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## **KAZIA ENROLS FIRST PATIENT TO EVT801 PHASE I CLINICAL TRIAL**

**Sydney, 4 November 2021** – Kazia Therapeutics Limited (NASDAQ: KZIA; ASX: KZA), an oncology-focused drug development company, is pleased to announce that it has commenced enrolment to a phase I clinical trial of EVT801, an investigational cancer therapy that Kazia licensed from Evotec SE in April 2021.

### **Key Points**

- EVT801 is a small molecule inhibitor of VEGFR3, and acts by inhibiting lymphangiogenesis, the formation of new lymphatic vessels around the tumour. It has shown compelling evidence of activity in a wide range of preclinical cancer models and appears broadly well-tolerated in animal toxicology studies.
- Kazia licensed EVT801 from Evotec SE, an international drug discovery alliance and development partnership company, in April 2021.
- The phase I study will focus primarily on understanding the safety, tolerability, and pharmacokinetics of EVT801 across a range of doses. It is also designed to explore preliminary signals of clinical efficacy, and to investigate the biological activity of the drug via a rich suite of sophisticated biomarker analyses.
- The lead clinical site in the study is L'Institut Universitaire du Cancer de Toulouse Oncopole (IUCT-Oncopole) in Toulouse, France. The lead investigator is Dr Carlos Gomez-Roca, a medical oncologist with a strong background in drug development and early phase clinical trials.
- The phase I study is expected to recruit a maximum of 60 patients, with the actual number dependent on the emergent safety profile of the drug. Timelines to completion will depend on the number of dose levels tested, and Kazia expects to provide further guidance on this as the study progresses.

Dr Carlos Gomez-Roca commented, “We are pleased to now be enrolling patients to this phase I study of EVT801. Despite great progress in the treatment of cancer over recent years, there remains a substantial need for new therapeutic options in a wide range of tumours. EVT801 has shown promising preclinical data, and we very much hope that it may now prove beneficial to our patients.”

### **Board of Directors**

**Mr Iain Ross** Chairman, Non-Executive Director

**Mr Bryce Carmine** Non-Executive Director

**Mr Steven Coffey** Non-Executive Director

**Dr James Garner** Chief Executive Officer, Managing Director

Kazia CEO, Dr James Garner, added, “in the six months since we licensed EVT801, the Kazia and Evotec teams have been working assiduously to execute a first-in-human study of this very promising drug candidate. It has been a privilege to work with the team at the IUCT-Oncopole site in Toulouse, which is one of the leading cancer centres in France, and we hope to add an additional centre in the new year. We are delighted that the study is now open to recruitment. All of us in Kazia firmly believe that EVT801 has enormous potential as a novel cancer therapy, and we look forward to working closely with the investigators to explore that potential.”

Dr Cord Dohrmann, Chief Scientific Officer of Evotec SE, said, “We are very excited to see EVT801 proceed to the clinic. The Phase I clinical trial will be conducted by Evotec, under the sponsorship of Kazia, at the renowned IUCT-Oncopole in Toulouse. Evotec will support the management of the Phase I clinical trial with analyses and biomarker development, which we anticipate will yield important data for the validation of the approach and to further contribute to the development of robust patient stratification strategies for the further clinical evaluation of EVT801.”

### **Phase I Study Design**

The phase I study of EVT801 is designed in two stages. The first stage is a multiple ascending dose (MAD) study, which is designed to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) for EVT801. Patients in the study will receive EVT801 at low doses, and this will be progressively escalated in subsequent cohorts as the safety profile of the drug is determined.

The second stage of the study will recruit twelve patients, of whom six will have been diagnosed with renal cell carcinoma and six with soft-tissue sarcoma. All twelve patients will receive EVT801 at the RP2D determined in the first stage. These patients will participate in intensive analyses to better understand the biochemical activity of the drug.

In addition to conventional measures of safety, efficacy, and pharmacokinetics, the phase I study will employ cutting edge biomarker technologies to provide early insights into the activity of EVT801. A rich program of tissue and blood biomarker analyses has been developed by Evotec scientists, in collaboration with the team at Oncopole. It is expected that these analyses will help to better understand the effects of the drug in human subjects and may also help to identify the most responsive patients and provide early predictors of clinical efficacy.

Kazia is also collaborating with Radiomics, an imaging analysis organisation based in Belgium, to apply sophisticated AI-based analyses to the CT and MRI scans collected during the study. Proprietary machine-learning algorithms developed by Radiomics can provide exceptionally detailed insights into the behaviour of the tumour while on treatment, and this information may help to predict and understand clinical response.

## Clinical Sites

The lead site in the study is the Institut Universitaire du Cancer de Toulouse Oncopole (IUCT-Oncopole) in Toulouse, France. IUCT-Oncopole combines several leading clinical cancer treatment facilities with a world-class research infrastructure, on an integrated campus that brings together public and private stakeholders, including industry participants. The centre treats more than 10,000 new patients each year, and more than one in eight patients are enrolled in clinical studies.

The lead investigator for the study is Dr Carlos Gomez-Roca, medical oncologist and Chair of the Early Phase Unit at IUCT-Oncopole, Dr Gomez-Roca's clinical research is focused on development of targeted therapies and immuno-oncology drugs. He is a member of ESMO, ASCO, FITC and AACR, and has contributed to more than 60 peer-reviewed publications, including as first or second author, in journals such as the *Journal of Clinical Oncology* and *Annals of Oncology*.

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## **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 immunology agents. A phase I study commenced recruitment in November 2021.

For more information, please visit [www.kaziatherapeutics.com](http://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.

## **About Evotec SE**

Evotec is a life science company with a unique business model that delivers on its mission to discover and develop highly effective therapeutics and make them available to the patients. The Company's multimodality platform comprises a unique combination of innovative technologies, data and science for the discovery, development, and production of first-in-class and best-in-class pharmaceutical products. Evotec leverages this "Data-driven R&D Autobahn to Cures" for proprietary projects and within a network of partners including all Top 20 Pharma and over 800 biotechnology companies, academic institutions, as well as other healthcare stakeholders. Evotec has strategic activities in a broad range of currently underserved therapeutic areas, including e.g. neurology, oncology, as well as metabolic and infectious diseases. Within these areas of expertise, Evotec aims to create the world-leading co-owned pipeline for innovative therapeutics and has to-date established a portfolio of more than 200 proprietary and co-owned R&D projects from early discovery to clinical development. Evotec operates globally with more than 4,000 highly qualified people. The Company's 14 sites offer highly synergistic technologies and services and operate as complementary clusters of excellence. For additional information please go to [www.evotec.com](http://www.evotec.com) and follow us on Twitter @Evotec and LinkedIn.

## CLINICAL TRIAL SUMMARY

<b>Study Title</b>	A Phase 1, First-in-Human, Open-Label Study to Assess the Safety, Tolerability, and Pharmacokinetics of EVT801 in Patients with Advanced Solid Tumours
<b>Investigational Product</b>	EVT801 (oral selective VEGFR3 inhibitor)
<b>Disease Area</b>	Advanced solid tumours
<b>Registration</b>	TBD
<b>Principal Investigator and Site</b>	Dr Carlos Gomez-Roca <i>Institut Claudius Regaud - IUCT Oncopole</i>
<b>Study Description</b>	This study is a phase I, first-in-human trial to establish the safety profile and dosing of EVT801.
<b>Number of Subjects</b>	<b>Stage 1</b> – up to 48 patients <b>Stage 2</b> – 12 patients
<b>Study Design</b>	This is an open-label, single-arm trial. The study comprises two stages, which will run sequentially.  <b>Stage 1</b> – a multiple ascending dose ('escalation') component. Enrolment will initially be via single-patient cohorts, expanding to a conventional 3+3 design once toxicity is encountered.  <b>Stage 2</b> – an expansion cohort for biomarker exploration.
<b>Patient Population</b>	Stage 1 will enroll patients with advanced solid tumours that are resistant or refractory to existing therapies. Stage 2 will enroll patients with renal cell carcinoma or soft-tissue sarcoma.
<b>Endpoints</b>	The primary endpoints of the study are safety and tolerability. The study will also assess key pharmacokinetic parameters to inform subsequent development of EVT801.  The study will explore preliminary signs of clinical efficacy, principally via measurement of Overall Response Rate (ORR). The study also includes a comprehensive suite of biomarker analyses, comprising blood, tissue, and imaging data, which will be used to better understand the activity of the drug.
<b>Start Date</b>	First Patient In: November 2021
<b>Duration</b>	Provisionally anticipated to be approximately two years, but will be more precisely assessed once study is well underway.

## Q&A

### What is the mechanism of action of EVT801?

Rapidly growing cancers require a substantial supply of nutrients, and so the tumour is obliged to generate new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis) to provide for its needs. Drugs which disrupt angiogenesis have been shown efficacious in a range of solid tumours, and several products are approved by FDA.

EVT801 is a small-molecule inhibitor of vascular endothelial growth factor receptor 3 (VEGFR3). VEGFR3 is integrally involved in lymphangiogenesis, the formation of new lymphatic vessels around a growing tumour. By inhibiting this target, EVT801 is expected to prevent the tumour from establishing and maintaining the network of lymphatic vessels required to sustain growth.

In addition, emerging data has shown that drugs targeting VEGF receptors can change the balance of immune cells in and around the tumour.<sup>1</sup> It is therefore anticipated that EVT801 may potentiate the activity of immuno-oncology therapies such as Keytruda<sup>®</sup> (pembrolizumab), Opdivo<sup>®</sup> (nivolumab), and Yervoy<sup>®</sup> (ipilimumab).

### What are similar products in this class of therapies, and how does EVT801 compare?

The first mainstream pharmaceutical product to target angiogenesis was Avastin (bevacizumab), which was brought to market by Genentech in 2004. It is currently approved by FDA for the treatment of a wide range of cancers, including colorectal cancer, lung cancer, recurrent glioblastoma, cervical cancer, ovarian cancer, renal cell carcinoma (kidney cancer), and liver cancer.<sup>2</sup> Avastin has sales of approximately US\$ 7 billion per annum.<sup>3</sup>

Avastin acts via inhibition of vascular endothelial growth factor (VEGF), a signalling protein that it is intimately involved in angiogenesis. Several pharmaceutical products are available which target the VEGF receptors (VEGFR), which are embedded on the surface of cells and which bind to circulating VEGF to trigger angiogenesis. These drugs are often referred to as 'angiokinase inhibitors' and an abbreviated listing is provided below.

Manufacturer	Product	Targets	Indications
Bayer	Nexavar (sorafenib)	VEGFR, PDGFR, RAF kinases	Liver cancer; renal cancer; thyroid cancer
Pfizer	Sutent (sunitinib)	VEGFR, PDGFR	Renal cancer; GIST
Novartis	Votrient (pazopanib)	VEGFR, PDGFR, FGFR, c-Kit	Renal cancer; soft-tissue sarcoma
Pfizer	Inlyta (axitinib)	VEGFR, PDGFR, c-Kit	Renal cancer
Exelixis	Cometriq (cabozantinib)	c-Met, VEGFR2, AXL, RET	Thyroid cancer; renal cancer; liver cancer

<sup>1</sup> C Tacconi et al. *Cancer Research* 2019;79:4196–210

<sup>2</sup> FDA-approved Prescribing Information

<sup>3</sup> Forbes, 17 January 2020

EVT801 is distinguished from all marketed angiokinase inhibitors by its high degree of specificity for VEGFR3. One consequence of this is that EVT801 is likely to act predominantly via inhibition of lymphangiogenesis rather than angiogenesis, and this may be associated with less development of drug resistance. More importantly, the selectivity of EVT801 is expected to result in a lower incidence of toxicity compared to existing therapies.

### **Are there other selective VEGFR3 inhibitors on market or in development?**

To Kazia's knowledge, there are no selective VEGFR3 inhibitors in clinical development in the global pipeline, and none have been approved for marketing by regulatory agencies.

A monoclonal antibody targeting VEGFR3 was previously developed through to phase I clinical trials by Lilly. LY3022856 (also referred to as IMC-3C5) was found to be well-tolerated but showed limited evidence of clinical activity in phase I.<sup>4</sup> This program was discontinued by Lilly following completion of phase I.

Kazia has carefully evaluated the IMC-3C5 data prior to in-licensing EVT801 from Evotec. Research has shown that VEGFR3 activation requires the presence of VEGFR2, forming a three-way complex between VEGF, VEGFR2, and VEGFR3 (heterodimerisation).<sup>5</sup> To be successful, a new drug needs to block both the VEGFR2-VEGFR3 complex and the VEGFR3-VEGFR3 homodimer. IMC-3C5 only blocks the homodimer, but not the heterodimer, and the company believes that this is the primary reason for its failure in the clinic. EVT801 is able to block both homodimer and heterodimer.

### **In which tumour types is EVT801 expected to ultimately be used?**

The phase I study will be conducted in patients with 'advanced solid tumours', a group which comprises patients with any non-haematological malignancy which has spread ('metastasised') and which is resistant to existing treatment. This very broad patient population is typical for 'first-in-human' studies of a new cancer drug.

The study includes an expansion cohort which will specifically examine the activity of the drug in renal cell carcinoma (cancer of the kidney) (RCC) and soft-tissue sarcoma (STS). These cancers have been chosen because they are generally responsive to existing angiokinase inhibitors, and they also provide rich opportunity to better understand the biological activity of EVT801.

The eventual commercial indication for the drug may include these groups, but it may also include other cancer types such as lung cancer, bowel cancer, or liver cancer. Kazia expects to consider the promising target populations after completion of phase I, in consultation with clinicians and advisors.

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<sup>4</sup> MW Saif et al. (2016) *Cancer Chemotherapy and Pharmacology*. 78:815–824

<sup>5</sup> A Alam et al. (2004) *Biochemical and Biophysical Research Communications*. 324(2):909-915

### **Will EVT801 be combined with paxalisib?**

Kazia does not at this stage plan to combine EVT801 with paxalisib. The two drug candidates are independent within Kazia's pipeline, and there is limited scientific data at present to support the combination.

However, it is anticipated that both drugs will be used substantially in combination with other drugs. In the case of EVT801, the most promising combination agents are likely to be immuno-oncology therapies such as Keytruda® (pembrolizumab), Opdivo® (nivolumab), and Yervoy® (ipilimumab).

### **Why is the study being conducted in two stages?**

The primary purpose of a phase I study is to understand the safety, tolerability, pharmacokinetics, and dosing of a new drug. Stage 1 of the EVT801 phase I study is designed primarily to support this purpose.

In addition, Kazia has emphasised a substantial 'translational medicine' component in the design of the study. The objectives here are to better understand the intricate biological activity of the drug so as to better inform its use, and to de-risk its further development. Stage 2 is designed primarily to support that purpose. However, both Stages will collect full safety and pharmacokinetic data, as well as providing biomarker analyses, and so there is considerable overlap in practice.

### **Kazia previously alluded to a planned third stage. Why has this not been included?**

Kazia had originally envisaged combination with immuno-therapy to represent a third stage of the study, which would have taken place after completion of Stage 1. During regulatory review, the French competent authority raised operational questions in relation to this stage which may require some time to fully resolve. As a result, Kazia has temporarily removed the third stage of the study in order not to delay the first two stages. In parallel to Stage 1, the company will discuss Stage 3 with clinicians and regulatory advisors and consider how best to re-introduce this component at a later date.

### **Kazia licensed EVT801 from Evotec in April 2021. How has it been possible to commence a clinical trial so quickly after completion of the licensing transaction?**

While conducting due diligence and negotiating the license agreement, Kazia began planning a potential phase I study in parallel and at risk. As a consequence, work was able to commence almost immediately after contract execution.

Moreover, the study is being implemented by Evotec, in a very tightly integrated collaboration with Kazia, and the efficiencies of this innovative operating model have allowed for considerable acceleration of the program. In addition, had manufactured investigational product prior to the licensing transaction, and that material will now be used in the phase I study, substantially reducing timelines.



## **Why is the study being performed in France?**

In general, France is a highly attractive location for clinical trials, with first-class medical infrastructure, high-quality data, and a well-designed regulatory environment.

In the case of the EVT801 study, initiating clinical development in France was considered to provide considerable timing advantages relative to commencing elsewhere. In addition, the co-location of Evotec laboratories on the Oncopole campus allows for rapid, real-time performance of sensitive biomarker analyses that would be challenging with an international study.

Kazia anticipates the inclusion of other countries later in the clinical development.

## **Why did Kazia select Evotec as the clinical CRO for this study?**

Although the licensing agreement between Kazia and Evotec envisages ongoing collaboration between the two companies, Kazia has no contractual obligation to work with Evotec on any specific project.

In the case of the phase I study, Kazia sought proposals from several CROs in a competitive bidding process. Evotec was selected on the basis of the extensive experience of its clinical team, the high degree of senior management engagement, the availability of resources proximal to, and with experience of, the chosen clinical sites, and its competitive cost.

The selection of Evotec as the clinical CRO has yielded great efficiencies in the conduct of the study, since there is substantial familiarity with EVT801 in that organisation. In particular, the rich program of biomarker work that has been included in the study benefits greatly from close integration between the clinical CRO and Evotec's own laboratories.

## **What is the nature of the biomarker work in this study?**

As part of the study, Kazia will examine a comprehensive suite of 'biomarkers', sophisticated laboratory assessments designed to better understand how EVT801 works in human patients, how the most responsive patients may be selected, and how the greatest efficacy may be obtained from the drug. In broad terms, the biomarkers fall into three main categories.

First, analyses of tumour tissue samples will be performed, primarily with the objective of identifying responsive patients. This work will be conducted by Evotec scientists.

Second, analysis of blood samples during the study will be conducted to understand how EVT801 is modifying the behaviour of the tumour and of the patient's immune system. This work will also be led by Evotec scientists, in collaboration with a research team at Oncopole.

Third, CT scans from the study will be subjected to 'artificial intelligence' (AI) analysis to better detect the effects of the drug on the tumour. This work will be performed by Radiomics, an AI-powered analysis and consulting firm based in Belgium.

**What is the projected cost of this study?**

In common with most biotech companies, Kazia does not itemise specific per-project costs. In general, phase I studies have a wide range of potential costs, due to the fact that they can recruit variable numbers of patients. However, the overall costs of the project are considered highly cost-effective in the context of industry benchmarks.

**When is initial data expected?**

Kazia expects to provide regular updates to the market on operational progress with the study. Provisionally, initial data is anticipated within 12-18 months of study commencement.