



## **IMPORTANT**

**This document is an unofficial translation of the Hebrew original Barnea report (Description of Company's Activities), December 31, 2010 from the financial report of Hadasit Bio-Holdings Ltd. that was submitted to the Tel-Aviv Stock Exchange and the Israeli Securities Authority on March 31, 2011.**

**The Hebrew version submitted to the TASE and the Israeli Securities Authority shall be the sole binding legal version.  
This translation is for the convenience of English readers only.**

## **Description of the Company's Activities 2010**

**This description of the Company's activities includes forecasts, assumptions and estimates whose realization is uncertain, and which are outside of the Company's control. In light of the fact that the Company maintains holdings in several technological companies (the "Project Companies") which are currently in various stages of performing research and development on their base ideas, the Company has no measure of certainty regarding the realization of forecasts and of projections made with regards to the developments and technologies constituting the base ideas of the Project Companies. The progress of research and development depends, inter alia, on the rate and amount of financing raised by the Project Companies.**

### **1. 5.1 Description of the Company's Operations and of the Development of its Business Activities**

#### **5.1.1 General**

[A] The Company was founded on September 19, 2005 by Hadasit Medical Research Services & Development Ltd. ("**Hadasit**").

On December 28, 2005, the Company published a public offering prospectus of its shares (the Company was founded as a research and development company, and intends to continue engaging in research and development in the fields of medicine and biotechnology). The aforementioned report was the initial offering of the Company's securities to the public. From the first report date until the date of this report, the Company has made additional public offerings, and has also raised financing within the framework of private issuances.

As part of a financial round conducted during August 2010, the Company raised approx. NIS 11,325 thousand (oversubscription of the public offering amounted to approx. 143%). As of the reporting date, the Company's cash balance amounts to approx. NIS 8.8 million.

[B] Near the date of the IPO's completion according to the report, Hadasit transferred to the Company its full holdings in 9 information-rich companies engaged in research and development in the fields of medicine and biotechnology

(the "**Portfolio Companies**"). Apart from the aforementioned transfer of holdings, no additional rights or contractual undertakings were transferred by Hadasit to the Company. Some of the Portfolio Companies are related to the Company's controlling shareholder (Hadasit) through agreements involving the performance of trials for and by the Company at Hadassah hospital. In the Company's opinion, its proximity to Hadassah Ein Kerem hospital, and to the hospital's researchers, laboratories and research infrastructure, constitutes a significant contribution to and promotion of the activities of the Portfolio Companies, and adds significant, unique value to the capital investments made by the Company in the Portfolio Companies. The Company's audit committee has decided that the contractual undertakings for provision of services to the Portfolio Companies are done in conditions which do not fall short of those offered to other external, unrelated companies, in competitive conditions.

One of the Portfolio Companies, the holdings in which were transferred to the Company shortly after completion of the public offering according to the report, Hapto Biotech Inc. ("**Hapto**"), merged into a subsidiary of Ortech Technologies Ltd. The Company's holdings in Hapto were replaced by financial holdings in Ortech. In January 2008, Ortech changed its name to Forticell BioScience Inc. After Portisal entered into and exited from a procedure in the USA for protection from its creditors (Chapter 11), the Company's full investment in Portisal was erased from the Company's books.

In July 2009, the Company announced that an additional Portfolio Company in which the Company has holdings - TK-Signal Ltd. - decided to terminate its operations.

After the balance sheet date (in January 2011), an additional Portfolio Company in which the Company has holdings (Conjugate Ltd.) decided to liquidate and terminate its operations.

The Company also has holdings in a publicly traded company in Israel (BioLineRx Ltd.).

[C] As of the reporting date, the Company maintains holdings in 7 active private Portfolio Companies, and also holds stakes in two public companies (BioLineRx Ltd., whose securities are traded on the Tel Aviv Stock Exchange Ltd., and Portisal - in which the Company's full holdings have been erased).

[D] As of the reporting date, four companies in which the Company has holdings (Verto, Enlivex, Thrombotech and Biomarker) have entered the human clinical trial phase. Thrombotech received authorization to begin a more advanced phase of clinical trials (Phase IIa), and intends to begin a second human clinical trial during the second quarter of 2011.

[E] Companies in which the Company has holdings, as specified in this section, are information-rich companies engaged in research and development in the fields of medicine and biotechnology. In most of the Portfolio Companies, the knowledge base is held by researchers who are currently employed, or who were employed as of the date of delivery of this information, by the hospitals of the Hadassah Medical Organization ("**Hadassah**") in Jerusalem. The Company will review its investment and holdings in additional information-rich companies using this and other criteria which have been determined, and will be determined in the future, by the Company's board of directors. In parallel, the Company is also reviewing products and companies based on intellectual property which did not originate from Hadassah hospital and its researchers, although at this stage the Company believes that, in light of the advantages inherent in its proximity to Hadassah and its researchers (including the added value obtained by the reviewing of projects done by Hadassah and its researchers), any clinical trial or research cooperation will be done with Hadassah and its researchers as a condition for an investment being made by the Company. The Company hereby clarifies that the foregoing does not constitute a definite policy, and that, in consideration of the relevant circumstances, the Company's Board of Directors will consider any investment framework or type presented to it for evaluation.

Hadassah is a medical institution based in Jerusalem that is international in its scale and standing and which includes, inter alia, two university hospitals in Ein Kerem and Har Hatzofim, five schools for medical professions, outpatient clinics, research centers, and more.

Hadassah is a company limited by guarantee founded in 1935. As such, it has no share capital or shareholders. According to the Companies Law, its members are to be considered as shareholders. The members of Hadassah are HMRA (Hadassah Medical Relief Association Inc.) and at least seven executives in HWZOA (Hadassah Women's Zionist Organization of America), who serve as ex-officio members. HMRA and HWZOA are both not-for-profit American organizations.

HMRA and HWZOA are related companies - the members of HWZOA's board are ex officio members of HMRA (in other words, HWZOA's board of directors is subject to the general assembly of HMRA; the executive committee of HWZOA serves as the board of directors of HMRA ; and both companies share the same company officers).

Since its founding, Hadassah has benefited from significant annual contributions from HMRA, both for current and development budgets.

By force of Section 132 of the Patents Law, 5727 - 1967, and by force of the agreements and terms of employment of Hadassah employees, including forms regarding notification of invention of services on which Hadassah researchers are signed, all inventions discovered during and as a result an employee's work at Hadassah belong to Hadassah. Inventions which have commercial potential are delivered for handling and commercialization to Hadasit - a company fully owned by Hadassah. In accordance with the management agreement signed between the Company and Hadasit, and which is described below in this section, Hadasit provides the Company management services (for the description of the management agreement, see Section 5.13 of this report).

Similarly to the mechanism in place in other scientific institutions, Hadasit is Hadassah's technology transfer office, and is the entity that acts to raise resources and commercialize the scientific discoveries produced by Hadassah's researchers (mostly doctors who, in parallel to their ordinary work, are also engaged, inter alia, in clinical research).

Hadasit also works to commercialize additional services provided by Hadassah under commercial conditions, including consulting provided by doctors / other Hadassah experts, performance of clinical trials at Hadassah through the Hadassah Clinical Research Center (HCRC), and services provided in other frameworks, including use of the institution's infrastructures (animal house facilities, manufacturing under GMP conditions, etc.).

Hadassah has assigned to Hadasit all rights held by it that pertain to the developments of the Portfolio Companies. The rights to the scientific developments transferred to Hadasit by Hadassah were transferred to the Portfolio Companies, as described in Section 5.3 below.

Apart from the holdings of Hadasit in the Portfolio Companies transferred to the Company, Hadasit also has holdings in additional Portfolio Companies, and notified the Company that it intends to continue operating in the fields of medicine and biotechnology. Hadasit has not undertaken to transfer its holdings in additional portfolio companies to the Company, including companies which, at present or in the future, fulfill the two cumulative conditions, due to which Hadasit chose to transfer its holdings in the Portfolio Companies to the Company. In addition, Hadasit has no undertaking to transfer additional intellectual property to the Company, and has notified the Company that it to continue operating in the field (including founding additional companies or transferring research information by way of licensing to other companies, through means other than the Company). Any transfer to the Company of Hadasit's additional holdings, or any provision of license from Hadasit to a Portfolio Company specified in this report (or which may be subsequently consolidated with the Company) will be subject to commercial-business negotiations between the parties and to the receipt of all authorizations legally required for this purpose.

The Company's Board of Directors has established criteria for the Company's performance with regards to investments in new companies (target companies). These criteria are based on the source of the intellectual property developed, the company's degree of relation to Hadassah, the technology's scientific attractiveness, the product's target market, the degree of scientific / technological maturity of the Portfolio Company in question, and the Company's planned stake in the target company following performance of the investment.

**[F]** Subject to the ability of the Portfolio Companies to successfully raise the amounts required by them for performance of the advanced phases of their products' development, the Company will work to ensure that the Portfolio Companies adopt exit strategies upon completion of the first significant human clinical trial. The intention is that during Phase I/II of the clinical trials, and during the preparations for Phase II of the clinical trials, the Portfolio Companies (all or some) will hold meetings with entities considered to be appropriate for the purpose of investing in the continued development process and / or for strategic cooperations, and especially with multi-national pharmaceutical companies. As of the reporting date, Verto Ltd., which completed a Phase I/II clinical trial conducted on 12 lupus patients, and Thrombotech Ltd., which completed a Phase I clinical trial, are the

Portfolio Companies for which the Company intends to implement the aforementioned strategy. It is hereby emphasized that a Phase I/II clinical trial (if successful) proves the safety of using the product under development, and also demonstrates a preliminary direction regarding the product's efficacy.

According to information received by the Company, in accordance with Hadasit's experience in the relevant field, the multi-national pharmaceutical companies repeatedly emphasize, in meetings held with them, that the presentation of Phase I/II clinical trial data (that is, presentation of at least safety results in human clinical trials) is the optimal stage for the creation of a strategic cooperative relationship between the pharmaceutical companies and the development companies.

In the event that the results produced by such a trial demonstrate efficacy as well, the company and the product it is developing become, in the company's opinion, even more attractive from the perspective of the pharmaceutical companies (the potential partner).

[G] From the date of its founding until today, the Company has not distributed any dividends to its shareholders. As of the reporting date, there exists no distributable balance which could be distributed to the Company's shareholders in accordance with legal requirements. It is hereby noted that in 2010, the Company presented significant capital gains (approx. NIS 13 million) as a result of an investment transaction of partners in one of the Portfolio Companies (Protab Ltd.).

### **5.1.2 Hadasit Medical Research Services and Development Ltd.**

As of the reporting date, Hadasit is the controlling shareholder in the Company, and holds approx. 36% of the Company's issued capital (approx. 37.17% at full dilution).

Hadasit is a private company founded in Israel on December 7, 1986 by Hadassah, and is fully owned by it.

As noted above, Hadasit's area of operation is the promotion and commercialization of the intellectual property and research and development capabilities in the fields of medicine and biotechnology which are produced, in whole or in part, by Hadassah and its employees (mostly doctors).

The commercialization of scientific ideas is generally done through the granting of licenses to pharmaceutical companies or other technological or biotechnological companies for the use of the information and intellectual property (or license) in exchange for agreed-upon payments (royalties), or through the founding of a subsidiary, to which license is granted to use the intellectual property, and which works to commercialize the scientific discoveries. Hadasit is involved in these companies through its holdings in their shares, its participation in their boards of directors, its participation in the creation of its work plans and budgets, and its participation in their administrative decision making processes.

As specified below, the majority of licenses for use of the information and intellectual property granted to the Portfolio Companies included in this report are exclusive licenses, unrestricted by time or location, which may be revoked in extraordinary cases such as the insolvency of the Project Company in question. The license agreements state that Hadassah and Hadasit have the right (license from the Project Companies) to make use of the intellectual property transferred to the Portfolio Company or developed by it, for the purpose of medical treatment of patients at Hadassah, for the purpose of research, non-commercial use, or for the purpose of professional publications (subject to arrangements in place with the Portfolio Companies with regards to the provision of early notice, and allowance of reasonable opportunity to arrange for the registration of patents for publications which may harm the possibility of such registration). In general, the protection period granted to a patent owner for the development specified in the patent is 20 years from the date of submission of the first application for the patent's approval.

For the purpose of the Company's tracking and monitoring of the activities of the Portfolio Companies, the Company approved on January 6, 2008 a contractual agreement for the leasing of offices in a biotechnology park whose construction was completed in April 2009. The Company's offices were relocated to the technological park during June 2009, and five of the Portfolio Companies relocated their operations (offices and laboratories) to the park. After the reporting date, one of the Portfolio Companies (Protab Ltd.) notified the Company of its realization of the "exit window" provided to it in the sublet contract, and that due to leasing costs, it intends to leave the leasehold area in June 2011. At this stage, the parties are conducting negotiations to evaluate the possibility that Protab will remain in the leasehold until the completion of a total lease period of 5 years.

The Company also entered into an agreement with an external company which will rent unused areas in the leasehold of Enlivex Ltd.

The Company believes that its physical proximity to the Portfolio Companies facilitates its supervision of the Portfolio Companies and its promotion of their activities, and significantly helps to create an appropriate environment to facilitate the exchange of ideas, problem solving, the creation of an appropriate and advanced infrastructure for the research and development activities, and the provision of assistance for the various activities of the Portfolio Companies, thus enabling them to focus on their activities in the best possible manner. The advantages of size and close supervision enable better use of the financing transferred by the Company to the Portfolio Companies.

For details regarding the management agreement signed between the Company and Hadasit, see Section 5.13.

### **5.1.3 The Group's holding structure**

The following are details regarding the Company's holdings in the Portfolio Companies as of the reporting date:<sup>1</sup>

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<sup>1</sup> For details regarding the dilution source of each company in which a gap exists between the rate of holding and the rate of holding at full dilution, please see the details presented regarding each of the Portfolio Companies in Section 5.3 below. For details about loans convertible to shares in the Portfolio Companies, see Section 5.3 below.

Name of Portfolio Company	The Company's Rate of Holding as of the Reporting Date	The Company's Rate of Holding at Full Dilution	Total Amounts Provided by the Company to the Project Company <sup>2</sup> (ss of December 31, 2010 and the reporting date) (Thousands of NIS)	Worth of the Portfolio Company in the Company's Books as of December 31, 2010 (Thousands of NIS)	The Company's Right to Nominate Directors in the Project Company	The Portfolio Company's Area of Operation and Current Phase
<b>A. Subsidiaries</b>						
<b>Kahr Medical (2005) Ltd.</b>	76.05%	68.40%	8,200	1,274	Nominated by the general assembly of Kahr. The Company is party to a shareholders' agreement (see Section 5.3.5).	Development of a new type of protein, for the treatment of autoimmune diseases and cancer. Completion of animal trials, manufacturing of the protein under development for the purpose of the clinical trial, and contacting the regulatory authority.
<b>Enlivex Ltd.</b>	91.99%	83.63%	8,668	(534)	Nominated by the general assembly of Enlivex. 3 serving directors nominated on behalf of the Company.	Development of a cell-based treatment for graft-vs.-host disease in grafts and in inflammatory and auto-immune diseases. Performance of human clinical trials in three centers in Israel.

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<sup>2</sup> Includes amounts provided through share capital and convertible loans.

Name of Portfolio Company	The Company's Rate of Holding as of the Reporting Date	The Company's Rate of Holding at Full Dilution	Total Amounts Provided by the Company to the Project Company <sup>2</sup> (ss of December 31, 2010 and the reporting date) (Thousands of NIS)	Worth of the Portfolio Company in the Company's Books as of December 31, 2010 (Thousands of NIS)	The Company's Right to Nominate Directors in the Project Company	The Portfolio Company's Area of Operation and Current Phase
<b>Biomarker Ltd.</b>	87.49%	91.77%	4,130	224	Nominated by the general assembly. Two of the three directors of Biomarker serve on behalf of the Company.	Kit for detection of cancer (breast and colon) using blood tests. Advanced trial in patients and healthy individuals towards the preparation of a kit for multi-center trial.
<b>Verto Ltd.</b>	74.60%	67.32%	2,917	12	Nominated by the general assembly of Verto. So long as the Company holds at least 2% of Verto's issued capital, it has the right to nominate one director. 3 serving directors nominated on behalf of the Company.	Development of instruments and drugs for the treatment of lupus erythematosus. Completion of phase I human clinical trials.

Name of Portfolio Company	The Company's Rate of Holding as of the Reporting Date	The Company's Rate of Holding at Full Dilution	Total Amounts Provided by the Company to the Project Company (As of December 31, 2010 and the reporting date) (Thousands of NIS)	Worth of the Portfolio Company in the Company's Books as of December 31, 2010 (Thousands of NIS)	The Company's Right to Nominate Directors in the Project Company	The Portfolio Company's Area of Operation and Current Phase
<b>B. Associates</b>						
<b>Cell Cure Neurosciences Ltd.</b>	26.28%	24.54%	17,014	8,535	7 board members, of which 2 are nominated by the Company.	Cell-based treatment of age related macular degeneration (AMD), as well as Parkinson's disease and neurodegenerative diseases. Animal trials. Production of cells as the basis for the drug under development; contacting regulatory authorities in Israel and around the world.
<b>Thrombotech Ltd.</b>	24.77%	23.43%	2,958	959	So long as the Company holds at least 3% of Thrombotech's issued capital, it has the right to nominate one director. As of the reporting date, one director of Thrombotech's 5 directors is serving on behalf of the Company.	Development of drugs for the dissolution of blood clots and other indications. Clinical trials (safety) have been completed, with preparations underway for an additional trial (efficacy).

Name of Portfolio Company	The Company's Rate of Holding as of the Reporting Date	The Company's Rate of Holding at Full Dilution	Total Amounts Provided by the Company to the Project Company (As of December 31, 2010 and the reporting date) (Thousands of NIS)	Worth of the Portfolio Company in the Company's Books as of December 31, 2010 (Thousands of NIS)	The Company's Right to Nominate Directors in the Project Company	The Portfolio Company's Area of Operation and Current Phase
<b>Protab Ltd.</b>	69.79%	50.10%	10,368	12,198	Nominated by the general assembly of Protab. 2 serving directors nominated on behalf of the Company.	Drugs for the treatment of rheumatoid arthritis, inflammatory bowel diseases and other auto-immune diseases. Production and preparation for human clinical trial.
<b>C. Other Companies</b>						
<b>BioLineRx Ltd.</b>	0.25%	0.25%		991	Nominated by the Company's general assembly.	Development of drugs for a variety of diseases, from early development stages to advanced clinical trial stages. A public company whose shares are traded on the Tel Aviv Stock Exchange Ltd.
<b>Total</b>			54,305	23,659		

The continuation of the Company's current holding rate in the Portfolio Companies is conditional upon financial needs, the Company's strategy, and the financial ability held by and made possible for the Company, subject to the investment principles of the Portfolio Companies as specified in this report, for participation in investment rounds for the Project Companies. It is quite possible that, in additional financial rounds, the Company will not have the required means to maintain its current rate of holdings in the Portfolio Companies (all or some) and it is also possible that, in these rounds, a decision will be reached by the Company stating that it would be inappropriate or unprofitable to participate in such rounds.

As of the reporting date, the great majority of funds provided to the Project Companies by the Company are done through the provision of convertible loans. The Company considers these loans as an instrument enabling the Portfolio Companies to continue their activities and move towards the achievement of their goals as specified in Section 5.3 below, while granting the status of protected creditor to the Company, with the ability to convert the loan into shares in the event that the Portfolio Company raises financing from external sources. It is hereby noted that, in the investment rounds for the Portfolio Companies in which the Company participated in 2010, in which external partners in the Portfolio Companies were also involved (the investment transactions in Protab and Cell Cure), the Company converted the convertible loans it provided to the Portfolio Companies according to the terms specified in the loan agreements to shares identical to those received by the external investors.

The researchers of Hadassah's Portfolio Companies specified in Section 5.3 are entitled to receive a certain proportion of the income received by Hadasit in respect of the Hadasit's realization of its holdings in the Company, and in respect of the income received by Hadasit from dividends paid to it by the Company.

According to agreements between Hadasit and the Researchers, Hadasit has undertaken towards the aforementioned Researchers not to sell more than 60% of its holdings in the Company, in their rate that will be current after completion of the IPO according to the report (excluding the forced conversion). As of the reporting date, Hadasit has not sold Company shares.

## **5.2 The Company's activities - Investment in Information-Rich Companies**

**5.2.1** As noted above, the Company maintains holdings in 7 information-rich companies operating in the field of medical and biotechnological research (hereinafter, above and below: the "**Project Companies**").

Over the course of 2010, one Portfolio Company (which was not included among the 7 companies in which the Company maintains holdings as of the reporting date) - Conjugate Ltd. - decided to terminate its operations.

**5.2.2** The Company is interested in performing continuing investments in the Portfolio Companies, or in other companies. The investments are performed, and will be performed, following commercial negotiations between the Company and the Portfolio Company in which it decides to invest. The Company requires financial sources for the purpose of making the aforementioned investments. The Company is not financed by loans from external entities, and to date all financing made available to it was received from its shareholders.

For the performance of investments, the Company's board of directors consults with the scientific advisory committee described below, and determines - at its sole discretion - the manner and scope of investments performed by the Company in the Project Companies, while also reviewing the possibility of investing in other companies in which the Company does not have holdings, but which operate in the fields of medicine or biotechnology. All investments are evaluated on their own merits, taking into account the maximum potential benefit for the Company, and the criteria established by the Company's board of directors. The role of the scientific advisory committee is to advise the Company. Accordingly, the Company's board of directors is not required to receive its approval for the purpose of performing an investment or any other operation.

As of the reporting date, the scientific advisory committee, whose responsibility is to advise the board of directors with regards to proposed investments in the Portfolio Companies or regarding other investments in companies engaged in the field of medical and biotechnological research, and in which the Company is considering investing, is comprised of the following members: (no minimum or maximum number of members has been established by the Company for the advisory committee, though the Company intends to maintain a situation whereby, at any given moment, the number of members in the advisory committee is no less than 3). It is hereby noted that that none of the members listed below serve as a director or manager at Hadasit (Prof. Ruth Arnon serves as a director of Hadassah).

**[A] Prof. Ruth Arnon**

Prof. Ruth Arnon is a senior researcher at the Weizmann Institute of Rehovot in the field of life sciences, with a particular emphasis on immunology. Prof. Arnon has been serving as a professor at the Weizmann Institute for over thirty years, including ten years (1984 - 1994) as the Head of the Immunology Department. From 1995 to 1997, Prof. Arnon served as the Institute's Vice President. In addition to the senior positions held by her at the Weizmann Institute, Ruth Arnon also serves in several other organizations, including some of the most important scientific organizations in the world, the Israel Academy of Sciences and the World Health Organization. In Israel, Prof. Arnon also served as a senior advisor to the Israel's President regarding the formation of a national strategy, and as President of the Association of Academies of Science in Asia.

Prof. Ruth Arnon has been awarded several prestigious prizes, including the Wolf Prize, the Rothschild Prize and the Israel Prize for Achievements in Science.

In recent years, Prof. Arnon has been serving as a member in several boards of directors in Israel and around the world, and has also been active as an initiator of startup companies in the fields of life sciences, particularly in the field of the development of immune compounds. Prof. Arnon serves as a director of Hadassah.

Prof. Arnon is a partner in the development of Copaxone, a leading drug for the treatment of multiple sclerosis.

**[B] Steven Brill**

The founder and CEO of San Francisco's Brill and Co., a company engaged in the field of life sciences. Mr. Brill and his staff focus on risk capital investments and mapping of the biotechnology industry and its future trends.

Mr. Brill is very active in assisting companies in various stages of development which are engaged in the field of life sciences, from the companies' launch stages, through the cultivation of stable growth, to assistance in planning realization processes. In 2002, Mr. Brill won the "Man of the Year" prize in the field of vision and initiative in biotechnology investments, awarded by Scientific American magazine.

Mr. Brill serves on several boards of directors of biotechnology companies, some of which are traded on the NASDAQ.

Mr. Brill serves, among other roles, as a business development consultant regarding the life sciences industry for several governments, including the governments of Japan, Singapore and Malaysia. He also serves as a senior consultant to several companies, including Hadasit.

Prior to the founding of Brill and Co., Mr. Brill served for 28 years as the head of the life sciences financial and professional consulting division at E&Y, and holds a degree in Accounting from the University of Wisconsin in Madison, Wisconsin.

From time to time, the Company also consults with other advisors who are invited, as necessary, to the meetings of its scientific advisory committee, including Mr. Jonathan Silverstein, a partner in the New York risk capital fund Orbimed, Mr. Jonathan Fleming, a partner in the Boston risk capital fund Oxford Bioscience, and Adv. Cheryl Reicin - a partner in the international law firm Torys LLP, with offices in New York and Toronto.

**[C] Prof. Tak W. Mak**

Prof. Mak is an expert in immunology, a member of the Department of Medical Biophysics and Immunology at the University of Toronto in Canada, and the Director of the University's Advanced Medical Research Institute. From 1993 to 2002, he also served as Founding Director of the Amgen Institute in Toronto.

In 1984, Prof. Mak presented a significant breakthrough in the world of science, when he led a team of researchers that was the first to clone the human genes of T-cell antigen receptors. This research served as the basis for the understanding of immune response signals, and was quoted in over 1,200 medical studies. Prof. Mak has also published approx. 500 scientific articles on various topics, many of which appeared in prestigious journals, including Cell Science and Nature.

These research articles have been quoted in over 40,000 scientific articles. Beginning in 2004, he began focusing his research on breast cancer, for which he took on the role of Director of the New Institute for Breast Cancer Research in Toronto.

Prof. Mak has been awarded honorary doctorates in the USA and in Europe, is a member of the Royal Society of Canada, the Royal Society of London, and the Order of Canada, and serves as a foreign member in the National Academy of Sciences in the US. He has also been awarded several prizes, including the E.W.R Steacie Prize of the National Science & Engineering Research Council in Ottawa, the Ayerst Prize of the

Canadian Biochemical Society, the Robert Noble Prize of the Canadian Cancer Association, the Gairdner Foundation International Award, the Sloan Prize of the General Motors Cancer Foundation, and the Novartis Prize for Immunology.

Prof. Mak holds degrees in Biochemistry and Biophysics from the University of Wisconsin, and a PhD in Biochemistry from the University of Alberta.

There are also three other members with whom the Company consults from time to time as part of the activities of the Company's scientific advisory committee: (1) Jonathan Fleming - founder and partner in the risk capital fund Oxford BioScience Partners, with offices in Boston; (2) Dr. Howard Fillit - a senior director of the Institute for the Study of Aging in New York, an Estée Lauder family foundation; (3) Adv. Cheryl Reicin - a partner in the international law firm Torys LLP, with offices in New York and Toronto.

### **5.3 Project Companies**

5.3.1 The Company's purpose and one of its operational strategic elements is promoting the Portfolio Companies from the pre-clinical trials through the completion of the clinical trials.

In March 2007, Verto Ltd. began Phase I/II of clinical trials, which were completed in the second quarter of 2009. Enlivex Ltd., which received approval in April 2009 from the Ministry of Health to enter the phase of clinical trials on humans, began to experiment in the third quarter of 2009, and is expected to complete the experiments in the third quarter of 2011. Thrombotic Ltd. received approval in February 2010 to enter the clinical trial phase on humans and completed the clinical trials (Phase I – Safety) held at Hadassah Ein Kerem Hospital. Thrombotic is expected to begin another trial (Phase IIa – Efficacy) in Israel, and two additional locations abroad, over the course of the second quarter of 2011. Biomarker has been testing its diagnostic marker on blood samples of breast cancer patients, a process classified as a clinical trial, since October 2009. After the report date (January 2011), Biomarker received permission to enter into an additional clinical trial (blood samples for the early detection of colon cancer) – an experiment that began in the first quarter of 2011. Other

Portfolio Companies included in this report are currently in various stages preceding the human clinical trials (pre-clinical). Three major companies (ProtAb, Cell Cure and Kahr) are expected to begin clinical trials over the next 18 months.

The following is a description of the activities of each of the Portfolio Companies (the description below does not include a description of the Portfolio Companies in which the entire investments on behalf of the Company have been erased; does not include a description of the activities for Conjugate, which has decided to cease its operations; and does not include a description of Bioline's business and activities, whose company holdings are minor and whose reports, as a public company, are delivered to the Israeli public.<sup>3</sup>)

The descriptions that follow regarding the timeframes in which the Portfolio Companies are expected to begin their clinical trials and submit appropriate requests for such, are forward-looking statements, forecasts and estimations of the Company alone, based on investigations conducted on the Portfolio Companies and the researchers working in these Companies. The aforementioned are only projections and estimations, and there is no measure of certainty regarding their realization or regarding the date on which they will be actualized. The existence of these projections and estimations is conditional, inter alia, on the successful completion of the pre-clinical trials by the Companies, that they will possess sufficient financial resources in order to begin the clinical trials, and that no new technological developments will appear that may nullify or uproot the necessity or the developments of any of the project companies.

### **5.3.3 ProtAb Ltd. (Hereinafter – “ProtAb”)**

#### **Glossary for this Section**

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<sup>3</sup> Unless otherwise specified regarding any of the project companies, the information regarding the extent of their potential market value and competition is based on public information gathered by the Company.

**Biologics (Biological Materials)** - a wide range of medicinal products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins, such as antibodies, created by biological processes (non-chemical).

**Immunological (Treatments)** - treatments designed to suppress over-activity in the body's immune system.

**Antigen** – any foreign substance, that when penetrating the human body, stimulates an immune system response.

**Humanization of Antibodies** – chemically modified antibodies designed to be suitable for use in humans.

**Passive Immunization** – a type of vaccination achieved by injecting prepared antibodies taken from humans or animals that have been vaccinated against a particular antigen, and have been processed in preparation for injection.

**Active Immunization** – a type of vaccination that causes the body to produce its own antibodies by injecting an antigen which stimulates a reaction that produces antibodies in the human body.

**Protein** – an organic compound built of folded chains of amino acids connected by polypeptides. Proteins are among the most important compounds that make up the organism and are found in all living cells.

**HSP Proteins** – a group of unique proteins called HSP – Heat Shock Proteins, which protect the three-dimensional structure of proteins in the cell, thereby insuring the proper functioning under conditions of stress. These HSP proteins exist in cells of all organisms, including humans.

**Autoimmune Disorders** – diseases characterized by immune system cells losing their immunotolerance and attacking the body's own tissue and cells.

**Inflammatory Bowel Disease** – a group of diseases and inflammatory conditions of the colon and sometimes even of the small intestine.

**Segments** – in this context, it is an antigenic determinant (also known as an epitope). It is a specific part of the antigen molecule which causes an immune response. Antigens usually include many epitopes, each of which triggers a response, or activates T lymphocytes, of a different kind. The immune system is triggered by segments. The body identifies them as non-self (foreign), and different cells participate in an immune system response and begin to act against them.

**Antibodies** – protein molecules belonging to the immune system. The role of antibodies is to bind to antigens – molecules found on the surface of potentially harmful pathogens invading the body. The connection between the antibody and the antigen allows for the elimination of the invading pathogen in a number of ways.

**Human Antibodies (Humanized)** – an antibody based on an artificial protein engineered using molecular biology from a number of DNA sequences belonging to genes coded to a number of different proteins, engineered to be fit for human use.

**Chimeric Antibody** – antibodies based on artificial proteins engineered using molecular biology from a number of DNA sequences belonging to genes coded to a various proteins, which are possibly originating from different organisms. The name is based on a figure named “Chimera” from Greek mythology, who is described as being formed from body parts of different animals.

**Monoclonal Antibodies (Monospecific)** – antibodies that are identical, as they were produced by the same type of immune system cells which originated in one cell and have created clones. Monoclonal antibodies may be artificially created with particular affinities (affinity, binding capacity) for almost all materials. In medicine, monoclonal antibodies are used for diagnostic and treatment purposes.

**Diabetes** – diabetes is a metabolic disease which is characterized by a high concentration of glucose in blood and urine.

**Type 1 Diabetes (“Juvenile Diabetes”)** – approximately 10% of diabetes patients suffer from this type. It appears mostly in patients under the age of 30, particularly immediately before the age of schooling and again in adolescents.

**Psoriasis** – a chronic skin disease in which skin cells rapidly accumulate at a great pace. The disease is manifested in layers of skin, usually in a reddish-purple color, covered with scales. The disease occurs in 1-3% of the population.

**Cytokines** – small proteins that form the basis for communications between immune system cells and between cells belonging to the body's tissue.

**Receptors** – proteins found on the cell membrane or cytoplasm, which respond to ligands – molecules that bind to them and initiate a response. There are several types of receptors, including immune system receptors, which respond to cytokines and chemokines.

**TNF-Alpha (Tumor Necrosis Factor)** – cytokines secreted by white blood cells. A delay in the secretion of these materials allows for a decrease in the inflammatory process. These cytokines are able to activate various inflammatory cells and complex systems found in them. Similarly, they are able to modify these cells to particularly violent cells. These cytokines can recruit additional inflammatory cells and transport them to the inflammation site, and are also able to activate cells that may dissolve functioning bone, which could harm use of the joint. The use of antibodies against TNF is part of the currently recognized therapy process used against arthritis of this type.

#### **[A] A Description of ProtAb's Activities and the Technology Developed by it**

ProtAb is a private company incorporated in Israel which commenced business activity in August, 2005.

ProtAb is developing a novel therapeutic approach for the treatment of rheumatoid arthritis, inflammatory bowel disease (including Crohn's disease, and ulcerative colitis) and other autoimmune diseases. The development is based on discoveries made by Professor Yaacov Naparstek from the Hadassah Ein Kerem Hospital.

Rheumatoid arthritis, and other diseases that affect the immune system, are chronic diseases related to the group of autoimmune diseases in which the body activates the immune system against itself. Rheumatoid arthritis, for example, occurs when the immune system attacks the joints in the body, causing inflammation and destroying

the healthy tissue of the joints. During a normal inflammation process, it is necessary to balance the signals encouraging the inflammatory process (pro-inflammatory signals) and the signals that suppress the inflammatory process (anti-inflammatory signals). Imbalance between these signals can lead to an uncontrolled inflammatory process and subsequent development of the disease.

ProtAb is developing a novel therapeutic approach which is based on encouraging anti-inflammatory signals. It has found a way to seemingly delay the disease, which is based on increased secretion of a substance called cytokine IL-10, an anti-inflammatory signal. According to ProtAb's theory, there is significantly less production of antibodies against the protein segments of HSP (Heat Shock Protein) in patients with rheumatoid arthritis, and as a result, the level of IL-10 is lower and causes an uncontrolled inflammation which develops into an autoimmune disease.

The researchers at ProtAb have proven that active immunization with a segment of HSP, known peptide 6, and passive vaccination with antibodies against peptide 6, suppress arthritis and inflammatory bowel disease in animal models, and suppress diabetes in experimental models of type 1 diabetes. Additionally, the researchers have shown that the blood of rheumatoid arthritis and juvenile diabetes patients contains a low level of these antibodies. In light of the findings made by the ProtAb researchers, ProtAb seeks to develop immunological treatments that promote the secretion of the anti-inflammatory signal, IL-10, by the development of humanized monoclonal antibodies (proteins derived from the immune system that are able to protect the body against foreign substances in a very specific manner, which are produced through an industrial process) against peptide 6.

In order to develop the humanized monoclonal antibodies against peptide 6, the antibodies must be "translated" from their animal-based structure to a humanized structure, suitable for use in humans, through a process called humanization. The humanization process is a crucial process in ProtAb's preparations for clinical trials on rheumatoid arthritis patients with its leading product (a monoclonal antibody against peptide 6).

Accordingly, ProtAb has entered into a research and development agreement, with the possibility of attaining a future license, with a British company known as Antitope

Ltd. – a leading company engaged in carrying out humanization of antibodies through a unique and patent-protected technology. At the end of 2007, the first stage of the humanization process was successfully completed and the chimera antibody was produced (an engineered antibody consisting mostly of human origin, but still containing elements from mice).

In early 2008, experiments were successfully carried out which confirmed that the chimera antibody did in fact preserve the original antibody features, in terms of efficacy in treating rheumatoid arthritis (tested on animals). The success of the trials on the chimera antibodies formed a basis for future implementation of the humanization process for the development of antibodies that will eventually undergo a full humanization process, and the decision was made to continue the humanization process of the antibody in accordance with the aforementioned agreement with Antitope, the British company. Later that year, they successfully completed the final stage of the humanization process and efficacy tests indicated that the antibody maintained its own qualities, even subsequent to the completion of the humanization process.

During 2009, ProtAb expanded its pre-clinical trials of the humanized antibody, and tested the antibody's activities in an animal model of inflammatory bowel disease. Since the mechanism of action used by the antibody is the promotion of anti-inflammatory signals, the antibody has potential for treating a wide range of autoimmune diseases. Initial efficacy tests have indicated that the antibody inhibits the disease significantly, specifically reducing intestinal inflammation. These findings present the possibility for treatment of a wide range of autoimmune diseases, with use of the leading antibody developed by ProtAb.

In addition to the above, during 2009, the properties of the humanized antibody were examined in depth in different models of arthritis in animals and in an animal model of Inflammatory Bowel Disease, in various doses and methods of administration. These tests are a necessary step in preparing the antibody for production and treatments of patients with arthritis and additional autoimmune diseases. These tests showed positive results and indicated efficacy of the antibody in suppressing various

anti-inflammatory diseases. These findings support the possibility of treatment of a wide range of autoimmune diseases with ProtAb's leading antibody.

At the end of 2009, ProtAb began developing the early stages of the production process for the humanized antibody, in cooperation with the Antitope company (Britain). In light of the fruitful cooperation between ProtAb and Antitope in the humanization of the antibody, ProtAb entered into an agreement with Antitope to develop the early stages of production of the humanized antibody, in preparation for the clinical trials on humans. This process continued through the first half of 2010.

2. During the second quarter of 2010, ProtAb completed the early stages of development for the production processes of its leading antibody, in cooperation with Antitope (Britain), and selected Xcellerex in the United States to continue the production of the humanized antibody for the toxicological experimentation stage and the clinical trials on humans. ProtAb formed a manufacturing service agreement with Xcellerex and began developing the necessary processes for the scale-up and manufacturing in compliance with the GMP principles with Xcellerex. ProtAb enlisted a Vice President of Research and Development, Dr. Dorit Landestein, to lead its entrance into the advanced stages of production of the antibody for the toxicological trials, its submissions to the regulatory authorities, and preparation for the beginning of the clinical trials of its leading antibody. Dr. Landestein is a great degree of experience in the industry in various fields, including antibody-based drug development and analytical methods in the field of antibodies.

During the third quarter of 2010, ProtAb continued its development of the processes required for scale-up and production, in compliance with the GMP principles, with Xcellerex (in the USA). During this period, ProtAb completed a technology transfer to Xcellerex and chose a cell-line and conditions appropriate for the maximal expression of the medical antibody.

In the third and fourth quarters of 2010, along with the entrance of ProtAb into advanced production processes of the antibody, ProtAb was aided by global experts (Key Opinion Leaders) in Israel and abroad in the development of biological drugs to treat autoimmune diseases, in order to formulate a strategy for the preliminary trials

on humans. This process was prepared for submission to the regulatory authorities that will allow for the commencement of clinical trials of ProtAb's leading antibody.

In addition, throughout this period, ProtAb continued to complete research on deciphering the mechanism of action of its leading antibody.

#### Forecasts and Estimates for 2011 and 2012

The following information is forward-looking information, whose realization, in whole or in part, is uncertain, and is conditional, inter alia, upon the realization of the results of the research conducted, and that ProtAb attain the funding required to perform the research, development and experimentation on humans, in accordance with its plans:

ProtAb intends to commence the first trial (Phase I/II) with the peptide-6 antibodies, in the first stage on healthy volunteers, and in the second stage on patients with rheumatoid arthritis and inflammatory bowel disease during the fourth quarter of 2011. The experiments are expected to continue during 2012. The delay in ProtAb's forecast to begin the clinical trials on humans comes as a result of a setback in obtaining a contract with Xcellerex for developing manufacturing processes, scale-up and commercialization under GMP principles, and lengthening the preparatory stage and the scale-up of the manufacturing process itself. ProtAb intends to submit an application to the relevant Helsinki Committee for approval of the clinical trials, after completing the toxicological experiments in the third quarter of 2011<sup>4</sup>. Additionally, ProtAb intends to apply for a preliminary meeting (Pre-IND) with the FDA during the third-fourth quarter of 2011.

#### **[B] Relevant Potential Market and Competition**

The Company estimates that the treatment of rheumatoid arthritis has been, and will remain, one of the most profitable areas of the pharmaceutical industry. Rheumatoid arthritis, and other related diseases, cost the United States' economy, according to

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<sup>4</sup> The specific delay in the forecast of the date for beginning the clinical trials is a result of advancement in the development of the monoclonal antibody which ProtAb estimates has greater business potential, but requires complex research and development processes, including work with subcontractors abroad for a variety of stages in addition to the manufacturing required for entry level clinical trials in humans.

estimates and various publications, over \$65 billion each year, in direct and indirect expenses.

Rheumatoid arthritis is an extremely common disease, affecting approximately 1% of the world's population. According to the publications, sales of treatments for rheumatoid arthritis in the global market have reached approximately \$35 billion in 2008. ProtAb estimates that the market volume will only grow, and that the growth trend is expected to continue at a rate of 14% per annum in the coming years<sup>5</sup>.

The anti/pro inflammatory materials that inhibit the production of TNF-Alpha (Tumor Necrosis Factor) are in great demand, and include the following monoclonal antibodies (the manufacturer's names will be specified in parentheses) Remicade (Centocor) with sales of \$6.5 billion in 2008, Humira (Abbott) with sales of \$4.5 billion in 2008, and the soluble TNF receptor, Enbrel (Amgen), with sales of \$7.4 billion in 2008. In addition to these drugs, in 2006, two additional drugs were added to the market – Orencia (Bristol-Myers Squibb) with sales of \$0.44 billion in 2008, and MabThera/Rituxan (Roche) with sales of \$5.6 billion in 2008. To the best of ProtAb's knowledge, during 2009, new drugs intending to delay TNF-Alpha received approval to be marketed in the United States- Cimzia (USB/Celltech) and Simponi (Centocor Ortho Biotech), and approval for marketing in the United States for the monoclonal antibody against IL-6 (Interleukin-6) was received by Actemra (Roche) in January 2010.

The Company estimates that the potential market value of pro/anti inflammatory materials, such as anti-peptide-6 monoclonal antibody (an antibody against part of the HSP protein, which ProtAb intends to begin preliminary clinical trials on as mentioned above), are similar in size, when being used as individual material and when being used as a facilitator for another anti/pro inflammatory material.

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<sup>5</sup> Information regarding the market size and the expected market growth is included in the market research: IXIS Securities Sector Report, April 2006.

Among other biological materials to treat rheumatoid arthritis undergoing clinical trials are, for example, (manufacturer names provided in parentheses)<sup>6</sup>: AMG108 (Amgen, MedImmune); HuMax CD20 (Genmab); Ocrelizumab (Roche); Eculizumab (Alexion Pharmaceuticals); Denosumab (Amgen); BMS-561392 (Bristol-Myers Squibb); LymphoStat-B™ (Human Genome Sciences/GSK) and VX702 (Vertex). The Company is unaware of products that compete with ProtAb as pro/anti inflammatory material based on HSP (heat shock protein).

Like rheumatoid arthritis, inflammatory bowel disease (IBD) and psoriasis are common autoimmune diseases that have potential market value for ProtAb<sup>7</sup>. In 2006, over a million people in the United States were affected by inflammatory bowel disease. That same year, about 7.8 million people were affected by psoriasis alone. The global market value for drugs treating IBD was \$2.7 billion in 2007<sup>8</sup>, and the market value for drugs treating psoriasis was about \$2 billion in 2005. In addition, the anti/pro inflammatory materials that inhibit TNF-Alpha production have entered these markets and their market value is steadily increasing.

### **[C] Human Capital**

ProtAb is based on the research of Professor Yaakov Naparstek from the Hadassah Ein Kerem Hospital. ProtAb is dependent on the continuous involvement of Professor Naparstek and his team in the early stages of the continued research and development.

Ms. Shira Yair serves as a General Manager of ProtAb. In addition, in 2005 ProtAb expanded its research team and recruited a Vice President of Research and Development who has a great deal of industry experience in various fields, including

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<sup>6</sup> The information regarding the products in development has been taken from research called Rheumatoid Arthritis Therapeutics: Market Trends and R&D Insights published in September 2006 by Arrowhead Publishers.

<sup>7</sup> The information regarding Inflammatory Bowel Disease (IBD) and Psoriasis was taken from: Commercial and Pipeline Insight: Psoriasis – Anti-TNF's lead another indication (December 2006) and Commercial and Pipeline Insight: Inflammatory Bowel Disease Competition increases for the biologics (November 2006).

<sup>8</sup> Bharat Book Review (September 2008)

the development of antibody based drugs and analytical methods in the field of antibodies.

In addition to the senior researcher recruited in the past and whose role is to explore the antibody's mechanism of action, a research assistant was recruited who is involved in developing analytical methods required to test different batches of the medical antibody in the production process. This researcher works in ProtAb's laboratories in the biotechnology park complex in Hadassah Ein Kerem.

### **[D] The Right to Appoint Directors, Convertible Loans and ProtAb's Share Capital**

In accordance with ProtAb's bylaws, ProtAb's directors are appointed by its general assembly. As of this report's date, there are six directors serving on the board of ProtAb, three of which serve on behalf of the Company.

On April 12, 2010, ProtAb entered into an agreement to issue shares to existing and new investors (The Pontifax Fund and a general biotechnology company). During the investment round that the Company participated in, the Company converted convertible loans available to ProtAb. After upholding the pre-conditions stipulated in the agreement, the issuance was completed as follows:

The investors pumped \$4 million into ProtAb. In return, ProtAb allocated 111,111 preferred A shares par value of 0.01 NIS each, in accordance with the relative investment contributed by each investor.

In addition, the investors were given 88,888 options to purchase preferred A shares, which can be exercised for three years or until certain conditions are met, whichever is sooner, plus an additional \$45 for the exercise of the option. New investors who participated in the investment round were allocated an additional 12,858 options for ordinary shares par value 0.01 NIS each.

In the framework of the investment, the Company converted all of its convertible loans to ProtAb, including the accrued interest for the loans.

As part of the agreement, ProtAb updated its bylaws. In the update, it was stipulated, inter alia, that certain actions enumerated in the bylaws would require the consent of

all preferred A shareholders holding more than 7.5% of ProtAb's share capital, after issuing the shares.

### **[E] Patents, Intellectual Property and Intellectual Property Development Cost**

ProtAb's main intellectual property is the structure of the humanized monoclonal antibody. During the third quarter of 2009, ProtAb filed a new patent application protecting its leading antibody, the monoclonal antibody after the humanization process, which is found at the forefront of ProtAb's developmental efforts. The application is designed to protect various sequences of the humanized antibody, and their uses for treatment of patients suffering from autoimmune diseases in general, and in the treatment of rheumatoid arthritis and inflammatory bowel disease patients specifically. ProtAb estimates that this application strengthens and widens ProtAb's intellectual property, and protects the product that will be tested in the human clinical trials for commercial purposes. During the third quarter of 2010, ProtAb filed the PCT application for the abovementioned patent.

ProtAb holds an exclusive license to use the patents and patent applications owned by Hadasit pertaining to peptides for the treatment of autoimmune disease. This exclusive license applies to the set of patents and patent applications in the field of innovative amino-acid sequences, their antibodies and usages. The set of patents and patent applications protects the novel protein segments, the antibodies against them, and the use of all of them in treatment of patients with autoimmune diseases in general, and in treatment of patients with rheumatoid arthritis in particular. ProtAb holds a license on 19 patents, whose requests were filed in 1999, and were received in the United States, Australia, Israel, Canada and Europe (Austria, Belgium, Switzerland, Germany, Spain, France, Britain, Ireland, Italy, the Netherlands, Sweden, Denmark, and Finland), and three patent requests submitted in the United States, Japan and Israel (part of these applications were submitted in 1999, and part of them were submitted in 2008).

As part of its continuous research and development, ProtAb has made significant progress in understanding how the antibody's mechanism of action against peptide-6 is able to increase the anti-inflammatory signal known as IL-10. Consequently, ProtAb filed a new patent application over the course of August 2007, which includes

dimensions of the mechanism of action, and an innovative element of the IL-10 gene, increasing ProtAb's intellectual property. Consequently, ProtAb filed a PCT application in August 2008. In addition, ProtAb filed a new patent application (US Provisional) in the first quarter of 2009, which protects ProtAb's leading antibody's target protein, and soon thereafter filed a PCT application on the matter during March 2010.

Part of the funding for the research carried out in ProtAb's first period was financed by an association engaged in promoting useful scientific research in Israel (hereinafter: **"the Association"**). The Association provided ProtAb, in the framework of Hadasit, with a sum of \$550,000 in order to fund its research and development, but only once the Association's Review Board found ProtAb's primary research proposal to be worthy of financial support. In accordance with the terms of the financing agreed upon by the Association, it was stipulated that if, as a result of the research conducted by ProtAb, any financial rights are created for Hadassah or Hadasit, the financial rights shall be divided between Hadassah and Hadasit, and the Association, as follows: of all initial money received by ProtAb, 50% will be transferred to the Association, with a cap of 10 times the amount of the grant provided by the Association for the research through which the right to the monies was acquired. To the best of the Company's knowledge, these abovementioned sums may be received by Hadasit (and later by Hadassah) only as dividends distributed by the Company. On September 4, 2007, ProtAb filed and received approval for a support grant for its research and development activities from the Office of the Chief Scientist in the Ministry of Industry, Trade & Labor. The grant includes a participation certificate for 60% of the R&D budget of 1 million NIS for expenses in Israel, plus the participation certificate for 30% for a similar budget for expenses relating to subcontractors abroad. These grants have been determined for the period from June 2007 to May 2008. On November 25, 2008, ProtAb filed and received approval for a continuous support grant for its research and development activities from the Office of the Chief Scientist in the Ministry of Industry, Trade & Labor. The grant includes a participation certificate for 60% of a R&D budget of 1.9 million NIS for expenses in Israel, plus a participation certificate for 30% for an R&D budget of 2.6 million NIS for subcontractor expenses abroad. These grants were provided for the period of months

from June 2008 to May 2009. Over the course of the second quarter of 2009, ProtAb filed and received approval for an extension of the above stated grant through to the end of October 2009. The grant, after its changes and the extension, includes a participation certificate for 60% of an R&D budget of 2.4 million NIS for expenses incurred in Israel, and it also includes a participation certificate for 30% of an R&D budget totaling around 1.3 million NIS for expenses relating to subcontractors abroad.

During May 2010, ProtAb filed and received approval for a continuous support grant for its research and development activities from the Office of the Chief Scientist from the Ministry of Industry, Trade & Labor. The continuous grant from the Chief Scientist is based on a budget of about 4.7 million NIS, and the amount of the grant is weighted at 50% for the development of the monoclonal antibody, Proximab, for the treatment of rheumatoid arthritis and inflammatory bowel disease. In December 2010, the term of the grant was extended for an additional four months, through the end of February, 2011. ProtAb's management estimates that ProtAb will utilize approximately 90% of the abovementioned budget, and accordingly, around 90% of the total sum of the grant shall be used by ProtAb for the implementation of this plan.

In 2007, ProtAb entered into two agreements with Hadasit: a service agreement (conducting research and development on one of ProtAb's leading products including additional experiments on animals and preparations for clinical trials) and a consultancy agreement involving Professor Yaakov Naparstek. In August 2008, both agreements were extended until the end of May 2009, and then were extended for a period of development based on permits by the Chief Scientist, until February 2011. ProtAb paid Hadasit a sum total of 581,884 NIS for the agreement between them in 2007; a total of 841,936 NIS during 2008; a total of 1,098,082 NIS during 2009; and a total of 924,674 NIS during 2010.

In June of 2009, ProtAb moved its offices from the biotechnology park complex in Hadassah Ein Kerem, in accordance with a sublease agreement signed between ProtAb and the Company. The ProtAb grounds include a broad foundation for laboratory. ProtAb's laboratories in the biotechnology park were initiated in the last quarter of 2010 after recruiting a research assistant dealing with the development of analytical methods under the direct supervision of the Vice President of R&D.

In July 2010, ProtAb entered into an agreement with the subcontractor Xcellerex for the production of ProtAb's monoclonal antibody. The total contract amount ranges between \$1.3 million to \$1.8 million, for a period of up to three years.

ProtAb continues to conduct business dealings with a variety of venture capital funds to execute investments in ProtAb that will allow it to conduct clinical trials.

### **[F] Investments in R&D**

During the past three years (2008 – 2010), a total of 10,205,000 NIS were invested in ProtAb for research and development, as follows (in thousands of NIS):

<b>Period</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Total</b>
<b>Investment in R&amp;D before the Scientist's participation <u>completed</u> at ProtAb</b>	2,370	2,388	5,497	10,205
<b>Excluding participation by the Scientist, net</b>	(901)	(376)	(1,637)	(2,864)
<b>Investment in R&amp;D, net</b>	1,469	2,012	3,860	7,341

### **5.3.4 Enlivex Ltd. (hereinafter – “Enlivex”)**

#### **Glossary for this Section**

**Inflammation** – inflammation is the immune system's reaction against injury, certain stimuli, and against contaminants that invade the human body or a life form.

**Leukemia (Blood Cancer)** – a severe disease that causes abnormal formation of blood cells in bone marrow. At first, the cells behave almost normally, but with time displace the white and red blood cells and platelets. The cancer is divided into two types: chronic leukemia and acute leukemia.

**Apoptosis** – Programmed cell death. Unlike necrosis – which is a traumatic death of cells after an infection or injury - the process of apoptosis is gradual, orderly, and consistent.

**Autoimmune Disease** – autoimmune disease is characterized by cells of the immune system which lose immunotolerance and attack the body's own cells and tissue. A typical expression of these diseases is the death of cells and the destruction of body tissue that occurs anywhere in the body without a clear cause. Examples of these types of diseases are multiple sclerosis and arthritis.

**Hematopoietic Diseases** – diseases characterized by a defect in the production of blood components.

**Immunotolerance** – the immune system can distinguish between “self” and “foreign”, i.e. between molecules and cells belonging to the body itself, and between molecules and cells from a foreign source in a manner that ensures that the immune response is only achieved against a foreign body. The distinction between “self” and “foreign” is called immunotolerance and is an essential mechanism that prevents damage to the body. When there is a defect or flaw in the immunotolerance system, autoimmune system diseases may be developed in which the immune system attacks the body's own components.

**Bone Marrow Transplant** – bone marrow is spongy tissue located in the bones which creates cells in the blood system – red blood cells, white blood cells and platelets. Bone marrow transplantation is now an accepted medical approach to approximately 100 different diseases that affect the system that produces blood cells and that damage the immune system (diseases of the neoplasm such as leukemia, and conditions such as bone marrow deficiency that are congenital or acquired).

**Allogenic Bone Marrow Transplant** – a condition in which the patient receives stem cells from his brother, sister, or parent. A non-relative of the patient may also be suitable for allogenic transplantation. This is unlike autologous bone marrow transplantation, in which the patient receives his own stem cells.

**Graft-versus-Host Disease** – transplanted stem cells may cause adverse reactions within the body. This phenomenon is called graft-versus-host disease (GvHD) and may appear up to six months after transplantation.

**Immunosuppression** – is an act that reduces the activation of the immune system. Particular sections and specific responses of the immune system may cause immunosuppression of other parts of the immune system itself. Targeted immunosuppression is performed in order to weaken the immune system, to prevent or reduce a graft rejection response, anti-graft disease and against autoimmune diseases.

**Stem Cells** – cells found in bone marrow that can produce various kinds of blood cells in the body.

#### **[A] A Description of Enlivex's Activities and the Technology Developed by it**

Enlivex is a private company incorporated in Israel under the name Tolarex Ltd. which commenced business activity in September, 2005.

Enlivex is developing an innovative system that includes a drug called ApoCell for the treatment of graft-versus-host disease in bone marrow transplantation, Crohn's disease and other autoimmune diseases by inducing immunotolerance, as a substitute for conventional immunosuppression.

The development is based on discoveries made by Prof. Dror Mevorach and his laboratory at Hadassah Ein Kerem Hospital.

Transplantation of bone marrow or stem cells donated by non-relatives (a procedure known as allogeneic) is a treatment given in cases of hematopoietic diseases, such as cancer of the blood – leukemia, multiple myeloma, etc. In 30% - 70% of transplants (depending on the disease and circumstances of the case), patients develop a disease called graft-versus-host disease (GvHD) in various degrees of severity, in which the newly implanted cells attack the transplanted tissue (the “host”). GvHD is manifested by rashes, diarrhea, skin problems, liver dysfunction, and is sometimes even life-threatening. There is currently no specific and particular treatment for GvHD, and it is a significant barrier in successful allogeneic bone marrow transplants.

Enlivex is developing a drug to treat autoimmune diseases, while focusing on the first stage of GvHD. The system treats the blood taken from the patient (or donor in a case of GvHD), by inducing controlled cell death, and then returns the blood to the patient. These cells have anti-inflammatory properties and reduce inflammation and autoimmune processes, and leave immunotolerance in the patient's body in a natural and physiological way. The treatment developed by Enlivex is apparently safe, and not expected to cause any side effects because the intended use is only for cells taken from the patient (or from the donor, who in any case is donating bone marrow cells to the patient). This treatment is tailored to the patient (adjustment of the tissue in a case of GvHD, or cells of the patient himself in other diseases such as Crohn's). Concurrent to the development of ApoCell, the Company is exploring the development of a universal cell product (VerCell) as a "shelf" drug which does not require compatibility between the donor and the patient.

In addition to ApoCell, the cellular technology, Enlivex has also identified and begun to isolate molecules that have escaped during the programmed cell death procedure (apoptosis). Based on Professor Mevorach's research, these molecules also may have an effect of inducing immunotolerance when combined with ApoCell or as an independent treatment.

In August 2009, Enlivex began performing Phase I/II clinical trials in GvHD to test the safety and to provide a preliminary evaluation of the efficacy of ApoCell in treating the disease. The experiment is performed in two hospitals in Israel (Hadassah Ein Kerem and Rambam) and is expected to include 12 – 18 patients. As of early February 2011, at least six patients have been enrolled for the trials and treated, and the trial is currently at the stage whereby the third dosage group is awaiting the completion of the first and second groups as they are evaluated by the external safety committee which can approve the dosage for the next group. As of the date of this report, the clinical trial has continued as usual in accordance with the plan and the approval of the Ministry of Health and the local Helsinki Committees.

On February 28, 2011, Enlivex completed the third year of its R&D program approved by the Office of the Chief Scientist in the Ministry of Industry, Trade & Labor, and intends to apply for support for the fourth year thereafter. The approved

budget of three programs (during some years the program was extended for longer than a year) and has totaled about 10,430,000 NIS of which the Company has been approved for support, according to applicable law, for R&D amounting to 60% from the Chief Scientist.

### **[B] Relevant Potential Market and Competition**

As of the date of this report, the Company is unaware of specific treatments against GvHD. To the best of Enlivex's knowledge, the current treatments are based on immunosuppression with drugs such as Methotrexate and Cyclosporine.

In the field of treatment for apoptotic cells (undergoing programmed cell death), the Therakos Company (Johnson & Johnson) uses in vitro photopheresis<sup>9</sup>, which is a cellular treatment that causes, inter alia, programmed cell death (apoptosis) in white blood cells. As of the date of this report, the group is in Phase III of the clinical trials to treat acute GvHD.

Osiris Therapeutics in Baltimore, Maryland has completed Phase III of the clinical research of its leading product (Prochymal) – a drug based on the technology of human stem cells which is used to treat GvHD, and has recently reported completing its experimentation while not achieving the primary objective of the clinical trials, and at this stage it is still unclear, at least to the public, what will become of the medication that, according to Osiris, is being developed to treat children with GvHD.

Other than the treatment of GvHD, the Company believes that the technology in its possession may adjust the treatment of other autoimmune and inflammatory diseases such as preventing or reducing the effect of transplanted organ rejection, treatment of Crohn's disease, and other diseases, such as multiple sclerosis. Parallel to the clinical development of ApoCell for the treatment of GvHD, the Company is investigating the effect of ApoCell's treatment on these additional diseases in animal models and will consider an expansion of ApoCell's development for these diseases as well.

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<sup>9</sup> Treating the patient's blood by giving a photoactive drug, taking a blood sample rich with white blood cells, exposure to harmful ultraviolet radiation, and returning the blood cells will stimulate an immune response where beneficial.

The global market for GvHD is estimated at approximately \$300 million each year<sup>10</sup>, and the Company sees an opening to the greater market of autoimmune diseases.

The Company estimates that in accordance with recent publications<sup>11</sup>, new therapeutic approaches will lead to market growth of 15% for autoimmune disorder treatment, until the market scope exceeds \$20 billion in 2012. The third largest group of diseases in the industrialized world, after heart disease and cancer, is autoimmune disease, and it is currently the focus of increased research and funding, which leads to various successful product development.

### **[C] Human Capital**

Enlivex is based on the research of Professor Dror Mevorach of Hadassah Ein Kerem Hospital and continues to be developed by him. Enlivex is dependent on the continuous involvement of Professor Mevorach in the early stages of the rest of his research.

As of June 2007, Mr. Alon Moran (former CEO BioMass Ltd.) has acted as the CEO of Enlivex.

### **[D] Patents and Intellectual Property**

In July 2006, a license agreement was entered into, in which Enlivex was provided with an exclusive license and the patent application filed in the United States and Europe owned by Hadasit and Yissum, a research and development company of Hebrew University Ltd. (“Yissum”) (the application was filed in 2005). The application pertains to a method for monitoring the immune response of patients with various diseases, including immune diseases and cancer, through the activity of specific cellular target sites.

In return for Yissum granting the license, Enlivex has allocated 6.25% of its allocated shares to Yissum. In addition, Enlivex owns two patent applications, which are Enlivex’s main applications, which have been filed in a number of countries in the

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<sup>10</sup> [http://www.bizjournals.com/baltimore/stories/2005/10/10/daily31.html?from\\_rss=1](http://www.bizjournals.com/baltimore/stories/2005/10/10/daily31.html?from_rss=1)

<sup>11</sup> DataMonitor research regarding the market for immune system diseases (2008).

world (USA, Canada, Europe, Japan, Israel and India) for treatment through cells found in the process of death. The company is expanding its intellectual property, and estimates that additional patent applications will be filed with the progress of their research and subject to budgetary constraints.

In the framework of expanding their intellectual property, in April 2008 an agreement was entered into between Enlivex and Tolaren Ltd. (hereinafter – “**Tolaren**”), which provided Enlivex with a global license, exclusive and free of obligation to pay royalties, to develop, manufacture and market the intellectual property developed by Tolaren which is owned by Tolaren, or which is under Tolaren’s control based on licensing agreements.

The agreement states that all development, concepts, methods, etc. developed by Enlivex which are related to the intellectual property that Tolaren has provided a license for, shall be owned solely by Enlivex. Enlivex undertook to incur patent-protection costs for which it was awarded with the abovementioned licenses.

Tolaren is a private company incorporated in Israel, whose sole activities are holding shares in Enlivex. The company holds 96.5% of the issued share capital of Tolaren.

In return for granting the license, and soon after signing the agreement, Enlivex allocated 50,050 regular shares to Tolaren which gives Tolaren a retention rate of 50% of Enlivex. With such, the company owns around 91.99% of ownership of Enlivex.

### **[E] Right to Appoint Directors, Convertible Loans and Share Capital**

In accordance with Enlivex’s bylaws, the Company’s directors are appointed by its general assembly. As of the date of this report, Enlivex’s share capital is comprised only of ordinary shares.

As of the date of this report, the sum of all convertible loans that the Company has provided for Enlivex is 8,549,000 NIS including accrued interest.

In March 2010, the Company signed an agreement with Enlivex for a convertible loan totaling \$100,000 USD. The term of the convertible loan was set until January 1, 2013. The loan was granted under the usual conditions in which the Company grants

convertible loans to Portfolio Companies (LIBOR interest plus the agreed upon rate, the right to conversion with a discount, determining a conversion rate in a case where there is no fundraising round during the term of the loan).

In July 2010, an agreement was entered into between the Company and Enlivex for a convertible loan up to \$180,000 USD. The period of the convertible loan was set until June 1, 2012. This convertible loan was also given under the usual conditions in which the Company extends convertible loans to Portfolio Companies.

In December 2010, an agreement was entered into between the Company and Enlivex for a convertible loan in the sum of 400,000 NIS. The period of the convertible loan was set until June 1, 2013. This convertible loan was also given under the usual conditions in which the Company extends convertible loans to Portfolio Companies.

In December 2010, a framework agreement for the provision of a convertible loan was entered into between the Company and Enlivex totaling up to 637,000 NIS. The period of the convertible loan was set until June 1, 2013. This convertible loan was also given under the usual conditions in which the Company extends convertible loans to Portfolio Companies.

#### **[F] Investments in R&D**

During the past three years (2008 – 2010) a total of 9,114,000 NIS was invested in research and development at Enlivex without the Scientist's participation and minus the participation of the Scientist respectively, as follows (in thousands of NIS):

<b><u>Period</u></b>	<b><u>2008</u></b>	<b><u>2009</u></b>	<b><u>2010</u></b>	<b><u>Total</u></b>
<b>Investment in R&amp;D before the participation of the Scientist completed in Enlivex</b>	3,023	2,908	3,183	9,114
<b>Minus the participation of the Scientist, net</b>	-1,127	-1,798	-1,294	-4,219
<b>Investment in R&amp;D, net</b>	<b>1,896</b>	<b>1,110</b>	<b>1,889</b>	<b>4,895</b>

### **5.3.5 KAHR Medical Ltd. (2005) (hereinafter – “KAHR”)**

#### **Glossary for this Section**

**Autoimmune Diseases** – a series of very common diseases (5% of the population) in which the immune system attacks the body’s own tissues. As in various cancers, autoimmune diseases also begin by a malfunction in the body’s cells, in this case in the immune system. The difference between the various autoimmune diseases is the tissue that the disease is attacking.

**Chimera Protein** – a protein consisting of parts of proteins from different sources that are adjoined by using genetic engineering techniques.

**SCP: Signal Converter Proteins** – modern and complex chimera proteins comprised of Type I and Type II receptors. This structure enables, for the first time, the creation of proteins with two biologically functional ends.

**Psoriasis** – a chronic skin disease which creates layers of red skin covered in thick scales which become a silvery color when they dry on the elbows, knees, scalp, and sometimes other parts of the body. The rash is usually symmetrical. The cause is known. The disease is hereditary and may erupt in situations of anxiety. It is most common in children and adolescents. Sometimes it is related to arthritis. There is no specific cure and existing treatments are for relief.

**Multiple Sclerosis** – a chronic disease of the nervous system affecting adults and youth. Damage is caused to the myelin surrounding the nerves in the brain and spinal cord which affects the functioning of these nerves. The disease is characterized by intermittent seizure attacks. Symptoms include unstable walking, shaking movement of the limbs (ataxia), involuntary movements of the eye (nystagmus), and speech disturbances and weakness. Cause of the disease is unknown.

**Myelin** – a fatty substance that surrounds the axons of specific neurons, which provides them with protection and isolation. Nerves with myelin sheaths allow neural signals to be transmitted more quickly than those without the myelin surrounding.

**Axon** – a projection from the neuron that conducts electrical impulses away from the neuron’s cell body.

**[A] Description of the Activities of KAHR and the Technology Developed by it**

KAHR is a private company incorporated in Israel which commenced business activity in September, 2005. KAHR is developing innovative therapies to autoimmune diseases and cancer, which are based, inter alia, on the discoveries of Dr. Michal Daranitzki Elhalel at her laboratory at Hadassah Ein Kerem Hospital and Professor Mark Tykocinski<sup>12</sup> (formerly of University of Pennsylvania in the US (in this section “**the Foreign Inventor**”)).

KAHR was founded in order to develop leading technology invented by the Foreign Inventor based on the creation of new protein molecules to treat autoimmune diseases and different types of cancer. This technology is based on chimera proteins that may cause modulation (changes intended to make planned improvements) of the immune system in order to modulate it for the treatment of autoimmune diseases, diseases in which the body activates the immune system against itself, such as multiple sclerosis, psoriasis, or rheumatoid arthritis, and to treat various types of cancer.

In June 2007, Dr. Noam Shani (former VP of Research and Development at Biogenics and Compugen) was recruited to serve as KAHR’s CEO and replaced Professor Eitan Galon as a board member of KAHR. In August 2009, Attorney Ofir Shahav joined the board, and in August 2010, Dr. Einat Zisman (the CEO of Hadasit) replaced Dr. Noam Shani as a member of the board.

KAHR has a license to a number of patents from the Foreign Inventor and the University of Pennsylvania for technology called SCP (Signal Converter Proteins), which in KAHR’s opinion, are a technological breakthrough. The aforementioned are exclusives licenses and are not limited in time for use of the patents and for providing sub-licenses. In the agreement, KAHR undertook to keep up with the reasonable rate of development and pay milestone payments and royalties from product sales to the University of Pennsylvania.

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<sup>12</sup> 250 shares were allocated to Dr. Tykocinski (19% from KAHR’s issued share capital). Dr. Tykocinski is on KAHR’s board of directors.

Unlike conventional biological medicines, which contain one active site, SCP proteins are chimera proteins containing two active sites on both sides of the protein. The advantage is that it allows molecules to bind to two target sites simultaneously, thereby changing the standard signal transmitted between the cells – such as changing a signal that would usually activate the immune system cells to a signal that would suppress them. The medical potential of such molecules has been demonstrated in the last decade through numerous scientific articles by researchers at Hadassah and the Foreign Inventor.

After extensive investigation, KAHR has chosen four potential SCP products for KAHR's development line. All of these developments are molecules that are candidates to be drugs that treat immune system disorders such as multiple sclerosis and chronic arthritis, in addition to various types of cancer. Two of the products, called KAHR-101 and KAHR-102 have been selected for immediate development for clinical trials and the processes to do so are being developed by Cobra Biomanufacturing in England. KAHR-101 is KAHR's leading product.

During 2008, the cell line development for the creation of KAHR-101 was completed, as was the molecule cleaning process. A significant amount of the product was manufactured and the material was tested and found to be active in laboratory experiments and preliminary experimentation on mice, designed to determine the doses required for activity. Significant<sup>13</sup> activity of the product was found in sub-scan injections at long concentrations. In 2009, a number of significant experiments were conducted in Hadassah on animal models for rheumatoid arthritis and multiple sclerosis. The experiments showed that the Company's leading product, KAHR-101 was active in both models. Additionally, a large number of experiments were conducted on cell cultures with different types of human cancer. These experiments proved that KAHR-101 shows high and significant activity in killing cancer cells. Initial trials on models of human cancer in mice have also shown high levels of activity. During 2010, KAHR completed a large number of experiments on models of liver cancer and kidney cancer in animals. The experiments showed that KAHR-101,

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<sup>13</sup> A number of experiments were conducted on animal models for autoimmune diseases. All of the experiments conducted on molecule KAHR-101 showed long-term and significant therapeutic activity.

the Company's product, was active in both models and that a correlation exists between the dosage of the drug and its activity in animals. In addition, the Company tested the activity of the product known as KAHR-102 on cell lines of different types of cancer and showed that KAHR-102 was also active in indications of cancer in addition to previously released autoimmune indications.

In 2008, KAHR founded the Scientific Advisory Board which has been joined by a number of world-renowned scientists in the field of drug development for autoimmune diseases and cancer, such as Professor Mark Feldman from the Imperial College in London, and Lawrence Steinman, from Stanford University. In October 2008, the first meeting of the Scientific Advisory Board was held, during which KAHR's development strategy was formed for the clinical trial phase. In January 2010, the board met again.

KAHR entered into an agreement to perform research and development work with the controlling shareholder of Hadasit, in accordance with the terms of the agreements approved by the Audit Committee and the Company's board of directors. In consideration for the services granted by Hadasit, KAHR paid Hadasit a total 723,000 NIS during 2010.

In addition, KAHR has entered into an office space rental agreement (for a sublease) for office space and laboratories that the Company is renting in Bio-Park.

An agreement was entered into between KAHR and the University of Pennsylvania (through a trustee on behalf of the University) in 2008, whereby the University will grant KAHR a worldwide exclusive license unlimited in time, to use the intellectual property developed by the Foreign Inventor in the University. The parties agreed that other than KAHR, the University would be permitted to allow non-commercial entities to use the property for which the license was granted for educational and research purposes alone. The agreement provides that KAHR shall be permitted to grant sublicenses, but only under various commitments required for the approval of sublicensing (reports, sales, etc.).

The parties agreed that KAHR will act to the best of its ability in order to meet the milestones set forth in the agreement, including milestones regarding fundraising for

KAHR. In the case of failure to meet a milestone, the University maintains the right to bring the license to a close.

The parties agreed that KAHR will pay the University a one-time payment of \$80,000 for granting the license (payment to be paid gradually in accordance with prescribed milestones). It was also agreed that KAHR will allocate its shares to the University in order to give the University a 5% holding in KAHR (on a fully diluted basis as of January 1, 2009). Provisions were determined that limit the dilution of the University's holdings to no less than 2% of KAHR, until the fundraising totaling \$4 million has been completed for KAHR. Moreover, it was agreed that KAHR shall pay the University a total of \$10,000 per year for the costs of conservation and maintenance of the patents included in the license. Additionally, payments to the University were determined in the case in which commercial and developmental milestones are met, and the rate of royalties to be paid by the Company for product sales derived from the license was stipulated.

A shareholder agreement was also signed by KAHR's shareholders (Dr. Tykocinski, the University of Pennsylvania, and the Company). In the shareholder agreement, provisions were included regarding the sale of shares, right of first refusal, right to join the sale, and the right to obligate a sale. It was determined that the Company has the right to appoint three members to the board of directors, and that as long as Dr. Tykocinski holds at least 7% of the Company's issued capital – he has the right to appoint one additional board member.

### **[B] Relevant Potential Market and Competition**

KAHR focuses on markets of drugs and treatments for autoimmune diseases and cancer. The global market for autoimmune biological drugs is expected to reach \$20 billion in 2009. The scope of sales of biological drugs prescribed for the treatment of autoimmune diseases reached \$16 billion in 2006 and is expected to double by 2013 (DataMonitor Report 12/07 "Commercial Insight: Autoimmune Review"). However, KAHR assesses that the popular biological drugs today provide only a partial solution to the enormous demand for treatment of autoimmune diseases.

The global pharmaceutical market for the treatment of cancer was estimated to be about \$70 billion in 2008, which was an increase of 7% from the previous year. The three most profitable drugs in the market (Rituxan, Herceptin, and Aston), which have each sold billions of dollars, are biological drugs (protein based, similar to SCP products). The leading drug in this market – Rituxan – has been approved to treat cancer in autoimmune diseases – similar to the clinical course of KAHR-101.

Based on the sales of similar drugs in the market in question, the drugs developed by KAHR, if their development is completed and they can be marketed in central markets while receiving insurance coverage, have market potential of billions of dollars per year.

### **[C] Convertible Loans**

As of the date of this report, all of the convertible loans that the Company has provided to KAHR, including accrued interest, total 5,958,000 NIS. In December 2010, the Company provided KAHR with a convertible loan for the sum of 200,000 NIS to continue financing its operations. The period of the loan was set until November 25, 2013. This convertible loan was provided under the regular conditions under which the Company provides Portfolio Companies with convertible loans.

In June 2010, the Company provided KAHR with a convertible loan for the sum of \$150,000 USD in order to continue financing its operations. The period of this loan was set until June 25, 2013. This convertible loan was provided under the regular conditions under which the Company provides Portfolio Companies with convertible loans.

In March 2010, the Company provided a convertible loan to KAHR for \$100,000 USD in order for it continue financing its operations. The period of this loan was set until March 13, 2013. This convertible loan was provided under the regular conditions under which the Company provides Portfolio Companies with convertible loans.

In January 2010, the Company provided a convertible loan to KAHR for \$150,000 USD in order for it continue financing its operations. The period of this loan was set until January 18, 2013. This convertible loan was provided under the regular

conditions under which the Company provides Portfolio Companies with convertible loans.

### **[D] Investments in R&D**

During the past three years (2008 – 2010) a total of 7,846,000 NIS was invested in research and development at KAHR, as follows (in thousands of NIS):

<b>Period</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Total</b>
<b>Investments in R&amp;D before the Scientist's participation completed in KAHR</b>	2,824	2,657	2,365	7,846
<b>Excluding the Scientist's participation, net</b>	-265	-435	-475	-1,175
<b>Investments in R&amp;D, net</b>	<b>2,559</b>	<b>2,222</b>	<b>1,890</b>	<b>6,671</b>

### **5.3.6 Cell Cure Neurosciences Ltd. (hereinafter – “Cell Cure”)**

#### **Glossary for this Section**

**Neurodegenerative Diseases** – a series of diseases in which one of the critical cell types of the central nervous system is damaged or dead. Examples: Parkinson's, ALS, multiple sclerosis, and Alzheimer's.

**Parkinson's Disease** – a disease in which the nervous cells the brain that are responsible for dopamine production, among other things, die. The disease is characterized by shaking in various parts of the body and can lead to death.

**Pigment Cells or RPE Cells (Retinal Pigmented Epithelium Cells)** – cells in the back of the retina that provide nutrients and remove waste from the cells that absorb light in the eye.

**Embryonic Stem Cells** – a unique cell that has the ability to breed and develop each of the 220 cell types in the human body.

**Dividing Father Cells** – part of the stem cells that are in the initial development stage.

**Dopaminergic Neurons** – cells that are part of the central nervous system that produce the chemical dopamine.

**Macular Degeneration or AMD (Age Related Macular Degeneration)** – the degeneration and death of cells which are located in the center of the retina (which has the highest concentration of vision cells) and which are responsible for distinguishing details (macula). As a result of this, the patient suffers from blurriness in the central field of vision.

**OpRegen™** - the first product developed by Cell Cure to treat retinal degeneration, including macular degeneration, based on the RPE cells in suspension.

**OpRegen Plus™** - a product for the treatment of retinal degeneration, including macular degeneration, which is based on the RPE cells in the membrane.

### **[Introduction] Establishment and the Commencement of Cell Cure's Operations**

Cell Cure is a private company incorporated in Israel in November 2005. When it was incorporated, Cell Cure was under the complete control of the Singapore company known as ES Cell International Pte Ltd. (hereinafter – “**ESI**”).

In accordance with the agreement signed between Cell Cure and ESI, on November 20, 2005, ESI undertook to grant Cell Cure an exclusive worldwide license to their intellectual property in the field of treatment in neurodegenerative diseases through cell replacement therapy in humans (hereinafter – “**the ESI License**”). The ESI License was granted, and its extent would depend on the investment of the company and/or external fundraising for Cell Cure, conditions which were met fully. The ESI License was granted to the company based on an agreement dated March 22, 2006 (the “**ESI License Agreement**”) and Cell Cure has been an active company since that date.

In the second quarter of 2010, ESI was acquired by the American Stock Exchange company Biotime Inc. (hereinafter – “**Biotime**”) (AMEX: BTX).

### **[A] Investments in Cell Cure in 2010**

Based on an investment agreement signed in October 2010, Cell Cure raised a sum total of \$7.1 million USD. Teva invested \$2 million in Cell Cure, the Company invest \$1 million in Cell Cure (including a conversion of around \$100,000 loaned to Cell Cure) and Biotime invested \$4.1 million in Cell Cure (including a conversation of \$250,000 loaned to Cell Cure) (hereinafter – “**the 2010 Round**”). In the framework of the 2010 Round, the shareholders of Cell Cure authorized splitting Cell Cure’s share capital, such that each ordinary share with a par value of 1 NIS will be converted to 100 regular share par value 0.01 NIS.

In addition, in the framework of the 2010 Round, the shareholders signed an amended shareholder’s agreement with Cell Cure and replaced Cell Cure’s bylaws with an amended version.

Following the 2010 Round, ESI and its parent company, Biotime, hold over 50% of the issued and paid up capital of Cell Cure. The Company holds around 26% of Cell Cure’s issued and paid up capital.

### **[B] Intellectual Property – Licenses and Research and Development Agreements**

ESI granted a worldwide exclusive license to Cell Cure to develop, market, trade, exploit, and use the intellectual property that ESI possessed at the time, in the field of treatment for neurodegenerative diseases by using Cell Replacement Therapy in humans, including the right to grant sublicenses to third parties, subject to certain conditions, as customary. The ESI License obligates Cell Cure to pay royalties to ESI in respect of income arising from the provision of sublicenses.

In March 2008, the ESI License was expanded to include factors leading to macular degeneration. Also, ESI granted Cell Cure with an additional and non-exclusive license, under the same intellectual property, to research, develop, and make use of embryonic stem cells for testing toxicity and the effectiveness of drugs, in the framework of the FP7 consortium (ESNATS) (mentioned below) and for other needs.

In September 2006, a licensing and sponsored research agreement was signed between Cell Cure and between Hadasit Medical Research Services Ltd. (hereinafter

– “**Hadasit**”) by which Cell Cure leased the research services of Hadasit in order to carry out the Cell Cure’s research program in the field of the original ESI License (which did not include activities in the field of RPE cells).

In November 2006, Cell Cure announced that a patent cross-license agreement was signed between Cell Cure, ESI, and GERON (hereinafter – “**the Cross-Licensing Agreement**”). The Cross-Licensing Agreement applied to the specific patent rights pertaining to the separation of nerve cells from the embryonic stem cells of human origin. The Cross-Licensing Agreement granted all parties a worldwide license to use, unexclusively, the patents owned by GERON and ESI. The commercial terms of the Agreement were not disclosed. GERON and ESI also agreed, inter alia, to mutually withdraw oppositions to patent registrations filed against each other in Australia.

In 2007 (and in the framework of the fundraising round that Teva partook in), Teva was awarded with a preliminary right to bid on the purchase of usage rights on Cell Cure developments, as long as Cell Cure decides to transfer or grant rights to third parties.

In August 2009, a research and licensing agreement between Cell Cure and Hadasit became effective (hereinafter – “**the Hadasit License Agreement of 2009**”). The Hadasit License Agreement of 2009 granted Cell Cure an exclusive and worldwide license (including a right to provide sublicenses, subject to conditions) to use certain inventions developed by the researchers from the Hadassah hospital, in the field of development and exploitation of embryonic stem cells and RPE cells derived from embryonic stem cells to treat degenerative diseases of the retina by using the Cell Replacement Therapy (hereinafter – “**the Hadasit License**”). At the same time, another product development agreement came into effect between Cell Cure and Hadasit by which Hadasit performs research and development for Cell Cure in the field of the Hadasit License.

In October 2010, in the framework of the 2010 Round, a new agreement was signed between Cell Cure and Hadasit which replaced the Hadasit License Agreement of 2009 (hereinafter – “**the Hadasit License Agreement of 2010**”). The Hadasit License Agreement of 2010 redefined the business conditions for granting a Hadasit License (including royalties, milestone payments, carrying costs, etc.). Also, in the

Hadasit License Agreement of 2010, special conditions were set for granting a sublicense to Teva.

Parallel to the Hadasit License Agreement of 2010, a number of related agreements were signed in the 2010 Round: (1) an additional research service agreement by and between Hadasit and Cell Cure, under the supervision of Professor Binyamin Rubinoff from the Hadassah Hospital staff (“**Prof. Rubinoff**”) for a term of five years and a scope of \$300,000 a year starting in 2011 (hereinafter – “**the Additional Research Agreement**”). The specific research topics that will be studied in the framework of the Additional Research Agreement have not yet been determined, and will be determined from time to time by the parties based on the mechanisms stipulated in the Additional Research Agreement; (2) a consultancy service agreement, by which Prof. Rubinoff and Professor Eyal Banin (who is also from the Hadassah Hospital staff) will provide Cell Cure with consultancy services in developing OpRegen™ (hereinafter for matters pertaining to Cell Cure, known as “**the Consultancy Agreement**”). As part of the proceeds paid to Hadasit and to Prof. Rubinoff and Prof. Banin based on the Consultancy Agreement, Hadasit, Prof. Rubinoff, and Prof. Banin received options to purchase Cell Cure shares at a rate of 5% of the issued capital of Cell Cure at the 2010 Round closing date.

In the 2010 Rounds, another research and option for an exclusive license agreement was signed between Cell Cure and Teva (hereinafter – “**the Teva Options Agreement**”) pursuant to which Teva was granted with an option for a worldwide and exclusive license in return for royalties (with a right to grant sublicenses) to develop and commercialize OpRegen™. The option is valid as of October 18, 2010 and ending 60 days after IND for the abovementioned product. Teva was granted with an option to receive a license under the same conditions, to develop and to commercialize OpRegen Plus™. It was agreed upon, that should Teva choose to exercise the option to receive the licenses as stated, from that point onward, Teva would bear the costs of research and development of the license at hand. It is noted that the granting of such licenses is subject to the approval of the Chief Scientist and that the transfer of certain materials for the licenses at hand to Teva is subject to the approval of the Health Ministry. It shall be further noted that ESI and Hadasit both authorized their approval for the Teva Options Agreement in writing and the granting

of sublicenses by it, and that the Hadasit License Agreement of 2010 contains special conditions that apply to this sublicense if Teva chooses to exercise it.

In the investment agreement of the 2010 Round, conditions were set by which Cell Cure can receive licenses to use specific intellectual property owned or controlled by Biotime.

**[C] Description of Cell Cure Activity and the Technology Acquired and Developed by it**

During 2010, Cell Cure focused on developing a cellular product for the cure of AMD while continuing to develop the cell research to cure Parkinson's Disease.

Cell Cure's developments in the field of AMD are based on the joint findings of the research staff run by Prof. Rubinoff and Prof. Banin from the staff of Hadassah Hospital. To the best of Cell Cure's knowledge, there is currently no effective treatment for AMD. The main cause for this disease is the death of RPE cells beneath the retina which are supported by it. The cells required to heal AMD are retinal pigment cells derived from embryonic stem cells.

The healing process is a process in which RPE cells are injected in order to renew and replace the RPE cells which are atrophying in the patient's eye, and to stop the progression of the disease.

Cell Cure is developing two formulations of RPE cells – one is RPE cell suspension (OpRegen™), and the second are cells placed on a membrane (OpRegen Plus™). Both products are designed to move transplanted cells under the retina which act as a replacement for the dead cells. Cell Cure creates the RPE cells from human embryonic stem cells by a method called Directed Differentiation Method – a unique protocol developed in laboratories in the Hadassah Ein Kerem Hospital. The method allows for directed differentiation of human embryonic stem cells to targeted RPE cells.

Embryonic stem cells are a major source and basis of stem cells for medical treatment. Cell Cure's goal is to reach a level of embryonic stem cell production under cGMP conditions (sterile conditions) in order to perform clinical trials on humans. As of the

date of this report, Cell Cure does not have enough adapted cells for human clinical trials, and Cell Cure is currently in the development process for the production of cells under cGMP conditions.

In addition, Cell Cure continues to develop cellular treatment products for Parkinson's disease and other neurodegenerative diseases, based on the discoveries of Prof. Rubinoff and his laboratory at Hadassah Ein Kerem Hospital in the field of embryonic stem cells.

Parkinson's disease is a degenerative disease of the brain caused by gradual damage to nerve cells that produce a neural transmitter chemical called dopamine, which is responsible for controlling body movement. Following the injury and death of these cells, classic symptoms of Parkinson's disease are expressed, including tremor, rigidity, slow movement, and lack of coordination.

To the best of Cell Cure's knowledge, there is currently no drug or surgery that prevents the death of dopamine producing cells and the progression of the disease, and in Cell Cure's opinion, the hope lies in a therapy that can restore lost nerve cells that create dopamine, a treatment known as cell therapy. In recent years there has been a significant improvement in some Parkinson's patients treated with a transplantation of dopamine-secreting cells derived from embryos from abortions. A significant improvement appeared mainly in patients under the age of 60 who showed significant improvements in symptoms of stiff limbs and slow movement, when tested in the morning before receiving their daily medication. Other patient groups and other conditions did not see such a significant improvement. These results were published in an article in the New England Journal of Medicine.<sup>14</sup>

Another article published in September 2003 in the Annals of Neurology<sup>15</sup> showed no significant improvement in another experiment with Parkinson's patients two years after transplanting dopamine secreting cells derived from embryos, however a deeper

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<sup>14</sup> Transplantation of Embryonic Dopamine Neurons for Sever Parkinson's Disease, N Engl J Med, Vol. 344, No. 10 March 8, 2001.

<sup>15</sup> A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease, Ann Neurol 2003; 54: 403 – 414.

analysis of these results shows that the patients did indeed show clinical improvement during the nine months following transplantation, when the patients received drugs that suppressed the immune system.

Notwithstanding the above, this treatment has severe restrictions, such as a shortage of cells for transplantation and the inability to meet mass production as required by standards and quality control<sup>16</sup>.

Of the potential sources of cellular treatment, human based embryonic stem cells (hESC) are considered by Cell Cure to be the best source since they can be differentiated into any type of cell in the human body, and have the potential to serve as an inexhaustible source of various cell types, including dopamine producing neurons.

Cell Cure intends to continue developing methods in the coming years for differentiation of hESC cells and performing experiments in animal models.

From the time of the Company's investment in Cell Cure to the date of this report, Cell Cure has completed a mapping process of its intellectual property. Also, Cell Cure has established a basis for its administrative actions (including appointment of a CEO), has improved its development plan, has completed the construction of an anticipated and planned budget for a term of five years, and has won research grants from relevant research bodies in the field (ALS Foundation; Michael J. Fox Foundation for Parkinson's Research; Genesis Consortium<sup>17</sup> for Cellular Therapy, and the Chief Scientist).

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<sup>16</sup> This research was summarized in a summary from one of the leading medical journals (THE LANCET, *Neural Transplantation for the Treatment of Parkinson's Disease*, Neurology (Vol. 2) July 2003). Two of the abovementioned researches were done at the initiative of the National Institute of Health in the USA. Additional significant research was published in articles in the New England Journal of Medicine 2001.

<sup>17</sup> The Genesis Consortium is a collaboration between a number of companies that deal with cellular therapy and develop generic technologies together in this field, and in the area of stem cells. The Consortium operates within the framework of the MAGNET program in the Office of the Chief Scientist in the Ministry of Industry, Trade & Labor, and was established in 2003.

In 2008, Cell Cure began working jointly in the ESNATs program – an affiliate program for a framework project for research and development of the European Union (FP7). The program includes 30 academic research groups from the research field of stem cells who examine the manners in which to use these cells for the purpose of drug development.

Cell Cure explores various markers on the cell's surface that would allow for the distancing of dividing father cells from the population of cells designed for transplant. Distancing the dividing cells will prevent the formation of large implants or growths that are currently the main stumbling block in implementing a transplant of cells classified from human embryonic stem cells.

During the fourth quarter of 2008, Cell Cure developed a quantitative test to diagnose whether cells have the potential to develop tumors following transplantation, due to the presence of unclassified stem cells. To do so, Cell Cure began a series of experiments that examine the application of the test with father cells from the nervous system. This test will be useful to examine the safety of classified cell transplantation generated from embryonic stem cells in order to ensure that they transplanted cells do not have the potential to produce tumors. Cell Cure also developed standard operating procedures (SOPs) to create father cells of the nervous system from human embryonic stem cells to test the genetic health of the cells, to characterize their rate of division, and to freeze them. These procedures bring Cell Cure closer, in Cell Cure's estimation, to being able to use transplanted cells in the future in patients with Parkinson's disease and patients with multiple sclerosis. Cell Cure intends to continue its activities in the fields of research and treatment using embryonic stem cells for Parkinson's disease, and during the course of 2011, Cell Cure intends to focus on developing cells to cure disease associated with retinal degeneration.

In 2009, Cell Cure began research to treat AMD disease using human embryonic stem cells. In 2009, Cell Cure began developing methods to produce cells with cGMP conditions and completed the development of the abovementioned method in 2010. Cell Cure began to produce cells with cGMP conditions intended for use in clinical trials.

Today, there is no medical treatment for dry AMD, and to the best of Cell Cure's knowledge, there is no current research process that can lead to a satisfactory medical solution. The entrance of Cell Cure into this field will be possible, according to Cell Cure's forecasts, thanks to the development of the Hadassah researchers of the method that allows the targeting of differentiation of embryonic stem cells to pigment cells, which after transplantation can replace the targeted pigment retinal cells. Transplantation of these pigment cells in patients with dry AMD can prevent the retinal degeneration of the eye resulting from a lack of function in the patient's pigment cells. Towards the end of 2009, Cell Cure proved the medical efficacy of Cell Transplantation Therapy in animal models of AMD disease.<sup>18</sup> Cell Cure will continue its activities in this field for the purpose of reaching the quality and safety testing stage expected in 2012 (Phase I clinical trials in humans). As noted, the above is forward-looking information and is contingent on the results of experiments and the favorable outcomes of research, and that Cell Cure will have the financial resources required to do so.

#### **[D] Grants Received by Cell Cure as of the Date of This Report**

Until the date of this report, Cell Cure has received various commitments for financing (from which monies have been transferred to Cell Cure in accordance with the terms of the grants) from a number of sources, as follows:

[1] The Chief Scientist (the Ministry of Industry Trade & Labor) – in March 2007, Cell Cure was given a commitment to receive a grant from the Chief Scientist for the study of Parkinson's disease. The grant was given for the period between December 2006 and November 2007, and was about 2.2 million NIS. The Company was financed by about 60% for the research totals for that period. A grant for around 3,000,000 NIS was approved for Cell Cure for the period between December 2007 and November 2008 at a financing rate of 60%. In January 2009, Cell Cure filed an application for an additional research period for the months of January through December 2009 totaling about 3.1 million NIS, with a requested participation rate of 60%. In May 2009, the requested budget was approved for the said research period for

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<sup>18</sup> Idelson et al. Cell Stem Cell. 2009, Oct 2;5(4) p. 396.

a total of 3 million NIS. The development focus of the Chief Scientist's project was the development of transplanted embryonic stem cells for Parkinson's disease.

In 2008, Cell Cure reached most of its research objectives, except for one. The main objectives included identifying factors that would enhance differentiation for dopaminergic neurons, improving the survivability of transplanted dopaminergic neurons, endorsing reagents in differentiation protocols to reagents suitable for clinical use, the preparation of protocols for the production of dividing father cells from embryonic stem cells and freezing them, and developing quality control tests for the father cells. In January 2009, Cell Cure began the RPE project for the cure of AMD disease, in accordance with the development plan filed to the Chief Scientist. In September 2009, the plan was approved by the Chief Scientist for the year of 2009. In May 2010, the company received written confirmation from the Office of the Chief Scientist in which the Company was entitled to a grant totaling 6,237,000 NIS at a participation rate of 60%. According to the written approval, the Company is entitled to receive research and development grants totaling up to 3,742. In May 2011, they should receive refunds from the Office of the Chief Scientist in the Ministry of Industry, Trade & Labor for Company expenses from 2010. Cell Cure applied for support from the Office of the Chief Scientist in 2011.

[2] ESNATS Consortium within the FP7 program – Cell Cure participated in this consortium on behalf of the European Union. The grant was given towards research testing usage of stem cells and testing the toxicity of new drugs in the nervous system. The grant is for a total of about 175,000 Euros and covers a period of five years. The project began in April, 2008. Cell Cure is not obligated to return the grant.

### **[E] The Relevant Potential Market and Competition**

#### **AMD**

About 20-30 million people in the United States are at risk for AMD disease (this is an aggregate figure and not the amount of new patients per year, or any other period, and the forecast is that the number of patients will grow as long as the population increases). About 7.3 million people in the US are in an early stage of the disease, at least in one eye. In addition, about 1.75 million people in the US have an advanced

stage of the disease and this number is expected to grow by the year 2020 to about 2.95 million patients. In general, among the patients with AMD in the United States, about 973,000 of them are in the geographic atrophy stage and are suitable to receive the treatment that Cell Cure will offer in the future, as long as its research and experiments are successful and it has the necessary financial resources for the commercialization and development of the product<sup>19 20</sup>.

Within the AMD market, one potential competitor is a company called Advanced Cell Technology Inc. (OTCBB:ACTC). This company is developing a product based on RPE cells, and in 2011 it plans to begin carrying out clinical trials.

Other competitors are the academic group of Professor Peter Coffey from the University College of London, and the group receiving funding from the state of California (CIRM), led by Professor Clegg. These groups, to the best of Cell Cure's knowledge, intend to enter the phase of clinical trials on humans during 2012.

Cell Cure estimates (based on Cell Cure's best understanding and the knowledge in its possession), that Cell Cure's advantages over the other groups as specified above are expressed as follows: [A] the differentiation process of human embryonic stem cells, which is unique and developed by Cell Cure; [B] the ability to produce embryonic stem cells under cGMP conditions, both due to the proximity to the Hadassah Medical Center and because of the ability and existing access that Cell Cure has to embryonic stem cells at a level suitable to produce cells for human clinical trials; and [C] the scientific excellence of Prof. Rubinoff and Prof. Banin's research groups, who are leading the research for Cell Cure.

### **Parkinson's Disease**

In light of the data that there are 3 million patients with Parkinson's disease in the world, and that 300,000 new cases are diagnosed each year, the market potential for the therapeutic method based on embryonic stem cells for Parkinson's disease, in particular, and to neurodegenerative diseases in general, is very large.

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<sup>19</sup> N Engl J Med 2008;358:2606-17.

<sup>20</sup> Arch. Ophthalmol. 2004;122:564-572.

Assuming that the cost of a one-time treatment through the use of embryonic stem cells for a Parkinson's patient is estimated at \$25,000 (a sum equivalent to three years of medication), the estimated value of the potential market is about \$7.5 billion per year, based only on the number of new cases annually. However, in light of the preliminary stage of developments in the field of embryonic stem cells in the world, this is only an initial evaluation, and difficulty exists in assessing the extent and exact size of the potential market. However, the Company believes that the markets are very large.

The field of stem cells is a complex field, both in terms of the science and the investments required. Stem cell companies in the US have managed to raise \$441 million from venture capital funds alone; on the other hand, the 10 companies engaged in this field in Israel have raised approximately \$75 million from private investors, government agencies and corporations alone. In light of the differences between the US and Israeli markets, and in light of the enormous gaps in available financing sources, the amount of capital raised in Israel shows lively activity and progression in the field.

The main potential competitor of Cell Cure known the Company is the Geron Corporation<sup>21</sup> - a leading company in human embryonic stem cells (hESCs) (hereinafter "**Geron**"). In 2003, Geron announced that its researchers have shown that hESCs can undergo differentiation to dopamine producing neurons and these cells can be transplanted into brains of rats of Parkinson's disease model animals.

As detailed above, in November 2006, Cell Cure signed a patent Cross-Licensing Agreement with ESI and Geron.

In addition, there are several companies developing cell therapy products for the treatment of Parkinson's disease based on different types of stem cells. Companies of this type include Reneuron Ltd. and StemCell Inc.

### **[F] Human Capital**

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<sup>21</sup> NASDAQ: GERN

Activity at Cell Cure is based on the research and continued development of Professor Rubinoff from Hadassah Ein Kerem Hospital. Cell Cure is dependent on the further involvement of Professor Rubinoff, and the involvement of Professor Banin and Tamir Ben-Hur in stages of research and development in animal models. Accordingly, it is expected that Cell Cure will continue to be involved in a service agreement with Hadasit that will ensure the continued participation of these entities in Cell Cure's activities.

As of the date of this report, about 14 scientists are working at Cell Cure, under the professional guidance of Professor Rubinoff and Professor Banin.

### **[F] Patents**

In accordance with the License Agreement with ESI, Cell Cure was awarded an exclusive license regarding, inter alia, a number of patent applications and patents owned by ESI (submitted between 2000 and 2003). These patents and applications for the registration of patents, as stated, relate to: (1) embryonic stem cells and dividing father cells derived from them; (2) improved methods for growing cultures with embryonic stem cells; and (3) embryonic stem cells that dopamenergic neurons are derived from.

The Company estimates that the abovementioned technology is a breakthrough in the treatment of central nervous disease (CNS) neuro-degenerative diseases, and is an important step in developing technology based on the ability of stem cells to become desired target cells and to be reproduced in a controlled manner, so that in practice, damages caused by the disease can be repaired. For the license conditions of ESI, see subsection [A] above. The ESI License also applies to this patent.

In August 2009, Cell Cure received an exclusive intellectual property license from Hadasit related to the Directed Differentiation of embryonic stem cells to RPE cells.

### **5.3.7 Verto Ltd. (hereinafter – “Verto”)**

#### **Glossary for this Section**

**Colona** – tube/filter used to filter various elements of the blood or plasma.

**Peptide** – short protein.

**Auto-Antibodies** – immune system proteins developed in the patient's body, that act against it and cause disease.

**Rebound** – an increase in the amount of antibodies, such that the amount of antibodies is higher following the treatment, than prior to the treatment.

**Lupus Nephritis** – inflammation of the kidneys caused by systemic lupus erythematosus.

**Human Anti-DNA Antibody** – proteins developed by the immune system in the patient's body that act against genetic material (DNA) in the body of the patient.

**Plasmapheresis** – a process by which the blood is removed from the patient's body, separated into parts, undergoes a cleaning or enrichment process, and then is returned to the body.

**[A] Description of Verto's Activities and the Technology Developed by it.**

Verto is a private company incorporated in Israel which commenced business activity in September, 2003. Verto develops innovative devices and drugs used to treat lupus (systemic lupus erythematosus). Verto's developments are based on the discoveries of Professor Yaakov Naparstek and his laboratory at Hadassah Ein Kerem Hospital in Jerusalem.

Lupus is a chronic disease which belongs to a group of autoimmune diseases in which the body activates the immune system against itself. Lupus disease creates "auto-antibodies" that bind to specific areas of normal body tissue, such as joints and kidneys, causing inflammation and destruction of these target organs. Causes of the disease are still unknown, and there is currently no specific medication against the disease. The standard treatment today, accompanied by severe side effects, uses drugs which suppress the immune system in a non-specific manner, or alternatively, a procedure in which the patient's blood is removed together with the auto-antibodies and is replaced with normal blood, a process called plasmapheresis.

In its first stage, Verto developed a column, called LUPUSORB™, which is used as a means to improve the standard plasmapheresis process for lupus patients. The LUPUSORB™ contains a short peptide VRT101 which binds and specifically targets only the auto-antibodies from the blood, thus improving the patient's condition, without causing the side effects that accompany plasmapheresis. The development is based on the discovery of the peptide called VRT101, which targets the specific regions of the body's tissue that the antibodies bind to in lupus disease. In January 2007, Verto received the regulatory approval required to perform initial experimentation (Phase I) in patients in order to test the safety and toxicity of LUPUSORB™ and the short-term effectiveness of the proposed treatment.

The clinical trial (Phase I/II) whose purpose, as stated, is to test the safety and efficiency of the product, began in March 2007.

In 2008, Verto announced the successful completion of the human clinical trials (Phase I/II) for the treatment of patients of systemic lupus erythematosus (lupus disease). The experiment was performed on 10 SLE patients in the Hadassah Ein Kerem Medical Center, and the safety and efficacy of the LUPUSORB™ device was tested.

During the experiment, a plasamapheresis process was carried out on 10 patients with the disease. For two months afterward, patients arrived for follow up visits which included blood and urine tests and doctor visits.

The results of the experiment were successful in both safety and efficacy. In terms of efficacy – the developed product was able to cause a significant reduction in the amount of the antibody present, which is among the leading factors that cause lupus disease. Antibody levels declined and did not return to the level existing prior to the treatment (i.e. no rebound effect was observed – a phenomenon occurring during other drug-based treatments). In terms of safety – no significant negative side effects were observed as a result of the product's use.

According to the exit strategy of the Company, Verto is currently in a partnership or investor detection stage in order to continue carrying out the clinical trials.

Verto signed an agreement with The Sage Group – a technology oriented and senior company in the field of healthcare, which specializes in strategy and commercialization of intellectual property. To the best of the Company's knowledge, The Sage Group has extensive knowledge in the fields of diagnostics, pharma, biopharma and biotechnology.

In accordance with the agreement, The Sage Group will help Verto shorten the time required to display the new technologies in the global market and find potential business partners. The Company estimates that the experience of Sage and its connections as mentioned above can assist Verto in finding a suitable strategic partner in order to continue the pivotal study.

### **[B] Relevant Potential Market and Competition**

To the best of the Company's knowledge, there is no specific drug treatment against systemic lupus erythematosus (SLE). The treatment existing in today's market is based on non-specific immunosuppression, such as steroids and chemical substances, leading to serious side effects in the patient's body. As mentioned, the treatment may lead to severe infections which are among the main causes of morbidity and mortality in patients with lupus. Existing drugs have other serious side effects, such as broken bones, premature atherosclerosis, malignant tumors and fertility problems. A more gentle and specific approach is to reduce the amount of auto-antibodies causing the disease by filtering plasma (plasmapheresis). However, this treatment is not common because of the need to replace the plasma and its central components after each treatment.

Many companies, whose drugs are in Phase III, have announced in recent years that they are ending the experiments due to lack of product efficacy. For example, Rituxan of the Biogen and Genentech companies for the treatment of lupus nephritis was found by publications to be non-effective in treating the disease<sup>22</sup>; Phase III experiments for Riquent from the BioMarin company in corporation with La Jolla, for treatment of kidney disease that accompanies Lupus, was discontinued due to a lack

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<sup>22</sup> <http://www.biovalley.ch/content.cfm?nav=4&content=10&command=details&id=9148>

of efficacy<sup>23</sup>. Another disappointing trial was CellCept from the Roche and Aspreva companies for the treatment of lupus nephritis<sup>24</sup>.

To the best of the Company's knowledge, Teva Pharmaceutical Industries is currently in the development stage of Edratide, a peptide based on CDR1 which produces human anti-DNA antibodies, in an innovative approach for specific regulation of autoimmune processes in SLE. Belimumab from the Human Genome Sciences Company and GSK for the treatment of lupus was found to be, to the best of the Company's knowledge, effective during the Phase III trials conducted. The Company understands that the board is recommending to the FDA in the United States to market Belimumab. FDA approval has yet to be provided.

SLE is a chronic disease, often lifelong, affecting millions of people worldwide. The population of patients with lupus in the United States, at all stages of severity of the disease, is estimated at about 450,000 patients. The market potential for lupus patients in the main European markets – Britain, Germany, France and Italy – is around 390,000 patients.

Kidneys are the main organ affected in much of the population suffering from systemic lupus erythematosus. The autoimmune antibodies sink into the kidneys and cause a condition called lupus nephritis. Of approximately 450,000 lupus patients in the United States, around 225,000 suffer from lupus nephritis, of which around 112,500 have significant damage caused to their kidneys.

LUPUSORB™, developed by Verto, is specifically designed for the population of patients with severe kidney infection, estimated at around 112,500 patients in the United States and around 97,500 in the European markets. Under the expectation of meeting around 10 treatments per year at a price of approximately \$1,000 per treatment, LUPUSORB™ has the market potential of \$1.2 billion in the United States and \$975 million in Europe. Verto estimates that there is potential to expand the market by use of LUPUSORB™ as a preventative treatment.

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<sup>23</sup> <http://www.reuters.com/article/pressRelease/idUS157018+12-Feb-2009+PRN20090212>

<sup>24</sup> <http://www.fiercebiotech.com/story/aspreva-roche-put-cellcept-ice/2007-09-10>

**[C] Human Capital**

Verto is based on the research and continued development of Professor Yaakov Naparstek from the Hadassah Ein Kerem Hospital. Verto depends on the continuous involvement of Professor Naparstek in the early stages of the ongoing research. As of the date of this report, Mr. Stuart Bernstein serves as the Company's CEO.

**[D] The Incubation Period, Patents and Intellectual Property**

Verto's research projects were approved by the Chief Scientist, and beginning in September 2003 and until August 2005, were carried out as part of a business incubator found in the area of Upper Nazareth – Nayot Technology Center Ltd. – in the “incubation track”, according to the rules of the Chief Scientist. For the obligation to pay royalties applicable to companies undergoing the business incubator process, see section 5.6 below.

Verto's intellectual property includes an exclusive license from Hadasit for the family of patents and patent applications.

The patents are in the field of treatment for lupus disease (SLE). This patent family protects innovative peptides and their usage for the treatment of lupus, both in the drug form and by their incorporation into medical devices. In this field, Verto has an exclusive license for 19 patents received in the United States, New Zealand, Europe (Austria; Belgium; Switzerland; Germany; Denmark; Spain; Finland; France; Britain; Greece; Ireland; Italy; Netherlands; Portugal and Sweden), Australia and in Israel (all of the applications were filed in 1998, except for the application filed in Israel in 1997). Verto also holds exclusive licenses on the patent application in the United States (which was filed in 2001) and on the patent application filed in Canada (which was filed in 1998) for the use of peptide treatments for treating lupus disease. The patent application from 2001 (peptide + column) was rejected by the American reviewer citing a lack of innovation. Verto appealed, but the application was again rejected.

At the end of 2009, Verto filed new patent applications in the United States, Europe, Japan, China, and India in order to protect the results of the clinical trial phase.

At the end of 2009, Verto decided to return the rights to the second family of patents to Hadasit who had granted it a license, pertaining to the field of instrumentation and diagnostic and monitoring methods of lupus disease. This was done in order to focus its resources and means of activities to the fields of treatment.

All of the patent applications and patents are owned by Hadasit.

**[E] The Right to Appoint Directors, Convertible Loans, Share Capital and Main Shareholders**

As long as the Company holds at least 2% of Verto's issued share capital, it is entitled to appoint one (1) director on Verto's board of directors. As of the date of this report, all three of Verto's directors serve on behalf of the Company.

Verto has two types of shares: ordinary shares and preferred type-A shares. All of the shares provide their owners with the same rights, except for Liquidation Preference given to preferred type-A shares. During an event allocating Liquidation Preference, the preferred shareholders are entitled to a first payment at the share price (in this section, the term "share price" means \$0.75 per share), plus an annual interest rate (the semi-annual LIBOR rate) plus 4%. The Company holds ordinary and preferred type-A shares of Verto.

As of the date of this report, the total loans on behalf of the Company to Verto, including accrued interest and linkage to the dollar, is about 2,910,000 NIS.

In 2010, the Company did not provide funding resources to Verto, including not lending convertible loans for securities of Verto.

**[F] Investments in R&D**

During the past three years (2008 – 2010), a total of 1,005,000 NIS was invested in research and development and the entrance into the clinical trial stage in Verto, as follows (in thousands of NIS):

<b>Period</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Total</b>

<b>Investment in R&amp;D before the Chief Scientist's participation in Verto</b>	740	210	55	1,005
<b>Excluding participation of the Scientist, net</b>	0	0	0	0
<b>Investment in R&amp;D, net</b>	<b>740</b>	<b>210</b>	<b>55</b>	<b>1,005</b>

### **5.3.8 Thrombotech Ltd. (hereinafter – “Thrombotech”)**

#### **Glossary for this Section**

**Deep-Vein-Thrombosis – DVT** – the formation of a blood clot in a deep vein, usually in the legs or pelvis.

**Fixed Dose Combination; FDC2** – a combination of two or more substances/drugs in a predetermined manner and dose, in a form of administration determined in order to improve drug activity.

**Naturally Derived** – a peptide segment whose source is a PAI protein that has not been chemically modified to improve stability or dissolution features.

**Characterization of Formulations** – a process in which analytical methods determine the level of salts binding to peptides during the manufacturing process and are necessary for its dissolution.

**Short Protein (Peptide)** – a molecule composed of two or more amino acids, bound by a peptide bond.

**Rat Stroke Model** – a model developed in rats as a basis for testing chemical or mechanical triggers that lead to stroke in the animal (blockage of blood vessels in the brain) to determine the efficacy of the drug in development.

**Orphan Drug** – a medication designated for a very small market (under 200,000 patients in the United States) which is therefore entitled to certain benefits from the

regulatory authority (abbreviated approval process and market exclusivity for seven years).

**Receptor** – a cell or group of cells that can detect environmental changes and can produce neural signals in response. All edges of the sensory nerve act as receptors, whether they detect touch (on skin), chemicals (in the nose or on the tongue), sound (in the ear), or light (in the eye).

**Protein Complexes** – when the protein is connected to other proteins, it creates a chain called an active protein complex. The special structure of the complex determines its activities and interactions with other cells.

**Urokinase** – a protein produced in the kidney that can dissolve blood clots. The protein is excreted in urine if it is not required in the body.

**[A] A Description of Thrombotech's Activities and the Technology Developed by it**

Thrombotech is a private company incorporated in Israel which commenced business activity in September, 2000.

Thrombotech's field of activities is the development of drugs designed to dissolve blood clots for the treatment of a stroke, heart attack, deep vein thrombosis and similar indications. The abovementioned development is based on the discoveries of Professor Abd Higazi and his laboratory at the Hadassah Ein Kerem Hospital.

Treatments to dissolve blood clots (thrombolytic treatments) are the main treatment in the case of a stroke or heart attack when there is a block of blood flow to the areas of the brain or heart. The Company estimates that today's efficacy of the existing drugs used to dissolve blood clots is limited and accompanied by side effects, some serious, such as a stroke, and thrombolytic treatment must take place within three hours from the onset of symptoms. In addition, there is a probability for bleeding, including bleeding through strokes. Thrombotech's purpose is to develop a new generation of thrombolytic drugs which are more efficient, safer (i.e. with fewer side effects) and appropriate for the large number of stroke and heart attack patients.

Thrombotech initially dealt with the development of two drug platforms that showed great potential for meeting these needs. The first platform is its leading compound called “TB101”, which is based on the discovery of a mechanism that can only dissolve new blood clots (blood clots formed in a relatively short period of time before their treatment) with no known side effects. Compared to the thrombolytic drugs used today, TB101 is seemingly more efficient and has an enhanced safety profile. As part of the reorganization of the research and development activities that occurred in late 2007, Thrombotech’s management decided to focus on developing the second platform detailed below (and not the above platform).

In the second platform, Thrombotech discovered a section of a protein (“THR-018”) which can seemingly prevent the side effect of bleeding associated with the current thrombolytic medications, when this protein segment is given together with these drugs. Based on this platform, Thrombotech aims to develop drugs to treat patients with stroke, heart attack, and similar occurrences.

During the laboratory experiments, Thrombotech found that a segment of a short protein (peptide) that the company developed, and which was given in combination with an existing drug for the treatment of stroke or heart attack (TPA – manufactured by Genentech), can prevent the side effects and significantly reduce cerebral hemorrhage associated with the administration of drugs today. Also, it was found that this protein reduces up to three times the space created from the existing drugs.

The Company estimates that Thrombotech’s developments, if they are able to be developed into a drug, can be administered independently or in conjunction with other products.

In February 2010, Thrombotech received approval to begin implementation of clinical trials on humans in Israel. The experiment was conducted on 40 healthy volunteers to assess the safety of the material.

In light of the new focus implemented by Thrombotech, and after significant testing and potential clinical development systems, Thrombotech planned a meeting with the American Food and Drug Administration (FDA) in 2008 in order to obtain approval of the requested development strategy. The meeting with the FDA took place in early

2009 due to administrative considerations of the FDA. The Company continued regulatory activities designed to explore the possibilities of developing THR-018 (orphan drug) in 2010.

Moreover, during the remainder of 2009 and during 2010, Thrombotech carried out comprehensive toxicology tests on the THR-018 – the leading compound and a primary candidate for treatment, and at the same time to improve the database regarding the effectiveness of the activities on animals.

#### **[A] Development during 2010 – 2011**

During 2010, the following major developments took place at Thrombotech:

**Regulatory Activity** – during the first quarter of 2009, Thrombotech held a Pre-IND meeting with the FDA. The meeting was described by the regulatory advisors as an extremely positive meeting, in which the FDA proposed to help develop the product in the accelerated development track (fast track). In addition, pre-clinical supplementary tests, which were required for initiating the clinical trials until the point of the second phase, were concluded in the United States. The FDA accepted the Phase I clinical trial outline and approved the production plan (CMC. Throughout 2010, after discussions with the FDA, the Company decided, at this stage, not to continue the process of developing the product as an orphan drug (within the current time window of tPA – up to 3 hours from the onset of symptoms of a stroke)).

**Preclinical Activities/CMC** – during 2009, Thrombotech completed additional safety tests and completed the pharmacological safety tests. Thrombotech completed the development of bio-analytic methods required for clinical trials on humans and the manufacture of peptide markers required for the clinical trials. Valid methods were developed to determine the level of peptides in the serum for rats, dogs and humans. These methods allowed for measurement of blood peptide levels in clinical trial toxicity tests in humans.

**Finances/Investments/Grants** – Thrombotech submitted a grant request to NIH (the National Institute of Health, U.S.). If approved, the grant is expected to support a portion of Thrombotech's R&D budget for 2011 – 2012. The Company expects that an answer will be received during the second quarter of 2011. A scientist grant was approved for Thrombotech for about 3.5 million NIS with a participation rate of about 30%-50% (50% activities in Israel and 30% abroad). In December of 2010, the Company received approval from the Chief

Scientist for additional support by the investment budget of 3.4 million NIS and at an average participation rate of 43%. In addition, a round of internal investments was completed totaling about \$800,000 USD in September 2010. Also, the shareholders converted options to company shares.

Clinical Activity – in August 2010, Thrombotech completed its initial clinical trials on humans conducted in the Phase I unit of Hadassah. The trials were conducted on 40 healthy volunteers and demonstrated that the peptide is safe in the tested doses. Similarly, it was expected that the physiological activity indicating that the mechanism of action demonstrated in animals also existed in humans. The positive test results allowed Thrombotech to continue its clinical developments of the product. Thrombotech expects the clinical trials to begin in stroke patients in 2011.

Patents – during 2009, patent applications were filed to register the TRMB-008 patent in several territories including China. In addition, another U.S. Provisional patent [asthma] was filed. During 2010, some of Thrombotech's patents entered the international exam phase and an additional patent was filed to test the possibility of use of the peptide to treat blood pressure.

Business Development – during 2010, continuation requests were made to many national pharma companies and the first article reporting on the activity of THR-18 was printed. Two additional articles are currently in the advanced stages of being written and are expected to be published in 2011. The Company introduced the results of the activities in two major international conferences in the field of strokes.

### **[B] Relevant Potential Market and Competition**

As mentioned, Thrombotech focuses on the development of drugs whose purpose is to dissolve recently created blood clots in the bodies of patients.

The market research company, "Frost & Sullivan" conducted tests on the American stroke market, and found that in 2007, the U.S. market volume for drugs treating strokes was approximately \$4.1 billion, and is expected to grow at a rate of about 6% per year until 2012<sup>25</sup>.

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<sup>25</sup> Medtech Insight/Elsevier Business Intelligence, December 2008

Strokes are the leading cause of disability among adults in the western world. The ability of treatments to reduce disability is a major competitive factor among market participants. The development of drugs that dissolve blood clots (thrombolytic) causing strokes increases the importance of an immediate diagnosis and treatment. Since a vast majority of stroke patients arrive at the emergency room at a delay exceeding six hours, medication to dissolve blood clots is only given to about 3% of all patients suffering from an acute stroke. For this reason, it is important to develop drugs to dissolve blood clots that are administered without risk of bleeding as soon as possible.

As of the date of this report, there are hundreds of products that are currently being studied for accompanying a stroke. Most of the molecules are in the pre-clinical stage.

To the best of the Company's knowledge, the main drug approved to dissolve blood clots at this time by the American FDA, and which is directed to the relevant market, is a drug called TPA (Tissue Plasminogen Activator) from the Genentech Company, one of the oldest and leading biotechnology companies in the world. To the best of the Company's knowledge the drug in question is effective, but in order to guarantee that the patient does not suffer side effects characterized by bleeding, there is a narrow window of efficiency for treatment estimated to be three hours from the onset of the incident. The drug being developed by Thrombotech, in accordance with the findings of the trials on animal models in a case of stroke, is expected to be far more efficient, but is designed so that the timeframe of efficiency will be longer and will extend for a period of nine hours from the onset of the incident. The abovementioned difference in terms of efficiency is mainly due to the difference in the mechanism of action between Genentech's drug and the development of Thrombotech's drug.

Thrombotech's laboratory results in the animal experiments show, with high certainty<sup>26</sup>, that the administration of TPA together with THR-018 developed by Thrombotech: (A) may be an effective treatment for up to six hours after the stroke incident; (B) reduces the area of cerebral necrosis by more than 50% than the reduction with the TPA treatment alone; (C) substantially reduces (up to 80%) cerebral hemorrhages in comparison to the TPA treatment alone.

In addition to the TPA drugs, a number of additional drugs are being studied for heart attack, and may be relevant for the treatment of strokes:

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<sup>26</sup> Statistical significance above 0.99.

Activase, Tenecteplase and Cathflo Activase from the Genentech Inc. company; Reteplase from the Centocor company; and Streptokinase from the Aventis Behring company.

Thrombolytic drugs attract a great amount of attention and have a substantial market, but most were developed for ischemia (inadequate flow of blood) in the heart muscle. The number of drugs found in development for a stroke is limited to a small handful of molecules.

### **[C] Human Capital**

Thrombotech's leading technology is based on the research of Professor Abd Higazi from Hadassah Ein Kerem Hospital and requires the researcher's knowledge for further development.

During November 2007, Dr. Itzhak Lamensdorf was appointed as the CEO of Thrombotech and Professor Marian Gorecki was appointed to serve as the chairman of Thrombotech's board of directors. In addition, the Company has senior consultants in the field of drug development and regulation.

During 2009, Dr. Arnon Aharon joined Thrombotech and served as Thrombotech's clinical leader and will soon lead the company's clinical trials.

In addition, Thrombotech signed an agreement for the provision of management services with Pharmaseed – a company specializing in the development of technology for the central nervous system – and is not a controlling shareholder in the company.

Thrombotech's agreement as stated above for the provision of management services costs a total of \$10,000 per month.

### **[D] Incubation period, Patents and Intellectual Property**

Thrombotech's research project was approved by the Chief Scientist in the Ministry of Industry, Trade & Labor (hereinafter – “**The Chief Scientist**”). Beginning in October 2000, Thrombotech acted in the framework of a technological incubator found in the Upper Nazareth area – Nayot Technology Center Ltd. – for a three year period in an “incubation track” in accordance with the rules of the Chief Scientist. For the obligation to pay royalties, applicable to companies operating in a technology incubator, see below.

Thrombotech has ownership of, or an exclusive license for, the use of a variety of patent applications and patents that protect the protein complexes and peptides and their uses to dissolve blood clots. The patents and patent applications are divided into three main groups.

The first group protects two protein complexes included in the urokinase (an enzyme that acts to dissolve blood clots) and its receptor and applications for dissolving blood clots in several diseases such as strokes. Thrombotech has an exclusive license on patents owned by Hadasit as follows: patents received in the U.S. (the patent applications were filed between 1999 – 2001), in Europe (the patent applications were filed in 1997) and in Australia (the patent applications were filed in 1999 and 2000). Likewise, Thrombotech has an exclusive license for patent applications owned by Hadasit which were filed as follows: patent applications in Canada, Israel, Japan and Australia (submitted since 1997); applications in Canada and Israel (applications submitted in 2000). Due to the change in Thrombotech's focus as explained above, Thrombotech stopped developing the first group of patents, and they were returned to the ownership of Hadasit.

The second group contains patent applications and patents regarding protein complexes that include the urokinase and its receptors that bind with a specific connection and which are used to dissolve blood clots for the treatment of a number of diseases such as a stroke. This group contains a United States patent (the patent application was filed in 2001) and applications in Europe and in Canada (submitted in 2002). Due to the changes in Thrombotech's focus as above specified, Thrombotech stopped the development of the second group of patents, which returned to the ownership of Hadasit.

The third group contains patents for the dissolving of blood clots and preventing brain injuries in conjunction with coagulation solvents such as TPA. This group contains patent applications filed in Canada, Europe, Israel and Japan (the patent applications were filed in 2002), applications to Australia, Canada, Europe, Israel, and the U.S. (the patent applications were filed in 2003 – 2004), and two additional applications filed in the U.S. (filed in 2005 – 2006). During 2009, Thrombotech filed patent applications for the TRMB-008 drug in several territories. Also, a U.S. Provisional

application was filed (the field of asthma). During 2010, following the pre-clinical/clinical results, a U.S. Provisional patent application was filed for further treatment for blood pressure.

### **[E] The Right to Appoint Directors, Thrombotech's Share Capital and Major Shareholders**

As long as the Company holds at least 3% of Thrombotech's issued share capital, it is entitled to appoint one (1) director for Thrombotech's board of directors. As of the date of this report, one of the five directors on Thrombotech's board of directors serves on behalf of the Company. Of the additional directors who serve on Thrombotech's board, there is a director on behalf of "Clal Biotechnology Industries", a director appointed on behalf of Ofer Technologies, Thrombotech's CEO, and Professor Marian Gorecki, who was appointed to serve as the chairman of the board.

In September 2010, the Company's shareholders converted 11,824 options (out of 28,374 options in circulation) to series A-2 shares of Thrombotech, in consideration of 3.9 million NIS, around 3.4 million NIS of which were received in cash. At the time of the conversion, the Company extended the exercise period for the 16,550 options remaining until December 29, 2011. Extending the option period increased the fair value of the options presented by long-term commitments totaling 382,000 NIS, parallel to the reduction in the company's equity.

As part of this round, the Company participated in the relative portion and invested \$200,000.

In December 2010, the Company received approval from the Chief Scientist for support in an R&D program on the treatment of strokes for a retroactive period that began in June 2010 until May 2011. The approved budget for the plan was up to 3,355,000 NIS with an average participation by the Chief Scientist of about 40% of the approved R&D budget.

### **[F] Investments in R&D**

During the past three years (2008 – 2010), a total of about 9,259,000 NIS was invested in research and development at Thrombotech, as follows (in thousands of NIS):

<b>Period</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Total</b>
<b>Investment in R&amp;D before the Chief Scientist's participation in Thrombotech</b>	2,896	3,152	3,211	9,259
<b>Excluding the participation of the Chief Scientist, net</b>	- 579	- 598	- 495	- 1,672
<b>Investment in R&amp;D, net</b>	<b>2,317</b>	<b>2,554</b>	<b>2,716</b>	<b>7,587</b>

### **5.3.9 BioMarCare Technologies Ltd. (hereinafter – “BioMarCare”) (formerly called Incure Ltd.)**

#### **[A] Description of BioMarCare's Activities and Technology Developed by it**

BioMarCare is a private company incorporated in Israel which commenced business activity in August 2002.

In October 2009, BioMarCare renewed its activities with a new name – BioMarCare Technologies Ltd., and is in the business of unifying a number of technologies and intellectual properties in the field of advanced markers (biomarkers) for the early detection of various cancers. In this framework, BioMarCare raised a convertible loan

totaling \$300,000 USD from the Company, an investment totaling \$400,000 USD and recruited a staff, as detailed below.

BioMarCare focuses on locating and developing cancer diagnostic technologies and methods based on intellectual property, which is essentially based on the findings of the Hadassah researchers. Its aim is to leverage these diagnostic technologies, with the common denominator of being in the field of cancer, to support the development of a number of projects simultaneously.

Biological markers detect the cancer's progress at an early stage, allowing one to track the process of treatment for each patient individually, so that the efficacy of treatment will be increased and the side effects involved reduced. The development process of diagnostic tools and biomarkers is a relatively short process for the manufacture of drugs (pharma) and therefore, the process requires professional and focused management.

As of the date of this report, BioMarCare is focusing on the development of two diagnostic sets for the detection and diagnosis of breast cancer and colon cancer:

[A] The first product, Breast PARpanel™ is a diagnostic method for the early detection and monitoring of the metastasis distribution process in breast cancer. BioMarCare is developing a simple immunological blood test, which will help determine the quantitative level of onco-genetic markers of the Protease Activator Receptors group, which are released into the blood stream during the disease. Preliminary clinical findings which compared with blood samples of cancer patients at different stages of the disease with blood samples of healthy women indicated a specific marker for cancer and the clinical benefit expected as prognosis markers, to select and monitor treatment of breast cancer.

In December 2009, BioMarCare received the approval of the Helsinki Committee to expand the trials that it is performing in the Institute of Oncology at the Hadassah Ein Kerem Hospital and in Hadassah Har Tzofim on a large number of blood samples from breast cancer and colon cancer patients in order to confirm the initial findings and to determine accurately the sensitivity and specificity of the simple blood test.

BioMarCare has built a database of about 500 blood samples which will be tested during 2011.

[B] The second product, Colon-MarCarePlex™ - in August 2010, BioMarCare signed a memorandum of understanding for a worldwide and exclusive license agreement for the development and commercialization of a molecular marker for the early diagnosis of colon cancer by using the simple blood test. The memorandum of understanding was signed with Hadasit and with the Ludwig Institute for Cancer Research Ltd., of New York, and is based on the CCAT1 marker, the result of joint research between the two institutions and the transportation of senior oncology surgeons at Hadassah Hospital. The abovementioned MOU was a precursor to a final licensing agreement, which is currently being negotiated for a signature.

Following the signature of the MOU, BioMarCare began the development of its second product based on a panel of molecular markers with a simple blood test, rather than an evasive test. The blood tests use the RT-PCR method (a molecular method commonly used for diagnosis) which aims to identify with a high precision the presence of a CCAT1 marker and additional marker which express cancerous growths in patients. The combination of markers is expected to provide extremely high levels of protection. Routine use of this new test will allow for the alert and referral of the patient for further testing and more comprehensive diagnosis, and life saving treatments.

Following the date of the report, BioMarCare received approval of the Helsinki Committee and began carrying out wide clinical trials (about 500 blood samples) for this product, in conjunction with the Oncology Department of the Hadassah Hospital, which aims to examine the efficacy of the new method for the early detection of colon cancer.

### **[B] Organization**

BioMarCare's activities are conducted from the Bio-Park in the Hadassah Hospital complex and use the administrative and logistical infrastructure of Hadasit.

BioMarCare's management team appointed the CEO, Ms. Dana Cohen, and Dr. Ouriel Faktor, the VP of Research and Development.

BioMarCare is assisted by research and development services from the scientists at the Oncology Institute, directed by Professor Tamar Peretz, a senior oncologist and leader in the international cancer research community. BioMarCare appointed Professor Peretz as its Medical Director to lead BioMarCare's clinical trials. In addition, BioMarCare recruited clinical trials monitors, clinical trial coordinators, and researchers. For its first product, BioMarCare is working with subcontractors in order to prepare the development of test kits.

### **[C] Development Status**

BioMarCare found that the gene known as PAR is overexpressed in malignant tumors and is directly proportional to tumor malignancies. PAR (the Protease Activator Receptor) (also known as the thrombin receptor) is located on the cell's surface and expressed in high levels in solid malignant tumors of various types; these findings provide a basis for developing an estimate. According to biopsy tests performed on patients, the said gene is overexpressed in a variety of cancer types such as: prostate cancer, breast cancer, colon cancer, and ovarian cancer.

The receptors from the PAR family have a unique mechanism which, on the one hand, when the receptor is activated, releases a short peptide into the blood, and on the other hand, the activated receptor is involved in cancerous and invasive processes. This mechanism of cutting into the cardiovascular system is different and unique compared to biomarkers, as opposed to other markers which are released into the blood as a result of the mortality and disintegration of the cancerous cell, separate from the cell or a few of them are actively secreted.

As a result of this mechanism, the measured level of PAR peptides in the blood is a mirror image of the process of the intracellular process leading to cancer, when there is a close biological and chronological relationship between the cancerous process and release of the peptide.

BioMarCare is developing a kit to detect peptides secreted from the PAR family (thrombin) in the blood of the patient as a diagnostic test that allows for the identification of metastatic cancers and the monitoring of the disease progression in different types of tumors. This kit uses a simple blood sample received from the

patient at clinics, HMOs, or Hospitals and the test itself can be carried out in main laboratories.

Clinical findings to date have demonstrated the inherent benefits in PAR1 and PAR2 markers:

[A] The PAR1 marker is detected in a group of over 70 breast cancer patients compared with the absence in healthy subjects; [B] the marker was detected in all four stages of the disease (I-IV) and not only in advanced stages; [C] contrary to the assumption that as the severity of the cancer increases the quantity of the marker increases, a high quantity of the marker was identified in some patients found in stages I-II, which provides the ability to diagnose a more severe course of the disease; [D] biopsies of breast cancer patients reveal PAR markers as a negative prognostic factor in patients receiving hormone therapy.

It was also found that in a group of 160 biopsies from women in early stages of the disease, about 85% were identified by a combination of PAR markers in tissue, compared with only 19% in women identified by commercial markers approved today.

BioMarCare began to develop a simple blood test kit that works with the "Competitive ELISA" method, which allows for the detection of different stages of cancer from solid tumors, and for follow-up treatment of the disease. The essence of the test is in measuring the PAR peptide levels in the tested blood sample, by the immunological symbols (antibodies) and a signal system (e.g. Fluorescence, color reading).

The Company believes that this discovery may allow the combination of simple diagnostic tools prior to the treatment process, immediately after the initial drug treatment and during all monitoring stages of the disease.

With a summary of the clinical trial results, BioMarCare is intending to prepare for a multicenter control trial as a basis for filing an application for marketing approval for the diagnostic kit to receive regulatory approval for sales in Europe and the United States. The forecasts, estimations, and intentions of BioMarCare described above are forward-looking information based on its estimations. The information in its possession is correct as of the date of this report and its work plan. These estimations

may not materialize, entirely or partially, or conversely may be realized in a substantially different manner than observed herein. This is due to various circumstances which may alter the markets in which BioMarCare operates, the failure to meet targets, the results of experiments, regulatory changes, technological changes, changes in the work programs (due to external factors), changes in the approvals of grants and a lack of additional sources of funding.

#### **[D] Relevant Potential Market and Competition**

Cancer markers currently approved for medical use are not unique for a particular type of cancer, are characterized by a low sensitivity and sometimes are expressed in healthy tissue. In the absence of a more specific diagnostic tool, these markers are usually used in order to monitor later stages of the disease and even then, not always successfully. The global market for the molecular diagnosis was approximately \$18 billion in 2006, and is expected to reach \$92 billion by 2016. The overall biomarker market was about \$5.6 billion U.S. in 2007 and is expected to reach about \$12.8 billion U.S. by 2012. The market segment reviewed for colon cancer is about \$3.75 billion U.S. and the target population are 50 years of age and older.

Each year, about one million people worldwide suffer from colon cancer. In the U.S. alone, 140,000 new cases are diagnosed annually. Most patients are diagnosed during advanced stages of the disease. The chance for curing colon cancer reaches 90% when the disease is discovered at an early stage. Conversely, if the discovery is made at an advanced stage when there are metastases, the chance of recovery is very low. Therefore, in the western countries, nationwide prevention programs for early detection are common.

Currently, the early detection of CRC is done by an annual national survey of people over the age of 50 with the help of a method of detection on a fecal occult blood sample, and a recommendation for a colonoscopy every few years.

The method to detect occult blood requires that the subject follow a special diet for a number of days before the test, self-preparation of the sample and full compliance for the test (the United States has about a 40% compliance rate). The method has low sensitivity and the specificity is strictly dependent on following the diet properly.

A colonoscopy provides a highly reliable level of diagnosis but is an invasive test and the response to undergoing the method in the absence of symptoms of the illness is very low. Therefore, although these methods have already led to early detection and have reduced the mortality rate from the illness, there is still a need to increase early detection, before colonoscopy, by the initiation of additional products. In the field of blood tests, there is currently no blood test with FDA approval or recommended by the American Society of Clinical Oncology (ASCO) for the purpose of early detection or monitoring of colon cancer.

In addition, blood tests based on biomarkers (CEA tests) are not sensitive and precise, and are therefore not recommended for diagnostic testing or monitoring. Therefore, diagnosis of the disease is currently done by using fecal occult blood (survey) or by colonoscopy, and not by blood tests. Monitoring of the disease is currently done using imaging.

BioMarCare is developing a simple and non-invasive blood test, while offering the patient comfort in providing a sample. This allows for serial or periodic tests, and has high specific sensitivity values compared with existing markers.

In addition, about 30% of patients diagnosed are in stage II of the disease. The percentage of post-operative healing in this group stands at 75% – 80%. However, for a significant number of the patients, the disease recurs. There are no approved blood tests targeting chemotherapy stage II patients after surgery.

In Israel, colon cancer is the most deadly form of cancer with the highest mortality rate, relative to other cancer diseases. About 3,000 people are diagnosed each year as patients of the disease, and about 1,500 people die as a result of it.

Breast cancer is considered to be the second most common among women. According to the current market assessment, in 2009, about 200,000 women were diagnosed with breast cancer and about 40,170 will die from the disease. Detection at an early pre-metastatic stage increases the survival rate in the first five years to 100%. Colon cancer is considered to be the third most common cancer with the amount of 1.1 million new cases per year of which 723,000 cases occur in developed countries and

153,700 in the United States in 2007. Pre-metastatic early diagnosis increases the survival rate in the first five years to 90%.

Biomarkers are also intended for the companion diagnostics market and are used for drug development, monitoring drug safety and efficacy and as a prognostic marker, or as a parameter that predicts the success of a drug treatment.

Today, breast cancer detection and monitoring after chemotherapy/surgical treatment/radio therapy are performed using imaging (MRI, PET/CT) once per 12 weeks, which exposes the patient to radiation. Also, such aforementioned imaging has a very high cost.

In the field of biomarkers for cancer there are a number of commercial kits used to identify markers; however, to the best of BioMarCare's knowledge, these are approved for use only in later stages of the disease. As a group, these markers are characterized by low specificity and sensitivity, and therefore their clinical usefulness is limited. As a result, there is a need for new markers with good clinical performance during early and late stages of the disease. To the best of the Company's knowledge, dozens of immunoassays and molecular markers for cancer new markers are being developed in the coming years. However, it seems that BioMarCare has a unique market potential both because of having developed blood-based panels based on specific cancer markers, using simple blood tests appropriate for any diagnostic laboratory. Unlike companies that develop diagnostic instruments or technology platforms, the BioMarCare Company specializes in clinical validation of the markers in defining the clinical benefits, and in developing the diagnostic kits.

### **[E] Human Capital**

BioMarCare is based on the research performed in the laboratory of Dr. Rachel Bar-Shavit and the research of Dr. Aviram Nissan, an oncology surgeon at Hadassah Hospital. The chief researcher for the PAR clinical trials is Dr. Beatrice Uziely, Director of the Institute of Ambulatory Services at the Institute of Oncology in the Medical Center of Hadassah Ein Kerem.

BioMarCare recruited a management team which includes Ms. Dana Cohen, the CEO of BioMarCare and Dr. Ouriel Faktor, both of whom have seniority in the biotech industry in the field of diagnostics.

As stated, BioMarCare recruited Professor Tamar Peretz to its services, Director at the Institute of Oncology in the Hadassah Hospital, and the director of the Center for Breast Cancer Disease, as the Advisor and Clinical Manager of BioMarCare.

As of the date of this report, BioMarCare employs four employees and receives the services of one employee as a subcontractor.

### **[F] Incubation Period, Patents and Intellectual Property**

BioMarCare's research project for its first product was approved by the Chief Scientist and began in June 2003 and until August 2005, BioMarCare acted in the framework of a technology incubator found in Jerusalem – the high-tech Technological Entrepreneurship Center Ltd. (as it was formerly known, today it is known as “Van Leer”), in the “incubation track” in accordance with the rules of the Chief Scientist. The obligation to pay royalties applies to companies operating in a technology incubator.

In the beginning of 2010, BioMarCare received a grant of 1,800,000 NIS from the Chief Scientist for the development of the PAR marker kit. BioMarCare has yet to submit a plan for the second year for this marker to the Scientist.

In October 2010, BioMarCare submitted a plan to the Scientist for the second product. It has not yet received approval for the grant by the Scientist.

### **[G] Patents**

The company has two families of patents:

The first family – BioMarCare has an exclusive license from Hadasit for two groups of patents and patent applications pertaining to the PAR marker.

The first technological group in this family is regarding the method and kit to identify the disease the evaluation of metastatic tendency and follow-up treatment. These patents protect the unique method of diagnostics of malignant tumors associated with

overexpression of PAR1. This group includes an exclusive license from Hadasit for use of the two patents registered in the U.S. The first patent is based on the molecular marker overexpressed in malignant tumors in 2002. The second patent - on February 7, 2008, a U.S. provisional patent application was filed which was titled: Immune-Detection of a Cancerous State in a Subject. The patent is intended to protect the immunological identification of the peptide released from PAR-1 in the serum of cancer patients. The identification distinguishes between healthy and sick patients, allows for blood tests which measure the degree of malignancy (levels 1-4) as well as tracking the efficiency of the treatment provided to the patients. The patent has entered the international stage (PCT) on February 5, 2009.

In November 2010, a U.S. Provisional patent application was filed. The patent was designed for use of PAR1 in panels with other markers.

The second group in this family includes the cancer treatment method by regulating gene expression (silencing) of PAR-1. BioMarCare Technologies has an exclusive license from Hadasit on the patent applications entitled: Gene Silencing of Protease Activated Receptor 1 (PAR1), registered in the United States and Europe. The patent intends to protect the silencing process of the gene to PAR-1 by using nucleic acid bearing identifiers of the PAR1 gene sequence which bind to it and paralyze the gene's expression, thus delaying the cancer process.

The second family of patents includes an exclusive license from Hadasit and the Ludwig Institute that is currently being negotiated for a signature, for the use of a patent that binds the CCAT1 marker to cancer. This patent was filed in February 2008 with a U.S. Provisional patent application titled: Colon Cancer Associated Transcript 1 (CCAT1) as a Cancer Marker.

The patent in question entered the international stage (PCT) on February 5, 2009.

Also, in this family a U.S. Provisional patent application was filed in November 2010. The patent is designed for use on a CCAT1 panel with other markers.

**[H] Right to Appoint Directors, Share Capital and Convertible Loans.**

In accordance with BioMarCare's bylaws, all shareholders that may be, together or separately, who hold 12.5% of BioMarCare's issued share capital (excluding shares issued to a trust not for the benefit of a specific person), will be entitled to appoint one director to serve on the board. As of the date of this report, two of the three directors serving on BioMarCare's board have been appointed on behalf of the Company. As of the date of this report, BioMarCare Technologies has only one type of share (ordinary shares par value 0.01 NIS each).

As of the date of this report, the total of all convertible loans provided by the Company to BioMarCare, plus accrued interest and linkage differentials, is approximately 2,532,000 NIS. The Company has also invested in BioMarCare's shares during 2010 in the amount of \$400,000 USD.

In June 2010, an investment agreement was signed between the Company and BioMarCare, according to which the Company will invest \$400,000 USD in exchange for 89,888 ordinary shares of BioMarCare. Under this agreement, the investment was transferred to BioMarCare in payments, where \$200,000 USD was transferred to BioMarCare following the signature on the investment agreement, and an additional \$200,000 USD was transferred during November and December 2010, following the completion of milestones as determined in the investment agreement (signature on an MOU to receive an exclusive license of the CCAT marker).

### **[I] Investments in R&D**

During the past three years (2008 – 2010) a total of about 2,501,000 NIS has been invested in research and development at BioMarCare, as follows (in thousands of NIS):

<b>Period</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Total</b>
<b>Investment in R&amp;D before the participation of the Chief Scientist at</b>	299	463	1,739	2,501

<b>BioMarCare</b>				
<b>Excluding the participation of the Chief Scientist, net</b>	0	0	-474	-474
<b>Investment in R&amp;D, net</b>	<b>299</b>	<b>463</b>	<b>1,265</b>	<b>2,027</b>

### **5.3.10 Conjugate Ltd. (hereinafter – “Conjugate”)**

Conjugate is a private company limited by shares which was incorporated in Israel on November 21, 2005.

Conjugate dealt with the development of drugs for treatment against systemic fungal infections, based on technology that links active ingredients and existing drugs to chemical compounds, to reduce drug toxicity while maintaining efficacy.

As part of the development process, in 2010, Conjugate attempted to scale-up the production process in order to produce large amounts of the Amposol product to be used for GLP trials on large animals and clinical trials on humans. During the production and scale-up stage, they encountered difficulties in recovering the experimental results of the original product in terms of safety and efficacy.

In light of the above, the board of directors of Conjugate decided to cease its activities and dismantle in January 2011.

In total, the Company invested around \$800,000 (investments made since 2008).

### **5.3.11 Company Holdings in BioLine RX Ltd.**

Bioline RX Ltd. (hereinafter – “**BioLine**”) is an Israeli public company traded in the Tel Aviv Stock Exchange Ltd. BioLine is engaged in the development of drugs and products in various fields, including cardiology, psychiatry, and oncology.

In January 2007, the Company participated in the tender phase of a public offering of BioLine. The Company also participated in the tender stage of issuing of BioLine's IPO. In total, the Company has invested 2,274,000 NIS in BioLine. The Company holds 308,750 ordinary shares of BioLine. Since acquiring the shares in BioLine, the Company has not sold, whether in the Stock Exchange or out of it, any shares of BioLine. As of the date of the financial reports, December 31, 2010, the stock market value of BioLine shares held by the Company is approximately 991,000 NIS.

The Company has no ability to influence BioLine's activities or direct its business in any manner. As of the date of this report, the Company's board of directors considers the BioLine holdings to be financial holdings.

BioLine is a publically traded company in the Tel Aviv Stock Exchange Ltd. and its reports are published publically.

#### **5.4 Investments in the Company's Capital During 2010**

According to a shelf prospectus for the Company published on August 31, 2009, the Company published, on August 29, 2010, a shelf prospectus report for issuance and registration for trading on the Tel Aviv Stock Exchange Ltd. As part of the offering report, the Company allocated 88,477 units, comprised of approx. 8,848 thousand shares and approx. 8,848 warrants (Series 4) in consideration of NIS 128 per unit. The warrants are unlinked, and are exercisable until August 30, 2013, with unlinked exercise money of NIS 1.75.

The total net consideration received as a result of the issuance amounts to approx. NIS 10,092 thousand.

#### **5.5 Dividends and Dividend Distribution Policy**

- 5.5.1 Since the date of its founding, the Company has not distributed any dividends.
- 5.5.2 The Company's dividend distribution policy, as specified in the Company's Articles of Incorporation, is that, at any such time as the Company is in possession of a distributable amount as defined in law, 75% of the amounts determined to be distributable to shareholders in the Company as dividends will be distributed, on the

condition that the Company will retain a surplus of funds that is sufficient to meet the payments specified in the management agreement over a period of two years (or over a shorter period, if the management agreement specifies a shorter validity period, or in the event that the balance for the period in which the management agreement was to be valid is less than this time period). It is hereby clarified that, in subsequent periods, the remainder of the aforementioned amount which remained undistributed (in other words - 25% of the amount) will not be considered a distributable amount, even if the distribution conditions specified in the Companies Law are fulfilled, and this amount will be available the Company in accordance with the decisions reached by the Company's board of directors (which will also have the right, following a decision reached on the matter, to order distribution of the amount to the shareholders).

## **5.6 Research and Development**

- 5.6.1 All of the Portfolio Companies engaged in the field of medical and biotechnological research.
- 5.6.2 The main area of operations in which the Company is engaged, through the Portfolio Companies, and in which it intends to continue to engage, is research and development in the field of medical and biotechnological research and / or production and distribution of the results of the research and development done in these areas.
- 5.6.3 The Encouragement of Industrial Research and Development Law, 5744-1984 (hereinafter: the "**R&D Law**") provides that any entity which was given the approval of the Chief Scientist as noted above will pay the State Treasury royalties from any revenue arising from a product developed as part of the program or resulting from it, including accompanying services for the product or involved therein, whether the revenue was created by the entity that was granted the authorization, or by a related person or entity.

The rate of royalties specified in R&D Law was set forth in the Regulations established based upon it. In accordance with the Encouragement of Industrial Research and Development Regulations, 5756 - 1996, the entity that received the authorization must pay the State Treasury royalties up to the amount specified in the Law and the Regulations established based upon it.

As of the reporting date, the following Portfolio Companies have received funds from the Chief Scientist, subject to the provisions of the R&D Law:

(1) Protab; (2) Cell Cure; (3) Enlivex; (4) Thrombotech; (5) Verto; (6) Biomarker; (7) Kahr Medical (2005) Ltd.; (8) Conjugate.

## **5.7 Stages of Development and Regulatory Approvals Required for the Development of Drugs and Medical Products**

### **[A] Introduction**

- 5.7.1 The approval of medical products for distribution is subjected to stringent regulations (legislation). Regulation is relatively strict in Israel (by the Ministry of Health), in the United States, (by the Food and Drug Administration) (hereinafter: the "FDA") and in Western Europe (by the European Medicines Agency) (hereinafter: the "EMA").
- 5.7.2 The regulatory requirements differ from country to country, and authorization provided by one country does not necessarily guarantee authorization by a different country. However, an authorization given by a regulator which is considered stricter (such as in the USA or Western Europe) will usually facilitate the process of receiving authorizations in difference places around the world. In addition, authorization granted by the EMA is valid for all of its member countries<sup>27</sup>. It is generally accepted that after FDA approval is received for a product, EMA approvals will also be received a relatively short time later. This assumption is based on the similar level of requirements of these authorities, which eliminates the requirement for significant additions in order to meet the requirements of one authority after receiving approval from the other.
- 5.7.3 The process of receiving the required regulatory approvals in each of the countries result in significant expenses, including nominating a local representative and investing in skilled, professional personnel, and continue over a relatively long period which may reach several years, especially in countries where stringent regulations are in place. In contrast, the process may be significantly shorter in countries with more lenient regulations. The Company focuses on receiving authorization in countries that have the biggest markets for the products developed by the Portfolio Companies, especially the USA and European countries, in addition to the performance of clinical trials in Israel.

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<sup>27</sup> According to information appearing on the organization's website at <http://www.emea.eu.int/hums/aboutus/emeaoverview.htm>, 27 countries are members of the organization as of July 2009.

- 5.7.4 Each groups of products in the field, and at times even a single product, requires unique development and production facilities that are specifically designed to meet the regulatory requirements, and must undergo a lengthy approval process which includes testing of the product's development processes, testing of the consistency and reliability of the development processes, and testing of the laboratory. Ethical tests and reviews must also be passed. Periodic reviews are conducted by the authorities (such as the Ministry of Health and the FDA) after the product is approved, at a frequency of once every year or two. These reviews include a review, among others, of the Company's fulfillment of cGMP principles, as specified below.
- 5.7.5 For procedures involving the development, manufacturing, storage and transportation of drugs, the regulatory authorities specify current Good Manufacturing Practices ("cGMP") in order to ensure that development is performed in a safe and monitored environment. These principles are updated from time to time, and include methods for documenting, supervising and monitoring the manufacturing processes and their supporting systems. The performance of clinical trials is also subject to a similar system of strict principles ("GCP").
- 5.7.6 Similarly, the regulatory authorities specify guidelines for the proper handling of human cells or tissue intended for grafting, introduction or transfer into humans (hereinafter: "HCT/P"). Their main purpose is to prevent the spread of infectious diseases.
- 5.7.7 The regulatory process, inasmuch as it is relevant to this report, is divided into two main tracks: the approval of drugs and the approval of devices. Reference is also made to the approval of HCT/P, in addition to the process required for the approval of medical devices.
- 5.7.8 The registration process for drugs includes clinical trials which the company must perform (in humans) with the goal of evaluating whether approval can be given for the treatment of the patient population using the drug. Prior to the commencement of clinical trials, preliminary trials must be performed on laboratory animals.

#### **[B] The Helsinki Committee**

- 5.7.9 Before commencing human clinical trials in all countries signed on the Helsinki Committee for Human Rights (including Israel), approval must be received from the entities authorized to approve performance of human clinical trials.

- 5.7.10 The trials must fulfill the principles of the Helsinki Declaration, and must receive the approval of the ethics committee of each medical institution in which they are conducted (the "Institutional Helsinki Committee"). The doctor and / or committee of doctors with which the company is collaborating present the trial protocol to the medical institution's ethics committee.
- 5.7.11 After holding a deliberation in which the committee reviews, inter alia, whether the trial protocol fulfills all ethics guidelines, a decision is reached regarding the protocol's approval. Any changes made to the protocol require making an updated submission to the ethics committee for their approval. As of the reporting date, all the Portfolio Companies included in this report are required to obtain, in addition to the approval of the Institutional Helsinki Committee, the approval of the executive Helsinki committee at the Ministry of Health, for the purpose of commencing the human clinical trial phase.
- 5.7.12 The approval of the Helsinki committee is a necessary condition for receiving approval for the use of medical drugs and / or devices from Western health authorities, including the Israeli Ministry of Health.
- 5.7.13 In order to conduct human clinical trials in Israel, a permit must be received based on the research plans (protocol) (hereinafter: the "**Permit**") from a committee (named, as noted above, the Helsinki Committee), which acts by force of the Public Health Regulations (Clinical Trials in Human Subjects), 5741 - 1980 (hereinafter: the "**Public Health Regulations**"). Permits are granted subject to the following conditions: that the application for approval be submitted by a qualified doctor who will be serving as the chief researcher responsible for the trial; that the researcher participating in the human clinical trial be possessed of the skills and experience in their field required for conducting the trial in question; and the trial fulfill the following conditions:
- (1) The expected advantages gained by a participant in the trial and by the Company must justify the risk taken by and discomfort caused to the participant involved in the trial;
  - (2) Existing medical and scientific knowledge must justify conducting the clinical trial being requested;
  - (3) The clinical trial must be planned in a scientific manner which enables it to find an answer to the issue being tested, and its process must be described in a clear, detailed and precise manner in the trial protocol;

- (4) The risk to participants in the trial must be as low as possible, due to the use of proper research methods, and the use, as much as possible, of procedures which have already been tested on humans or animals; In addition, the monitoring and supervision of trial participants must be of optimal quality;
- (5) The trial participants must be chosen in accordance with inclusion and non-inclusion guidelines as specified in the trial protocol;
- (6) An informed consent form for the trial must be filled out by at least subjects, including all required details as specified in the policy;
- (7) The trial plan must include instructions regarding the methods in place for guarding the privacy of participants and the confidentiality of information collected;
- (8) The trial plan must include an orderly mechanism for supervision of the trial;
- (9) The trial initiator must have obtained appropriate insurance coverage for the trial participants;
- (10) The initiator and chief researcher must be capable of allocating the resources required to properly conduct the trial, including skilled personnel and the required equipment;
- (11) The type of commercial relationship existing between the researcher and with the institution in which the trial is conducted must not adversely affect the proper performance of the trial;
- (12) To the degree that trial participants, jointly or individually, may be exposed to pressure or undue influence in order to persuade them to participate in the trial, the appropriate measures must be taken to prevent such pressure or to minimize the aforementioned influence.

**[C] Description of the process by which regulatory approval for the distribution of drugs is received:**

5.7.14 The development process for a drug is complex, and usually includes <sup>28</sup>the following main phases in which criteria established by the health authorities must be fulfilled in order to pass on from one phase to the next<sup>29</sup>, as described below:

5.7.15 Animal trial phase - A phase in which research and development for the drug is performed by the Company by means of animal trials:

Pre-clinical trials include a laboratory evaluation of the product under development and animal trials. These trials are intended to test the product's chances of becoming an effective, safe drug.

5.7.16 Pre IND Meeting Phase - In this phase, meetings are held with expert representatives of the regulatory authority for the purpose of presenting the development processes for the drug and the Company's plans for continued development and performance of clinical trials.

5.7.17 IND Submission Phase - This phase involves submitting a program file for Phase I of clinical trials. This file includes details regarding the locations in which the clinical trials will be conducted, and information about the manufacturing and clinical batch data testing processes (a drug's manufacturing series) that will be specifically used in the clinical trial in question.

5.7.18 During the clinical trial phase, the experimental drug is given to patients or healthy individuals under the supervision of a doctor-researcher who is qualified to supervise human clinical trials. Each clinical trial must pass review testing and receive the advance approval of the independent Helsinki Committee in the institution where the trial is being conducted ("Helsinki Committee"), as described above. The number of subjects in each trial is established in coordination with the competent licensing authorities.

5.7.19 Phase I Clinical Trial - After receiving approval from the regulatory authority for the commencement of clinical trials, as well as additional approvals required pursuant to

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<sup>28</sup> Subject to differences between countries and between the particular provisions in effect therein.

<sup>29</sup> The description of phases is general, and may from time to time be different for different drugs. For example, in certain cases, phases II and III or phases I and II can be combined.

the Helsinki Declaration, the Phase I clinical trial begins. The trials are for the most part intended to test the product's safety, and sometimes also to test the drug's dosage against the amount of the drug present in the subject's body. Specific biological indicators are also analyzed using blood tests in order to ascertain the drug's safety. The number of patients is determined, as noted above, by the regulatory authority, and differs between products. However, in most cases, this phase includes a smaller number of subjects in comparison with later phases.

- 5.7.20 Some trials are defined as Phase I/II; in these trials, the drug is given to patients. In this manner, after the trial's success, the product's safety can be proven, and presented along with data to support its efficacy. Post Phase I - IND Amendment Phase - This phase includes a summary report of the first clinical trial, a summary of development works, and plans for the Phase II clinical trial.
- 5.7.21 Phase II Clinical Trial - in the Phase II clinical trial, trials are conducted on a defined population of patients, and testing is done of the drug's degree of efficacy for the treatment of a specific indication (disease or symptom), and of the tolerance of different doses in order to determine the product's optimal dose. Possible negative side effects and health risks are also tested. At times, in cases where an identical drug already exists on the market which has received approval from the relevant regulatory authority, this phase is not required, since the required dosage is already known based on the existing drug.
- 5.7.22 After conclusion of the Phase II clinical trial, the regulatory authority is presented with a summary report of the clinical trial, a summary of development works, and plans for the third phase of the clinical trial - Post Phase II IND Amendment.
- 5.7.23 Before commencement of Phase III of the clinical trial, a preliminary meeting is held with the regulatory authority (Pre Phase III Meeting), after which the Phase III clinical trial begins. This phase involves testing of the drug's efficacy, based on the results of the Phase II clinical trial. The trials are conducted on a broader scale, in order to provide additional proof of the efficacy and safety of the drug in question in a greater number of patients, and is conducted in a number of different centers.
- 5.7.24 In the next phase, the regulatory authority is presented with a file containing a description of all development process, manufacturing processes and clinical trial results (BLA-Biologics License Application). After the regulatory authority conducts comprehensive pre approval inspection, the product is given FDA Approval.

5.7.25 At times a fourth phase of trials is also conducted subsequent to the drug's approval.

In most cases, these are life-saving drugs for which approval was given in an accelerated process, and for which the regulatory authority is still interested in receiving the results of additional clinical trials in order to gather more information about the treatment results for the approved indication. In this case, the entity requesting approval must complete Phase IV trials within a set period of time, with failure to meet one or more of the conditions of the approval process possibly resulting in revocation of the drug's license.

5.7.26 It is hereby clarified that there exists no assurance that a drug which is currently undergoing registration procedures will receive approval within a set time period, if at all. Moreover, even if approval is granted, it may be limited or restricted.

**[D] Description of the procedure for obtaining regulatory approval for the distribution of a medical device:**

5.7.27 The Company's activities in the field of medical devices are subject to various legislative provisions, including the provisions of the Department of Medical Devices of the Ministry of Health's Pharmaceutical Division. On the international level, the company's activities are subject to international standards, including FDA standards in the USA, CE standards in Europe, and ISO quality assurance standards.

5.7.28 Procedure for obtaining FDA approval for distribution of a medical device in the USA:

Foreign companies manufacturing medical devices which they intend to export to the USA must comply with FDA regulatory requirements prior to exporting those medical devices, since the FDA does not recognize regulatory authorizations granted by institutions in other countries. FDA requirements include, among others, the manufacturing of medical devices in accordance with quality assurance regulations, the receipt of scientific reports for the medical devices, the nomination of an American agent, and the provision of opportunity to FDA representatives to supervise the manufacturing procedures being used in the plant.

FDA approval for medical devices is given only upon fulfillment of a number of conditions, depending on the process in question. The Premarket Notification 510 process is a relatively short one, in which the FDA is shown that the medical devices for which approval is requested are safe and efficacious, are comparable to other products of various areas which are legally distributed in the USA, and do not require a

process of PreMarket Approval (PMA). The PreMarket Approval process requires, inter alia, performance of clinical trials at a larger scale, which may prolong the time period until receipt of regulatory approvals, and may increase the costs required to receive them.

Due to the innovative nature of the device technologies developed by the Portfolio Companies included in this report, and due to the fact that the Company is not aware of any similar technologies currently existing on the market, the Company believes that the FDA will instruct the Portfolio Companies developing medical devices to begin the process of regulatory approval through the PMA, which is, as noted above, a lengthier, more expensive regulatory track (though also more reliable and well-founded).

#### 5.7.29 **CE Marking:**

To the Company's knowledge, based on public announcements, the CE Marking is a European product standard which serves as a manufacturer's declaration stating that the product meets the required criteria and the technical specifications issued by the relevant authorities, including health, safety and environmental authorities. The standard guarantees free trade among EU and EFTA countries (Iceland, Lichtenstein and Norway), and permits the licensing and customs authorities in Europe to not approve distribution of similar products which do not bear the CE Marking, in accordance with the European Conformity guidelines regarding medical devices. Beginning on June 14, 1998, manufacturers of medical devices are required to act in accordance with the European Conformity provisions.

Medical devices are defined as equipment or material used in the treatment of humans, including for the purposes of diagnosis and treatment.

As part of the process of testing medical devices, the European Conformity reviews the product's technical features and the manufacturer's quality control system, such that, at the end of the process, the manufacturer receives the CE Marking and the ISO 14385 standard for the quality control process.

#### 5.7.30 **Description of the procedure for obtaining approval from the Ministry of Health for distribution of a medical device in Israel:**

The Company's activities in Israel are subject to the issuance of a permit by the Ministry of Health for human clinical trials, requiring the approval of the Medical

Devices Department ("**MDD**") and the approval of the Helsinki Committee, as described above and below:

(1) Medical Devices:

A medical device is defined as a device, chemical material, or biological or technical product which is used for medical treatment, or which is required for the operation of a device or tool used in treatment, and whose main purpose is not to affect the human body as a medicinal tool. The Medical Devices Department at the Ministry of Health is the entity responsible for granting import permits of different kinds for medical devices, for monitoring the distribution of medical devices, and for approving clinical trials of medical devices.

(2) The Public Health Regulations (Human Clinical Trials), 5741 - 1980 (the "**Regulations**") and Policy no. 14 of the Ministry of Health's Pharmaceutical Division - Human Clinical Trials (the "**Policy**"):

(3) The Regulations and the Policy provide the procedures for approval of performance of a clinical trial, and for trials of medical devices defined as special human clinical trials. According to the Policy, all medical trials are subject to the regulations for human clinical trials, to the provisions of the policy, to the current Good Clinical Practice guidelines provided by the International Conference on Harmonisation (research devices), and to the provisions of the current standard for human clinical trials of medical devices. The Regulations provide that human clinical trials may not be approved unless the Helsinki Committee of the hospital which intends to conduct the trial has approved its performance, and has delivered notification of it in writing to the medical director of the hospital in which the trial is being conducted, and that the hospital director has agreed that the trial is not opposed to the Helsinki Declaration, and is not in violation of the Regulations. In specific cases specified in the Regulations, the opinion of the upper Helsinki Committee (administered by the Ministry of Health) is also required to approve the performance of human clinical trials.

**[E] Description of the procedure for obtaining regulatory approval for the distribution of HCT/P:<sup>30</sup>HCT:**

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<sup>30</sup> In this report, this approval is relevant only to the products developed by Cell Cure.

5.7.31 Description of the procedure for obtaining regulatory approval for distribution of HCT/P in the USA:

Humans cells or tissue intended for grafting, introduction and transfer into humans are subject to supervision as cells, tissue or human cellular and tissue-based products, or using the abbreviated term - HCT/P.

To the Company's knowledge, the Center for Biologics Evaluation and Research (CBER) supervises HCT/P in accordance with federal regulations. Examples of tissue that is subject to these Regulations include bones, skin, cornea of the eye, ligaments, tendons, dura mater, heart valves, and hematopoietic stems / progenitors produced by peripheral blood, cord blood, ova and sperm.

The implantation of organs containing blood vessels, such as kidneys, liver, heart, lungs and pancreas, are subject to the supervision of the Health Resources and Services Administration (HRSA) and not CBER.

In accordance with the provisions of the aforementioned federal regulations, an institution that handles human tissue must select donors and test them, must prepare written procedures for the prevention of infectious diseases, and must act in accordance with those procedures and maintain orderly registration of its activities.

The American Food and Drug Administration (FDA) has published three final guidelines which expand the types of products requiring supervision, including comprehensive requirements to prevent the transfer, infection and spread of infectious diseases.

- (1) The first guideline requires companies to register all of their HCT/P products with the FDA.
- (2) The second guideline requires institutions handling human tissue to evaluate donors based on selection and testing processes, with the intention of minimizing the transfer or infectious diseases through the grafting of tissue.
- (3) The third guidelines specifies procedures for the handling of human tissue used in HCT/P.

The new requirements are intended to improve public health protection, while also minimizing the regulatory burden.

5.7.32 The procedure for obtaining regulatory approval for the distribution of HCT/P in Israel is as follows:

- (1) Importing of tissue: Circular instruction no. 9/96 issued by the Director of the Ministry of Health provides precise requirements for the importing of human tissue. In addition to the regular registration documents for medical devices, the importer is required, inter alia, to provide documents which prove the source of the tissue, its storage conditions, the date of the tissue's handling and the manner in which it was processed, test results, and other information of this kind.
- (2) Production of tissue: In addition to the policy in place for human clinical trials, the Ministry of Health specifies additional requirements for trials involving HCT/P in Israel. These requirements specify, inter alia, the provision of information regarding the product's features, its operational mechanism, the manner in which it is to be introduced into the subject's body, a survey of the existing technology on the issue, information regarding the tissue donor, and more.

## **5.8 Competition**

The Company is not aware of any direct and immediate competition in its area of operation, other than competition with additional entities which invest, and intend to invest, in the Portfolio Companies' areas of operation.

Several additional groups which are active as holding groups for companies / projects in the field of life sciences are traded on the Israeli stock exchange (Biocell, Biolight, Biomedix, Clal biotechnology, BioLineRx, and others). The Company believes that its uniqueness results from its method of operation, the types of companies operating in collaboration with it, and its unique connection with Hadassah hospitals as a source for intellectual property, and for research and development expertise and infrastructure. In the Company's opinion, these characteristics provide it with a significant advantage over other holding companies in the field of biotechnology.

Moreover, a large number of companies are traded around the world in the biomedical field which constitute an investment alternative for investors looking to invest in this field.

For details regarding the markets in which each of the Project Companies operates, see the section dealing specifically with each of the Portfolio Companies in Section 5.3 above.

## **5.9 Employees and Workforce**

As of the reporting date, the Company does not employ employees other than Mr. Ophir Shahaf (an attorney holding a Master's in Business Administration), who serves as the CEO of the Company (and whose salary is paid by the parent company, Hadasit, within the framework of the agreement for provision of management services, as specified, inter alia, in Section 5.13.1 below).

The management services are provided to the Company through Hadasit, according to the management agreement signed between the two companies. Subsequent to the reporting date, a new management agreement, approved by the general assembly, was signed on February 27, 2011. All management services are provided to the Company by Hadasit, other than employees and company officers which the Company must employ pursuant to the law (see below for details regarding the internal auditor nominated for the Company) .

## **5.10 Financing and Credit**

The Company has to date not required loans or credit for the purpose of its operations, apart from the issuance of bonds to the public as noted above, half of which were converted to Company shares, while the other half (mostly interest payments) was repaid in August 2008. For the purpose of meeting the targets of the Portfolio Companies, the Portfolio Companies will require funds in addition to those provided to date by the Company, and which it will currently be able to provide to it in the future, and will need to raise financing from additional, significant external sources other than the Company, as specified in this report.

As of the reporting date, the Company has financed its operations by raising funds from its shareholders, and as a result of the conversion to Company shares of half of the bonds issued by it.

## **5.11 Taxation**

See Note 25 to the Company's financial statements as of December 31, 2010.

As of December 31, 2010, the Company's total cumulative losses amounted to approx. NIS 14,173 thousand.

## **5.12 Insurance**

As of the reporting date, the Company has not yet entered into insurance agreements of any kind, other than a policy to insure its directors and company officers. To the best of its knowledge, the Company is not currently underinsured.

Along with the request for approval of a clinical trial which was submitted to the ethical committee of Hadassah, the initiator of the trial must also sign a Ministry of Health form, in which they declare that they: "commit to insure the patients, the medical staff conducting the clinical trial, and the medical institution, against third party lawsuits resulting from the trial, whether submitted during the trial's performance or after its conclusion, to an amount that is at least equal to the insurance amount by which State doctors are insured at that time for the insurance purchased by the State for them, and to the fund maintained for them. In addition, in the event that clinical trials are conducted in Hadassah facilities following an external order (in other words, not initiated by a Hadassah doctor without the involvement of an external orderer), the external orderer will be required to sign letters of indemnification and undertaking towards Hadasit, Hadassah, and the Hadassah Researchers.

Clinical trials that are conducted following an initiation made by a Hadassah doctor, without the involvement of an external orderer, are covered by the professional insurance policy for Hadassah doctors. The Portfolio Companies conducting clinical trials in Hadassah (including companies which are held, or will be held, by the Company at 100%) will be required to enter into an insurance agreement which covers the requirements specified above.

## **5.13 Significant Agreements**

### **[A] Management Agreement**

- 5.13.1 From the date the Company became a public company until today, a management agreement has been in effect between the Company and its controlling shareholder, Hadasit.
- 5.13.2 On February 27, 2011, the general assembly approved (after receiving approval from the Company's audit committee and board of directors) the new management agreement between the Company and Hadasit.
- 5.13.3 **Terms of the management agreement:**
- 5.13.3.1 The management agreement was set for a period of 4 years, beginning January 1, 2011. Notwithstanding the above, the parties agreed that the Company's board of directors will have the right, at its discretion and after receiving recommendation from the audit committee for this purpose, to terminate the management agreement after a period of 12, 24 or 36 months from its date of authorization (hereinafter: the "**Exit Dates**") (in other words, on January 1, 2012, January 1, 2013 and January 1, 2014). In the event that the agreement is terminated as above, the agreement states that Hadasit will not have the right to raise any claims or suits against the Company. Announcement of termination of the agreement as above will be possible on the condition that the Company provides written notice to Hadasit no later than 4 months before each of the Exit Dates. The management agreement will not be automatically extended, and any extension added to the validity period of the management agreement will require the consent of both parties, and receipt of all legally required authorizations for this purpose (inasmuch as these may be required).
- 5.13.3.2 **Management services:** The agreement states that, during the term of the management agreement, Hadasit will provide the Company, through its employees and consultants, ongoing management services to facilitate the Company's operations and activities in the field. In all matters relating to the provision of the aforementioned management services, the operations of Hadasit will be done in accordance with, and under the supervision of, the Company's management and board of directors. The management services will include the following services (above and below in this document: the "**Management Services**"): [A] General management services to assist with the Company's current and regular operations. For the purpose of providing the Management Services, Hadasit will provide the Company with the services of Mr. Ophir

Shahaf, at the Company's request (see Section 3.5 above); [B] consulting services to facilitate the Company's investments in the Portfolio Companies, and in other companies in the field (whose sources are either in Hadassah or outside it), in which the Company will review investment opportunities; [C] Hadasit will provide the Company with accounting services, office services, computing services, and all other services required for the Company's current and regular operations. The Company will be the one to choose its auditors, and all expenses arising from the preparation of financial statements, as well as accountants' fees, will be paid by the Company. The wages of directors, of the internal auditor, of lawyers providing services to the Company, and of any other company officer or employee who can and does work at the Company will be paid by the Company; [D] Hadasit will provide the Company, through employees possessed of expertise in the field, with consulting services in the field of the intellectual property; [E] at the Company's request, and in accordance with the personnel available at Hadasit, Hadasit will nominate, pursuant to the provisions of the law, directors in the Company and / or in the Portfolio Companies from among Hadasit's managers and employees; [F] in addition to the consulting services provided by its manager and employees, and subject to the above terms, Hadasit will have the right, at such time as it deems necessary, to arrange for external professional consulting services for the Company and / or for the Portfolio Companies, for the purpose of fulfilling its responsibilities. The Company will bear these costs, inasmuch as Hadasit will deem them necessary for the Company's operations; [G] within the framework of the provision of services, Hadasit will invest its best efforts in order to provide the Company access to leading doctors and scientists employed at Hadassah, and who have bearing on the area of operation of one of the Portfolio Companies, or of a different new company in which the Company may consider performance of a new investment. Hadasit will invest its best efforts to create a situation whereby the Company receives consulting and accompaniment services from those senior doctors and scientists, and, if necessary, will assist the Company in conducting negotiations with those doctors and scientists for the purpose of involving them in the new Portfolio Company, or for the purpose of arranging terms whereby services can be provided by them for the purpose requested by the Company. The consulting fees paid to doctors and scientists, if any, for the consulting and accompaniment services provided by them to the Company, will be paid by the Company directly or through Hadasit. In this latter case, the Company will repay Hadasit for any

such payment; [H] the Management Services will be provided pursuant to the provisions of all laws, to the provisions of the Company's Articles of Incorporation, as these may exist from time to time, to the Company's budget, to any order and / or decision and / or policy determined the Company's board of directors, and with the full cooperation of the Company, of the organs operating within it, and of the advisory committee nominated by the Company (insofar as the latter will be in operation).

**5.13.3.3 The consideration:** In consideration of the provision of management services, the Company will pay Hadasit a total of NIS 620,000 **per year**, and will bear the full cost of Mr. Ophir Shahaf's wages, who will provide the Company with general management services. This amount will be CPI-indexed, with the base rate for any payment made being the known index on the date the parties signed the management agreement. The consideration was determined, inter alia, on the basis of the proportion of work provided by the employees of Hadasit who will be providing the Company with the aforementioned management services. VAT as required will be added to the consideration amount. In addition, the Company will repay Hadasit, against presentation of proper invoices which Hadasit will present to the Company, for any payment and expense financed by Hadasit for the Company, including travel expenses in Israel or abroad for Mr. Shahaf, in his service as the Company's CEO. In the event that, for the purpose of providing the Management Services pursuant to this agreement, any of the employees of Hadasit who provide the Management Services will be required to travel abroad, the trip in question will only be made after approval is given by the Company's board of directors, with full repayment of the travel expenses. The Company will fully repay Hadasit for Mr. Shahaf's employment costs, including bonus payments and social benefits, whether these were accrued or actually paid, with the addition of VAT as required. Payment for the Management Services will be paid at the beginning of each quarter, for that quarter. The Company has undertaken not to distribute dividends to its shareholders, and not to invest funds in the Portfolio Companies, or to make any other investment, in a manner that results in it being left without sufficient self-funding for the payment of the Management Services for a period of 12 months, or for a shorter period, in the event that the management agreement between the parties (in accordance with its validity, from time to time) is set to expire within a period shorter than that specified above. Subject to the receipt of all required authorizations, including

the authorization of the Company's audit committee, board of directors and general assembly, the parties agreed that the Company will review an allocation of options to the employees of Hadasit who will be providing the Management Services specified in this agreement. The number of options allocated, and their terms, including the exercise terms and exercise price, will be decided at the Company's discretion, and will be subject, as noted above, to the receipt of separate proper authorization for this purpose.

5.13.3.4 **Main terms of Mr. Shahaf's employment:** In addition to the management agreement, an employment agreement was also signed between Hadasit and Mr. Shahaf. The agreement states that Mr. Shahaf's entire time and work at Hadasit will be spent for the purpose of providing general management services to the Company. Hadasit will not employ Mr. Shahaf for any other or additional purpose not involved in the provision of general management services to the Company. As part of the management agreement signed between the parties, it was established that the Company will bear the full cost of Mr. Shahaf's employment at Hadasit. For the fulfillment of his responsibilities, and with regards to any professional decision which he will be required to make with regards to his responsibilities, Mr. Shahaf will be directly subordinate to the Company's board of directors. The employment agreement has no predefined period of validity. However, Mr. Shahaf and Hadasit will have the right to terminate the transaction agreement, at their sole and exclusive discretion, following delivery of an announcement 90 days in advance. Mr. Shahaf will have the right to receive monthly wages in the amount of NIS 48,000, as well as social benefits (directors' insurance, provident fund and other terms which do not exceed the standard (annual vacation, sick days, convalescence pay, vehicle, telephone and the return of regular and recognized expenses). The Company's board of directors will have the right to determine an annual bonus to be paid to Mr. Shahaf in accordance with the criteria established for this purpose by the Company's board of directors. Mr. Shahaf will also be entitled to receive an allocation of 525,195 options (non-marketable) in the Company.

**It is hereby emphasized that the Company does not have control, neither directly or indirectly, of the operations of all of the Portfolio Companies. In light of the above, it is hereby emphasized and clarified that it is possible that some of the Portfolio Companies will not operate in accordance with the Company's**

**recommendations or suggestions, both in terms of science, and in terms of marketing / distribution / finance.**

**[B] Undertakings to pay royalties to the Office of the Chief Scientist**

Five (5) of the Portfolio Companies held by the Company are companies which have operated as part of the greenhouse plan operated by the Office of the Chief Scientist. In light of this, these companies are required to make royalty payments to the State of Israel - the Office of the Chief Scientist, as specified above in Section 5.3.

**[C] Leasing agreement**

On February 5, 2008, a leasing agreement was signed between the Company and Unihad Biopark Ltd. ("Unihad") for the leasing of approx. 860 sq. m. in the biotechnological park whose construction was completed in early 2009. The leasing agreement was set for a period of 5 years, with an option available to the Company to extend by an additional 5 years, at higher rent.

The leasing agreement states that the Company will pay monthly leasing fees in the amount of NIS 64 per sq. m. (approx. NIS 55 thousand per month). In addition, the Company will pay, over the lease period and the option period, NIS 43 for adjustment works performed by the other company.

Parts of the leasehold were subleased out to the Portfolio Companies under the same conditions at which the Company leases the leasehold. Negotiations are currently being held between the Company and each of the Portfolio Companies for the continued subletting and its terms.

**5.14 Legal Proceedings**

- 5.14.1 As of the reporting date, no legal proceedings are currently being conducted on behalf of or against the Company.
- 5.14.2 To the Company's knowledge, no legally formed authority is considering, reviewing or planning any legal proceedings against the Company.

**5.15 Summary of the Company's Forecasts for Expected Developments in the Portfolio Companies During 2011**

The following data is presented as the Company's projections and forecasts only, and should be evaluated accordingly. The Company has no measure of certainty that these will be the actual amounts required for the Project Companies. It is possible that the Portfolio Companies will require higher or lower amounts than those specified below. Moreover, the Company has no obligation or undertaking to deliver the amounts presented to the Portfolio Companies (or any amount required, inasmuch as it may be required, to complete the presented amounts):

<b><u>Project Company Name</u></b>	<b><u>The Company's estimate for 2011</u></b>	<b><u>Forecast and projection for the Company's investments in the Portfolio Companies over 2011, for the purpose of meeting predefined targets<sup>31</sup></u></b> <b><u>(In thousands of USD)</u></b>
<b>Thrombotech</b>	Beginning of Phase IIa clinical trial for an original indication (stroke). An additional indication, for hypertension, is also being tested.	<b>200</b>
<b>Verto</b>	Identification of a strategic partner for continued trials and commercialization of the technology.	<b>0</b>
<b>Cell Cure</b>	Continued work with the new partners. Completion of cell production under GMP conditions; pre-clinical animal trials; regulatory preparations for clinical trials.	<b>0</b>

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<sup>31</sup> It is hereby clarified that the amounts included in this table are presented as the Company's estimates and forecasts with regards to the amounts required by the Portfolio Companies for the purpose of meeting their predefined goals for 2011. The Company has not undertaken to deliver the required amounts to the Portfolio Companies, either in whole or in part.

<u>Project Company Name</u>	<u>The Company's estimate for 2011</u>	<u>Forecast and projection for the Company's investments in the Portfolio Companies over 2011, for the purpose of meeting predefined targets<sup>31</sup></u> <u>(In thousands of USD)</u>
<b>Protab</b>	Work with partners, preparation for future fundraising, manufacturing of the Company's leading antibody under GMP conditions in preparation for clinical trials, performance of pre-clinical trials for two indications, regulatory preparations for a clinical trial.	<b>0</b>
<b>Biomarker</b>	Completion of the process of adding an additional marker to the Company's services basket. Expansion of the sample base on which the trial of the leading product is being conducted. Beginning work on "kitization". Identification of an external investor.	<b>350</b>

<b><u>Project Company Name</u></b>	<b><u>The Company's estimate for 2011</u></b>	<b><u>Forecast and projection for the Company's investments in the Portfolio Companies over 2011, for the purpose of meeting predefined targets<sup>31</sup></u></b> <b><u>(In thousands of USD)</u></b>
<b>Kahr</b>	Completion of a transaction with an external investor. Manufacturing of the leading product. Pre-clinical trials for treatment of cancer and immune system diseases - start of Phase I trial.	<b>500</b>
<b>Enlivex</b>	Identification of an external investor and participation in fund-raising. Completion of the clinical trial in patients, and analysis of the results. Preparations for the next trial (regulation and manufacturing). Beginning business development to find a partner for commercialization of the technology.	<b>500</b>
	<b>Total investments in the companies</b>	<b>1,550</b>

<u>Project Company Name</u>	<u>The Company's estimate for 2011</u>	<u>Forecast and projection for the Company's investments in the Portfolio Companies over 2011, for the purpose of meeting predefined targets<sup>31</sup> (In thousands of USD)</u>
<b>Hadasit</b>	Management fees, overhead, offices in the biotechnological park. The calculation is derived from the new management agreement, which is based on the proportion of work provided by Hadasit employees.	<b>620</b>
	<b>Total</b>	<b>2,170</b>

## **5.16 Business strategy and goals; Forecasts and estimates regarding the target markets of Portfolio Companies**

- 5.16.1 The information in this section presents forecasts, business strategies and estimates made by the Company, whose realization is uncertain. The information included in this subsection is not based on any facts or concrete information held by the Company. Due to various factors, including the development of the fields in question, failure to meet targets, failure to realize technologies, changes in technology or technical breakthroughs, lack of actual feasibility of the technologies specified, or due to other reasons resulting from the technology base of the Portfolio Companies or of the manner in which they are actually managed, these forecasts and estimates may not be realized.
- 5.16.2 The Company was founded as a fully owned subsidiary of Hadasit - the technology transfer office of Hadassah hospital. As part of its role as a technology transfer office, Hadasit is responsible for the registration of patents, for the protection of intellectual

property that created by Hadassah, and for concentrating the effort to commercialize the intellectual property.

- 5.16.3 In general, the commercialization method utilized by Hadasit is achieved through the granting of licenses (exclusive or otherwise) to entities who intend, and have the capability, to move the projects towards becoming a final, marketable product. In the past (until the early 1990's) most licensing agreements made were between Hadasit and multi-national pharmaceutical companies. Beginning in the early 1990's, a change began occurring in the perspective of pharmaceutical companies, with the latter establishing development arrays of their own, while disconnecting themselves from external sources of intellectual property such as Hadasit. In light of this change, technology transfer offices were required to develop new commercialization tools, and the mechanism chosen by Hadasit was to create start-up companies which would handle the various topics at the forefront of applicational research at Hadassah. The pharmaceutical companies currently require that products be in later phases of development than those required by the start-up companies with which they enter into licensing agreements, which means that the Company's financing must promote the Portfolio Companies at least until the preliminary clinical phases.
- 5.16.4 The main features of the mechanism currently used by Hadasit are as follows: Hadasit works to submit and register patents in order to protect intellectual property; Hadasit founds a company, to which it transfers the exclusive license for the handling of the patent for the intellectual property; Hadasit receives holding of the founded company and allocates to external entities who are prepared to invest in the founded company (funds specializing in early-phase biotechnology, greenhouses, etc.); the founded company begins operating as an independent unit, with a management staff and researchers. At times, the founded company performs its work within Hadassah, using the infrastructure relevant to the scientist around which the company was founded.
- 5.16.5 The main goal towards which the Company strives is enabling the Portfolio Companies to enter into a Phase I human clinical trial, completing the Phase I human clinical trial within the company, and entering into collaboration agreements or performing the realization of holdings in Portfolio Companies that successfully completed the Phase I human clinical trial. The intention is for these trials to be conducted, as much as possible, on patients, so that the company conducting the trial can prove efficacy as well as safety.

5.16.6 As noted above, Hadasit founded the Company, and transferred its full holdings to it in 9 Portfolio Companies which were founded in accordance with the process described above. The Company also performed an investment issuance in another Portfolio Company - Conjugate Ltd.

5.16.7 The Portfolio Companies in which Hadasit had holdings which were transferred to the Company are companies which fulfilled, in Hadasit's opinion, the following two cumulative conditions:

- (1) The maturity criterion (all of the companies successfully performed the part of the stage involving performance of animal feasibility trials for the relevant diseases and treatments for which the Portfolio Companies are attempting to create solutions).
- (2) The products are intended for markets in which the business potential is large, in Hadasit's opinion.
- (3) The Company holds, in the Portfolio Company, significant holdings (over 30%) and significant managerial influence.

1.1.1. The Company's future holdings in the project.

5.16.8 The Portfolio Companies in which Hadasit held holdings which were transferred to the Company are companies in preparations for a Phase I clinical trial, and for the completion of feasibility trials in animals. For this purpose, they require a considerable amount of additional funding.

5.16.9 The Company's business strategy is such that, in addition to the investments made by it, additional investments will also be made in the Portfolio Companies by the Portfolio Companies' existing shareholders, and by new investors recruited for this purpose.

#### **Planned exit strategy**

5.16.10 The intention is that, at the end of Phase I, and during the preparations for Phase II, the Portfolio Companies (all or some) will hold meetings with entities deemed to be appropriate for the purpose of strategic collaborations, especially multi-national pharmaceutical companies.

- 5.16.11 In accordance with Hadasit's experience in the relevant field, multi-national pharmaceutical companies repeatedly emphasize, in meetings held with them, that the presentation of Phase I/II clinical trial data (in other words, the presentation of safety results in addition to beginning efficacy testing in humans) is the optimal stage for the creation of a strategic relationship between pharmaceutical companies and development companies.
- 5.16.12 There are a number of well-known methods of actualizing the aforementioned collaborative relationships, including granting a license for usage and distribution, merger, acquisition of operations, etc.
- 5.16.13 **The Company again emphasizes that all of the above are estimates and forecasts made by the Company. There exists no measure of certainty that all or some of the Project Companies will penetrate their potential markets, nor any measure of certainty regarding the market share of all or some of the Project Companies in the event that they do penetrate those markets, either on their own or with the assistance of others. All of the above is intended to provide the Company's non-binding estimate regarding those markets it considers to be potential markets. The market sizes were presented based on the Company's estimates, and have no basis in any formal or approved documents held in its possession.**

## **5.17 Risk Factors**

- 5.17.1 Since the Company engages in investments in Project Companies, most of the Company's risk factors are derived from the risk factors of the Project Companies.
- 5.17.2 The following is a description of the Company's risk factors resulting from its holdings in the Portfolio Companies, and from its dealing in the field of investment in the Project Companies:
- A. Due to the concentration of the Portfolio Companies' activities in Israel, any change for the worse in the national and security situation, and any slowing of the economy caused as a result thereof, including as a result of a military reserve call-up of the Project Companies' employees, may have a negative impact on the position of the Portfolio Companies, and as a result, also on the Company's position.

- B. The main assets held by the Portfolio Companies are the intellectual property, knowledge and research in their possession, and which can for the most part be protected by the registration of patents. Any delay, completion, assault on legality, or claims of breach of existing patents, or patents for which a patent registration application has already been submitted by any of the Project Companies, may have a negative impact on the position of that Portfolio Company, and on the Company's position.
- C. The investment in the Portfolio Companies is a high risk investment, which at times may be completely lost, due to the possibility that all or some of the Project Companies may not reach their predefined targets, including due to difficulties in recruiting the appropriate personnel, in raising the required financing, due to the eventual non-development of products or devices which they are engaged in developing, or due to such development encountering difficulties or delays which incur additional costs whose scope cannot be estimated, due to technical difficulties encountered during the development process, due to a discovery resulting in the impossibility of developing the technology, due to a discovery that it will not be possible to commercialize, distribute or sell the developments, due to a limited ability to recruit appropriate patients for the purpose of performing the clinical trials, or due to failure during the clinical trial phase.
- D. Since the Portfolio Companies were generally founded on the basis of knowledge and studies performed by Researchers within Hadassah, the Portfolio Companies are dependent, for the purpose of their continued operation, both on the continued collaboration with those researchers, and on their collaboration with Hadassah. Any loss of collaboration with a researcher who is significant to the continued research and development of the product may adversely affect the position of the relevant Portfolio Company, and of the Company.
- E. The Portfolio Companies are companies on the beginning of their path, and in stages of research and development. The Company has no source of revenue from the sale of products or arising from its research and development activities.
- F. Technical changes are possible which may result in the economical or technological unfeasibility of completing development of the products, or which may result in the developments becoming archaic. Future developments in the medical and biotechnological products field are not predictable, although there

does exist certainty of the fact that various entities around the world are attempting to develop solutions for the diseases and needs for which the Portfolio Companies are attempting to create treatments. Competition in the field of the Project Companies' developments may result in the Portfolio Companies' developments becoming redundant, due to the priority of technologies developed by competitors, or to the competitors' developments being cheaper to distribute or easier to commercialize (both in terms of regulatory authorizations, and in terms of development costs).

- G. Investment in the securities of Portfolio Companies is, for the most part, investment in securities that are unregistered for trading on the stock exchange or in an orderly market. For this reason, difficulties may be encountered in selling these securities, or in realizing them by other means. Furthermore, investment in the Portfolio Companies is an investment in companies which generally do not distribute dividends, but instead usually have a sale exit strategy. The Company's success depends on its ability to enter into agreements with manufactures and distributors for the purpose of manufacturing the developments, and with large pharmaceutical companies for the purpose of completing clinical trials and commercialization of the developments.
- H. As noted above, the Company maintains holdings in the Project Companies, which at times do not grant it control and the ability to direct the activities of the Project Companies. Due to the foregoing, the Company may at times encounter difficulties in obtaining information and current updates about the progress of the Portfolio Companies, and current information about the financial position of the Project Companies. This may influence, inter alia, the manner in which decisions are reached in the Company regarding investments in the Portfolio Companies or in the realization of its holdings in the Project Companies. The Company's rate of holding in the Portfolio Companies generally does not grant it the ability to direct the activities of the Portfolio Companies or to take part in their management.
- I. The products of the Project Companies, inasmuch as these may pass the research and development phases, are subject to the regulations of the health authorities in the target countries, resulting in the possibility that regulatory developments or changes in standardization may present difficulty for the Portfolio Companies in completing their developments and in the marketing of a drug or medical product. Changes in the regulatory environment relating to the marketing of drugs,

including changes made to the Portfolio Companies, or to any manufacturer of theirs, or to any other entity working on their behalf, may impose various restrictions upon the activities of the Portfolio Companies, including failure to obtain approval for their products.

- J. Due to limited financial sources, it is possible that during the investment rounds performed by the Portfolio Companies (especially investment rounds dealing with large amounts), the Company may not have, even if it intends to participate in the rounds, the required means to preserve its rate of holdings in some or all of the Portfolio Companies.
- K. The Company is largely dependent on its ability to raise financing from external sources for the purpose of financing the research and development activities (including performance of the trials) done by the Project Companies. Due to the severe global economic crisis and the economic deceleration it caused, the various financing sources available to the Company have been significantly reduced, as well as other financing avenues, including financing through capital markets (by issuance of convertible bonds, etc.), which were also adversely affected by the worldwide economic crisis, and which cannot be effectively utilized. Sources of financing are the raw material used by the Project Companies, and without providing the flow of the financing required by the Portfolio Companies, it will not be possible to complete their developments, especially within their planned time frames..
- L. The Company's funds are deposited, among others, in USD deposits, though its liabilities and current expenses are mostly in NIS. The convertible loans provided by the Company to several of the Portfolio Companies are in USD. Fluctuations in USD exchange rates may affect the Company's position and the amount and rate of shares of Portfolio Companies to which the Company will be entitled in the event that it chooses to convert its convertible loans into shares in the Project Companies.

5.17.2 The following is a table of risk factors, according to their degree of influence:

<b>Risk</b>	<b>High influence</b>	<b>Medium influence</b>	<b>Low influence</b>
<b><u>Macro-economic</u></b>			
Economic deceleration	X		
Adverse changes in the national security situation		X	
Fluctuation in foreign currency rates			X
Deceleration of capital markets	X		
<b><u>Sector-based</u></b>			
Intellectual property	X		
Technical markets		X	
Fluctuations in the biotechnology sector and biotechnological markets		X	
Changes in legislation, standardization and regulation	X		
Competition		X	
<b><u>Specific to the Group</u></b>			
Share price on the stock exchange			X
Dependency on researchers and human capital	X		
Dependency on Hadassah	X		
Failure of the research and development process or of clinical trials, or prolonged delays in the development of products	X		
Dependency on the management of the Project Companies and other partners over which the Company has no control	X		
Lack of additional financing sources to complete the research and development and to conduct the clinical trials, resulting in the closing of companies.	X		

<b>Risk</b>	<b>High influence</b>	<b>Medium influence</b>	<b>Low influence</b>
Entry into contractual agreements with manufacturers and distributors for the manufacturing and distribution of drugs and products for development, difficulties in marketing and market penetration, and product liability lawsuits			X <sup>32</sup>
Limited ability to recruit patients for the purpose of conducting clinical trials.		X	

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<sup>32</sup> The Company attributes a low influence to this risk factor in consideration of its planned business strategy, according to which the Portfolio Companies will not reach the marketing and commercialization phase for the drug on their own, but instead will either grant license to multi-national pharmaceutical companies, or will be sold in an exit. In the event that any of the Portfolio Companies reaches the marketing and commercialization stage of drugs and products its has developed on its own, this risk factor will have a significant effect on the Company.