Reference – Opening of file

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| **Jerusalem District Court**Civil File 37155-09-18 Sarah Herzog Memorial Hospital Ezrat Nashim vs. Thursday 20 September 2018 Joit et al.Confirmation of opening of fileA confirmation has been given that on 20 September 2018 at 15:49 in this court Civil File 37155-09-18 Sarah Herzog Memorial Hospital Ezrat Nashim vs. Joit et al. was opened.The opening statement of contentions is to be produced for the opposing litigants within 5 days, by registered mail with confirmation of delivery, unless the court orders otherwise.Rulings and decisions are published at the website of the court system at the address [www.court.gov.il](http://www.court.gov.il)((https://www.gov.il/he/Departments/the\_judicial\_authority |

https://secure.court.gov.il/NGCS.Web.Secured/OpenCase/Pages/CaseComfirmationProofView.aspx

**The District Court Civil File \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**In Jerusalem**

**Sarah Herzog Memorial Hospital Ezrat Nashim**

Society number: 580082303

Represented by its attorney and patent attorney from the office of **Pearl Cohen Zedek Latzer Baratz**

Azrieli Sarona Tower, 121 Menahem Begin Road, Tel Aviv 6701203

Tel.: 03-3039000, Fax: 03-3039001

Email: ReceptionIL@PearlCohen.com **Plaintiff**

**- vs -**

1. **Prof. Daniel Joit**, passport number: 153130834

 58 Nahalat Binyamin St., Office 203

 Tel Aviv 6513316

2. **NeuroRX, Inc.**

 58 Nahalat Binyamin St., Office 203

 Tel Aviv 6513316

3. **Dr. Jonathan Joit**

 ID number: 336145768

 63 Hameyasdim St.

 Zichron Yaakov 3091097

 **Defendants**

**STATEMENT OF CLAIM**

Substance of the claim: intellectual property, declarative relief, mandatory order, the provision of accounts.

1. **“As the partridge sitteth on eggs, and hatcheth them not; so he that getteth riches, and not by right” (Jeremiah 17:11)**
	1. Against the background of this saying, we may describe the claim under consideration which deals with a blatant theft of inventions from Herzog Hospital – a psychiatric hospital in Jerusalem and nonprofit society, working to provide medical treatment to thousands of seriously ill patients while carrying out clinical research with the aim of bringing relief to patients across the world.
	2. The inventions and technologies stolen and which were developed with great effort in the framework of studies carried out at the hospital by the hospital researchers was meant to be owned by the hospital and commercialized via cooperation conducted in good faith and full trust with Defendant 1 – a researcher in the world of psychiatry, who was entrusted with the continuation of the development of the inventions and their commercialization.
	3. Within the framework of the cooperation between the parties, the hospital made information and data available to Defendant 1 and granted him full freedom of research activity, in the belief that he would act for the joint interests of the parties.
	4. Over time, it became clear, unfortunately, that over the years Defendant 1 was leading a “double life”, in which he was “smuggling” the Plaintiff’s inventions, abandoning the joint commercialization and development, making the hospital’s inventions and developments his own. Thus the Plaintiff discovered, to its astonishment, for the first time in the framework of a television interview, that **Defendant 1 had set up a partnership with his brother**, a commercial company dealing in the development of psychiatric products, **based on the same technology and the same research platform developed by the hospital, which was to have been jointly commercialized and developed**.
	5. Thus, instead of continuing to develop and commercialize the hospital’s inventions, Defendant 1 chose to establish a competing company in the dark together with his brother and to develop the technologies for their benefit. Bit by bit, the Plaintiff discovered the scope of the deeds and the theft, and the pattern of action became clear. Thus, over the years and while registering patents on the basis of the technologies which were developed at the hospital, and while “anesthetizing the Plaintiff”, Defendant 1 went to the trouble to file applications for the registration of patents based on that technology and even on the various aspects of those inventions, in his name only and far from the knowledge of the Plaintiff, without the Plaintiff being listed as owner and without its researchers being listed as the inventors.
	6. As if that were not enough, the patent applications on behalf of Defendant 1 with regard to the technologies on the basis of which the commercial company was formed with his brother were filed at the same time as the filing of the hospital’s patent applications for the exact same technology. If Defendant 1 had acted as required and as expected of him according to law, these applications would naturally have been filed as applications owned by the hospital or at the very least as continued applications from the partnership of the parties.
	7. Along the way, the Plaintiff discovered, to its astonishment, that in the framework of the contractual “family” connection between Defendant 1 and his brother, there was an agreement, *inter alia*, even on **an option to purchase a license on patents of the joint company** (and additional patents), without the knowledge of the Plaintiff. **In other words, in an extreme conflict of interest, Defendant 1 gave the company owned by him an option to purchase a license on patents of the joint company behind the back of the Plaintiff and without its knowledge.** Defendants 2 and 3 cooperated in the above-mentioned transaction with their eyes open and with the clear knowledge that the matter had not been discussed with or approved by the Plaintiff.
	8. And as if this were not enough, as time passed it became clear that during the examination of the applications of Defendant 1, Defendant 1 permitted himself to act with a conflict of interest and take positions with regard to the joint patent applications in order to promote his applications, all without the approval of the Plaintiff.
	9. Upon discovery of the theft, the Plaintiff, as could be expected of it, preferred not to stop the research and the commercialization, and to apply to the Defendants in an effort to arrange the restoration of ownership of the inventions to the hospital and to bring about a solution outside the walls of the courtroom.
	10. In the framework of the dialogue between the parties, and the moment when Defendant 1 understood that his actions had been exposed, he agreed immediately and over the years of contacts **that all the patents – the joint ones and those filed only by him outside the knowledge of the Plaintiff, would be returned to the full ownership of the Plaintiff (or of a company on its behalf), which, on its part, granted a usage license for them to the Defendants against the payment of suitable and reasonable royalties**. However, the central dispute between the parties revolved around the consideration owed to the hospital.
	11. Over all the years of the negotiations, the Defendants continued to conduct themselves with a lack of good faith, while concealing information relevant to the negotiations the whole time, taking unilateral steps with regard to the intellectual property and even making odd threats of one sort or another in an attempt to frighten the Plaintiff and prevent it from acting to protect its rights.
	12. Under these circumstances, the Plaintiff had not choice but to file this claim. Below is a more detailed account:
2. **The Parties**
	1. The Plaintiff, Sarah Herzog Memorial Hospital Ezrat Nashim (hereinafter: “**Herzog**” or “**Plaintiff**”) is a geriatric and psychiatric-general hospital (the first psychiatric hospital in the Middle East) as well as a nonprofit organization whose number is: 580082303. The medical center was established in 1894 with the name Ezrat Nashim with the purpose of assisting the mentally ill.
	2. The hospital consists of two central wards:

**The geriatric wards**, which specializes in problems connected with aging, including psychogeriatrics and diagnostics and the treatment of Parkinson’s and Alzheimer’s disease, complex medical and nursing care, chronic respiratory treatment, physical rehabilitation, etc. As a direct result of the expertise which the hospital has acquired in the field of respiratory treatment, a unit was also established for chronic respiratory treatment of children.

**The psychiatric ward**, which specializes in the treatment of patients suffering from schizophrenia and other mental illnesses.

* 1. At the same time, Herzog also operates outpatient clinics in the community, including the community center for mental health, which treats about 2,000 women, men and children per month and concentrates mainly on the treatment of the mentally ill and children suffering from ADHD.
	2. In addition, the hospital operates the Israel Psychotrauma Center, which treats PTSD resulting from terror attacks, violent incidents, natural disasters, etc.
	3. Herzog, which is the third largest hospital in Jerusalem, is a nonprofit organization and does not receive government funding. It is administered by a volunteer management committee, and its income is based on its medical activity and on donations.
	4. Together with treatment and clinical wards, based on the broad experience accumulated at Herzog with regard to psychiatric, neurological, geriatric and pediatric treatment, the center has unified all R&D in these fields in the Clinical  Research Center for Brain Sciences – a multidisciplinary research center for the human brain.
	5. The Herzog research unit has won international recognition thanks to its breakthrough work in the fields of behavioral genetics, schizophrenia, Alzheimer’s and Parkinson’s disease and ADHD. Herzog researchers have been given many, various research grants such as grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD) of the United States; the European Union; the Israel Society of Biological Psychiatry; the Israeli Ministry of Science and many other financing bodies. Herzog researchers have published many international articles, often in cooperation with other hospitals and universities throughout the world.
	6. The administrator of the mental health ward in Herzog Hospital for the past 14 years since 2014 is Prof. Uriel Heresco-Levy (hereinafter: “**Prof. Heresco**”) – a full professor of psychiatry in the Medical School of Hebrew University and Hadassah. Beyond the day-to-day and continuous psychiatric treatment given by Prof. Heresco to the patients in the ward suffering from difficult and complex illnesses, Prof. Heresco invests his energy and time also in research and development, in an attempt to find additional medicinal solutions and cures for his patients. Prof. Heresco is a leading researcher in the fields of treatment of schizophrenia and depression and over the years has won various prizes and grants for his research, including from: the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Stanley Fund, the European Union – Neuron 2017 and the Israel Academy of Science.
	7. Defendant 1, Prof. Daniel Joit (hereinafter: “**Prof. Joit**” or “**Defendant 1**”), is a psychiatrist and professor of neurology at Columbia University in New York.
	8. Mr. Daniel Joit is the joint founder of Defendant 2, the chairman of Defendant 2 and a member of the science advisory board of the company. A copy of the webpage from the website of Defendant 2 is attached and marked **A**; it describes the position of Prof. Joit in the company. Over the years, Defendant 1 has established various companies under his full ownership, which have served as “wallet companies” for various contractual connections and occasionally for holding intellectual property (including that under dispute). For our purposes, these two are relevant: Glytech, LLC (hereinafter: “**Glytech**”) and AminoAcid Solutions, Inc. (hereinafter: “**AASI**”).
	9. Defendant 2 is NeuroRX (hereinafter: “**NeuroRX**” or “**Defendant 2**”), an Israeli-American pharmaceutical startup company established by the two brothers – Defendants 1 and 3 – in 2015 for the purpose of developing drugs for the treatment of CNS disorders. According to the information on the company website, the company is now progressing in the development of drug therapy for depression in bipolar disorder, known also as manic depression. Attached herein and marked **B** is the webpage from the website of the company which offers a review of its activity. To the best of the knowledge of the Plaintiff and according to its examination, Defendant 2 was established on the basis of the intellectual property of the Plaintiff as will be detailed below.
	10. Defendant 3 is Dr. Jonathan Joit (hereinafter: “**Jonathan Joit**” or “**Defendant 2**”), an ophthalmologist by training and, to the best of the knowledge of the Plaintiff, is lacking any scientific experience in the field of activity of Defendant 2. Defendant 3 is the CEO of Defendant 2, and, as stated, the brother of Defendant 1.
1. **The chain of events**
	* 1. **Professor Heresco’s journey to a fellowship at the Einstein Medical Center**
	1. Prof. Heresco began his work as a clinical psychiatrist in the mental health ward of Herzog Medical Center in 1986. Upon starting his work in the ward, Prof. Heresco began to treat patients with schizophrenia – one of the more serious and complex mental disorders in the field of mental illness. Over the years, beside his ongoing clinical work, Prof. Heresco began to take an interest and carry out various studies with regard to the mapping and comprehension of the drug treatment for schizophrenia[[1]](#footnote-1).
	2. In 1991, his employment and interest in schizophrenia led Prof. Heresco to fly to New York as a research fellow in the Albert Einstein College of Medicine (hereinafter: “**Einstein**”). The fellowship program at Einstein was administered by Prof. Stephen Zukin, who was a pioneer in the field of research in schizophrenia, as will be detailed below.
	3. In the framework of the research conducted at Einstein, Prof. Zukin and Joit then examined the effect of the addition and modulation of the amino acid glycine, which is linked to N-methyl-D-aspartate nerve receptors (hereinafter: “**NMDA**”) found in nerve cells, on psychosis – which is a part of schizophrenia.

**NMDA receptors**

* 1. A receptor is a protein found on membranes of cells (or in the cell fluid), the function of which is to signal to the cell to execute a particular biological action, such as division, release or introduction of substances into the cell, etc.
	2. The transfer of the signal is done by binding a small molecule called a ligand to a designated target site on the receptor, whereby the binding of the ligand to the receptor (which is similar to the connection between a key and a lock) is mediated by a certain biological action in the cell. This biological action constitutes part of a biological signal transmission chain.
	3. The NMDA receptor, as stated, is a **nerve receptor** – a type of receptor found in nerve cells which responds to neurotransmitter ligands – nerve transmitters. The binding of the neurotransmitter to the receptor causes the transmission of nerve signals between one nerve cell and another. The transmission of the signal is done by means of the opening and closing of ion channels located on the cell membranes, where the ion flow causes a change in the electric voltage of the cell membrane which leads to the transition of the nerve signal.
	4. NMDA is a dedicated nerve receptor for glutamate. However, in addition to the glutamate binding site, additional dedicated binding sites are found on the surface of the NMDA receptor to additional ligands which mediate various neurological actions by means of their binding. The ligands which lead to the activation of the receptor are called **agonist** molecules, while ligands which delay the action of the receptor are called **antagonist** molecules.
	5. The NMDA receptor has a central function in the learning and memory processes and in the strength of the synapse (the meeting place between the nerve cell and the target cell). Over the years, it was also discovered that these receptors are involved in symptoms of a variety of illnesses connected with the central nervous system and mental illnesses, including Alzheimer’s and Parkinson’s disease and schizophrenia, and there is a clear effect on their activity as the result of the taking of various psychoactive drugs.
	6. When in 1991 Prof. Heresco went to the Einstein Medical Center, this, as stated, was in order to take part in work under the guidance of Prof. Pan Pereg, the head of the course at Einstein, and Prof. Zukin. At that time, Prof. Joit was a researcher at the start of his career, who was working with Prof. Zukin. Over the years, a large share of the research of Prof. Joit was devoted to the study of the NMDA receptors, mainly in the context of schizophrenia.
	7. In the framework of the research carried out at Einstein, Prof. Heresco and other researchers under the guidance of Prof. Joit studied the effect of giving glycine to 14 patients with schizophrenia. The results of this study showed an improvement in the symptoms of the disease following the addition of the glycine[[2]](#footnote-2).
		1. **The study of schizophrenia carried out by Prof. Heresco at Herzog and the discovery with regard to mobility.**
	8. Upon the return of Prof. Heresco to Israel in 1993, he returned to his clinical work in the psychiatric ward at Herzog. Together with his clinical work mainly with schizophrenics, Prof. Heresco decided not to neglect the research channel which he had begun at Einstein and continued **independently** in the research wing of Herzog, in the hope of finding new, alternative treatment discoveries which would aid his patients.
	9. Prof. Heresco then decided to plan an additional clinical study to be carried out at Herzog, the purpose of which was to examine how the addition of glycine to the existing drug regime given to schizophrenics would affect the course of the disease and its symptoms.
	10. Due to his ongoing clinical work, Prof. Heresco had the advantage, on a daily and independent manner, of clinically identifying the effect of one drug regime or another on the symptoms of the disease, which would not necessarily be identifiable in a laboratory.
	11. The studies planned and executed by Prof. Heresco showed that the addition of glycine to the existing drug regime being given to schizophrenics who developed a resistance to drug therapy caused a decline in the negative symptoms of the disease[[3]](#footnote-3).
	12. This study lead to an additional series of studies, in the framework of which Prof. Heresco researched the effect of additional agonists on the NMDA receptor on the symptoms of schizophrenia, including the amino acid **D-serine** and **D-cycloserine** (hereinafter: “**DCS**”) – a type of antibiotic for the treatment of tuberculosis – which is also known as a partial agonist for the NMDA receptor. These studies showed a symptomatic improvement in the patients who, in addition to the drug therapy, also received DCS, glycine or D-serine, in comparison with patients who received a placebo[[4]](#footnote-4).
	13. However, and this is the main point: the results of the trials also lead to a surprising and unexpected scientific discovery – Prof. Heresco discovered an unexpected clinical change in one of the drugs caused generally as a result of **receiving drug treatment for schizophrenia** – Prof. Heresco discovered that for patients who at the same time were receiving drug treatment, glycine or D-serine, a significant improvement was observed in involuntary excessive movement accompanying anti-psychotic drug therapy.
	14. Schizophrenics undergoing antipsychotic treatment frequently develop movement side effects similar to the symptoms of Parkinson’s disease (the phenomenon is called “**Parkinsonism**”), which includes shaking, stiffness and muscular hypertonicity, bradykinesia – the symptom of slowness of movement, as well as dyskinesia – a movement disorder characterized by involuntary muscle movements and a decline in the ability to execute voluntary movements[[5]](#footnote-5).
	15. As soon as Prof. Heresco discovered and identified the clinical improvement in movement symptoms, he decided to examine the subject with patients with Parkinson’s disease as well who suffer from the same symptoms as a result of the disease itself (and not as a result of the taking of the drugs). Therefore, Prof. Heresco carried out an additional clinical trial at Herzog intended to examine the effects of an addition of D-serine to the movement symptoms in **Parkinson sufferers**. The results of the study confirmed the conclusions of Prof. Heresco and demonstrated a significant improvement in the movement disorders accompanying the disease.
	16. Prof. Heresco made contact with Prof. Joit who, as stated, had experience in working with the NMDA receptor and in the study of schizophrenia and had cooperated with him in the surprising clinical improvement he had identified in the measurement of movement. Prof. Joit, sharing the enthusiasm of Prof. Heresco from the invention, wished to receive the results of the trials that had been done and asked to carry out the statistical processing of the results, so that it would be possible to demonstrate them in the framework of articles or a patent application.
		1. **Patent 105 – Patent #1**
	17. After Prof. Joit viewed the surprising results, the two researchers turned to Dr. Yehezkel Caine, CEO of the Herzog Medical Center, and asked to file a patent application on the basis of the research. Dr. Caine approved their going ahead and filing a patent application as stated. On 6 February 2003, patent application number IL154318 was filed for registration in Israel with the heading: “Pharmaceutical Compositions for the Treatment of Movement Disorders”. The application was filed of course in the name and under the full ownership of Herzog Hospital, where Prof. Heresco and Prof. Joit were registered as its inventors. This application was registered as a patent on 1 September 2010.
	18. On the basis of the Israeli patent application, that same year an American patent application was also filed in the name of Herzog, which was registered as Registered Patent No. US 8,629,105 under the heading “Pharmaceutical Compositions for the Treatment of Movement Disorders” (hereinafter: “**105**” or Patent “**1**”) (additional applications were also filed in other places in the world).
	19. The patent application explains that Parkinson’s is a neurological disorder accompanied by movement symptoms and that according to various theories, NMDA receptors have an important function in the development of Parkinson symptoms. The patent application explains that contrary to previous knowledge, it was discovered by chance in the framework of the study that **agonists** to the NMDA receptors (i.e. molecules which activate it), and primarily those specifically dedicated to the target site of the amino acid glycine, were discovered to be effective in the treatment of movement disorders. The patent application offers a number of examples which demonstrate clinical trials with glycine, D-serine and DCS in schizophrenics as well as trials with glycine and DCS in animals.
	20. This patent claims a system for treating the symptoms and dyskinetic side effects in patients with movement disorders by means of glycine or D-serine or blockers to the absorption of glycine or D-serine or combinations thereof, for the purpose of easing the movement symptoms.
	21. Over the years, the two researchers published a series of articles on the basis of the research carried out at Herzog[[6]](#footnote-6).
		1. **The establishment of SEROTECH**
	22. During 2004, Dr. Caine, the CEO of Herzog, and Prof. Joit decided that it would be appropriate to try and develop a product which could be commercialized and could offer a cure to many patients throughout the world. Since the Herzog Medical Center is a nonprofit clinical center and has little (if any) experience in commercialization, Prof. Heresco and Dr. Caine were pleased with the involvement of Prof. Joit, who up to that date had already filed a number of patent applications and was viewed by them as having commercial experience.
	23. The two of them, who had developed a great trust in Prof Joit, spoke with him of the possibility that the parties would continue to commercialize the technologies jointly. At that stage, Prof. Joit suggested establishing a commercial company which would be jointly owned by Prof. Joit and Herzog (by means of companies on behalf of both parties). For this purpose, Herzog established a commercial company fully owned by it under the name Teniv. It was agreed between the parties that Prof. Joit would be responsible for the commercialization of the discoveries developed at Herzog.
	24. On 22 October 2004, SEROTECH, LLC (hereinafter: “**SEROTECH**”) was established in Delaware, USA, as a limited liability company. On 9 February 2005, Teniv and AASI signed an agreement arranging the activity of SEROTECH under the title “Limited Liability Company Agreement of SEROTECH, LLC”. a copy of the agreement signed between the parties is attached and marked **C**.
	25. Within the framework of the agreement, the parties stated that the joint company would deal in the commercialization of the technology in American Patent Application Number US20040157926, which had been registered as Patent 105 (Patent 1). According to the agreement, the company would deal in the promotion of the commercialization of applications for the use of D-serine and related compounds for the treatment of Parkinson’s and related disorders.
	26. In this framework, it was agreed that 80% of the company would be owned by Teniv (the hospital’s company), which had brought the intellectual property and had invested the capital required for the registration of the patent, and of course the cost of the studies, while 20% would be owned by AASI (owned by Prof. Joit). This division, as was believed in real time by the parties, would correctly reflect the contribution of the parties to the inventions and the division of the economic risk between them in light of the belief that Prof. Joit would work to commercialize the technology.
		1. **The trial carried out at Herzog on DCS for the treatment of depression**
	27. After the establishment of SEROTECH, Prof. Heresco continued his ongoing clinical work in the ward while carrying out studies in the field of clinical applications of pharmacological modulation of the NMDA receptor in psychiatric diseases. In this context, he continued a series of studies intended to examine the effect of DCS as a possible treatment for depression.
	28. Studies up to the middle of the 1990s had demonstrated that various drugs delayed the activity of the NMDA receptor, brought about anti-depressive effects in laboratory animals, including drugs being used as partial agonists or antagonists to the NMDA receptor, although also in various target sites on the receptor other than the glycine (or glutamate) sites.
	29. In a study executed in 2000, it was demonstrated surprisingly that the use of the anesthetic **ketamine**, which constitutes an irreversible antagonist to the NMDA receptor (at a particular site on the receptor), was seen as having a significant anti-depressive effect. Additional studies carried out afterward also showed that giving ketamine significantly improves the symptoms of depression. Surprisingly, the studies also showed that the symptomatic improvement was observed only about two to three hours after a one-time intravenous dose of ketamine and was maintained several weeks thereafter.
	30. However, despite the surprising results, it was known at that time that the continued use of ketamine was impractical due to the serious side effects of ketamine – including confusion, a cognitive decline as well as an addictive tendency[[7]](#footnote-7).
	31. These studies excited the curiosity of Prof. Heresco. In addition, in the clinical field, Prof. Heresco knew that earlier reports from as far back as the 1950s and 60s carried out by a researcher named George E. Crane (hereinafter: “**Crane**”) had showed that the use of DCS, which had already been approved as an antibiotic treatment in the 50s for treating tuberculosis (Seromycin®) had demonstrated a clinical improvement in the mood of tuberculosis patients[[8]](#footnote-8). An additional study carried out by Crane, also in tuberculosis patients, reported an improvement in various symptoms of neurosis, sleep disorders, depression, etc. while receiving DCS[[9]](#footnote-9).
	32. Several decades later, it was discovered that DCS is a “**partial agonist**” to the NMDA receptor; i.e. a molecule which in low dosages functions as an agonist and activates the receptor, while in high dosages, it becomes an **antagonist** and delays its activity.
	33. However, even if a number of optimal phenomena were observed in laboratory animals, no studies have been done with DCS for patients diagnosed as suffering from depression. Moreover, it was known that high dosages of antagonists to NMDA have serious effects (psychosis), while serious effects are also known for DCS, including psychosis and seizures.
	34. Despite this, Prof. Heresco decided to examine whether DCS could turn out to be effective in the treatment of patients diagnosed scientifically as suffering from persistent depression (i.e. depression which does not respond to drug treatment), since it also constitutes an antagonist to the NMDA receptor like ketamine (although with a different mechanism), and it has already been demonstrated that it led in the past to a change in the mood of patients with tuberculosis, even when not diagnosed as suffering from depression.
	35. Against the background of these facts, in 2005, Prof. Heresco initiated a clinical proof of concept randomized control trial at Herzog, in the framework of which he added to the fixed drug treatment of 22 patients suffering from persistent clinical depression DCS in the low dosage of 250 mg. per day, for a period of 6 weeks.
	36. The results of the trial which were received were not unambiguous – on the one hand, an improvement was demonstrated in observed clinical symptoms, the DCS dosages were well received by the patients, but on the other hand, an improvement in the depression indexes measured in the patients during the trial did not show an unambiguous trend in comparison with the placebo.
	37. Prof. Heresco decided to share the trial results which he had received with Prof. Joit. The two again decided that Prof. Heresco would transmit all the data to Prof. Joit, and Prof. Joit would carry out the statistical analysis of the results received. In 2006, the two (and additional researchers at Herzog) published an article summarizing the trial carried out at Herzog[[10]](#footnote-10).
	38. Despite the lack of significance in the results received, Prof. Heresco decided not to abandon the direction of the study of DCS and to try to make use of additional dosages of DCS. However, due to the serious side effects known in use of antagonists to the NMDA receptor in general, and to DCS in high dosages, Prof. Heresco decided to construct a trial in the framework of which he would raise the DCS dosage gradually.
1. See, for example, the following publications and lectures, which indicate the activity of Prof. Heresco during those years: Heresco-Levy et al., ***Prescribing patterns of neuroactive drugs in 98 schizophrenic outpatients***, Israel Journal of Psychiatry and Related Sciences, 3:157-163 (1998); Heresco-Levy et al., ***Post dose reduction survival in the maintenance treatment of schizophrenia***, Schizophrenia Research, 3:39-40 (1990); Gropp C et al., ***Water intoxication with marked hyponatremia in two chronic schizophrenic inpatients***, Israel Psychiatric Association, 6th National Congress, Tel Aviv, Israel (poster 1988); Heresco-Levy et al. ***Psychotropic drugs: Survey of prescribing patterns in chronic schizophrenic outpatients***, Israel Psychiatric Association, 6th National Congress, Tel Aviv, Israel (lecture, 1988); Heresco-Levy et al. ***Low-dose strategies in the treatment of schizophrenia***, Israel Psychiatric Association Meeting, Assaf Harofe Medical Center 40th Anniversary, Tsrifim, Israel (lecture, 1990); Heresco-Levy et al., ***Low-dose maintenance treatment in schizophrenia***; University, ***Relapse in schizophrenia***, Department of Psychiatry and Human Behavior, Brown ***Predictors of*** Providence, Rhode Island (lecture, 1990); Heresco-Levy et al., ***Post dose reduction survival in the maintenance treatment of schizophrenia***, International Congress on Schizophrenia Research, Badgastein, Austria, (poster, 1990); ***Two years after maintenance neuroleptic dose reduction in schizophrenia***, Heresco-Levy et al. ***Predictors of relapse*** Israel Psychiatric Association, 7th National Congress, Jerusalem, Israel (lecture, 1990). [↑](#footnote-ref-1)
2. Javitt DC et al. Heresco-Levy U., ***Amelioration of negative symptoms in schizophrenia by glycine***, American Journal of Psychiatry 1994, 151(8), 1234-6. [↑](#footnote-ref-2)
3. 3Heresco-Levy U., et al., ***Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia***, The British Journal of Psychiatry 1996, 169(5), 610-617 ; Archives of General Psychiatry, 1999, 56, 29-36 (1999); Heresco-Levy., et al., ***Efficacy of High-Dose Glycine in the Treatment of Enduring Negative Symptoms of Schizophrenia***, Archives of General Psychiatry, 1999, 56, 29-36 (publication accompanied by editorials). [↑](#footnote-ref-3)
4. Heresco-Levy U. Javitt DC et al., ***Double-blind, placebo-controlled, crossover trial of D-cycloserine adjuvant***

***therapy for treatment-resistant schizophrenia***, The International Journal of Neuropsychopharmacology 1998, 1, 131-135; Heresco-Levy U. ***N-Methyl-D-aspartate (NMDA) receptor-based treatment approaches in schizophrenia: the first decade***. The International Journal of Neuropsychopharmacology 2000, 3, 243-258; Heresco-Levy U, Javitt DC., et al., Pla***cebo-controlled trial of D-cycloserine added to conventional neuroleptics, olanzapine and risperidone in schizophrenia***, American Journal of Psychiatry, 2002, 159, 480-482; Heresco-Levy U. Javitt DC et al., ***D-Serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia*** Biological Psychiatry, 2005, 57, 577-585. [↑](#footnote-ref-4)
5. See US Patent 8,629,105 below, on p. 1 line 59+. [↑](#footnote-ref-5)
6. Gelfin E, Heresco-Levy U. Javitt DC et al., ***D-serine treatment alleviates motor and behavioral symptoms in***

***Parkinson’s disease***, The International Journal of Neuropsychopharmacology 2012, 15, 543-549; Shoham S, Javitt DC, Heresco-Levy U, et al., ***Glycine and D-cycloserine attenuate vacuous chewing movements in a rat model of tardive*** ***dyskinesia***, Brain Research 2004, 1004, 142-147.; Heresco-Levy U. Javitt DC, et al., ***Glycine site agonists of the N-methyl-D-aspartate receptor and Parkinson's disease: a hypothesis***, Movement Disorders, 2013, 28, 419-424. [↑](#footnote-ref-6)
7. Heresco-Levy, ***Glutamatergic Mechanisms in Depression: Focus on D-cycloserine***, Current Psychopharmacology,

.2017, Vol.6, No. 2. [↑](#footnote-ref-7)
8. Crane, G.E. (1959) ***Cycloserine as an antidepressant agent***, Am. J Psychiatry, 1959, 115(11), 1025-1026. [↑](#footnote-ref-8)
9. Crane, G.E., ***The psychotropic effects of cycloserine: A new use for an antibiotic***, Comprehensive Psychiatry 1961, 2(1), 51-59. [↑](#footnote-ref-9)
10. See Heresco-Levy et al., C***ontrolled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder,*** Journal of Affective Disorders 93 (2006) 239–243. [↑](#footnote-ref-10)