BRAINSTORM CELL THERAPEUTICS INC.
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Registration Statement No. 333-186516

This issuer free writing prospectus relates only to the shares of common stock ("common stock"), par value $0.0005 per share, of BrainStorm Cell Therapeutics Inc. (the "Company"), and the warrants to purchase shares of common stock (the "warrants") described below and should be read together with the preliminary prospectus filed by the Company with the United States Securities and Exchange Commission (the "SEC") on August 6, 2013 (the "Preliminary Prospectus") included in the registration statement on Form S-1 (File No. 333-186516) (the "Registration Statement") relating to these securities .. The Registration Statement and the Preliminary Prospectus included therein can be accessed at the following website: http://www.sec.gov/Archives/edgar/data/1137883/000114420413043084/v351742_s1a.htm.

Investor Materials

This issuer free writing prospectus includes a power point slide presentation attached as Annex A below and is incorporated herein by reference.

Forward-Looking Statements

We make forward-looking statements in this free writing prospectus that are subject to risks and uncertainties. These forward-looking statements include statements regarding the progress and timing of clinical trials, the safety and efficacy of our product candidates, the goals of our development activities, estimates of the potential markets for our product candidates, estimates of the capacity of manufacturing and other facilities to support our products, our expected further revenues, operations and expenditures and projected cash needs. These statements relate to future events of our financial performance and involve known and unknown risks, uncertainties and other factors that could cause our actual results, levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. Those risks and uncertainties include, among others:

- our ability to obtain additional funding to develop our product candidates;
- the need to obtain regulatory approval of our product candidates;

- the success of our clinical trials through all phases of clinical development;

- any delays in regulatory review and approval of product candidates in clinical development;

- our ability to commercialize our product candidates;
- market acceptance of our product candidates;
- competition from existing products or new products that may emerge;
- regulatory difficulties relating to products that have already received regulatory approval;
- potential product liability claims;
- our dependency on third-party manufacturers to supply or manufacture our products;
- our ability to establish or maintain collaborations, licensing or other arrangements;
- our ability and third parties' abilities to protect intellectual property rights;
- compliance with obligations under intellectual property licenses with third parties;
- our ability to adequately support future growth; and
- our ability to attract and retain key personal to manage our business effectively.

Forward-looking statements include all statements that are not historical facts. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "bel "estimates," "projects," "predicts," "potential," or the negative of those terms, and similar expressions and comparable terminology intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. These forward-looking statements represent our estimates and assumptions only as of the date of this free writing prospectus and, except as required by law, we undertake no obligation to update or review publicly any forward-looking statements, whether as a result of new information, future events or otherwise after the date of this free writing prospectus. You should read this free writing prospectus and the documents referenced herein and filed as exhibits to the Registration Statement, of which the Preliminary Prospectus is a part, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

The issuer has filed a registration statement (including a prospectus) with the SEC for the offering to which this communication relates. Before you invest, you should read the prospectus in that registration statement and other documents the issuer has filed with the SEC for more complete information about the issuer and this offering. In particular, you should carefully read the risk factors described in the preliminary prospectus, in the final prospectus, in any related prospectus supplement and in the documents incorporated by reference in the preliminary prospectus, the final prospectus and any related prospectus supplement. The registration statement has not been declared effective by the SEC and the information contained therein, including information in the preliminary prospectus, is subject to change prior to the registration statement becoming effective and the filing of the final prospectus with the SEC. You may get these documents for free by visiting EDGAR on the SEC website at www.sec.gov. Alternatively the issuer and the underwriters will arrange to send you the prospectus if you request it by calling Roth Capital Partners, LLC Syndicate Department, 24 Corporate Plaza, Newport Beach, CA 92660, at 800-678-9147 or Maxim Group LLC, 405 Lexington Avenue 2nd Floor, New York, NY 10174 at 212-895-3500.

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cryopreservation and cell Banking for Autologous Mesenchymal stem cell-Based Therapies

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Abstract: As cell-based therapies begin to progress through Phase III clinical trials, there is an increasing need for the development of comprehensive cell banking strategies. In order to achieve commercial viability, both autologous and allogeneic approaches must have a comprehensive, end-to-end cell banking model—including proper collection, manufacturing and release criteria, cryopreservation and storage of cells, shipping, delivery, and logistics management of the final cell product. By developing an understanding of industry standards and best practices across these areas, companies can be better positioned to reduce research costs, improve efficiencies, create revenue streams, decrease time to discovery and, ideally, increase the likelihood and number of approved marketed products. The focus of this paper will be on cell banking strategies for autologous-based cell therapies with mesenchymal stromal cell**s,** which are the most widely used cell type in cell therapy clinical trials today**.**

Keywords: cryopreservation, cell banking, autologous, mesenchymal stem cells, cell therapy

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Introduction

Stem cell-based therapies have tremendous promise for patients.1 While there are a few cell-based products, which are commercially available, there are many more potential therapies in clinical development.2,3 The two major types of stem cell-based products are those of allogeneic origin and of autologous origin. There are several differences between these two products, many of which impact the business model that is eventually deployed.4,5 First and foremost is the purpose and approach to cell banking. In the allogeneic cell therapy model, cell banking is employed for manufacturing and storage of a large- scale inventory of a uniform, off-the-shelf product. In the autologous cell therapy model, cell banking is employed for manufacturing and storage of individual aliquots, to be used for the preparation of future, repeat doses for each patient. Nevertheless, there are several similarities in these business models, as both are highly dependent upon a comprehensive cell banking strategy in order to achieve commercial viability. This includes proper collection, manufacturing and release criteria, cryopreservation and storage of cells, shipping, delivery, and logistics management of the final cell product.6 As cell-based therapies begin to progress through Phase III clinical trials, there is an increasing need to develop an understanding of industry standards and best practices across these areas. This will enable companies to reduce research costs, improve efficiencies, create revenue streams, decrease time to discovery and, ideally, increase the likelihood and number of approved marketed products.7 In addition, it will drive further interest and investment from key stakeholders such as pharma companies.[8]

The focus of this paper will be on cell banking strategies for autologous-based cell therapies with mesenchymal stromal cells (MSCs), which are the most widely used stem cell type in cell therapy clinical trials today.[9]

MSCs are multipotent stromal cells capable of differentiating into a variety of cell types including osteoblasts, chondrocytes, and adipocytes. The most commonly used MSC tissue sources for autologous cell therapy are bone marrow (BM) and adipose tissue (AT). While the morphology and immune phenotype of the MSCs derived from both BM and AT sources are similar, there is a much higher concentration of MSCs inAT.10 However, BM-derived MSCs have been more widely used and there is a much greater quantity of data regarding clinical safety and practice.

For autologous BM-derived stem cell therapies, the low colony frequency of MSCs and their long doubling time represent particular challenges, which are addressed with cell banking. For example, once the MSCs are isolated from the mononuclear cell component of the bone marrow tissue and they undergo a first stage of characterization with release criteria such as fluorescence-activated cell sorting, visual checks, sterility testing, and so on, these steps need not be repeated for the preparation of additional doses. With well characterized and well identified aliquots frozen and banked, preparation of repeat doses can begin with expansion of these cells, saving valuable time and resources.

Figure 1 depicts a representative cell banking and cryopreservation process for repeat dosing of an autologous, MSC-based therapy. Once the source tissue is harvested from the patient, it is transported to a dedicated cGMP

(Current Good Manufacturing Processes)-compliant cell therapy processing facility, where the MSCs are isolated, cultured, and characterized to insure that only the desired cell type(s) has been cultured. Appropriate release criteria for fresh MSCs are required before moving to aliquot and cryopreserve the cells. Once cryopreserved according to the Food and Drug Administration (FDA) guidelines, the cells can be banked for subsequent doses for the patient. Thereafter, individual aliquots can either be sent frozen to a cell therapy processing facility at the medical center for thawing and for further processing into single doses, or they will more likely be thawed and processed within the external facility. In either case, after gradual thawing, the cells must be characterized using release criteria appropriate for thawed MSCs. The cells can then be expanded and activated, when applicable, into individual treatment doses, or recultured if needed, before being shipped to the medical center for injection into the patient. While autologous derived therapies have advantages over allogeneic derived therapies when it comes to immunogenicity, their primary disadvantage is in the potential for higher Cost of Goods (COGs) due to the individualized, rather than large-scale, processing and delivery.[11]

Cryopreservation and cell banking for cell therapies

Figure 1. cell banking process for autologous Msc therapy. (**1**) Tissue aspiration is performed at a medical center; (**2**) Shipping of the tissue sample at 4 °C in temperature controlled packaging, with a temperature recorder, to cell therapy processing facility; (**3**) mSC isolation and culturing in culture chambers (manual production) or bioreactor; (**4**) Cell characterization according to release Criteria for Fresh mSC's; (**5**) Aliquoting of mSC samples with cryopreservation medium for future repeat doses; (**6**) Freezing and storage at -196 °C in Vapor Liquid nitrogen Freezer as per FDA guidelines*; (**7**) Slow thawing at 37 °C in water bath; (**8**) Cell characterization according to release Criteria for Thawed mSC's; (**9**) expansion of thawed mSC's in incubator and/or bioreactor for processing into repeat dose; (**10**) Activation of MSC's into final cell therapy product; (**11**) Shipping of final product in optimized, approved delivery device to medical center at 4 °C in temperature controlled packaging with temperature recorder; (**12**) injection of the cell therapy product into patient.

notes: *In the event that a cGmP compliant cell therapy processing unit exists within the medical center, frozen mSCs could theoretically be shipped to the medical center for thawing and further processing at that unit before delivery to the patient.

Optimization of the elements of the process can minimize the COGs and, therefore, improve overall commercial viability of the product. However, optimiza- tion of the cell banking and cryopreservation processes must be based on industry requirements and/or stan- dards of practice, which are constantly shifting as the field and regulators learn more about autologous cell- based therapies. This analysis will perform a deep dive into some of the key areas depicted in Figure 1 in order to highlight the key challenges and opportunities.

cell characterization considerations for Fresh cells

As described in Figure 1, aspiration of BM or other tissue is performed at the hospital and the aspirate is shipped in controlled temperature packaging to the manufacturing site for processing. The cells are then cultured and characterized using appropriate methods to ensure the cells are what they are supposed to be (ie, release criteria for fresh cells). In fact, generating robust release criteria is becoming a large area of focus for the industry.12 According to the FDA guidance:[13]

The final product is the final formulated product used for administration to human subjects. Final product release criteria testing should be performed on each lot of product manufactured. In some situations, each dose could be considered a single lot, depending on the manufacturing process. The results from final product release criteria testing

should be available prior to administration to a human subject. We recommend that you provide, in table format, all of your proposed specifications (tests for safety, purity, potency, and identity as described in Section IV, test methods, and acceptance criteria), including test sensitivity and specificity, where appropriate, for the final product.[13]

As mentioned above, the key elements are the safety, purity, potency and identity tests that need to be employed for a particular product.14 Safety refers to confirmation that the cell-based product is not contaminated with bacteria, fungus, or other microbes. Purity is done to confirm that the product does not have any contamination from cellular or acellular material (eg, processing material). Potency is a test to confirm that the cell-based product actually has the biological functions that are required to successfully treat the relevant patients. Finally, identity testing is used to confirm that the specific components, cellular and other, are both present and in the correct quantities. These are becoming such large issues for the industry that entities such as the Alliance for Regenerative Medicine have begun to tackle some of these challenges by providing more detailed guidance to industry players, as well as playing an active role for the industry in discussions with the relevant regulatory authorities.[15]

cryopreservation considerations

Cryopreservation has been successfully utilized for the long-term storage of several different cell types for many years, and is considered the most effective method for cell preservation.[16–18]Cryopreservation is based on the principle that chemical, biological, and physical processes are sufficiently stopped at cryogenic temperatures (-196 °C) because liquid water does not exist at such low temperatures. In fact, the only physical states that exist at cryogenic temperatures are crystalline. Furthermore, there is insufficient thermal energy for chemical and metabolic processes to proceed at biochemical relevant rates.

Cryopreservation, if done appropriately, will involve the following basic process. During cooling, ice nucleation occurs in the extracellular environment while the intracellular water super-cools. Because of extracellular ice formation, solution concentrations are higher outside the cells than inside and, hence, water diffuses out of the cell. As the temperature continues to decrease, the unfrozen solution within the cells and the extracellular unfrozen fraction subsequently solidify into a solid-like state. The viscosity is sufficiently high to reduce molecular motion on a practical time scale, thereby providing long-term stable storage of the cells.[19]

Given the fact that the current process is not yet optimized for cell-based products, there is a significant need to further improve cryopreservation techniques in this area. For example, an ideal cryo- protection solution should be non-toxic for cells and patients, non-antigenic, chemically inert, provide a high survival rate after thawing, and allow immediate implantation into the patient without washing. However, cryopreservation protocols still often rely on 10% dimethyl sulfoxide (DMSO) as a cryoprotectant, due to its marked ability to penetrate cell membranes and prevent cell rupture. It is well known that DMSO is potentially cytotoxic, and transplantation of DMSO-preserved human BM cells has been shown to cause severe adverse reactions.20 Moreover, the use of human serum albumin, cerebrospinal fluid, fetal bovine serum, and bovine serum albumin as cryoprotectants is also problematic, due to the risk of contamination with human or animal viruses and the potential of infection with prions and other unidentified pathogens.21 In addition, these are potentially dangerous due to the possible induction of an allergic response.

As a result, efforts are being made to reduce the DMSO content of cryoprotection media as much as possible,22 in some cases by replacing a portion of it with alternatives such as hydroxyethyl starch,[23] and, in some cases, by replacing it completely.[24] In addition, serum-free cryomedia are increasingly being developed.[25,26]

Adhering to FDA cell Banking and storage standards

Another area in which adherence to FDA guidelines is critical to the cell banking and storage process is that of cGMP storage. Key elements include: cGMP monitoring, access and backup, cGMP record-keeping inventory and proper identification, and cGMP in reuse of samples and discarding of surplus.32 In addition, a related need is for traceability of the cells in the treatment, and follow-up with the donor and recipient, both of which are much easier for autologous products. Finally, these standards apply effectively to anything that will end up being used by, for, or on the cells during cryopreservation, storage, and subsequent thawing including equipment, reagents, and processes.[33]

The FDA guidance for cGMP is included in the “Compliance Program Guidance Manual.”34 A key quote from this section highlights the FDA’s guidance and where it can be found:

Biological drug products are subject to the applicable regulations promulgated under both Acts, including the Current Good Manufacturing Practice regulations (CGMPs), which are found in Title 21 Code of Federal Regulations (CFR), Parts 210 and 211, and the Biologics regulations, 21 CFR Parts 600–680. In addition to the above, human cells, tissues, and cellular and tissue- based products regulated as biological drug products are also subject to the Registration and Listing, Donor Eligibility, and Current Good Tissue Practice (CGTP) regulations in 21 CFR Part 1271. Section 501(a)(2)(B) of the FD&C Act requires that biological drug products be manufactured in compliance with CGMPs. CGMP regulations apply to the manufacture of biological drug products and CGMP principles apply for the manufacture of biological intermediates and drug substances under Section 501(a)(2)(b) of the FD&C Act, and the Biologics regulations under 21 CFR Part 600.[3,4]

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The European Medicines Agency has similar guidance to the FDA.35,36 The key is that companies understand the similarities and differences between the two agencies and ensure GMP compliance across their product lifecycle.

cell characterization and Release criteria for Thawed cells

Once the cell-based product has been thawed, the final characterization prior to expansion, activation, when applicable, and delivery to the patient must be performed.37 Post-thawing release criteria, like post- culturing release criteria, include parameters such as viability, recovery, doubling time, phenotyping, and differentiation capacity. In addition, analytical methods must be used to rule out the presence of residual growth media supplements. See above discussion on release criteria for more details.

These tests are focused on ensuring that the cells, post-thaw, have the same characteristics as they did prior to freezing and shipping. The time and costs involved in this step, as well as in the subsequent expansion and activation into the end product, could add significantly to COGs if performed within an on-site cell therapy processing unit of a medical center as opposed to an external processing facility, due to the need for specially trained and qualified personnel. If the banked cells can be thawed, characterized, expanded, and processed into the end-product before shipping to the medical center, this would be of significant benefit to both the COGs, as well as to the overall success of the product.

packaging and shipping considerations

The ability to preserve the integrity of the tissue sample and the final, autologous MSC-based cell product is critical to the shipping method used between the manufacturing site and the medical center. Key factors are the minimization of: loss of cell viability and potency, time the cells are in transit, temperature fluctuations of the cells, and appropriate media for transporting the cells. There are a variety of possible approaches for transporting cells, primarily dependent on temperature. For example, one could ship cells either in a frozen state, at a variety of temperatures including liquid nitrogen, -80 °C, -20 °C, or non- frozen at either 4 °C or 20 °C. Each of these has unique benefits and disadvantages that must be considered, including ease of maintaining the temperature during transit to the hospital, time that the cells remain viable, ease of preparing the cells for the patient at the hospital, and storage of the cell-based product at the hospital.

Today, many cell-based products, such as blood components, are shipped at -20 °C due to the current limitations of the manufacturing processes of early stage products, as well as due to the type of freez- ing equipment typically available in most hospitals. These limitations exist because companies with prod- ucts in early clinical trials have yet to optimize the process given limited funds and the relatively early stage of the asset. Whether this temperature will be viable in the market in the future remains to be seen, but will likely depend on the indication and where the product is

stored and administered. However, ship- ping autologous cell therapy products in non-frozen states is more likely to be adopted in the short-term until on-site cell therapy processing units become the norm in major medical centers.

Finally, a key consideration is the stability and viability of the autologous cell-based product during shipping, as this will impact the number and location of supplier manufacturing sites. For example, if the cell-based product is stable for 24 hours post- release from the manufacturing site, and assuming 8–12 hours of time is required on-site for delivery to the patient (less if shipped non-frozen, more if shipped frozen), then 12 hours of time is required to deliver the product to the medical center. This would likely require one to two manufacturing sites in the US, located at key airline hub metropolitan areas to enable coverage of the majority of the larger cities in the US. If the stability time is much less, then the number of processing sites must increase or the number of potential patients who could be treated will decrease (eg, limited to the east coast of Washington DC to the Boston corridor or California).

The actual logistics of moving the cells from one place to another can be challenging to ensure that the right patient gets the right cells at the right time.

Companies should look at entities that are expert in shipping blood/tissue/materials such as blood banks, specialized logistics companies, or companies that specialize in delivering peritoneal dialysis equipment and supplies to patients. While the logistics of shipping cell-based products can be challenging, many entities have already solved this.

storage and Delivery of cells to patient

The cell-based product that has been shipped to the hospital for delivery to the patient could be stored on site, frozen or fresh depending on the product, in the existing blood/tissue bank of the hospital for a few days if needed until the patient is ready for treatment. But allowing the medical team to receive the final end-product ready for treatment without having to depend on the hospital cell processing unit to perform thawing, characterization, expansion, and possible differentiation procedures on-site would be optimal. In the perfect world, a preloaded syringe of the ready dose would be shipped to the medical center, ready for the physician to administer to the patient. There is some learning that companies trying to develop cell therapy products could derive from companies that have marketed monoclonal antibody- based products regarding optimizing product delivery to the patient.38 While these are still early days for cell therapy products, logistical and cost-related benefits will determine commercial successes and differentiate between otherwise similar products.

Future Frontiers

From this discussion, it is clear that the provisioning of an autologous cell-based product is complicated and can be quite expensive using today's technology. Methods and techniques that both decrease the complexity and cost are welcomed and are being explored. In the future, an optimal product could actually resemble that of a biologic—where the ready-to-deliver end product is shipped for immediate administration to the patient with minimal complexity. This would be based on fully optimized cell banking protocols in which cryopreservation and storage of the patients' aliquots for future repeat dosing would be normalized, not unlike today's procedure for oocyte cryopreservation. In addition, significant advances might be made, perhaps in lyophilization of cells or even bone marrow, which could provide additional benefits such as significantly longer viability, simpler long-term storage, and less costly shipping.39 Finally, this future is not likely to happen until several autologous products are launched and can optimize the business model by reinvesting profits from the product. Time will tell, but early data are encouraging that cell therapy products may become a mainstream medical treatment in the near future.

Author contributions

Analyzed the data: AH. Wrote the first draft of the manuscript: AH. Agree with manuscript results and conclusions: AH. Developed the structure and argu- ments for the paper: AH. Made critical revisions and approved final version: AH. All authors reviewed and approved of the final manuscript.

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Disclosures and ethics

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