INNOMEDICA

Talineuren

Liposomal GM1 for the Targeted Treatment of Parkinson's Disease
March 2018

Talineuren uses the active substance GM1, whose protective and regenerative effect on the brain is already known. InnoMedica's liposomal transport system is to target GM1 into the brain and enable oral administration – an effective, long-lasting Parkinson's therapy.

Executive Summary

InnoMedica has set itself the goal of optimizing the biological distribution of active substances in the body with a liposomal transport system. Recent preclinical studies have now shown that InnoMedica's liposomes in a novel liposomal composition are able to cross the blood-brain barrier. This allows the use of this technology in another major area of medicine – neurology.

InnoMedica's therapy approach of treatment with endogenous active substances protects the nerve cells and reduces their continuous dying. The protective and regenerative properties of this treatment method are novel in the context of the therapies available today for neurological disorders. According to preliminary preclinical findings, InnoMedica's Talineuren can open up new therapeutic possibilities for a large number of Parkinson's disease patients and patients with other neurodegenerative diseases.

InnoMedica's transport system to overcome the blood-brain barrier offers great benefits, which can be used especially for the administration of GM1. GM1 is a ganglioside that is found in the grey matter of the brain and plays an important role in neuronal development and plasticity. Positive results from a clinical study conducted by Thomas Jefferson University (TJU) on the use of GM1 in Parkinson's patients have prompted InnoMedica to focus its research on this group of patients within neurology. In a human study, Prof. Jay Schneider of the TJU was able to show that the administration of GM1 significantly alleviates Parkinson's symptoms and slows down or stops the progression of symptoms in the long term.

However, the treatment was accompanied by severe side effects due to the form of administration. In order to deliver sufficient GM1 to the brain, the substance had to be injected under the patient's skin twice a day. By oral administration, free GM1 is poorly absorbed and does not reach the neurons of the brain in effective amounts. Despite promising results, this treatment approach has so far found no application in medicine.

Using InnoMedica's liposomal transport system, the administration of GM1 is now to be made available for first-line therapy of Parkinson's disease. By means of liposomes, GM1 can be brought to the brain, bypassing the previous side effects. When GM1 is packaged in liposomes, oral administration is possible. Preclinical data show that the liposomes are absorbed into the bloodstream via the gastrointestinal tract and bring GM1 through the blood-brain barrier to the neurons of the brain. This makes treatment considerably easier and viable for a large number of patients. In a recent preclinical study, the functional capability of the liposomal transport system and the overcoming of the blood-brain barrier has been demonstrated. As a next step, InnoMedica will carry out further preclinical studies as well as the toxicology study required prior to the clinical phase. In addition, the procurement of the necessary raw material quantities and the expansion of production capacities must be planned.

The novel liposomal formulation was noted down in a patent by InnoMedica and filed with the Patent Office in December 2017. The development of this treatment proves the innovative potential of InnoMedica's technology platform beyond of oncology.

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Talineuren: InnoMedica's Parkinson's Therapy

InnoMedica's liposomal technology platform allows the biologically targeted transfer of medical agents to diseased tissue. Following the technological breakthrough in the development of a nanocontainer that is able to cross the blood-brain barrier and thus deliver drugs directly to the brain, InnoMedica evaluated potential applications in neurodegenerative diseases. InnoMedica's latest development project uses the liposomal transport system to deliver a nerve cell regenerating agent into the brain and has therefore included a product prototype for the therapy of Parkinson's disease in its pipeline. Preclinical data reveal the following advantages of InnoMedica's Talineuren:

Regeneration
The active substance used is a natural component of nerve cells and does not only fight symptoms of Parkinson's, but also has a regenerative effect on the brain. This property of the drug has great advantages for the patient, as it can prevent or critically limit the continuous, disease-related dying of nerve cells. Instead of symptom treatment, a therapy that can provide a positive long-term effect on the course of the disease becomes possible.

Oral administration
Talineuren can be delivered in a vial and drunk by the patient. The liposome allows oral administration also for agents that cannot be absorbed by the body in their pure form by the oral route. Oral administration has the advantage that, unlike injections, the therapy is pain-free and can be administered without medical help. This means treatment is simpler with significantly less intervention in the patient's daily routine.

Crossing the blood-brain barrier
The nerve cells are particularly worthy of protection for the body, since they hardly divide after childhood. The skull serves as a mechanical protective barrier against external forces. The blood-brain barrier protects the nerve cells from inside the body against harmful toxins in the blood. Only a few molecules can cross this blood-brain barrier. Contrary to popular scientific belief that liposomes cannot penetrate into the brain, InnoMedica has been able to determine a specific composition of the liposome that allows it to cross the blood-brain barrier. Thanks to this nanocarrier, active substances can also enter the brain that without liposomal packaging would be held back by the blood-brain barrier.

Few side effects
The medications used today to fight Parkinson's symptoms often cause serious side effects. In the preclinical studies with Talineuren, no side effects of the product have been observed so far.

The research results of InnoMedica show that this therapeutic approach has great potential, and that with long-term neuroregenerative therapy a lasting treatment of Parkinson's disease becomes possible for the first time. Leading neurologists in the US, Germany and Switzerland also attest great potential for this therapy. A patent filed in December 2017 shall protect the intellectual property of this novel therapy in the future.

GM1 as a Regenerative Agent

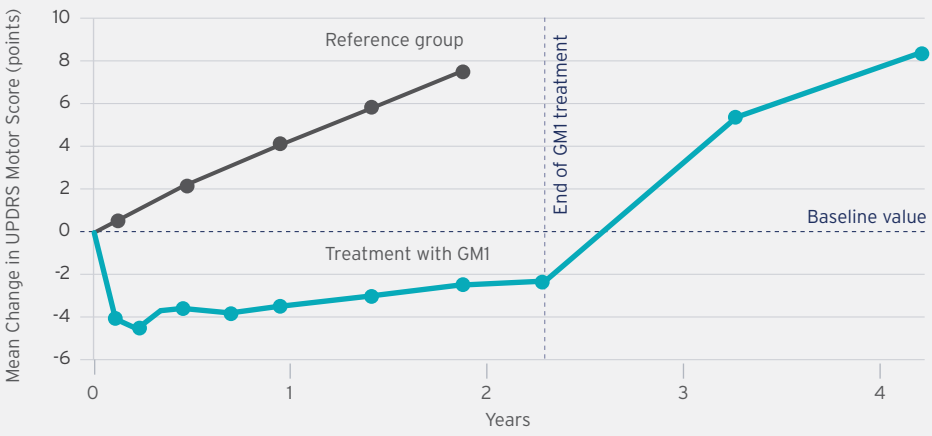
Today, Parkinson's disease is medically treated solely at symptom level. Therapies such as levodopa or dopamine agonists try to compensate the decreasing dopamine production in the brain with this symptomatic treatment. However, due to the steady dying of further nerve cells the patient's drug dose needs to be increased continuously. To date, there is still no satisfactory long-term treatment option due to the side effects. The characteristic movement disorders associated with Parkinson's disease, accompanied by non-motor symptoms, lead to great limitations in the everyday life of those affected.

In order to improve the current treatment options of Parkinson's disease patients, a medication is needed that approaches the disease as close to its cause as possible and supports the body's own dopamine production in the long run. Current research on Parkinson's disease shows that GM1 could be such an active agent. GM1 is a glycolipid naturally occurring in the brain, a so-called ganglioside. Gangliosides are particularly abundant in the membranes of nerve cells. An overview of the experimental research on externally supplied gangliosides and their effect on nerve cells shows that gangliosides play an important role in the functional restoration of damaged nerve cells: GM1 gangliosides seem to promote the survival and regrowth of damaged nerve cells.

In addition, GM1 has shown to have an immunoprotective effect, which manifests itself in the inhibition of immune cells. Neuronal structures are protected from the own immune system and it is prevented that these are attacked. However, if the GM1 concentration decreases in the brain, the immune cells multiply and destroy dopamine-producing nerve cells amongst others. Under the assumption discussed in expert circles that Parkinson's is caused by an autoimmune reaction or aggravated as a follow-up reaction, a reforestation of the brain's GM1 population could reduce this immune response.

Human studies investigating the effect of subcutaneously injected GM1 in Parkinson's patients confirm the hypothesis of neuroprotective effect in that an exceptional improvement in motor symptoms could

Strong, long-lasting improvement of motor score after treatment with GM1



Source: Schneider, Jay S. (2013): A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients, Journal of the neurological sciences 324(1–2).

Figure 1: Measurement of the change in motor score on the Unified Parkinson's Disease Rating Scale (UPDRS). An increase in the score indicates a worsening of the symptoms, a decrease in the score indicates an improvement of the symptoms. In addition to standard treatment, one group of patients was injected with GM1 subcutaneously twice a day for more than two years. The control group continued to receive their standard treatment only. Treatment with GM1 led to an immediate large improvement in symptoms (simplified and graphically revised illustration).

be achieved (Figure 1). In one of these clinical studies, Prof. Jay Schneider (Thomas Jefferson University, Philadelphia, USA) investigated the change in motor symptoms in Parkinson's patients over a period of four years. All participants received their standard therapy during this time. One group of patients was additionally injected with GM1 subcutaneously twice a day for 120 weeks.

After the start of the study, the symptoms of patients who were additionally treated with GM1 have greatly improved. Even over a period of more than two years, a comparison with the baseline values of patients shows an improvement in motor values. This long-term effect is particularly impressive as the reference group that did not receive GM1 showed a steady deterioration in symptoms. The data also indicate that the difference in symptom severity between the reference group and the GM1 group persisted for weeks after discontinuation of therapy with GM1, resulting in a sustained effect. This shows the great potential of treatment with GM1: at best the degeneration can be stopped, but at least the course of Parkinson's disease can be critically slowed down. Late effects of the disease would thus be delayed, and a higher quality of life maintained.

In addition to these promising clinical results on GM1, the study also revealed two unresolved issues, both of which can be attributed to the method of administration:

- In order to accumulate enough GM1 in the affected brain regions, GM1 had to be injected twice a day under the skin. These injections caused painful local skin reactions, which despite the strong symptom improvement usually were unbearable for the patient.
- This form of administration requires a subcutaneous injection twice a day, posing a significant intervention in the patient's everyday life.

Despite the strong therapeutic effect, no further trials with the free active substance GM1 could be carried out with patients due to these side effects.

GM1 in the Liposome: Crossing the Blood-Brain-Barrier when Administered Orally

InnoMedica's Talineuren combines the potential of GM1 in Parkinson's therapy with the benefits of liposomal technology. The combination of these two elements makes it possible to develop a new Parkinson's drug that can bypass the side effects. Figure 2 schematically shows a GM1-loaded liposome from InnoMedica.

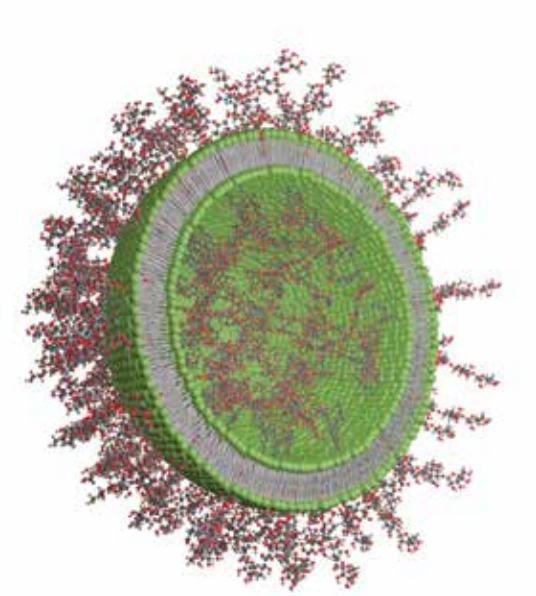


Figure 2: Schematic illustration of Talineuren. The liposome is loaded with the active substance GM1. The green lipids form a double membrane.

Thanks to the liposomal packaging a greater accumulation of GM1 can be achieved in the brain. This eliminates the need for subcutaneous administration. The liposomal formulation can be drunk, passes from the digestive tract into the blood and from there through the blood-brain barrier into the brain. Figure 3 shows the pathway of Talineuren through the patient's body. Once in the brain, GM1 will have a protective and regenerative effect on the nerve cells. Figure 4 illustrates how the GM1-loaded liposomes of Talineuren release their active substance in the dopamine-producing nerve cells.

Built up of the body's own molecules, the therapy is well tolerated by the organism and considered to be the body's own by the immune system. This neuroprotective as well as neuroregenerative treatment approach aims to achieve a long-term therapeutic benefit for the patient.

The liposomal formulation, combined with GM1 as active substance, has two key benefits:

Effect of GM1 proven in clinical studies

The potential of GM1 and its effect on Parkinson's disease has been extensively researched in several preclinical and clinical studies. There are proofs of efficacy in 94 patients with both short-term and long-term treatment success with GM1. With the liposome as a means of transport, the active substance can easily reach the brain without being held back by the blood-brain barrier.

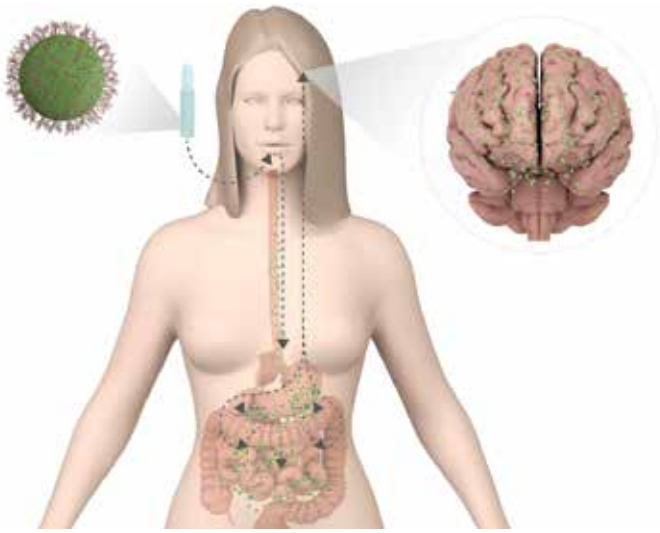


Figure 3: The schematic illustration shows Talineuren in the body after oral administration. Talineuren enters the bloodstream from the gastrointestinal tract, circulates and finally crosses the blood-brain barrier. Once in the brain, GM1 unfolds its regenerative effect.

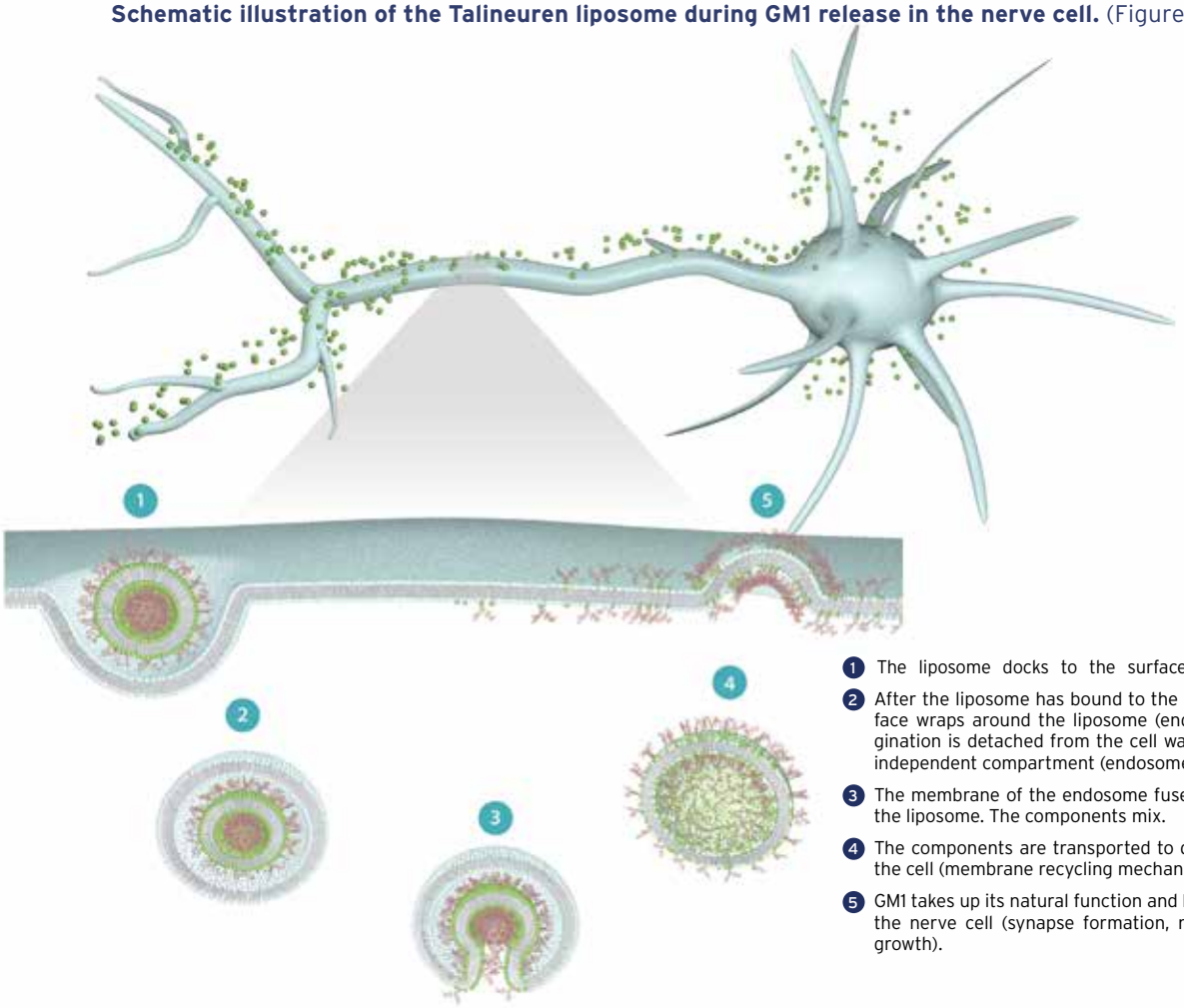
Oral administration avoids known side effects

The intolerable side effects in the form of painful skin irritations caused by the subcutaneous administration of GM1 have until today prevented further development of this therapy. However, InnoMedica's liposomal formulation now allows for oral administration and can thus make this highly effective therapy accessible to Parkinson's patients. In addition, oral administration is much more convenient for the patient than injection and is less arduous.

Furthermore, Talineuren treatment could substantially reduce the demand for conventional Parkinson's drugs. Standard therapy with levodopa causes long-term side effects in many patients, as the dose must be increased a lot over the duration of treatment. Side effects include dyskinesia (involuntary movements), on-off phenomena (strong fluctuations in motor skills), nausea and vomiting, circulatory problems, confusion, hallucinations and insomnia.

The therapy with Talineuren is thus able to elegantly circumvent the unresolved problems of the form of administration of the pure active substance and to maintain the regenerative effect of GM1 treatment.

Schematic illustration of the Talineuren liposome during GM1 release in the nerve cell. (Figure 4)



1. The liposome docks to the surface of the nerve cell.
2. After the liposome has bound to the cell surface, the surface wraps around the liposome (endocytosis). The invagination is detached from the cell wall and now forms an independent compartment (endosome).
3. The membrane of the endosome fuses with the casing of the liposome. The components mix.
4. The components are transported to different locations in the cell (membrane recycling mechanism).
5. GM1 takes up its natural function and begins to regenerate the nerve cell (synapse formation, neuron and dendrite growth).

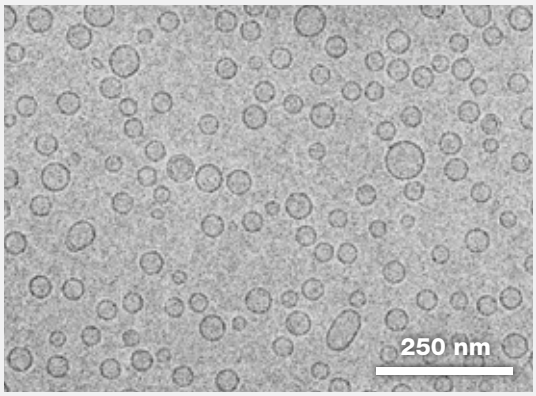
Preclinical Phase

InnoMedica has been developing the liposomal technology for several years and manufactures the liposomes itself in its own production facility in Marly. Experience in the design and production of liposomes contributes to a shortened development phase and has allowed speedy initiation of preclinical studies.

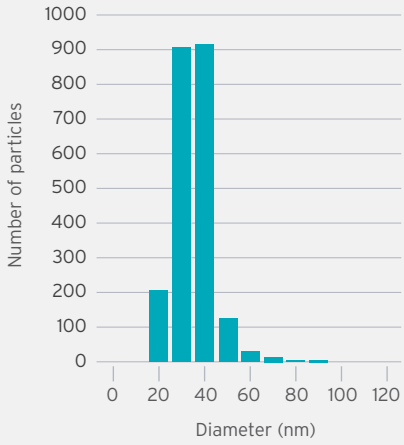
Using cryo-electron microscopy, InnoMedica was able to capture the Talineuren liposomes and visualize the structure of the liposomes and their components. It was possible to precisely determine the diameter of the liposomes in the electron microscope, which averaged 36 nm. The small size is important because it contributes to the fact that the liposomes of InnoMedica can pass the blood-brain barrier. In addition, it has been confirmed that the liposomes examined have a homogeneous round shape and consist of only one single lipid bi-layer membrane. These two characteristics are indicators of a robust and high-quality production (Figure 5).

Liposomal design of Talineuren
(Figure 5)

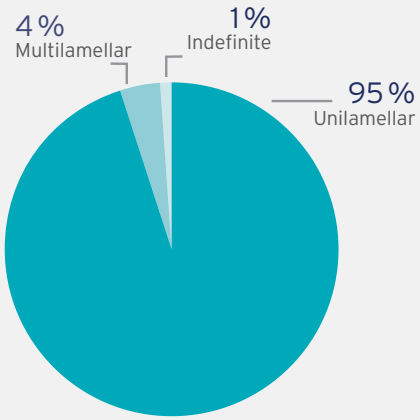
The picture on the right shows a section of cryo-electron microscopy of Talineuren. The liposomal membrane shells are recognizable as dark grey circles. The 20'000-fold magnification allows the visualization of the liposomes, even if they are smaller than 50 nm. By counting 2241 liposomes, properties such as size and structure could be determined. On average, Talineuren liposomes have a diameter of 36nm and are 95% unilamellar.



Liposome size



Liposome structure



The design of the Talineuren liposomes allows the crossing of the blood-brain barrier and thus a targeted transport of GM1 to the nerve cells of the brain.

Crossing the blood-brain-barrier

In several preclinical studies, the distribution of Talineuren in the body of mice was visualized by means of a near-infrared technique. In this study, Talineuren was administered intravenously and it was investigated whether InnoMedica's liposomal formulation of GM1 can pass the blood-brain barrier. An accumulation of Talineuren in the brain has been confirmed this way.

Figure 6 summarizes the results. The background fluorescence corresponds to the natural fluorescence signal of an untreated mouse. The fluorescence signals of liposome 1 and liposome 2 are not significantly different from the background fluorescence. In comparison, however, Talineuren has a significantly higher proportion of fluorescence signal in the brain. Thus, it has been demonstrated that thanks to the transport by the liposomal nanocarrier the liposome reaches the target site, the central nervous system, where GM1 is enriched.

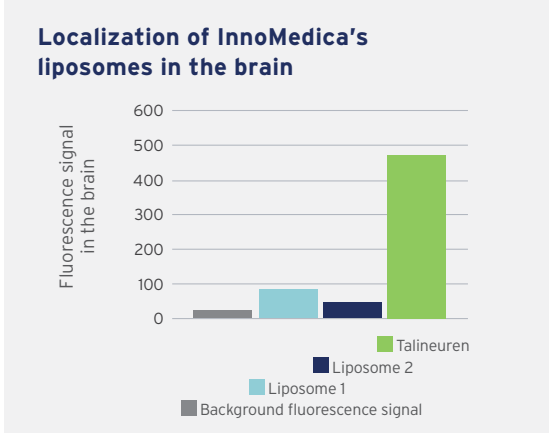


Figure 6: Measurement of the fluorescence signal of InnoMedica's fluorescence-labelled liposomes 24 hours after intravenous administration using near infrared technology. Talineuren shows the highest accumulation in the mouse brain.

Oral administration

To test oral administration, InnoMedica conducted a first preclinical study in an animal model for Parkinson's disease. There are different mouse models for the investigation of Parkinson's disease. InnoMedica deliberately chose a mouse model which was used in the preliminary studies for the humane application of GM1 in the context of the published research work of Prof. Jay Schneider. This mouse model has proven to be representative for the study of free GM1 and subsequent translation into the clinical phase. In addition, comparisons with the preclinical data of free GM1 are thus possible and have a high informative value.

The mouse model simulates a Parkinson-like disease course. In this process, dopamine-producing nerve cells in the brain die, causing the dopamine level to drop. The subsequent treatment of the animals with Talineuren and free GM1 took two weeks. The chromatographic analysis of the brain substance provides information on the amount of dopamine present after the treatment.

The results are shown in Figure 7. The key finding of the study is that oral administration of Talineuren always led to an increase in dopamine levels in the brain, which are typically low in Parkinson's disease. This increase is at least equal to and sometimes even significantly higher than the syringe-injected administration of free GM1. This is particularly noteworthy because the observed increase in dopamine levels in subcutaneously administered free GM1 could later be successfully translated into the human. The increase in the dopamine level during oral administration of Talineuren shows that liposomes are absorbed into the gastrointestinal tract and accumulate in the brain thereafter, where they develop their neuroprotective effect with the release of GM1.

The animal study further showed that in all animals treated with GM1 there was always an increase in dopamine levels measured, while the dopamine level remained low in the untreated group. When free, non-liposomal GM1 is administered orally, the increase in dopamine level is comparatively low. The strongest increase was seen in the groups treated with oral Talineuren at doses of 15 and 7.5 mg/kg. This proves the efficiency of the liposomal technology, as these two doses are 50 and 75 percent lower than with the free GM1.

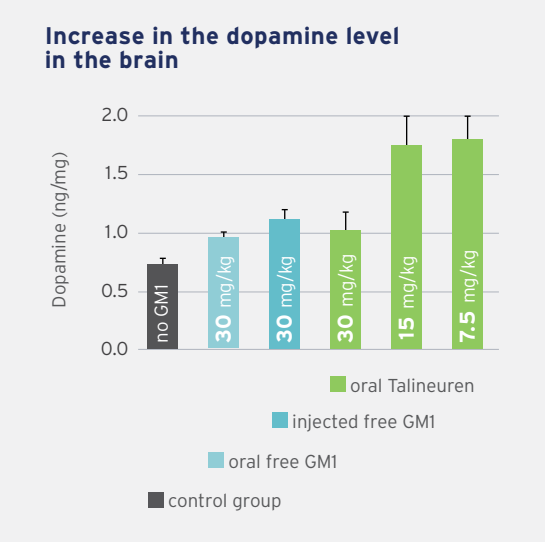


Figure 7: Talineuren orally administered at a dose of 7.5 mg/kg GM1 yields 2.5 times higher dopamine levels in the brain compared to levels of untreated mice.

In the mouse model, oral administration has proven to be an effective form of administration for Talineuren. In its therapeutic application, it offers the advantage of a simple and pain-free treatment that can be carried out without medical help. The patient can therefore largely maintain his independence during therapy, which is particularly desirable in a long period of illness such as in Parkinson's disease.

The use of the liposomal transport system shall be further explored in preclinical research to ensure that no adverse effects occur. In a next step, a comprehensive dose finding study will be carried out. It shall be clarified why in the cross-comparison of the Talineuren groups the smallest increase in dopamine levels occurred in the group receiving the highest dose of GM1. If this effect can be reproduced, possible explanations, such as blockage of absorption at higher doses in the intestine or at the blood-brain barrier, will be further investigated.

The risks of translation into humans are comparatively low, as the effect of GM1 is already known from clinical trials in humans. The existing data and the advanced state of the art of InnoMedica's technology are factors that have a positive effect on the cost and development time of the product.

Despite the mostly unknown cause, dopamine deficiency is observed in all forms of Parkinson's disease. To this day, no Parkinson's therapy is available to doctors that has a preventive or causative effect.

Parkinson's Disease: Cause, Treatment, Research

Parkinson's disease (also known as Morbus Parkinson) belongs to the group of neurodegenerative diseases and is also described as shaking palsy. With „shaking" and „palsy", this term refers to two hallmarks of the disease. In most cases, Parkinson's disease manifests itself in the form of gradual onset and increasing motor disorders over time, which include slowed movements, muscle stiffness, tremors and gait disturbances. The actual cause of the disease is unknown in most cases. Only one fifth of those affected have indications of possible triggers. Parkinson's disease patients may also experience non-motor symptoms such as pain and sensory disturbances, reduced sense of smell, vision problems, constipation or disturbances of blood pressure and thermoregulation. In advanced stages, patients also increasingly suffer from cognitive impairment and psychiatric disorders such as depression, listlessness or hallucinations.

Dopamine deficiency as a cause of symptoms

Despite the mostly unknown etiology, a characteristic neurological disorder in the form of a dopamine deficiency is observed in all forms of Parkinson's disease. Dopamine is a messenger substance that is involved in numerous biochemical processes in different brain regions and plays an important role in the regulation of emotions and impulse control. The dopamine deficiency is caused by the death of dopamine-producing (dopaminergic) nerve cells in the midbrain, where dopamine is needed to trigger and control conscious movements. First symptoms usually do not appear until 50 percent of the dopaminergic neurons have died. From then on, dopamine deficiency leads to motor impairments, which increasingly affect patients in their everyday lives and gradually lead to the loss of independence.

Drug therapies for the treatment of symptoms

A preventive measure or a therapy of the disease-causing factors is not available to doctors to date due to the lack of knowledge regarding the cause of the disease. After the diagnosis, an individual treatment is determined for each patient, which is adapted to his or her symptoms, age and the expected effect.

Currently, three groups of drugs are being used to treat Parkinson's, but these only relieve the symptoms of the condition and aim at increasing dopamine levels in the brain. Levodopa is today's standard therapy; other drugs belong to the class of dopamine agonists and monoamine oxidase (MAO-B) inhibitors.

Levodopa (L-Dopa): Precursor of dopamine

Since its introduction more than 50 years ago, levodopa (L-Dopa) has been the most effective way to reduce the typical movement slowdown in Parkinson's patients. Drug-supplied dopamine cannot enter the brain directly as it cannot penetrate the blood-brain barrier. Levodopa, however, is a precursor of dopamine, which can cross the blood-brain barrier. Converted into the messenger substance dopamine in the brain, it unfolds its biochemical effect. Levodopa is usually given in combination with a decarboxylase inhibitor in order to prevent the metabolism of levodopa in parts of the body other than the brain. The primary disadvantage of levodopa is often the shortening in effect duration over the course of Parkinson's therapy. In addition, the side effects often increase significantly with the duration of levodopa therapy. This can lead to confusion states, cardiovascular disorders and insomnia, among other things. Additionally, with high doses of levodopa given as the disease progresses, many patients experience involuntary movements (L-Dopa-induced dyskinesia, LID). Doctors therefore try to start this therapy as late as possible, especially in younger patients, given the anticipated longer treatment period.

Dopamine agonists: imitation of dopamine

The younger the patient is at the time of diagnosis, the more likely a dopamine agonist is given instead of L-dopa. The dopamine agonist is intended to mimic the effect of the messenger substance dopamine and at a later age is often administered in combination with L-dopa. The continuation of treatment with these drugs in combination with Talineuren is quite conceivable, provided that these agonists additionally reduce the symptoms.

MAO-B inhibitors and COMT inhibitors: inhibition of dopamine degradation

Another frequently used therapy option is the inhibition of dopamine degradation with MAO-B or COMT inhibitors. These block corresponding dopamine-degrading enzymes and thus increase the concentration of dopamine. Even with this approach, only a symptom control is achieved, and the continuous death of the neurons cannot be prevented.

Further therapeutic approaches in development

Stem cell therapy

Parkinson's disease is still an incurable disease. Doctors pay particular attention to research into stem cell therapy. Stem cells are transplanted, which are to entirely replace diseased nerve cells in the future. With this therapy, an effective treatment of Parkinson's disease would be quite conceivable. In other indications, similar approaches are already successfully being used in the clinic (for example, stem cell or bone marrow transplants in leukemia).

Although intensive research is being conducted into stem cells worldwide, the approval of possible therapy in Switzerland is still a long way off. Based on experience from other areas of medicine, it can also be assumed that stem cell transplantation is very costly and involves the following significant risks and uncertainties:

Limited efficacy in the treatment of Parkinson's disease: If only dopamine-producing stem cells are replaced, no improvement is to be expected for non-motor symptoms (digestive disorders, bladder disorders, depression, sleep disorders etc.). This method is not an alternative for symptoms that do not respond to dopamine replacement therapy (balance disorders, speech disorders etc.). In addition, Parkinson's disease not only causes dopaminergic neurons to die, but also other nerve cells inside and outside the brain.

Unclear cell behavior after transplantation: The lifespan and long-term behavior of stem cells in the brain are not conclusively explained. Besides, it is still unclear whether the cells in the brain of the affected patients actually network as much as it is hoped for. In animal experiments, an uncontrolled proliferation of the cells was observed, which indicates tumor formation.

Further risks: There is a possibility of transmitting diseases or triggering a rejection reaction of the transplanted cells in the transplant recipient. It may also be difficult to find a suitable donor for transplantation. Furthermore, in the absence of a transport method bringing stem cells into the brain, a surgical procedure would be necessary.

A comparison with a blood stem cell transplantation during an inpatient stay shows that costs of approximately CHF 330,000 could be incurred. Treatment with Talineuren would be much easier and far cheaper with oral outpatient administration.

Computer-controlled pump

Another possible therapy concept is the use of a computer-controlled pump, which controls the administration of Parkinson's drugs. By means of a probe in the small intestine, the dose fluctuations caused by tablets could be avoided. However, this is just another form of administration of existing drugs and not a novel mechanism of action or a cure for the disease.

Nanoparticles with repair genes

One last hope is research with nanoparticles. In preclinical studies repair genes have already been introduced into damaged dopamine neurons and the function of the nerve cells has been completely restored. In contrast to Talineuren it is to be assumed that the development of such a therapy will take longer time.

The response from neurologists to InnoMedica's regenerative approach with simple oral administration is extremely positive – Talineuren could fundamentally change the treatment of Parkinson's patients.

Outlook

Based on the promising results of the preclinical studies carried out so far, InnoMedica continues the development of Talineuren with great confidence. Knowing the efficacy of GM1 in humans, there is a good chance that Parkinson's patients will be able to benefit from the therapeutic potential of GM1 in the near future thanks to InnoMedica's liposomal formulation without injection-related side effects.

Complementary analyses to determine the number of living nerve cells will be carried out following the preclinical study on oral administration. Once the results are present, it will be possible to deduce to what extent InnoMedica's Talineuren could prevent the death of dopamine-producing nerve cells. In another histopathological study InnoMedica will determine the relationship between dead, inactive and active nerve cells after therapeutic treatment. In addition, the amount of GM1 in the blood and brain, as well as the amount of anti-GM1-antibodies is to be measured. The latter should help estimate the risk of an immune reaction to the drug.

In order to gain a better understanding of the mechanism of action of Talineuren, further studies are planned. In particular, the daily dose and the treatment regimen should be defined more precisely. First histopathological results are expected to be available in the first quarter of 2018 and will be included in both the design of the dose finding study in rats and the toxicology study.

For the translation of a drug from animal to human, a toxicology study is required whose purpose it is to demonstrate the dosage threshold to toxicity. This should show at which dose the test agent behaves toxic in healthy animals. The study assesses the tolerability of the product in relation to the dosage and must be carried out in accordance with legal standards (good laboratory practice, GLP).

InnoMedica took up dialogue with leading neurologists from various clinics in Switzerland and other countries in the autumn of 2017 to evaluate potential collaborations for the implementation of clinical phase I and II trials with Talineuren. The response from physicians to InnoMedica's long-term neuroprotective approach is extremely positive, because it is not limited to alleviating symptoms like current therapies but is intended to prevent the progression of the disease.

However, to start a phase I clinical study, the following steps must be taken: Talineuren must be produced in accordance with GMP standards, the preclinical phase must be completed up to and including the toxicology study in animals, and the study application must be approved by Swissmedic and the ethics committee. In addition, a production scale-up is necessary so that the quantities of Talineuren required for the clinical trial can be produced. As the production facilities have already been set up for InnoMedica's oncology product Talidox and equipment has been qualified for GMP production, a shortened procedure for achieving GMP readiness of Talineuren can be expected.

If the application for the clinical trial is granted, phase I clinical trials may begin. This serves to prove that Talineuren in humans can be used, without behaving toxic. Since Talineuren consists of endogenous molecules, the risk of such toxic behavior is generally lower, which may have a positive effect on registration for a phase I study. The data already available on the translation into humans from Prof. Jay Schneider, which showed a favorable therapeutic effect of GM1 in the absence of drug-related toxic side effects, should further facilitate the submission of the dossier of Talineuren to the authorities.

Nevertheless, there are some significant challenges associated with the project. GM1 is a biological raw material, which is purified in industrial processes and whose procurement is demanding, since the assurance of the necessary quality must be monitored throughout the entire supply chain. Furthermore, for daily oral intake the drug is needed in large quantities. For larger patient numbers, the procurement of GM1 requires a dedicated collaboration with one or more suppliers. But also, the filling of a large number of vials, due to the daily administration to the patient, is demanding and requires investments in automation.

To produce Talineuren clean rooms are needed in which no cytostatic is used. InnoMedica is therefore planning to commission a larger clean room for the

production of the oncology product Talidox. This would make the existing smaller clean room freely available for the Talineuren production. This is a good solution for the time being, but because of insufficient space reserves for bottling, it could quickly reach its limits. According to an agreement with the proprietor at the production site in Marly, however, additional rooms have already been reserved, which are suitable for the conversion to a large clean room for Talineuren. As a result, InnoMedica can continue to advance the toxicology study and clinical trial phase I planning, while steadily adapting the infrastructure to meet increasing demands. This is the only way to ensure that the necessary volumes can be delivered on time.

InnoMedica considers the starting position for Talineuren to be extremely attractive. The active substance is known from various preclinical and clinical studies and thus its translation from preclinical to human.

Regarding the manufacturing InnoMedica can draw on Talidox's scale-up experience, and its model can essentially be adopted. The lack of similar treatment options will further facilitate collaboration with public authorities and participating physicians. All of this creates optimal conditions for the launch of the new pipeline product and its preclinical and clinical development to market approval. InnoMedica is convinced that Talineuren will be a long-term effective therapy which, with its regenerative approach and simple oral administration, will fundamentally change the treatment of Parkinson's patients.

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The English version of InnoMedica's Talineuren brochure March 2018 was translated from the original German version which shall be binding in case of disparities.