ASX Announcement

Race Oncology Makes Breakthrough Composition of Matter Intellectual Property Discovery

- Bisantrene discovered to consist of three photoisomers with different biological and anticancer activities, which rapidly interconvert upon exposure to visible light
- Race has created a range of manufacturing and physical processes to enable the controlled infusion of the pure active (E,E)-bisantrene isomer into patients
- Three patent applications submitted, which if granted, will provide composition of matter intellectual property protection of (E,E)-bisantrene for 20 years.

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16 September 2025 – Race Oncology Limited ("Race") is pleased to announce significant scientific discoveries into the nature of bisantrene that have enabled the company to submit a new composition of matter patent application. If granted, this patent will protect the chemical structure of the active (E,E)-bisantrene isomer (Figure 1). Two additional patent applications covering the optimal manufacturing, formulation and uses of (E,E)-bisantrene were also filed.

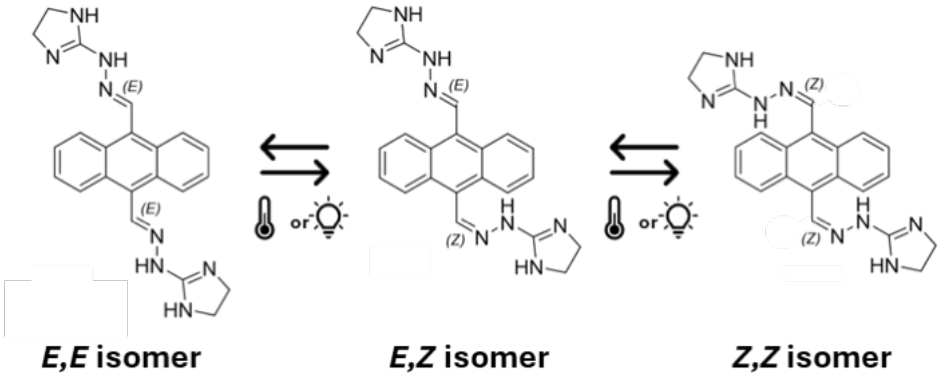


Figure 1. Interconversion between the different bisantrene isomers by visible light or heat.

This highly valuable new intellectual property (IP) is the result of extensive fundamental research undertaken by Race Oncology scientists over several years. Careful observations and follow-up of preclinical data anomalies by the Race team uncovered that bisantrene is composed of a mixture of three different *cis-trans* isomers ((E,E)-bisantrene, (E,Z)-bisantrene and (Z,Z)-bisantrene), with each isomer having differing biological properties and anticancer activity. These bisantrene isomers are generated during chemical synthesis, or by exposure to visible light and heat, with only the (E,E)-bisantrene ("all trans") isomer having significant anticancer activity.

Based on these discoveries, three patent applications were filed on 12 September 2025 covering the chemical structure, manufacture, formulation, storage, and uses of the active (E,E)-bisantrene isomer and isomeric mixtures. Race Oncology's IP advice is the patent applications meets all three fundamental requirements for allowance of a patent: novelty, non-obviousness, and utility. These patents, if granted, will provide composition of matter IP protection of (E,E)-bisantrene until 2045, with the potential for further extension via the patent term extension pathway available for pharmaceutical primary patents in some jurisdictions, including the USA.

These three patent applications add to the previously granted patents and patent applications held by Race covering the formulation and use of bisantrene (ASX announcements: 29 January 2018, 21 February 2018, 13 August 2019, 22 July 2020, 6 October 2021 & 19 October 2021). The company has requested accelerated examination of the new patent applications to aid pharmaceutical partnering discussions.

Race Oncology CEO and Managing Director, Dr Daniel Tillett commented, *"Being able to generate new composition of matter IP covering the active isomer of bisantrene fundamentally changes the commercial prospects of Race Oncology. We now expect to have 20 years of the strongest IP protection possible for the RC220 and RC110 formulations containing (E,E)-bisantrene. These discoveries highlight the commercial value of undertaking new preclinical research on clinically established pharmaceutical assets.*

I congratulate the entire Race preclinical team for their inspiration and extraordinary efforts in making this fundamental discovery and turning science into a valuable outcome for all our investors."

To avoid confusion in future announcements, the historical bisantrene isomer mixture developed by Lederle Laboratories will be referenced as 'bisantrene', while the all-trans isomer developed by Race will be referenced as either '(E,E)-bisantrene' or by the code 'RCDS1'.

Background

Composition of matter IP

Composition of matter patents, or primary patents, are the most valuable form of intellectual property in the pharmaceutical industry. These patents offer the strongest protection for new drugs because they protect the chemical structure of the active pharmaceutical ingredient (API) in a new drug product.

Regardless of how a chemical compound is synthesised, formulated, or used (whether in different dosages, forms, or methods), a composition of matter patent ensures exclusivity of the drug for a minimum of 20 years.

Isomers

Isomers are molecules that have an identical chemical formula, while having a distinct and different arrangement of the atoms within three-dimensional space. The different arrangement of atoms can result in isomers having different chemical, physical and biological properties. Isomers can be either structural, in which case the chemical bonds between the atoms differ; or stereoisomers, where the chemical bonds are the same, but the relative positions of the atoms in space differ.

In molecules containing a double bond between two atoms, two distinct configurations are possible. If atoms attached to the atoms comprising the double bond are on the same side of the double bond, the isomer is designated *cis* (from Latin meaning "on this side of"). If they are on opposite sides, the isomer is designated *trans* ("on the other side of") (Figure 2). In the International Union of Pure and Applied Chemistry's (IUPAC) recommended nomenclature, the letter E is used to symbolise *trans* and Z is used to symbolise *cis*. Conversion between these two forms (isomerisation) usually requires energy and temporary breakage of the double bond.

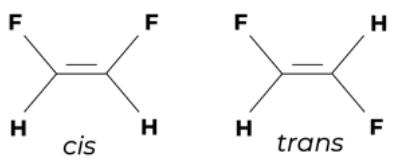


Figure 2. Example of double bond isomers: *cis*-1,2-difluoroethene (left) & *trans*-1,2-difluoroethene (right).

Photoisomers

In certain molecules, light can cause the interconversion between *cis* (Z) and *trans* (E) isomers. A well-studied example is the molecule that enables detection of light in the eye, retinal (retinaldehyde, a form of vitamin A). In the eye, retinal is found in the resting state in the *cis*-configuration as 11-*cis*-retinal. Upon capturing a photon of the correct wavelength, 11-*cis*-retinal converts to 11-*trans*-retinal. This 'photoisomerisation' event triggers a chemical signalling cascade in the retina, resulting in the perception of light by the brain.

Pharmaceutical isomers

Some pharmaceuticals are composed of two or more isomers. Each isomer of a drug can have different interactions with the intended target, as well as different absorption, distribution, metabolism, elimination, or excretion. In addition to their impact on therapy, isomers can have different off-target effects and toxicology, and it is not uncommon for a pair of isomers to display dramatically divergent safety profiles.[1]

Single-isomer drugs can provide several advantages compared to isomeric mixtures, including: reduced dosing requirements; reduced toxicity and side effects; reduced drug-drug interactions, and simpler, better-defined pharmacodynamics and pharmacokinetics.[2]

The importance of single-isomer drugs from a safety and efficacy perspective is reflected in the European Medicines Agency (EMA) not having approved a single new drug composed of a mixture of isomers since 2016.[2]

Three of the top-selling drugs in this century, Lipitor® (atorvastatin calcium), Plavix® (clopidogrel bisulphate) and Nexium® (esomeprazole magnesium) are examples of single-isomer drugs (Figure 3). Each of these drugs was protected via a composition of matter single isomer patent that superseded an earlier primary patent where the drug was first patented as an isomer mixture.[3]

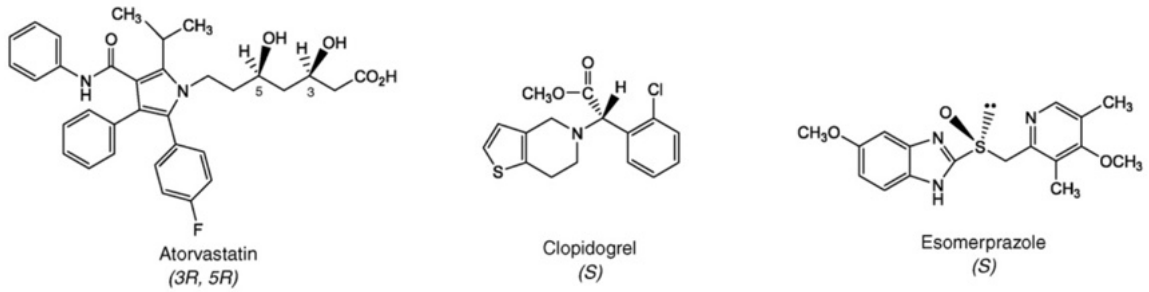


Figure 3. Chemical structures of single-isomer drugs claimed in isomer patents. Lipitor® (atorvastatin calcium), Plavix® (clopidogrel bisulphate), and Nexium® (esomeprazole magnesium). Reproduced from reference.[2]

Bisantrene

The original composition of matter patent for bisantrene (US4,258,181) was granted to American Cyanamid, the parent company of Lederle Laboratories, in 1981. This patent disclosed the discovery, chemical synthesis and anticancer activity of bisantrene, however, no photoisomers of bisantrene were disclosed by the inventors. Similarly, in the scientific and clinical literature from the 1980s, no photoisomers of bisantrene were noted by any researcher, nor was any special care taken by clinical investigators to protect infusion solutions of bisantrene from exposure to light.

The rapid photoisomerisation of bisantrene in solution (as high as 1% per minute under ordinary indoor light conditions), combined with a lack of protection of infusion solutions from light in historical trials, makes it highly likely that the bisantrene infused into patients in the 1980s consisted of variable mixtures of isomers. The exact dose of the active (E,E)-bisantrene isomer delivered would have depended on how much light the infusion solutions were exposed to before being given to a patient, with a consequential effect on efficacy and tolerability.

Importantly, all trials conducted using drug product manufactured by Race Oncology have used pure (E,E)-bisantrene, including the two Phase 2 Acute Myeloid Leukaemia (AML) trials, where the RC110 formulation was used,[4,5] and the current Phase 1 solid tumour cardioprotection/anticancer safety study of RC220 in combination with doxorubicin (ASX announcement: 1 May 2025).

Commercial significance of new composition of matter IP

The pharmaceutical industry places great value on composition of matter patent protection for externally acquired assets. Of particular importance is the remaining life of any composition of matter IP, given many new drugs have limited protection remaining at the time of market launch. It is not uncommon for new drugs to have less than 10 years of patent protection at the time of their first sale.

Pharmaceutical partners typically want a minimum of 8-10 years of patent life at the date of product launch as less than this makes it difficult to recoup the development and licensing costs and provide an attractive commercial return to their investors. Long patent life is considered highly desirable by the pharmaceutical industry – the longer the better.

The new composition of matter and associated patent applications provide several important value generators for Race Oncology (subject to patent approvals), including:

- Resetting of the patent clock with the strongest IP protection for the active (E,E)-bisantrene isomer until 2045.
- Preventing a generic version of bisantrene from being sold using the IP disclosed in the original Lederle primary bisantrene patent. This is because regulators will not approve any drug with an unknown and variable level of active API in any new or generic drug formulation.
- Minimising any dosing variability by ensuring patients only receive the active (E,E)-isomer of bisantrene.
- Strong IP protection of the RC110 formulation. This IP enables pharma licensing and/or partnership discussions to advance RC110 into a pivotal Phase 3 trial in AML without compromising the commercial value of RC220.

Next steps

Race management will be presenting a webinar on the significance of this discovery on Thursday, 18 September, 2025 at 6 pm AEST. To register for this webinar please use this link:

https://us02web.zoom.us/webinar/register/WN_3brVQ79-QNuuGy6pHaNvNg

References

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2. Ceramella, J. et al. A Look at the Importance of Chirality in Drug Activity: Some Significative Examples. Appl. Sci. 12, 10909 (2022).

3. Agranat, I. & Wainschtein, S. R. The strategy of enantiomer patents of drugs. *Drug Discov. Today* 15, 163–170 (2010).

4. Danylesko, I. *et al.* Bisantrene in combination with fludarabine and clofarabine as salvage therapy for adult patients with refractory or relapsed acute myeloid leukaemia (AML)—An open-label, phase I/II study. *Br. J. Haematol.* (2025)

5. Canaani, J. *et al.* A phase II study of bisantrene in patients with relapsed/refractory acute myeloid leukemia. *Eur. J. Haematol.* (2021) 106, 260–266.

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Q&A

Why didn't the original inventors of bisantrene, Lederle Laboratories, discover the different photoisomers of bisantrene in the 1980s?

The simple answer is we don't know. In the 1970s and 1980s, mixed isomer drugs were common and there was little concern or even interest in manufacturing pure isomer drugs. Additionally, the analytical techniques from that era were relatively crude compared to today, making it difficult to identify if multiple isomers were present in a particular drug formulation. The visible light-induced photoisomerisation seen with bisantrene is relatively rare in pharmaceutical chemistry and this may be why the Lederle chemists didn't look for isomerisation. It is possible that these (and other) factors played a role in Lederle's scientists not discovering the photoisomers of bisantrene.

Does this discovery invalidate the historical clinical data for bisantrene?

While the bisantrene used by Lederle in the 1980s was likely a mixed isomer formulation of unknown composition, it still contained the active drug (E,E)-bisantrene. The historical data remains highly relevant in terms of derisking our clinical programs.

How important is it to have new composition of matter IP over the active (E,E)-isomer of bisantrene?

Extremely important. Obtaining composition of matter patent protection over the active drug used in both the RC110 and RC220 formulations fundamentally increases the commercial value of Race Oncology in any pharmaceutical industry transaction, licensing deal or partnership discussion. It would prevent any other group developing their own formulation of bisantrene and clinically developing it in competition.

Could another pharma company sell the mixed isomer version of bisantrene?

No. Pharmaceutical regulators like the FDA and EMA will not approve a formulation of bisantrene where the level of inactive (E,Z)-bisantrene isomer is significant and variable. Attempting to sell a pure (E,E)-bisantrene formulation would infringe on our new composition of matter patent (assuming it is granted), as well as the various manufacturing, formulation, and use patents Race holds or is pursuing.

Was (E,E)-bisantrene used in the two Sheba Phase 2 AML trials?

Yes. The active drug used in the RC110 formulation supplied by Race Oncology for these trials was pure (E,E)-bisantrene.

Is (E,E)-bisantrene being used in the current RC220 Phase 1 solid tumour trial?

Yes. The active drug used in the RC220 formulation is also pure (E,E)-bisantrene.

How did you know to use only the (E,E)-bisantrene isomer in RC110 and RC220 trials if you're only filing the patent claims now?

We have known of the isomerisation of bisantrene for several years. To maximise the patent life, we chose to delay submission of the isomer and associated manufacturing and formulation patents. This approach is used widely in pharma, where the primary composition of matter patent is only filed once the molecule reaches the clinical trial stage.

What does RCDS1 stand for?

RaCe Drug Substance 1. This is an internal codename used by Race to distinguish the (E,E)-bisantrene isomer from the other isomers of bisantrene.

Is it possible to run a Phase 3 AML trial using the RC110 formulation?

Yes. Two successful Phase 2 Acute Myeloid Leukemia trials have been run using the (E,E)-bisantrene RC110 formulation. A pivotal Phase 3 trial in AML could be undertaken using the RC110 formulation. The cost of such a trial far exceeds the current resources of Race Oncology and would require external financial support, to be feasible in the short term, or out-licensing of RC110 to a pharma partner.

You mention you could take RC110 into a Phase 3 clinical trial. If you were to do that, what impact would that have on your licensing prospects for RC220?

The RC110 formulation is considered a separate drug to the RC220 formulation by regulators like the FDA, EMA and TGA. This means the two formulations could in theory be separately licensed to different pharma partners for different clinical indications. In practice, it is likely that any acquirer of Race's IP would want to own or license both formulations.

This announcement is so long – what is the short takeaway?

Race Oncology scientists have found a way of patenting the active chemical form of bisantrene despite its age and extensive clinical history. If granted, this composition of matter patent will last until 2045 and is the most valuable type of patent for new drugs, for which large pharma companies pay a premium to own.

About Race Oncology (ASX: RAC)

Race Oncology (ASX: RAC) is an ASX-listed clinical stage biopharmaceutical company with a dedicated mission to be at the heart of cancer care.

Race's lead asset, RCDS1 (E,E-bisantrene), is a small molecule anticancer agent. RCDS1 has demonstrated therapeutic activity in cancer patients with a well characterised safety profile.

Race is advancing a proprietary formulation of RCDS1 (RC220) to address the high unmet needs of patients across multiple oncology indications, with a clinical focus on combinations with anthracycline, where we aim to deliver both cardioprotection and enhanced anticancer activity in solid tumour indications. Race is also exploring the use of RC220 as a low intensity treatment for acute myeloid leukaemia and other cancers.

Race Oncology has collaborated with Astex, MD Anderson, Sheba City of Health, UNC School of Medicine, University of Wollongong and University of Newcastle, and is actively exploring partnerships, licence agreements or a commercial merger and acquisition to accelerate access to RC220 for patients with cancer across the world.

Learn more at www.raceoncology.com.

If you have any questions on this announcement or any past Race Oncology announcements, please go to the Interactive Announcements page in our Investor Hub announcements.raceoncology.com

Race encourages all investors to go paperless by registering their details with the Company's share registry, Automic Registry Services, at www.automicgroup.com.au.

Release authorised by:

Daniel Tillett, CEO
info@raceoncology.com

Media contact:

Jane Lowe +61 411 117 774
jane.lowe@irdepartment.com.au