to Phase-1 trials to confirm safety, tolerability and drug penetration (blood concentration, etc.) in human subjects. After that, in order to confirm clinical indications and efficacy, dozens of patients for each of the three indications will be subjected to Phase-2 treatment for about 2 to 3 months, following the results of which a licensing-out will be considered. Hisamitsu Pharmaceutical's HP-5000 is expected to complete Phase-3 in December 2022. HP-5000 will then be launched in the market, and the supposition is that it will take until around 2024 to 2025 for the market to be ready for knee osteoarthritis applications. Therefore, just as the market for diclofenac patches for Knee OA is expanding, the timing for out-licensing MRX-6LDT will coincide.



Source: Fair Research Inc.

In the area of Knee OA, surgery is the final option, and before arriving at surgery the most common treatment is to treat the pain accompanying this condition, more often than not with NSAIDs playing a central role

Opioids are central to pain management

Progress is being made in the development of alternatives, but there have been many dead-ends

Opioids and NSAIDs will continue for the time being to be central

Reference

The last line of treatment for Knee OA 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 non-opioid drugs with a new action mechanism.

However, the development of anti-NGF antibodies continues to be interrupted, making drug development in the pain field problematical. Non-steroidal anti-inflammatory drugs (NSAIDs) will therefore continue for the time being to play a central role.

Pain medicine - an area of many failures

Product	Company	Stage	Mechanism	Status
Tanezumab	Pfizer/Lilly	Ph3	Anti-NGF antibody	Failed; Oct. 2021
Fasinumab	Teva/Regeneron	Ph3	Anti-NGF antibody	Halted due to side-effects
Ampion	Ampio	Ph3	TLR7 agonist antibody	Phase-3 Failure for OA (August 2022)
LY3016859	Lilly	Ph2	TGFα & epiregulin antibody	Dropped in Q1 2022
ACP-044	Acadia	Ph2	Redox modulator	Failed: Aug. 2022
ETX-810	Eliem	Ph2	palmitoylethanolamide	Failed: Aug. 2022
NYX-2925	Aptinyx	Ph2	NMDA modulator	Failed: Aug. 2022
Resiniferatoxin	Grunenthal	Ph3	TRPV1 agonist	Internat. collab. with Shionogi or Sorrento on OA
MEDI7352	Astrazeneca	Ph2	AntiNGF/TNF antibody	Phase-2 by 2023
VER-01	Vertanical	Ph3	Cannabis extract	Dev. In Germany for lumbago, etc.

Source: Fair Research Inc, drawing on materials produced by Evaluate Pharma

(6) The second major product: microneedles

MEDRx microneedles come with an applicator, which allows injections to be administered in a reliable way with finger pressure alone

Patent applications increasing

MEDRx has for the past 16 years been doing research on microneedles in an effort to find a simple and reliable way of administering drugs. This means the needle must reach the dermis vertically and painlessly, but the key is in the shape of the needle tip and the attachment device (the applicator). For other companies the applicator is spring-loaded and pushed in, so more force is applied and the patient may feel pain, while the MEDRx device requires only hand strength. The shape of the MEDRx microneedles is patented, and the applicator's patent has been registered in Japan, the US and China. MEDRx also aims to secure rights in Europe in June 2022 and has applied for patents in India and Brazil. In addition, MEDRx has also secured a patent in the US covering the technology for securing the needles in the skin, which is needed to achieve easy and reliable drug administration. It was registered in Japan in July 2022.

Source: MEDRx briefing, February 2022

Research is going on worldwide to develop preparations using microneedles

There is currently a lot of work going on worldwide to develop medical products using microneedles. This has recently been seen in the development of COVID-19 vaccines in response to the new corona virus pandemic. However, two US companies, Zosano and Radius, leading the way in medical appliances, have been developing formulations for non-vaccine applications. In December 2019, Zosano submitted an unsuccessful NDA for a migraine treatment using microneedles. The company was in discussions with the FDA on supplementary tests but had to abandon this in June 2022 when shortage of funds forced it into Chapter 11 (although its development operations continue). In the case of Radius, their osteoporosis treatment was in Phase 3 but it appears to have abandoned development of a current generation microneedle after failing in December 2021 to demonstrate superiority versus injectables. It seems that microneedles generate varying doses and stabilizing the necessary amount is proving difficult.

In Japan, development aimed at vaccine formulation is underway

In Japan in December 2021, the Hokkaido University Hospital used microneedles to vaccinate 39 subjects against Japanese encephalitis. It was reported that this method was 10 times more effective than the conventional subcutaneous injection method (Phase-1). The microneedles used were developed by Fuji Film. In addition, microneedles (manufactured by GMP by Nipro), which Cosmedy Pharmaceutical is jointly developing with Osaka University, are being developed with an influenza vaccine in mind, and clinical trials are scheduled to start in 2023 (source: Yomiuri Shimbun, July 22 2022, evening edition).

MEDRx is conducting feasibility studies with Japanese and overseas pharmaceutical companies and vaccine ventures

In April 2020 MEDRx began operation of a microneedle pilot plant, and further, in January 2021, completed an upgrade of that facility to handle pathological bacteria and viruses used in vaccines, along with genetically modified organisms, with the emphasis centering on "diffusion prevention and other biosafety measures". Meanwhile MEDRx initiated feasibility studies with several Japanese and overseas pharmaceutical companies and vaccine ventures with a view to operational tie-ups. At present there are ten or so such studies underway.

The details of two of these studies have been made public. In August 2021 it was revealed that a feasibility study had been conducted on a formulation in which FunPep's antibody-inducing peptide was applied to MEDRx microneedles. Peptides are cheaper than antibodies and their use could help reduce cost. By administering

a peptide that produces the targeted antibody with a microneedle, long-term antibody production is possible and convenience is improved.

Reference: FunPep's pharmaceutical development pipelines

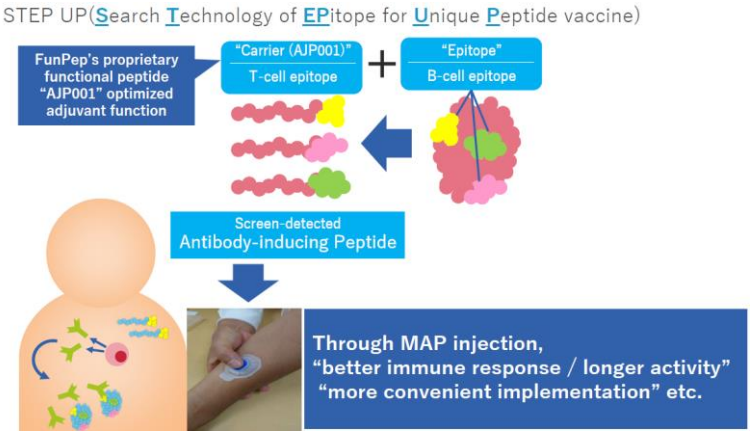
Development Pipeline

	Target Disease	Area	Discovery	Pre-clinical	Clinical Trial P-I	Clinical Trial P-II	Clinical Trial P-III	Alliance
SR-0379 Functional peptide	Skin ulcer	JP						Shionogi & Co., Ltd. (Global license agreement)
FPP003 Antibody inducing peptide (Target: IL-17A)	Psoriasis	AU						Sumitomo Pharma (Option agreement in North America)
	Ankylosing spondylitis	JP				*		
FPP004 Antibody inducing peptide (Target: IgE)	Pollinosis							TBD
FPP005 Antibody inducing peptide (Target: IL-23)	Psoriasis							TBD
FPP006 Coronapeptide vaccine	COVID-19							TBD

* Investigator initiated trial

Source: FunPep company briefing, August 2022

The FunPep antibody-inducing peptide and microneedle formulation



Source: MEDRx company briefing, August 2021

Note: Fair Research believes that FunPep antibody-derived peptides at the preclinical stage may be the subject of microneedle feasibility studies

The second study was conducted jointly with the Columbia University Irving Medical Center and published in March 2022. This was a study to explore the possible anticancer effects on breast cancer of administering the immuno-stimulant "7DW8-5" and the anticancer peptide "iRGD" using microneedles. The first step involved a test using mice, but the hope is that the next step will lead to physician-initiated clinical trials.

Note 1: 7DW8-5（a fluorinated phenyl ring-modified αGalCer analog）
A glycolipid that strongly stimulates natural killer T cells and increases antitumor activity
Note 2: iRGD（a cyclic peptide）
Cyclic peptide that specifically infiltrates tumor cells and tissues

Around 2024, there is a possibility that the stage succeeding animal testing will emerge.

Some of the ongoing feasibility studies (animal experiments) may evolve in 2023-2024 ready for the next stage (human trials).

2022 first half results and 2022 corporate plan

The company's forecast for sales in 2022 has not changed but could do so depending on negotiations with Cipla

Sales in the first half of 2022 came to only JPY9 million, all for iodine coat ointment sales, but the annual sales forecast is JPY289 million, because in addition to the iodine coat ointment the company is to receive JPY280 million from Cipla as a milestone payment when tizanidine tape enters Phase-2. Milestone income may change in light of how discussions with Cipla on Phase-2 costs and a rights buyback evolve.

The re-start of delayed product development could mean an expansion this year in R&D expenditures

R&D outlays in the first half of 2022 came to JPY274 million, below the level of the same period of the previous year. This is a reflection of the start of supplementary tests for lidocaine tape, the start of clinical trials for memantine tape, and the delayed development of fentanyl tape. For the full 2022 term, R&D costs are expected to expand to JPY1.085 billion (not including tizanidine tape Phase-2 costs) due to supplementary tests for lidocaine tape in the second half and the re-start of other tape developments which had been put on hold.

As shown above, full-year sales in 2022 are likely to exceed the previous year's figure by JPY281 million but, with R&D and other SG&A outlays set to rise JPY291 million, another operating loss is expected. At JPY1.002 billion yen this will be at roughly the same level as the previous year (JPY1.061 billion yen).

First half 2022 results and full year forecast

(JPY-mil)

	1H/2021	1H/2022	2021	2022 (Plan)
Revenues	7	9	8	289
Product sales	7	7	8	9
R&D income				280
SG&A	477	381	1,067	1,289
R&D income, etc.	331	274	794	1,085
Others	145	106	273	203
Operating losses	-471	-374	-1,061	-1,002
Recurring losses	-475	-382	-1,066	-1,003
Net losses	-473	-381	-1,059	-1,006

Source: MEDRx company briefing, August 2021

The company's "burn rate" gives it a little more than one year of cash

Cash in hand at the end of June 2022 stood at JPY1,269 million. Since the company continues to record losses in excess of JPY1 billion per year it has about one year's worth of cash reserves. In August 2022, the company announced a capital raising via the issue of its 25th new share subscription rights for an expected total of JPY737 million. As noted earlier, this was intended mainly to underwrite tizanidine tape Phase-2, so cash available for other product developments will last slightly more than one year. Fair Research infers that MEDRx will adopt a two-stage strategy of, firstly, "selection and concentration" in fields that can be out-licensed at an early stage, thus incurring low development risk, and secondly, building on that success to invest in the development of major projects.

Selective concentration necessary

End of June 2022 balance sheet

(JPY-mil)

	End Dec. 2021	End June 2022	Difference
Liquid assets	1,754	1,365	-389
Cash	1,703	**1,269**	-434
Others	51	96	45
Fixed assets	353	331	-22
Tangibles	270	248	-22
Investments, etc.	83	83	0
Total assets	2,108	1,696	-412
Liabilities	153	117	-35
Liquid liabs	125	90	-35
Fixed liabs	27	27	0
Net assets	1,955	1,579	-376

Source: MEDRx company briefing

	Conclusion: product selection and concentration help the company out of a rut
	It goes without saying that the company's top priority in terms of product is its lidocaine tape (Lydolyte), which is the closest of its products to approval and market launch. The costs associated with the required supplementary tests will depend on the response from the FDA but the company's own suggestions would cost just under JPY200 million. This sum has already been reflected in the company's 2022 budget.
Company's top priority: lidocaine tape	Next in terms of priority is tizanidine tape, so favoured because of its development status and marketability. It has already been decided to allocate the proceeds of the issue of the 24th stock subscription rights to promote the development of tizanidine tape
Second priority tizanidine tape	Fentanyl tape or memantine tape is next in line. In terms of marketability the memantine patch, which uses the NTCS® technology is the more promising. However, development risk considerations might favour the fentanyl tape, which uses the ILTS® technology. It is expected that around JPY200 million will be invested in the Pivotal BE fentanyl tape trials.
Next because of development risk considerations might be fenatanyl tape	Taking into account the JPY500 million yen that will be required annually for basic research and running the company's administrative side, the total funds required for next year will be about JPY900 million, excluding tizanidine tape. Even if the milestone income from Cipla fluctuates, cash will remain within the current range.
Milestone income on lidocaine tape from DWTI in 2023, and income elsewhere from licensing out sales rights	Within the next year, the regulatory approval and launch of the lidocaine tape (Lydolyte) is more or less a certainty and, in addition to the milestone income of JPY100 million from DWTI, opportunities to license out marketing rights will also emerge. The result will be a stabilization of income.
After that, hopes of income from licensing out fentanyl tape and a re-licensing of tizanidine tape	The company now plans to secure the funds necessary to validate fentanyl tape's safety and misuse prevention mechanism and, when that validation is positive (we think around 2023-2024), a licensing-out of fentanyl tape will be possible. As for tizanidine tape, the scenario envisaged is that Phase-2 will be executed using newly-raised funds, and with the success of Phase-2 a second licensing-out will occur with the licensee being responsible for Phase-3.
Optimism also for progress in the company's next two major product development projects	Fair Research believes MEDRx has overcome the problems so often faced by ventures through its strategy of "selection and concentration" and has now entered a growth stage where out-licensing opportunities emerge more continuously. We are optimistic that the development of the next two major projects (MRX-6LDT and microneedles) will progress and that corporate value will further expand.

Selection and concentration - image

		2022	2023	2024
Top Priority	Lidocaine tape (Lydolyte)	Extra tests	Re-applicatipn Milestone from DWTI Licensing of sales rights	Market launch Royalties income
Second Prioirty	Tizanidine tape （CPN-101（MRX-4TZT))	Start of Phase-2 Cash raising	Ph2	Ph3 Licensing-out
Third Priority	Fentanyl tape （MRX-9FLT）	Pivotal BE trials	Tests of misuse prevention function Long tem stability tests	Licensing-out
Or	Memantine patch （MRX-7MLL)	PK trials start	= > Pivotal BE trials	Safety & long-term stability

Source: Fair Research Inc.

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