SUDA PHARMACEUTICALS LTD

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ASX Release

PROGRAM UPDATE: ANAGRELIDE

Key points:

- Platelets are involved in cancer progression
- A reduction of platelets can help prevent tumour growth and metastasis
- Anagrelide prevents the production of platelets
- An oro-mucosal spray formulation of anagrelide could minimise dose limiting side-effects
- SUDA's anagrelide project to be used as an adjuvant or neo-adjuvant therapy

PERTH, AUSTRALIA – 21 February 2019: SUDA Pharmaceuticals Ltd (ASX: SUD), a leader in oro-mucosal drug delivery, provides the following update on its development of anagrelide, an anti-thrombotic agent, that has shown promise as a novel anti-cancer agent.

SUDA acquired the global rights for the use of anagrelide as an adjuvant/neo-adjuvant treatment for cancer in January 2018. During the past 12 months, the SUDA team has been working on the development of a formulation for the delivery of anagrelide across the oral mucosa. SUDA's plan is to formulate an oro-mucosal spray of anagrelide utilising the Company's OroMist® technology, which could potentially avoid the side-effects associated with the molecule when administered as an oral solid dose.

This project relates to the use of a radically new, first-in-class approach to the treatment of cancer, potentially applicable across a wide range of solid tumours. Currently, newer cancer treatments involve immunotherapy which stimulate the patients' own immune system. Anagrelide could be complementary to such treatments rendering circulating cancer cells more susceptible to attack by the body's own "killer" T cells and could thus offer a valuable new adjunctive therapy.

Anagrelide Overview

Anagrelide is currently used to reduce elevated platelets and lower the thrombotic risk in myeloproliferative diseases associated with high platelet counts. It is now recognised that platelets also play a key role in the growth and metastatic spread of tumours. At the last annual meeting of the American Society of Haematology, perhaps one of the most widely attended events in this field, several key opinion leaders presented data on the underlying mechanisms by which the platelet-tumour interaction is mediated and how the reduction of platelets could potentially help minimise tumour growth and metastasis.

Anagrelide is pharmacologically unique in its ability to modulate platelet production without impacting other blood cells. It does this by inhibiting expansion of the precursor cells that give rise to platelets (megakaryocytes (MKC)). Historically anagrelide was designed as a platelet anti-aggregatory agent but failed in this indication and was re-purposed as a platelet lowering drug in diseases marked by elevated platelets and increased thrombotic risk. However, the original classification of anagrelide as an anti-platelet/anti-aggregatory agents remained and caused much confusion. In December 2018, Professor Steven Watson (SUDA Scientific Advisory Board member) published an article in the journal "Platelets" setting straight the true classification of anagrelide as an anti-megakaryocytic agent, not an anti-platelet/anti-aggregatory agent for which it was originally intended. Anti-megakaryocytics represent an entirely new therapeutic class that currently hosts anagrelide as the only approved drug.

Anagrelide has the potential to be developed as an effective anti-cancer agent but is presently limited by the cardiovascular side effects seen after administration of the current capsule formulation. This gives rise to an initial first pass effect in the liver generating a cardio-stimulatory metabolite upwards of 40 times more potent than the drug itself. An oro-mucosal spray formulation of anagrelide could reduce these side-effects by avoiding first-pass generation of this highly potent cardio-excitatory metabolite.

The role of platelets in cancer

There is compelling experimental and clinical evidence confirming the crucial role played by platelets in cancer progression. Platelets accomplish this in a number of ways:

1) Immune system suppression
    a. Platelets physically cloak circulating tumour cells and shield them from the immune system's natural killer T cells.
    b. Platelet-derived transforming growth factor β (TGFβ) and lactate limit CD4+ and CD8+ T cell functions so constraining T cell immunity against cancer cells.
2) Tumour growth and metastases
    a. Platelet derived *adhesive* integrins enable cancer cells to attach to host cells and improve their ability to penetrate the host cell layers.
    b. Platelets then release further chemicals (such as vascular endothelial growth factor - VEGF) to help the tumour to grow its own blood supply (angiogenesis).
    c. The tumour then releases chemicals (cytokines such as IL-6) that tell the body to make more platelets so providing more growth factor and establishing a potentially fatal feedback loop.

As can be expected this results in more of the above resulting in faster growing tumours that are protected from the immune system that continue to generate more platelets.

Potential role of anagrelide in cancer treatment

Anagrelide by itself will not cure cancer. Anagrelide will slow the production of the platelets reducing the impact of these protectors of, and promoters of, tumour growth. Anagrelide is therefore proposed as an adjuvant or neo-adjuvant therapy (modifier/promotor of the effect of another drug). By reducing the production of platelets, anagrelide will stop or reduce the feedback loop discussed above and will further expose the cancer cells to the immune system. This means that by potentially slowing the growth of the tumours the existing cancer drugs have a greater chance of reducing the tumour burden. It also has the potential to improve the performance of some the most exciting new immunotherapies that are currently making their way onto the market.

The potential of reducing the platelet count in patients with solid tumours includes: greater progression free survival; reduced tumour burden; and even potentially greater cure rates.

Project Status

Anagrelide is a challenging drug to formulate. It is virtually insoluble in all major pharmaceutically acceptable solvents with a water solubility of just 0.002mg/mL, which is over 1000 times less than needed for an oro-mucosal spray which requires a concentration of ~2.5mg/mL. It is insoluble in most non-aqueous solvents as well. SUDA's technical team has been able to improve the solubility by greater than 10,000-fold using novel solvent compositions and solubility enhancers. Whilst this is impressive we are still working on developing a formulation with the solubility and stability characteristics required for a pharmaceutical product. The technical team are confident that they can achieve this and are currently testing a number of formulations that have shown promise.

Assessment and optimisation of the permeability of the product in vitro has begun using artificial membrane models. Preliminary flux rate estimates are very encouraging showing a high permeability for the drug. This is an ongoing process that will continue throughout the formulation development and optimisation stage of product development.

Once a suitable oro-mucosal formulation has been developed, pre-clinical testing will be conducted to confirm the ability of an oral spray formulation to reduce the formation of the cardio-toxic metabolite. This will pave the way for demonstrating proof of concept (POC) in man.

Intellectual Property

SUDA owns the global rights to the following patent:

"Prevention and treatment of metastatic disease in thrombocytotic cancer patients"
Priority date 22nd December 2014. PCT published June 30th 2016

The patent is in its National Phase and is undergoing examination in a number of key jurisdictions including the USA, Europe and Japan.

The patent claims are based around the treating or prevention of cancer in thrombocytotic cancer patients with solid cancers such as brain, GI, oral, head and neck, pancreatic, liver, colorectal, lungs, ovarian, cervical, endometrial, breast, prostate, kidney, melanoma, mesothelioma, multiple myeloma and gallbladder.

SUDA will add further patents to the portfolio to cover formulation and use of the drug.

Scientific Advisory Board (SAB)

As previously announced, SUDA is putting together a SAB of Key Opinion Leaders (KOL's) and industry influencers (II's). Currently three very strong members have joined the SAB and work is ongoing to identify further KOL's and II's to further strengthen the SAB.

Current members are:

- Steven Watson, professor, PhD | Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham UK.
    - Prof. Watson is the head of the Birmingham Platelet Group. The group undertakes a multidisciplinary approach to the investigation of platelet function in health and disease with a special focus on platelet receptors and their signaling pathways.
- Nailin Li, associate professor, MD, PhD | Karolinska Institute, Sweden

- Dr Li is an internationally recognized researcher in platelet functional studies and platelet-T effector cell interactions. His main research interests are thrombotic and inflammatory mechanisms in atherosclerosis, platelet angiogenetic activities in arterial remodeling and cancer progression, and clinical evaluation of anti-platelet drugs.

- Dr Richard Franklin PhD

  - Dr Franklin has worked for several major drug companies including Glaxo, Wyeth, Sterling Winthrop, & AstraZeneca. Latterly he was head of New Product Innovation at Shire Pharmaceuticals where he is credited with filing over forty patents on potential new drug products. Dr Franklin was closely associated with the original development and commercialization of anagrelide as an anti-thrombotic.

Business Development

SUDA's BD team are already in the process of identifying potential partners and introducing the project to them. Significant interest in the project has been received thus far and further efforts continue to focus Business Development activities in this direction. SUDA is working closely with KOL's to further the international understanding of the potential of anagrelide in cancer by instigating publications in international peer reviewed journals.

SUDA's preferred commercial outcome would be a global licensing arrangement with a mid to top tier pharmaceutical company with a strong oncology franchise. SUDA believes that this project should prove very attractive to immuno-oncology companies currently actively working in this area.

Project Funding

Anagrelide is a key project within the SUDA portfolio and as such the board has committed to self-fund the program from existing cash reserves and on-going income.

The project development is run through SUD 18 Pty Ltd, a wholly owned subsidiary of SUDA.

SUD 18 Pty Ltd has received a private ruling from the ATO that states that the company meets the criteria of an Early Stage Innovation Company (ESIC) (further validating the program) whereby the company can elect to raise money through this entity, with the investors receiving CGT exemptions and tax offsets.

This is a potential non-dilutive funding option for SUDA to expedite the program if it wishes to elect to use it.

Summary

An oro-mucosal spray of anagrelide should offer a much safer preparation, minimizing the risk of adverse cardiovascular effects while retaining the cytoselective anti-megakaryocytic properties of the drug. Furthermore, anagrelide's unique selectivity means it has no directly comparable small molecule competitors. A newly reformulated anagrelide would be potentially utilizable across a broad spectrum of cancers since there appears to be a common dependency on excess platelets to drive cancer establishment, growth and metastasis shared by many cancers.

Anagrelide would be complementary to many treatments by reducing the platelet numbers thereby reducing the proliferative and protective effect that platelets exhibit on metastatic cells and further rendering circulating cancer cells more susceptible to attack by the body's own killer cells. Thus, it potentially offers a novel and valuable first-in-class treatment option for cancer.

The global cancer market is currently forecast to be $138 billion by 2019 and is growing at 11%pa (*The Wall Street Journal Jan 27, 2019*).

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NOTES TO EDITORS:

About SUDA Pharmaceuticals Ltd

SUDA Pharmaceuticals Ltd (ASX: SUD) is a drug delivery company focused on oro-mucosal administration, headquartered in Perth, Western Australia. The Company is developing low-risk oral sprays using its OroMist® technology to reformulate existing pharmaceuticals. The many potential benefits of administering drugs through the oral mucosa (i.e.: cheeks, tongue, gums and palate) include ease of use, lower dosage, reduced side effects and faster response time. SUDA's product pipeline includes ZolpiMist™, a first-in-class oral spray of zolpidem for insomnia. ZolpiMist is marketed in the USA and SUDA has rights to the product outside of the US and Canada. SUDA has submitted a Marketing Authorisation Application to the Australian Therapeutic Goods Administration for ArTiMist®, its novel sublingual malaria treatment for children. In a Phase III trial, ArTiMist was shown to be superior to intravenous quinine. Other products in development include oral sprays for the treatment of: migraine headache; chemotherapy-induced nausea and vomiting; erectile dysfunction; PAH; epileptic seizures and pre-procedural anxiety; and cancer.

For more information, visit www.sudapharma.com

About blood platelets in cancer

Cancer survival across all solid tumour types has been shown to be related to the number of blood platelets a patient has, cells which are more usually associated with the clotting process. However, platelets are now known to provide essential growth factors that nourish cancer cells and enable them to take hold and develop into tumours. Hence, those patients with the highest platelet numbers are least likely to survive. This has been shown across a wide range of solid tumours including cancer of the brain, oral cavity, the head and neck, thyroid carcinoma, gastrointestinal cancers, pancreatic, hepatocellular cancer, colorectal cancer, cancer of the lungs and bronchus, cancer of the ovaries, endometrium, cervix, breast, prostate, kidneys, skin mesothelioma, melanoma and gallbladder.

About Anagrelide

The pharmacology of anagrelide enables the selective lowering of platelet numbers without significantly affecting clotting or the formation of other blood cell lines and, in this respect, is unique. Currently anagrelide is only available as a solid oral formulation and is used exclusively as an anti-thrombotic agent. The drug's fundamental limitation which precludes its use in the treatment of cancer is its cardio-stimulatory side-effect profile. These effects are known to be due to a highly potent cardio-excitatory metabolite of the drug, formed in large quantities during its initial passage though the liver after oral administration. The use of proprietary non-enteral formulation such as an oro-mucosal spray would minimise this first pass effect in the liver.