ASX RELEASE

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PHASE II CLINICAL STUDY AT WEILL CORNELL MEDICAL CENTER INVESTIGATING PAXALISIB IN COMBINATION WITH METFORMIN AND A KETOGENIC DIET ENROLLS FIRST PATIENT

Sydney, 28 February 2022 – Kazia Therapeutics Limited (NASDAQ: KZIA; ASX: KZA), an oncology-focused drug development company, is pleased to announce that a phase II study of Kazia's investigational new drug, paxalisib, in combination with metformin and a ketogenic diet for the treatment of newly diagnosed and recurrent glioblastoma, has been initiated at Weill Cornell Medicine, with the first patient successfully initiated in the study and a second patient already in screening.

Key Points

- Research by Professor Lew Cantley, who discovered the PI3K pathway, suggests that a low-insulin state may enhance the activity of PI3K inhibitors such as paxalisib. Inducing a 'ketogenic' state, in which the body is fueled by fats and proteins rather than by glucose, is a very effective way to reduce insulin levels.
- Patients on the study will also be treated with metformin, a common anti-diabetic drug, which is intended in this case to further reduce insulin levels.
- The Cornell study will explore this approach. One arm of the study will examine patients with recurrent disease, and the other will enroll newly diagnosed patients.
- Dr Howard Fine, founding Director of the Brain Tumor Center at New York-Presbyterian Weill Cornell Medical Center, will serve as Principal Investigator.
- The study is expected to recruit between 30 and 60 patients, and to take approximately two years to complete.
- Kazia will provide support, including study drug and a financial grant.

Dr Fine, Principal Investigator on the study, commented, "We have extensive and very convincing preclinical data to support this approach. My colleagues and I believe that administering paxalisib to patients in a ketogenic state may significantly enhance its efficacy. That in turn offers the potential to make a very significant difference in the treatment of glioblastoma, which remains one of the most challenging cancers in modern medicine."

Kazia CEO, Dr James Garner, commented, "We are delighted to have this study now underway and look forward to following its progress. This important milestone kicks off an exciting year for Kazia, with at least six potential data read-outs anticipated over the course of 2022. The GBM AGILE study continues to progress well, and additional studies, such as this one, have the potential to substantially extend and enhance the use of paxalisib in clinical practice."

Ketogenesis and Glioblastoma

Cells in the human body generally rely on glucose as 'fuel' for their energy requirements. However, when glucose is not readily available, cells can metabolise fats and proteins to provide energy. The fats and proteins are broken down to an intermediate form known as ketones, and so this biochemical pathway is referred to as 'ketogenesis'.

Unlike healthy cells, most tumour cells are poorly able to metabolise ketones, and so depend on glucose for their energy needs. Consequently, many researchers have experimented with 'ketogenic diets' as a potential treatment for cancer.[1]

In addition, scientists in Professor Cantley's lab have shown that insulin has the potential to counteract the anti-tumor effects of PI3K inhibitors[2]. In follow-up, Dr Fine's lab has shown that insulin can reverse the anti-tumor effects of PI3K inhibitors specifically in glioblastoma cells. Insulin is a hormone produced by the body in response to high levels of glucose. When the body is in a state of ketosis, glucose is absent, and so insulin falls to very low levels.

For these reasons, there is a sound rationale to explore a combination of ketogenic diet and paxalisib in glioblastoma. In this study, patients will also receive metformin, a common anti-diabetic drug, which will help to further lower fasting insulin levels.

Clinical Trial Design

This study will comprise two arms. The first will contain patients with newly diagnosed glioblastoma who have unmethylated MGMT promotor status. These patients have historically responded poorly to the current standard of care, temozolomide. The second arm will contain patients with recurrent disease, regardless of the methylation status of their MGMT promotor, who have progressed after taking standard-of-care therapy.

In each arm, paxalisib will be combined with metformin and with a ketogenic diet. The diet will be overseen by expert clinical dieticians to ensure that it is scientifically appropriate and that patients are compliant.

An initial cohort of approximately 16 patients will be recruited to each of the two study arms. If there are signals of activity in a given arm, that arm will be expanded to approximately 30 patients. The primary endpoint will be progression-free survival at six months (PFS6). In addition to efficacy and safety, the study will examine a range of

[1] A Kapelner & M Vorsanger (2015). *Medical Hypotheses*. 84(3):162-168
[2] B Hopkins et al. (2018). *Nature*. 560:499-503

metabolic, pharmacodynamic, and novel radiographic imaging biomarkers to inform future research and clinical practice. The study is expected to take around two years to complete.

Principal Investigator

Dr Howard Fine will serve as Principal Investigator to the study. Dr Fine is the founding Director of the Brain Tumor Center at New York-Presbyterian Weill Cornell Medical Center, Feil Professor of Medicine a Professor of Neurology at Weill Cornell Medicine. He is an internationally recognized leader in the field of neuro-oncology, with more than 30 years of experience in both laboratory and clinical research as well as in the care of patients with brain tumors. Dr Fine has built large multidisciplinary brain tumor programs at top academic institutions such as the Dana Farber Cancer Institute / Harvard Medical School and the National Institutes of Health, has cared for nearly 20,000 patients with brain and spinal cord tumors in his career, has conducted over 100 clinical trials, published over 250 papers and book chapters on brain tumors, and for over two decades has run a continuously operating translational genetic / molecular laboratory devoted to a better understanding of, and better therapies for, brain tumors.

Weill Cornell Medical Center

The Joan and Sanford I. Weill Medical College of Cornell University, known generally as Weill Cornell Medicine, is the medical school of Cornell University, based in New York, NY, and is one of the leading medical research centers in the United States. Its notable alumni include Dr Anthony Fauci, director of the National Institute of Allergy and Infectious Disease.

Paxalisib Clinical Program

The initiation of this trial in glioblastoma brings the number of ongoing clinical studies of paxalisib in brain cancer to eight.

Sponsor	**Phase**	**Indication**	**Registration**
Global Coalition for Adaptive Research	II / III	Glioblastoma	NCT03970447
Weill Cornell Cancer Center	II	Glioblastoma (*with ketogenic diet + metformin*)	NCT05183204
Alliance for Clinical Trials in Oncology	II	Brain metastases	NCT03994796
Dana-Farber Cancer Institute	II	Breast cancer brain metastases (*with trastuzumab*)	NCT03765983
Dana-Farber Cancer Institute	II	Primary CNS lymphoma	NCT04906096
Pacific Pediatric Neuro-Oncology Consortium	II	DIPG & DMGs (*with ONC201*)	NCT05009992
St Jude Children's Research Hospital	I	DIPG (childhood brain cancer)	NCT03696355
Memorial Sloan Kettering Cancer Center	I	Brain metastases (*with radiotherapy*)	NCT04192981

For More Information, Please Contact:-

In the United States:

Joe Green
Edison Investor Relations
jgreen@edisongroup.com
Phone: +1 646-653-7030

In Australia:

Jane Lowe
IR Department
jane.lowe@irdepartment.com.au
Phone: +61 411 117 774

About Kazia Therapeutics Limited

Kazia Therapeutics Limited (NASDAQ: KZIA; ASX: KZA) is an oncology-focused drug development company, based in Sydney, Australia.

Our lead program is paxalisib, a brain-penetrant inhibitor of the PI3K / Akt / mTOR pathway, which is being developed to treat glioblastoma, the most common and most aggressive form of primary brain cancer in adults. Licensed from Genentech in late 2016, paxalisib commenced recruitment to GBM AGILE, a pivotal study in glioblastoma, in January 2021. Eight additional studies are active in various forms of brain cancer. Paxalisib was granted Orphan Drug Designation for glioblastoma by the US FDA in February 2018, and Fast Track Designation for glioblastoma by the US FDA in August 2020. In addition, paxalisib was granted Rare Pediatric Disease Designation and Orphan Designation by the US FDA for DIPG in August 2020.

Kazia is also developing EVT801, a small-molecule inhibitor of VEGFR3, which was licensed from Evotec SE in April 2021. Preclinical data has shown EVT801 to be active against a broad range of tumour types and has provided compelling evidence of synergy with immuno-oncology agents. A phase I study commenced recruitment in November 2021.

For more information, please visit www.kaziatherapeutics.com or follow us on Twitter @KaziaTx.

This document was authorized for release to the ASX by James Garner, Chief Executive Officer, Managing Director.

CLINICAL TRIAL SUMMARY

Study Title	Paxalisib and Ketogenic Diet in GBM
Phase of Development	Phase II
Investigational Product	Paxalisib; metformin
Disease Area	Glioblastoma (WHO Grade IV Glioma)
Registration	NCT05183204
Principal Investigator	Dr Howard Fine *Weill Cornell Cancer Center, New York, NY*
Study Description	This is an open-label, phase II study to explore the efficacy of paxalisib in patients with newly diagnosed or recurrent glioblastoma when combined with a ketogenic diet and metformin
Number of Subjects	33-60 patients
Study Design	This is an open-label, two-arm study. **Cohort 1** will comprise newly diagnosed glioblastoma patients with unmethylated MGMT status **Cohort 2** will comprise recurrent glioblastoma patients (regardless of original MGMT status) Each cohort will include two stages: a first stage of approximately 16 patients to seek initial indications of activity, and then a second, confirmatory stage which will enroll approximately 15 further patients.
Patient Population	Newly diagnosed glioblastoma with unmethylated MGMT promotor status; Recurrent glioblastoma
Endpoints	The primary endpoint of the study is the proportion of patients alive and progression-free at six months (PFS6)
Participating Centres	Weill Cornell Medicine
Start Date	First Patient In: February 2022
End of Recruitment	Last Patient In (anticipated): 2H CY2023