No pain, certain gain

Novaremed

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Novaremed is a pharmaceutical company developing a number of new drugs against chronic diseases. At the head of the pack is their proposed treatment for neuropathic pain, known as NRD135S.E1. Here we discuss their plans and recent successes.

There are very few things in life worse than constant, unforgiving pain. Whether it occurs as the hitch in the small of your back as you sit down to work again, the creak in your knuckles as you go outside on a cold day, or even the deep burning within your bones from the chemotherapy, chronic pain continuously makes itself known to the sufferer.

Chronic pain can be divided, based on the causative reason, into two types, neuropathic and nociceptive. Neuropathic pain is a continuous pain where the damage has been done to the nervous system, making the specific cause difficult to identify and treat: think of back pain, of peripheral neuropathy in diabetics, shingles. Neuropathic pain makes up around 25-40% of chronic pain cases, depending on country, age group, etc. Nociceptive pain, by contrast, comes from damage to the body tissues, to muscles, joints, bones. Think of the pain you feel after breaking a bone, in arthritic joints, after an operation. This pain, thankfully, usually goes away once the underlying injury has healed.

The current state of treatment for chronic pain is less than optimal. Only a few drugs have actually been approved for use in humans, the big 4 being Gabapentin (Neurontin), Lyrica, Cymbalta and Lidocaine, all of which were launched between 1999 and 2004. Unfortunately, besides their limited efficacy, all of these drugs have significant side effects – most commonly dizziness, drowsiness, ataxia (lack of muscle control), and digestive problems. These side effects can sometimes be so bad that patients would prefer to drop the medication and simply cope with the pain itself. Beyond this there are three major factors which need improvement: current pills need to be taken several times a day; they do not have sustained medicine release for long term-treatment; and they often show unwanted interactions between different drugs.

To add to these difficulties, chronic pain is itself a growing problem. In 2008 there were between 9 and 16 million sufferers in the US and Western Europe. In three years, in 2018, there is expected to be between 16-22 million, a significant increase. This is also, naturally, a growing market for therapeutics, with the chronic pain field expected to have sales between 7-10 billion US dollars in 2018. It is this growing field, and knowledge that the current medication is somewhat lacking, which has brought new entrants into the field.

ENTERING THE RING...

One of these entrants is Novaremed, an Israeli company dedicated to developing drug for chronic pain with sustained efficacy. The company began, back in the early 90's, with an observation by the founder and CEO, Dr Eli Kaplan. At the time he was observing the common use of Antiviran as a remedy for hepatitis and various gastrointestinal disorders. Antiviran, before you ask, is the name given to a crude powder extracted from cultures of non-pathogenic microorganism, which has been used as an herbal tea/folk remedy for quite a long time. He suspected, as is often the case, that this mixture acted as a crude form of numerous interesting medicine-like molecules, and thus set out to purify and identify them.

After almost six years of teasing out the contents of this mixture, splitting it into fractions, testing each part, sub-dividing further, Dr Kaplan finally found the first of the active substances. A simple molecule, relatively small, it was neither a peptide, nor a lipid, not a lipoprotein, but chemically appeared to act by simulating a small peptide. Once this original compound had been identified, it was possible to use targeted molecular design to create a leaner, more effective version which was only half the size of the original substance (a mere 357 Daltons).

Novaremed itself was founded in 2008 to follow up on these early discoveries, with the initial work being performed in the Ashkelon Technology Incubator. These start-up incubators provide a vital role in helping innovative companies begin, providing facilities and equipment for early development and research. They were also assisted in this process by the traditionally entrepreneur-friendly Israeli government, as Michal Silverberg, Clinical Manger, commented "the continuous financial support of the Chief Scientist enabled Novaremed, like many other young companies, to cross the barrier of early product development".

Their current lead compound is known as NRD135S.E1, and has already shown extremely promising results in a number of tests. Indeed one of the only down-sides is that the name

itself is quite a mouthful, (Liat Hochman, Director of Clinical Operations, comments "internally we call it E1", which is definitely easier to say). E1 is what is known as a New Chemical Entity, a molecule that is unique and has not been previously seen in therapeutics. Alongside this E1 has a novel Mechanism of Action, (the manner in which it works), which relies on modulating the activity of a protein known as Lyn. Lyn is a tyrosine kinase, a type of signalling protein which acts as a mid-point between an outside stimulus (i.e. pain) and the cells own reaction to this occurrence. No other pain drug targets tyrosine kinases, nor does E1 bind to the common pain receptors – this means that it does not overlap with other treatments and thus could be extremely useful for patients who are not responsive to typical treatment.

"developing a first in class, efficacious and safe remedy, which has a unique mechanism of action, for this indication" (neuropathic pain)

ROUND 1

The process of developing a drug is long and often convoluted, but falls into three main stages. First come the pre-clinical experiments, making sure that your drug does what you want in cell lines, in biochemical assays, and in animal models. Next comes the First-in-Man studies, known as Phase I, which act as safety testing for the new drug: how well is it tolerated? How long does it stay in the body? How is it removed? Last are efficacy studies, Phase II and Phase III, which test how well the drug works at solving its target disease. As the potential medicine works through each stage more and more information is gathered, helping to inform the final use when it reaches the clinic.

Novaremed began with pre-clinical studies on E1, determining how it worked – not just that it affected Lyn, but how much, how quickly, and how long, all in excruciating detail. Once the biochemical characterisation was out of the way, they moved on to animal studies, examining various different models of chronic pain. Each of the studies showed not only that the drug was safe and well tolerated, but that it was often more effective at pain-reduction than a number of well-established medicines on the market.

ROUND 2

Following their excellent pre-clinical results, Novaremed moved on to the next stage, first-in-man trials. These trials, intended to determine safety and tolerability of a new drug, are usually entitled Phase I or, as in this case, Phase Ia. This was an ascending dose study, which means that the 32 healthy male volunteers (in 4 cohorts), were given gradually increasing doses of drug to see how it was tolerated. As would be expected, this is a slow and careful process, with a maximum level of care for the health of the volunteers. It was followed by a Phase Ib trial,

in which volunteers took a single dose for five days, to accurately model the typical chronic pain sufferer.

As expected, E1 was safe and well-tolerated, a few mild and transient side effects were seen in both the placebo and the drug group, indicating that they were most likely not caused by -E1-nerves. Alongside this, biochemical studies showed that E1 was rapidly absorbed into the bloodstream (within 1-3 hours) and then eliminated over the course of 24 hours. This is, naturally, exactly what the designers of a one-tablet-a-day medicine would like to see.

The next stage, Phase IIa, involves testing efficacy in actual patients. In this case the researchers are working with patients suffering from diabetes-associated neuropathic pain. This process has just begun, and results will not be known until the end of the process in March 2016, but everyone at Novaremed is confident that their initial observations will be borne out. As they comment, they are "developing a first in class, efficacious and safe remedy, which has a unique mechanism of action, for this indication".

ROUND 3, TAG TEAM?

So where to from here, for this company? Naturally there is the long process required to get their new drug, NRD135S.E1, to market. This not only requires human clinical trials, but also that they show the ability to safely manufacture their chemicals in the quantities needed. According to Neta Pessah, Pre-Clinical Manager, this is no problem, they have already "scaled up with relatively high yields, high purity, and under GMP (good manufacturing procedures) as required by ICH guidelines". Beyond this, from a purely prosaic view, the firm needs to defend its discoveries via patenting, and Noveremed has managed to secure strong patent protection for E1 until 2031.

Nor are the team at Novaremed happy to rest on their laurels after their success so far with E1. They are using it as a base to develop "other compounds in the pipeline that are chemically related to NRD135S.E1" comments Pessah, "which may be developed for indications other than neuropathic pain". The compound pipeline, of course, is one of the most important assets that a pharmaceutical company has, and thus the existence of these novel molecules is a strong sign for the company's future development.

Based on these strong fundamentals, and plans for the future, the founders of Novaremed are looking around for others with similar goals. As Liat Hochman, Clinical Operations, makes clear, "we are looking for collaboration with pharma companies interested in pain, and potentially other indications related to E1's mechanism of action." Their hope is that, by working with collaborators, they will be able to spread the benefits of their discoveries far further than otherwise possible. This is a company with lofty goals and a plan to launch themselves upwards. After all, once we can defeat pain, the sky is the limit.

Researcher Profile

Novaremed

Founded in 2008, the Israeli pharmaceutical company Novaremed is a rapidly impressing investors with their pipeline of compounds for treatment of chronic diseases. At the head of the list is their proposed treatment for neuropathic pain, known as NRD135S-E1. Headed by Dr. Eli Kaplan, and with members from well-known multinationals on their side, they are definitely a group to watch.

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