UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the month of June 2022

Commission File Number: **001-38764**

APTORUM GROUP LIMITED

17 Hanover Square
London W1S 1BN, United Kingdom
(Address of principal executive offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F: Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

We are filing this report to disclose certain power point presentations the Company shares with potential business partners; such presentations are incorporated herein by reference.

Neither this report nor the exhibits constitute an offer to sell, or the solicitation of an offer to buy our securities, nor shall there be any sale of our securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to the registration or qualification under the securities laws of any such state or jurisdiction.

The information in this Form 6-K, including the exhibits shall not be deemed to be "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and shall not be incorporated by reference into any filing under the Securities Act of 1933, as amended, except as shall be expressly set forth by specific reference in such filing.

This Form 6-K is hereby incorporated by reference into the registration statements of the Company on Form S-8 (Registration Number 333-232591) and Form F-3 (Registration Number 333-235819) and into each prospectus outstanding under the foregoing registration statements, to the extent not superseded by documents or reports subsequently filed or furnished by the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

EXHIBIT INDEX

Exhibit No.	Description
99.1	Power Point Presentation
99.2	Power Point Presentation

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Aptorum Group Limited

Date: June 9, 2022

By: /s/ Sabrina Khan
Name: Sabrina Khan
Title: Chief Financial Officer

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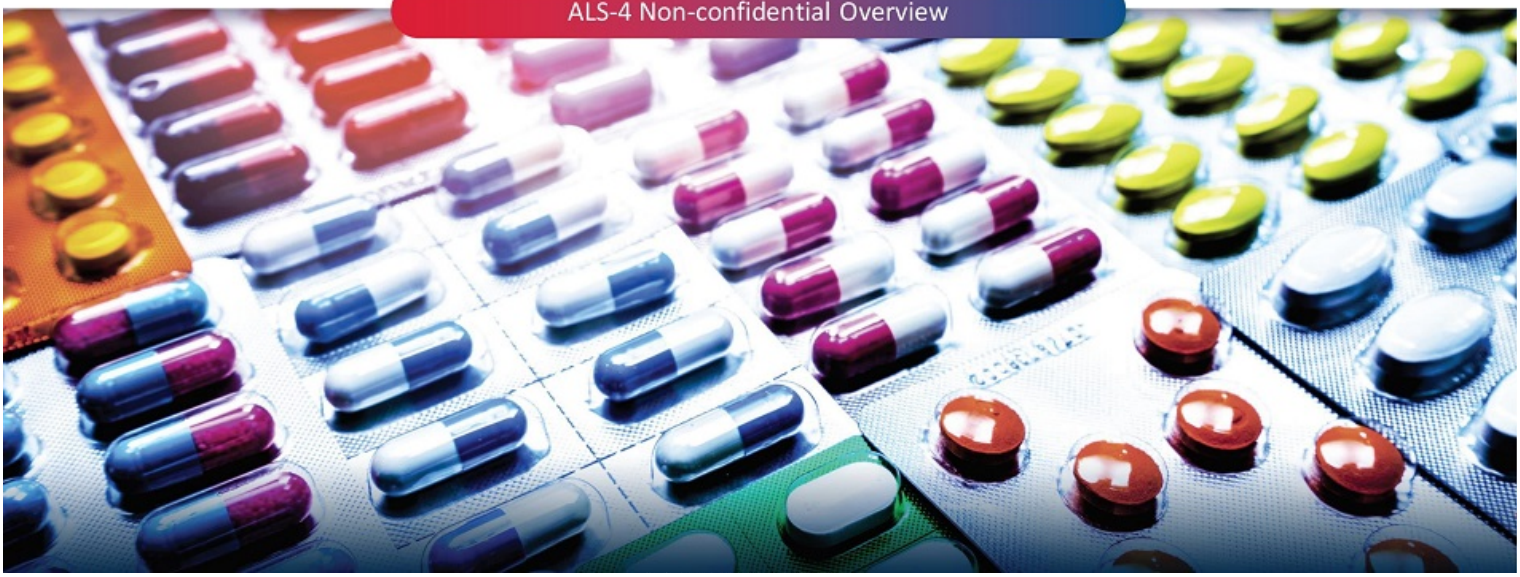
Facilitating Life Science Innovations to Serve Unmet Medical Needs

ALS-4 Non-confidential Overview



Disclaimer

This document includes statements concerning Aptorum Group Limited and its future expectations, plans and prospects that constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. For this purpose, any statements contained herein that are not statements of historical fact may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "should," "expects," "plans," "anticipates," "could," "intends," "target," "projects," "contemplates," "believes," "estimates," "predicts," "potential," or "continue," or the negative of these terms or other similar expressions. Aptorum Group has based these forward-looking statements, which include statements regarding projected timelines for application submissions, trials and commercialization and market potential of related products, largely on its current expectations and projections about future events and trends that it believes may affect its business, financial condition and results of operations. These forward-looking statements speak only as of the date of this document and are subject to a number of risks, uncertainties and assumptions including, without limitation, risks related to its announced management and organizational changes, the continued service and availability of key personnel, its ability to expand its product assortments by offering additional products for additional consumer segments, development results, the company's anticipated growth strategies, anticipated trends and challenges in its business, and its expectations regarding, and the stability of, its supply chain, and the risks more fully described in Aptorum Group's Form 20-F and other filings that Aptorum Group may make with the SEC in the future. As a result, the projections included in such forward-looking statements are subject to change and results may differ materially from those disclosed herein. Aptorum Group assumes no obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise. THIS PRESENTATION DOES NOT CONSTITUTE AN OFFER TO SELL OR SOLICITANT OFFER TO BUY NEITHER SHALL THERE BE ANY SALE OF THESE SECURITIES IN ANY STATE IN WHICH SUCH OFFER, SOLICITATION OR SALE WOULD BE UNLAWFUL PRIOR TO REGISTRATION OR QUALIFICATION UNDER THE SECURITIES LAWS OF ANY SUCH STATE.

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Antibiotic-resistant *Staphylococcus aureus* infections represent a significant unmet need

MRSA, VRSA and VISA are ranked as "high priority" development targets by the World Health Organisation[1]

- *Staphylococcus aureus* are gram-positive bacteria and the leading cause of skin and soft tissue infections, but can cause serious infections such as pneumonia, bacteraemia, and bone infections

- Vancomycin is the most frequently prescribed treatment for methicillin-resistant *Staphylococcus aureus* (MRSA); however, vancomycin has been >60 years in use and has been shown to have slow bactericidal activity, poor anti-staphylococcal activity, poor tissue penetration, high rates of infection relapse, and can cause resistance (vancomycin-intermediate (VISA) and vancomycin-resistant (VRSA))[4]

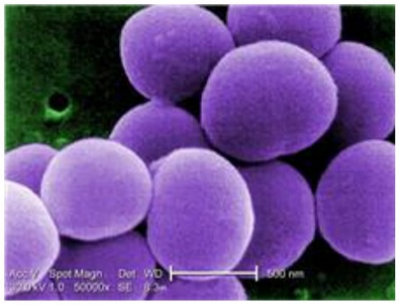

Image: CDC.gov

- MRSA (pneumonia) mortality rate is between 30% - 55.5%[2,3]

- MRSA (skin and soft tissue) recurrence rate is approximately 70%[2,3]

- New efficacious and safe therapeutics are urgently needed

1. https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed 2. "Methicillin-resistant Staphylococcus Aureus (MRSA) Drugs Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast, 2017-2025" (2018) https://www.researchandmarkets.com/reports/4853384/methicillin-resistant-staphylococcus-aureus-drugs. Transparency market research; 3. Clin Infect Dis. 2006 Jan 1;42 Suppl 1:S5-12; 4. https://pubmed.ncbi.nlm.nih.gov/25401098/

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- Developing non-antibiotics (non-bactericidal and non-bacteriostatic).
- **Targeting virulence factors** to disarm bacteria and thereby reducing pathogenicity.
- Potentially **less selective pressure** and **much less likely** for bacteria to **develop resistance**.

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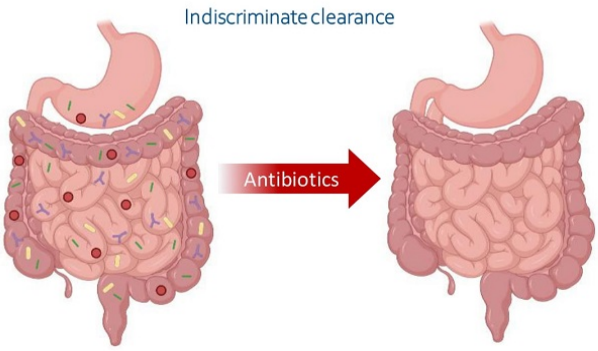
ALS program: Value proposition

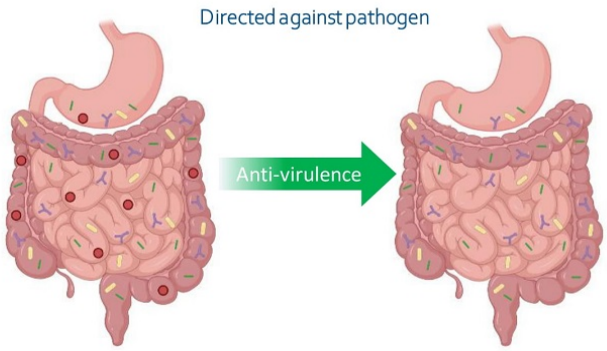
Antibiotic

- Antibiotic resistance in *S. aureus* has been discovered in most prescribed antibiotics for MRSA[1]
- Broad spectrum and indiscriminate[2]
- Commonly affect normal flora, may lead to superinfection in case of drug resistance[3]



Anti-virulence

- ✓ Not bactericidal, potentially less selective pressure and much less likely for bacteria to develop resistance[4,5]
- ✓ "Disarms" the bacteria by reducing pathogenicity[4,5,6]
- ✓ Bacterial clearing is mediated by host immunity[4,5]



1. Refer to "ALS-4: Approved Drugs for MRSA Infections" for complete set of sources; 2. P T. 2016 Feb; 41(2): 126–128; 3. J Infect Dis. 2018 Jan 30;217(4):628-636; 4. Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing; 5. MBio. 2017 Sep 5;8(5). pii: e01224-17; 6. J Exp Med. 2005 Jul 18;202(2):209-15.

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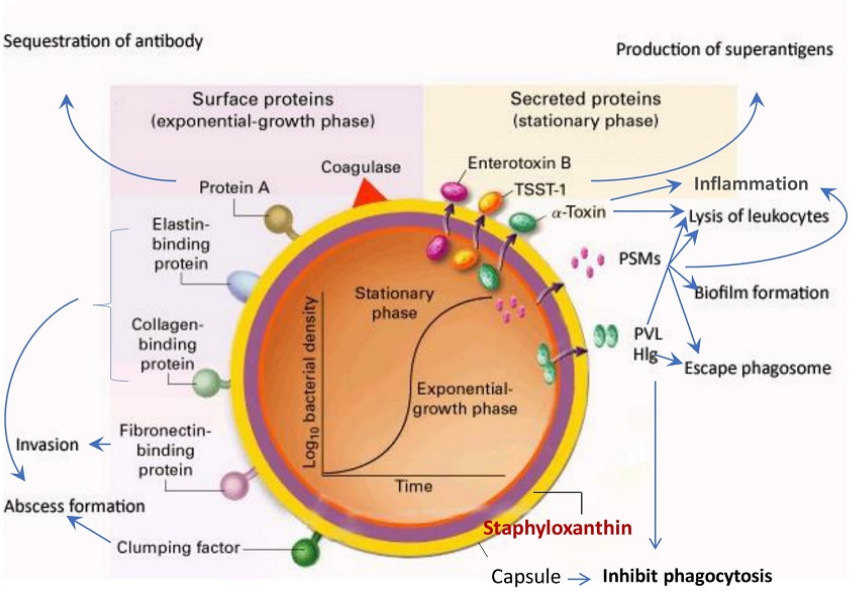

The figure is modified from Rachel J. Gordon, et al. Clin Infect Dis. (2008)

- Bacterial infections are mediated by pathogenic or opportunistic bacteria
- Successful infections depends on host immunity and the pathogen's virulence
- Virulence factors are the molecules that assist the bacteria to colonize the host at the cellular level; these factors are either secretory, membrane associated or cytosolic in nature
- Gram positive bacteria (e.g, Staphylococcus aureus) rely heavily on multiple arrays of virulence factors
- Targeting bacterial virulence is an alternative approach to antimicrobial therapy

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ALS-4, an anti-virulent, non-bactericidal drug candidate for *S. aureus* infections incl. MRSA

ALS-4 is a first-in-class, oral therapeutic that has the potential to complement vancomycin

- **Novel mechanism:** Anti-virulence, non-bactericidal approach as it targets virulence properties of S. aureus
- **Oral form**: An orally administered small molecule in line with "IV to oral antibiotic" switch policies; therefore, it has the potential for increased cost-effectiveness through out-patient treatment
- Potential as a mono- or combination therapy to overcome the shortcomings of vancomycin
- ALS-4 can potentially complement other bactericidal antibiotics as well; therefore, ALS-4 is not a direct competitor to antibiotics
- Potentially shows synergistic effects with other antibiotics

Desirable Characteristics	ALS-4	Vancomycin
Anti-virulent	✓	✗
Non-bactericidal	✓	✗ (Inhibits transpeptidation by binding to D-alanyl-D-alanine residues of the bacterial cell wall, leading to cell wall decomposition and bacterial lysis)
No observed resistance	✓	✗ (Vancomycin-resistant *S. aureus* discovered in 2002[1])
Orally bioavailable	✓	✗ (Oral only for gastrointestinal infection)
Good tissue penetration	✓	✗ (Large molecule)

Centers for Disease Control and Prevention. https://www.cdc.gov/hai/settings/lab/vrsa_lab_search_containment.html

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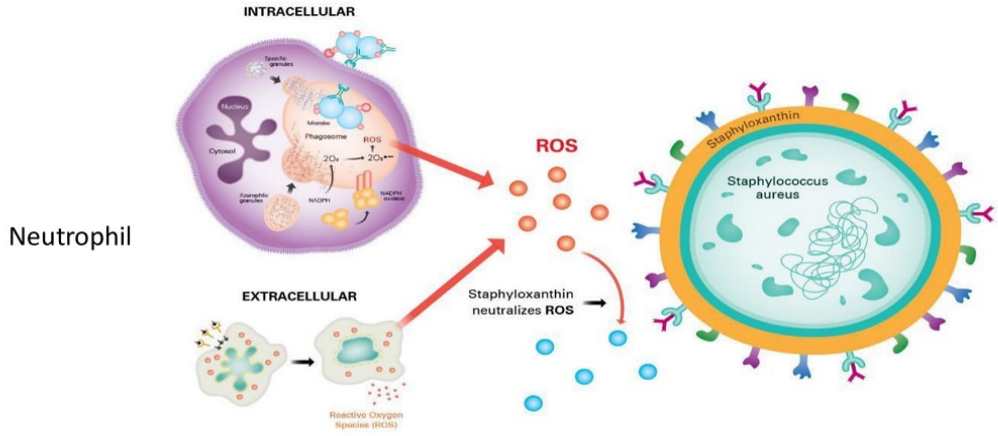
The role of staphyloxanthin in *Staphylococcus aureus*



- Neutrophils kill bacteria including Staphylococcus aureus intracellularly or extracellularly via Reactive Oxygen Species: ROS-oxygen radicals released by neutrophils trigger the subsequent bacterial damage processes.[1]
- To counteract, staphyloxanthin, a carotenoid pigment, protects the bacteria by serving as an anti-oxidant to neutralize the ROS secreted by neutrophils. [1]

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5975594/

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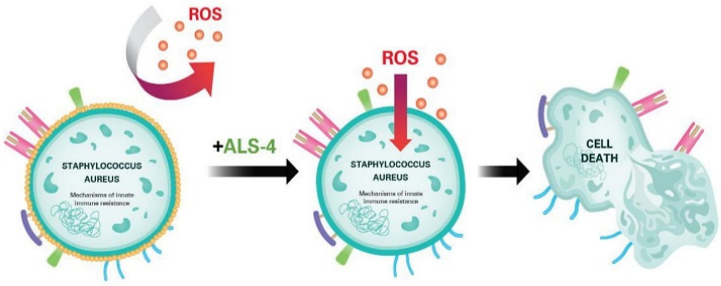
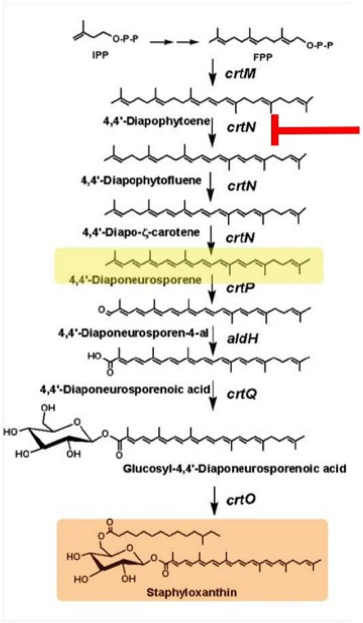
Mechanism of action: Targeting staphyloxanthin synthesis of *Staphylococcus aureus*[1]

- ALS-4 inhibits a key enzyme in the biosynthesis of staphyloxanthin.[1] In the absence of staphyloxanthin, the bacteria become susceptible to damage by ROS, triggering the usual series of mechanisms by neutrophils that ultimately leads to bacterial cell death.
- ALS-4 also shown that in the absence of staphyloxanthin, bactericidal activity is enhanced in the presence of antibiotics such as Vancomycin[2].





ALS-4 inhibits a key enzyme in the biosynthesis of staphyloxanthin[1]

1. Figure adapted from MBio. 2017 Sep 5;8(5). pii: e01224-17.
2. The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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Inhibition of staphyloxanthin synthesis by ALS-4

ALS-4

- Inhibits S. aureus pigment production (staphyloxanthin) with an IC_{50} = 20nM.
- This is visibly confirmed by the decolorization of the bacteria as ALS-4 is administered with increasing concentrations from 3.1 to 200nM.

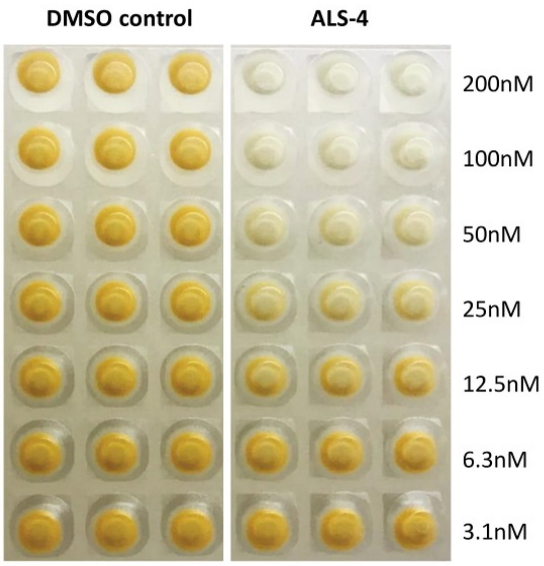

Figure adapted from MBio. 2017 Sep 5;8(5). pii: e01224-17.

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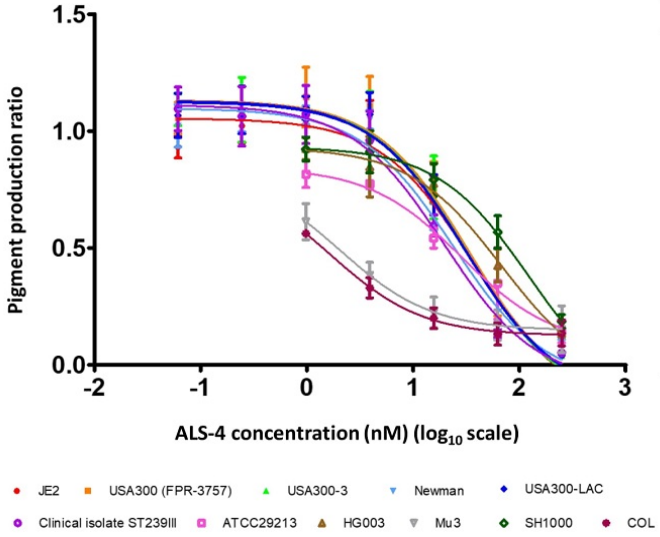
ALS-4 effectively inhibits staphyloxanthin formation across 11 strains of *S. aureus*

ALS-4 inhibits the production of staphyloxanthin in 11 common strains of *S. aureus in vitro*



Strain	Type	IC_{50} (nM)
SH1000	MSSA	70.5 ± 6
HG003	MSSA	54.4 ± 4
USA300-JE2	MSSA	37.7 ± 4
USA300 (FPR-3757)	CA-MRSA	30.8 ± 5
USA300-3	HA-MRSA	42.8 ± 6
Newman	MSSA	23.7 ± 1
USA300-LAC	MRSA	43.6 ± 5
ATCC29213	MSSA	30.0 ± 5
Clinical isolate ST239III	HA-MRSA	16.3 ± 8
Mu3	VISA	2.6 ± 1
COL	HA-MRSA	0.9 ± 1

ALS-4 can inhibit staphyloxanthin production in major MRSA strains and also VISA and MSSA strains. ALS-4 can address and compensate suffering from vancomycin resistant strains of staphylococcus aureus due to the targeting of different mechanisms[1].

1 The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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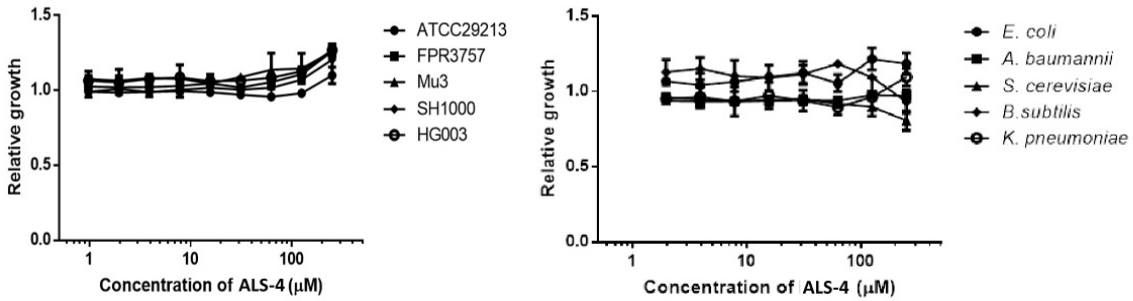
ALS-4 does not directly inhibit bacterial growth *in vitro*

- Lack of direct selection pressure significantly decreases the risk of emergence of drug resistance.
- In the absence of neutrophils, ALS-4 does not inhibit growth in 5 strains of *S. aureus* (left) and 5 different species of bacteria (right). However, ALS-4 reduces the virulence factors of *S. aureus,* significantly reducing risks of mortality and morbidity.



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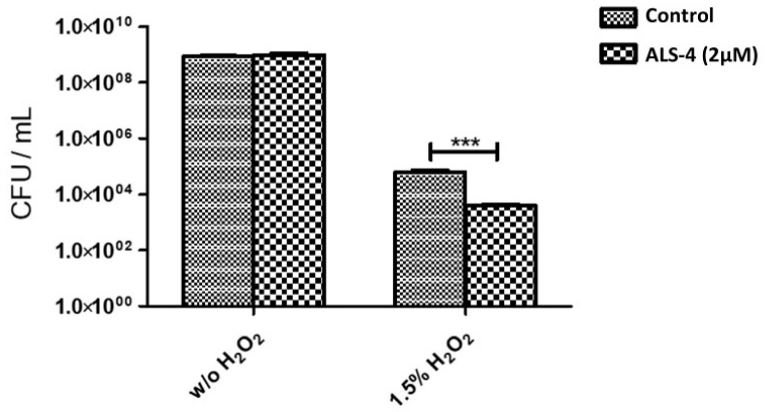
ALS-4 increases sensitivity of *S. aureus* to oxidative damage

- ALS-4 reduces bacteria number by an additional 10-fold in the presence of hydrogen peroxide (mimicking ROS production by neutrophils), as demonstrated in the below graph (p<0.001).



Statistical significance (p < 0.05) was assessed with unpaired student t-test. * *p* < 0.05, ** *P* < 0.01, *** *P* < 0.001, **** *P* < 0.0001.

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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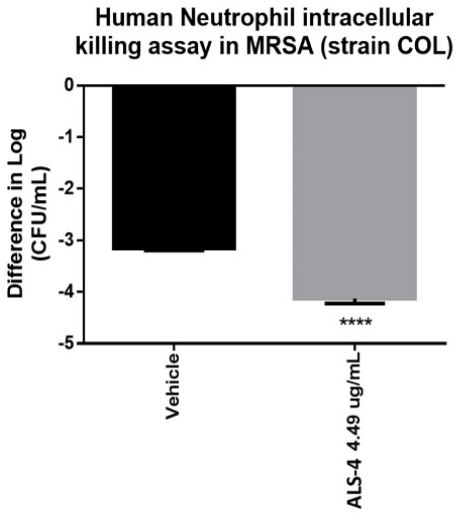

Bacterial density following treatment with human neutrophils in ALS-4 or vehicle treated MRSA (strain COL).

Data is presented as mean ± SEM. Statistical significance ($p < 0.05$) was assessed with unpaired student t-test. * $p < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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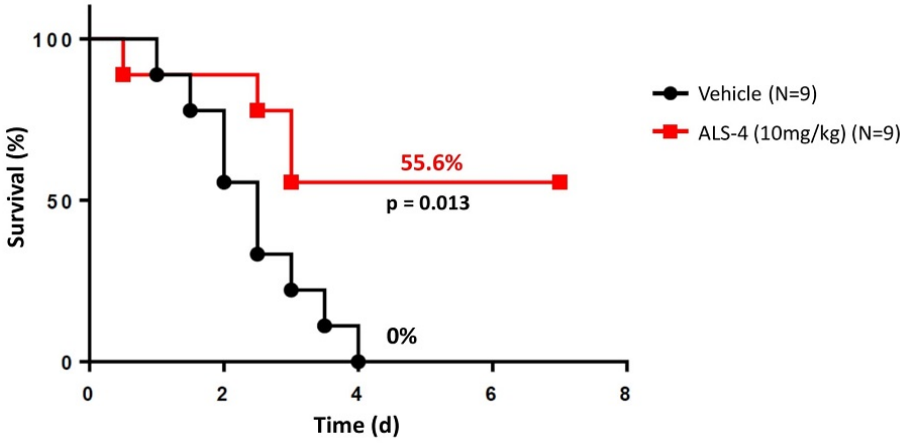
ALS-4 rescues rats infected with a lethal dose of MRSA in a bacteremia model

Oral administration of ALS-4 in a lethal MRSA (USA300) survival *in vivo* model.



- A lethal dose (10^9 CFU) of MRSA was introduced through the tail vein
- ALS-4 was administered **orally** 30 minutes after infection for twice a day thereafter

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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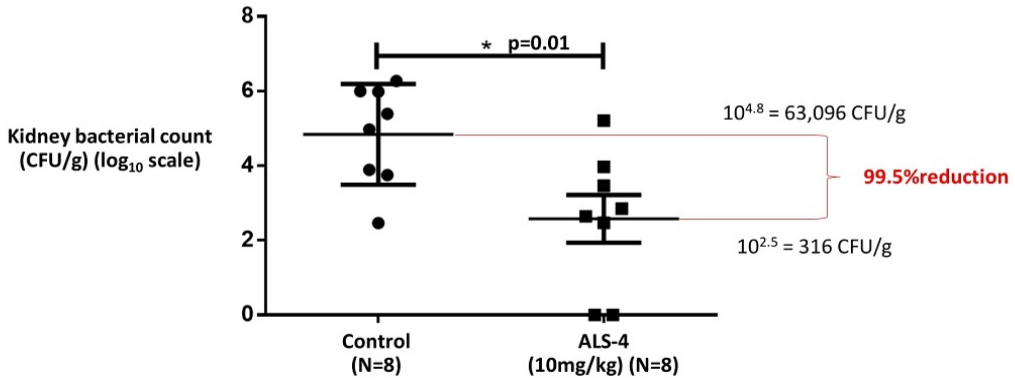
ALS-4 greatly reduces organ bacterial count in a bacteremia animal model

Oral administration of ALS-4 in a non-lethal bactaremia *in vivo* model.

- Rats were challenged with a non-lethal dose (10^7 CFU) of MRSA through the tail vein
- In order to simulate a more realistic clinical scenario, treatment was introduced 14-days after infection, where ALS-4 was administered orally twice a day at 10mg/kg per animal for 7 days
- Please see appendix for results in kidney, lung, liver, spleen in comparison to vancomycin



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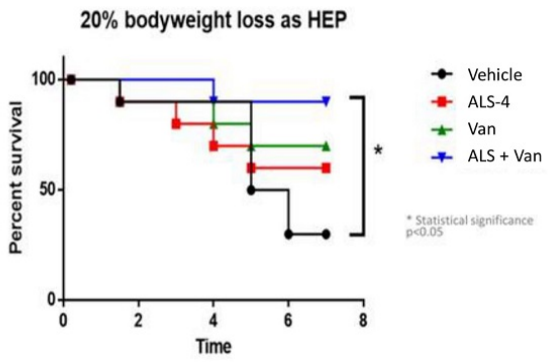
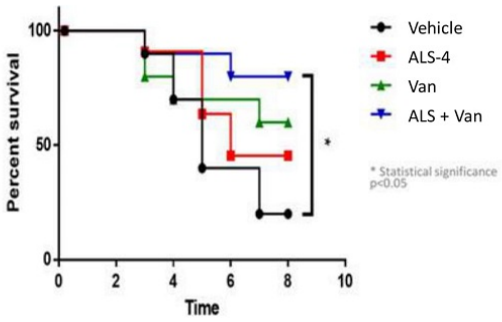
Immediate Treatment Post Lethal Dose



N = 10, CFU per mouse is 6 x 10^7. All of the treatments were administrated through i.p. 15 hours after infection;

(a) Vehicle
(b) ALS-4: 4.5mg/kg
(c) Vancomycin: 4.5mg/kg
(d) Combo: 4.5mg/kg LM32+4.5mg/kg Vancomycin

Delayed Treatment



N = 10, CFU per mouse is 6x10^7
ALS-4 at 6.75mg/kg/dose and treatment started 2 hrs post infection twice daily Vancomycin, 4.5 mg/kg/dose and treatment started 18 hrs after infection twice daily

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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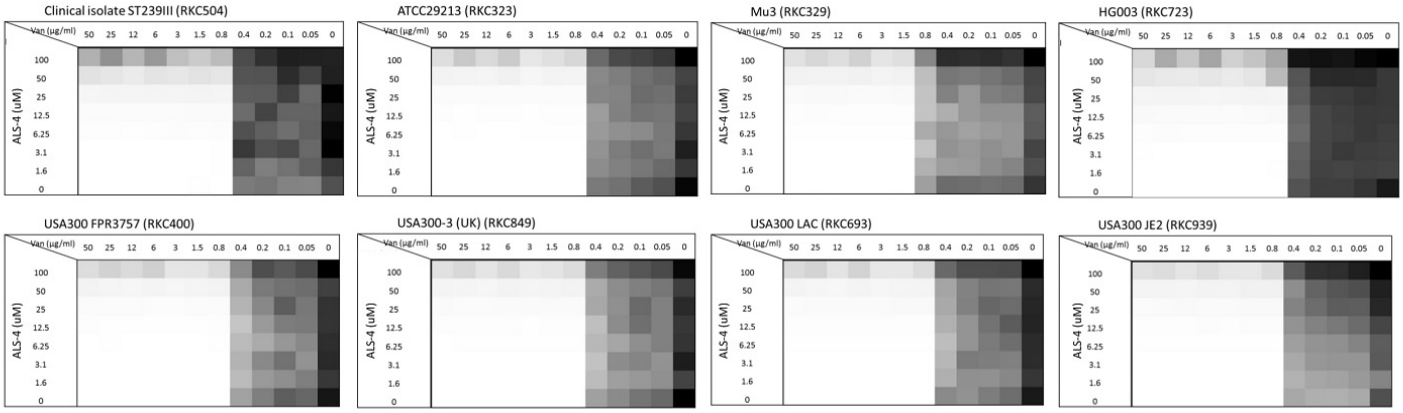
ALS-4 does not interfere with the action of vancomycin *in-vitro*

ALS-4 does not affect the minimum inhibitory concentration (MIC) of vancomycin in 8 strains of *S. aureus.*



- No effect on the MIC of vancomycin was observed *in vitro* when the concentration of ALS-4 was below 25µM
- ALS-4 is targeted to be efficacious at between 20-30nM, well within the above range.

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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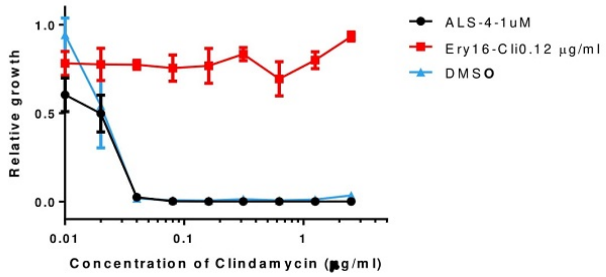
ALS-4 does not trigger antibiotic resistance in MRSA

Pre-treatment

Tubes	Day 1-4	Day 6-10
1	DMSO	DMSO
2	Ery 16 + CLI 0.12 µg/ml	Ery 16
3	ALS-4 1µM	ALS-4 1µM

(Clindamycin withdrawn between day 5-10)

Clindamycin resistance test after pre-treatment (BHI medium with 5 x 10^4/well bacterial inoculum)



- Clindamycin resistance (MIC from 0.12 µg/ml to >5 µg/ml) appeared rapidly after a 10-day intermittent treatment
- The use of Ery was to ensure no contamination of environmental bacteria as USA 300 (LAC) is resistance Ery
- Controls without the addition of antibiotics showed no resistance to clindamycin
- For the full protocol, please see appendix

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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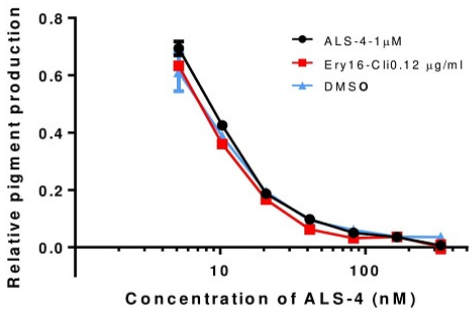
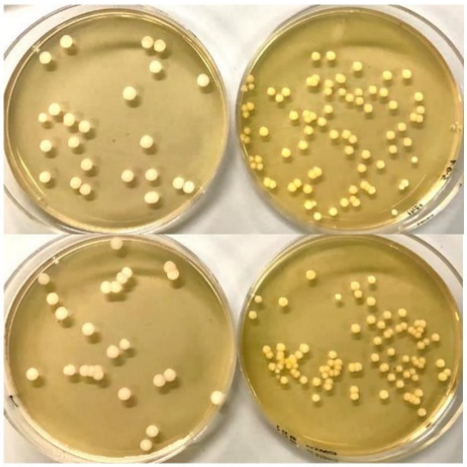
ALS-4 does not trigger its own resistance

ALS-4 efficacy test
(Bacterial inoculum: 4 x 10^7/ml)



BHI agar plates

	100nM ALS-4 (all colonies turned white)	**No ALS-4** (all colonies remained yellow)
Recovered bacteria after 11-day resistance-raising with 1µM ALS-4ca		
Recovered bacteria after 11-day resistance-raising with DMSO as control		



No bacterial resistance to ALS-4 detected after continuous incubation of the bacteria in the presence of 1µM ALS-4 for 11 days.

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

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ALS-4 is an attractive candidate for formulation

- Only 1 physical form identified from polymorph screening
- Physically and chemically stable
- Not hygroscopic

API (active pharmaceutical ingredient) manufacturing

- GLP toxicology batch of API has been completed
- GMP manufacturing of API has been completed
- GMP manufacturing of drug product has been completed for Phase 1

ALS-4 has low solubility in water

- Developed an enabling formulation to improve bioavailability
- An oral liquid formulation was used in Phase 1 clinical trial

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A P1 dose-escalation study in healthy volunteers is currently ongoing with positive interim results

Phase 1 trial in Canada (Completed)

A randomized, double-blind, placebo-controlled, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of single (SAD) and multiple ascending doses (MAD) of ALS-4 administered orally to healthy male and female adult volunteers

Aptorum Group has announced completion of the trial

- No subjects from both SAD and MAD cohorts dropped out of the studies and no Serious Adverse Events were observed
- In addition, no clinically relevant changes in respect of vital signs, electrocardiogram, clinical laboratory test results and physical examinations were observed compared to baselines

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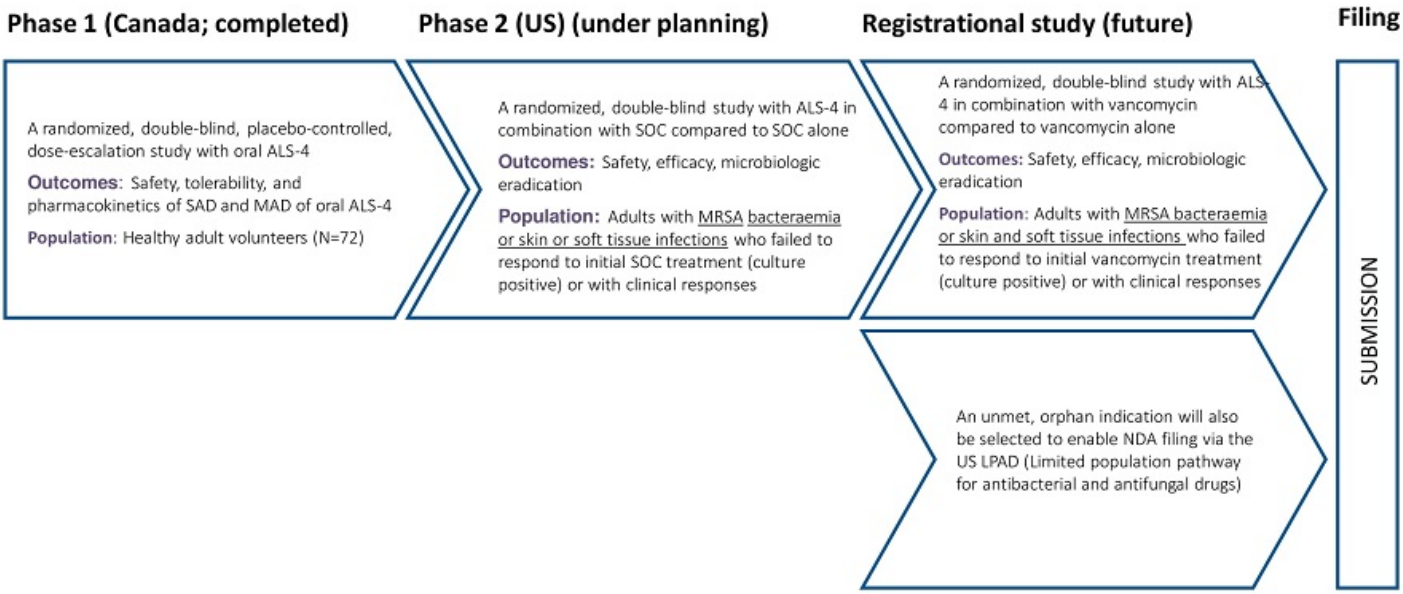
ALS-4: Targeted Clinical development



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- The global methicillin-resistant *Staphylococcus aureus* drugs market was valued at approximately US$ 2.9 Bn in 2016 and projected to each **over US$ 3.9** Bn by 2025[1]

ALS-4 market opportunities

Key indications	US LPAD opportunities	'Blue Sky' opportunities
ALS-4 in combination with SOC for MRSA (bacteraemia, pneumonia, skin & soft tissue, bone & joint, endocarditis)	A small subset of the key indications, for example, kidney failure patients suffering from MRSA bacteraemia, chronic MRSA bacteraemia, etc.	ALS-4 monotherapy as an outpatient prophylactic treatment in high risk population (e.g. aged patients undergoing surgery)

1. "Methicillin-resistant Staphylococcus Aureus (MRSA) Drugs Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast, 2017-2025" (2018).

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ALS-4: IP status

- The patent and patent applications cover the composition of small molecule compound and the method of treating microbial infection using same mechanism

ALS-4						
Patent Family	Compound / Composition	Method of Treatment	Formulation / CMC	Dosage	Physical Form	Other (e.g. Combination treatment or special route of administration)
Status	**Granted***	**Granted***	**Planned for filing**	**Not yet filed**	**Not yet filed**	**Not yet filed**
Expiration date	N/A	N/A	N/A	N/A	N/A	N/A
Region and term	*Patents have been granted in the U.S. (US Pat. No. 11,040,949 and US Pat. No. 11,052,078 titled "Compounds Affecting Pigment Production and Methods for Treatment of Bacterial Diseases"). National applications based on PCT application (PCT App. No. PCT/IB2018/055459) have been filed in major jurisdictions and regions including EP, China, Australia, Brazil, Canada, Chile, Eurasia, Israel, Japan, Malaysia, New Zealand, Singapore, South Korea and Hong Kong (all pending). ** The U.S. patents will expire in 2038, while any national patents based on the PCT application, if granted, will have a 20-year patent term from 2018.					

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APPENDIX

Approved drugs for MRSA Infections

The only 2 FDA approved antibiotics for MRSA bacteraemia

Frequently prescribed antibiotics for MRSA infections[1]

Product (Company)	Antibiotic Class	Indication(s)	RoA	Dose	Cost of Treatment (duration)	Notes
Vancomycin (Generic)	Glycopeptide	Severe infections caused by MRSA	IV / oral*	2g/day	USD 101-144 (7-10 days)	• **Currently, the most frequently prescribed** antibiotic for MRSA suspected infections[1,2] • In clinical use for >60 years[3], **vancomycin-resistant *S. aureus* (VRSA) was first discovered in 2002**[4]
Daptomycin (Merck)	Lipopeptide	ABSSSI, *S. aureus* bacteraemia	IV	4-6mg/kg/day	USD 6,736-23,710[5] (14-42 days)	• In clinical use since 2003[6] • **Daptomycin resistance described in S. aureus as early as 2006**[7]
Linezolid (Pfizer)	Oxazolidinone	ABSSSI, CABP, HABP, uSSSI	IV / oral	0.8-1.2g/day	IV: USD 1,920-5,376 Oral: USD 2,978-11,429 (10-14 days)	• In clinical use since 2003[8]. Entirely synthetic, not expected to develop clinical resistance[9], however • **Linezolid resistance encountered clinically since 2010**[9]
Ceftaroline fosamil (Actavis)	Cephalosporin	ABSSSI, CABP	IV	1.2g/day	USD 1,831-5,127 (5-14 days)	• In clinical use since 2010[10] • **Ceftaroline resistance encountered clinically since 2016**[11]
Tigecycline (Pfizer)	Glycycycline	ABSSSI, CABP, CIAI	IV	0.1-0.2mg/day	USD 1,888-4,977 (5-14 days)	• In clinical use since 2005[12] • **Tigecycline resistance encountered clinically in developing countries since 2017**[13,14]
Televancin (Theravance Biopharma)	Lipoglycopeptide	ABSSSI, HABP, VABP	IV	10mg/kg/day	USD 3,002-10,568 (7-21 days)	• In clinical use since 2009[15] • **Vancomycin resistance leads to a 4-8x increase in telavancin MIC** (minimum inhibitory concentration)[16]

ABSSSI: acute bacterial skin and skin structure infection; CABP: community-acquired bacterial pneumonia; HABP: hospital-acquired bacterial pneumonia; CIAI: complicated intra-abdominal infection; VABP: ventilator-associated bacterial pneumonia; * Only for intestinal infections; 1. Reproduced from" Companies Take Aim at MRSA Infections" P T. 2016 Feb; 41(2): 126–128; 2. Clin Infect Dis. 2011 Feb 1;52(3):e18-55; 3. Clin Infect Dis. 2006 Jan 1;42 Suppl 1:S5-12; 4. Centers for Disease Control and Prevention. https://www.cdc.gov/hai/settings/lab/vrsa_lab_search_containment.html; 5. Cost of treatment of Daptomycin for S. aureus bacteremia at a dosage of 6mg/kg; 6. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-572_Cubicin.cfm; 7. Int J Antimicrob Agents. 2006 Oct;28(4):280-7; 8. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-130s003_21131s003_21132s003_ZyvoxTOC.cfm; 9. Pharmaceuticals (Basel). 2010 Jul; 3(7): 1988–2006; 10. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200327orig1s000toc.cfm; 11. J Antimicrob Chemother. 2016 Jun; 71(6): 1736–1738; 12. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-821_Tygacil.cfm; 13. New Microbes New Infect. 2017 Sep; 19: 8–12; 14. Journal of Microbiology and Infectious Diseases 2017; 7 (4):173-177; 15.FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022110s000TOC.cfm; 16. Clin Infect Dis. 2015 Sep 15;61 Suppl 2:S58-68.

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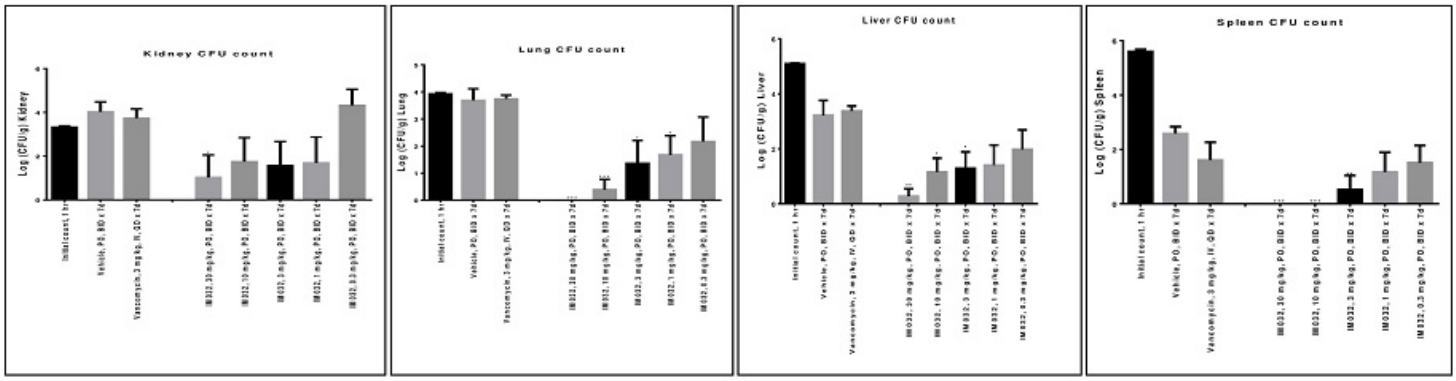
ALS-4: Oral administration in a MRSA non-lethal bacteraemia mouse model

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

- Dose-dependent efficacy of ALS-4 (compound IM032) shows a statistically significant reduction in bacteria count across major organs relative to vancomycin as a control.



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Protocol

1. Inoculum preparation: USA300-3 (LAC) was cultured overnight in BHI broth at 37˚C, 250 rpm.
2. Subculture preparation: 60 µl overnight culture was added to 6 ml BHI broth with different drugs.

Tubes	Day 1-4	Day 6-10
1	DMSO	DMSO
2	Ery 16 + CLI 0.12 µg/ml	Ery 16
3	ALS-4 1µM	ALS-4 1µM

3. Clindamycin (CLI): 0.12 µg/ml; Erythromycin (Ery): 16 µg/ml; ALS-4: 1 µM. The use of Ery was to ensure no contamination of environmental bacteria as USA 300 (LAC) is resistance Ery.
4. Culturing: during culturing, medium was changed everyday by centrifugation of the bacteria and replacing the supernatant with new medium plus DMSO or antibiotics or compounds as specified.
5. Bacteria collection: on day 11, 1 ml bacteria was centrifuged and resuspended in PBS with 10% DMSO for further testing.
6. MIC testing: in BHI medium in 96-well plate and cultured for 16h
7. Pigment production: in 96 deep-well plate and cultured for 36 h

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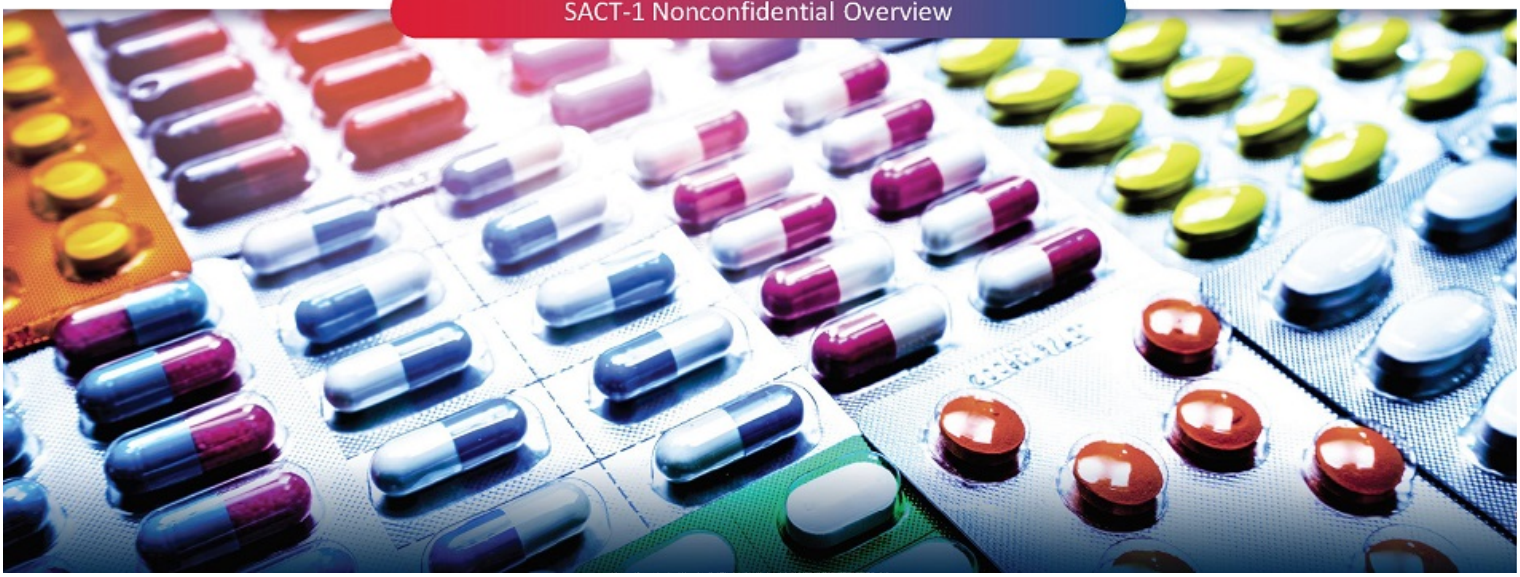
Facilitating Life Science Innovations to Serve Unmet Medical Needs

SACT-1 Nonconfidential Overview



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Executive summary

- SACT-1 is a repurposed oral suspension in development as an adjunctive therapy to standard of care in relapsed or refractory high-risk neuroblastoma in pediatric patients.
- SACT-1 targets the MEK5-ERK5 pathway and demonstrated to suppress MYCN expression, a poor prognostic factor of therapeutic outcome and resistance in neuroblastoma.
- SACT-1 has demonstrated remarkable potential in enhancing tumor cell death through different pathways.
- Preclinically, in combination with standard chemotherapy, SACT-1 provided enhanced efficacy in a xenograft mouse model of neuroblastoma. We propose the novel application of SACT-1 as a new treatment option for extending survival in high-risk neuroblastoma.

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- Our completed Phase 1 trial showed the safe use of SACT-1. The distinctive PK between SACT-1 and Edurant® further strengthen the advantage of our product.
- Aptorum is initiating an "End of Phase 1 (EOP1) Meeting" with the US FDA to seek approval to conduct a Phase 1b/2a trial.
- Received FDA orphan designation for the treatment of neuroblastoma in Jan 2022.
- Received in 2021 the first granted patent in treatment of various cancers including but not limited to neuroblastoma.

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MEK5 and ERK5 as potential therapeutic targets for cancers in recent years

Translational Oncology

Diverse and converging roles of ERK1/2 and ERK5 pathways on mesenchymal to epithelial transition in breast cancer

cancers

MDPI

Review

Clinical Significance and Regulation of ERK5 Expression and Function in Cancer

Matilde Monti [1,2], Jacopo Celli [2,3], Francesco Missale [1,2], Francesca Cersosimo [2], Mariapia Russo [2], Elisa Belloni [4], Anna Di Matteo [4], Silvia Lonardi [1], William Vermi [1,2], Claudia Ghigna [4,*] and Emanuele Giurisato [2,5,*]

Clinical, genetic and pharmacological data support targeting the MEK5/ERK5 module in lung cancer

Adrián Sánchez-Fdez, María Florencia Re-Louhau, Pablo Rodríguez-Núñez, Dolores Ludeña, Sofía Matilla-Almazán, Atanasio Pandiella & Azucena Esparís-Ogando

npj Precision Oncology 5, Article number: 78 (2021) | Cite this article

ORIGINAL ARTICLE | Open Access

ERK5 signalling pathway is a novel target of sorafenib: Implication in EGF biology

Marta Ortega-Muelas, Olga Roche, Diego M. Fernández-Aroca, José A. Encinar, David Albandea-Rodríguez ... See all authors

First published: 16 October 2021 | https://doi.org/10.1111/jcmm.16990

Oncoscience. 2021; 8: 64–71.
Published online 2021 May 18. doi: 10.18632/oncoscience.535

PMCID: PMC8131078
PMID: 34026925

Constitutive activation of MEK5 promotes a mesenchymal and migratory cell phenotype in triple negative breast cancer

Margarite D. Matossian, [1,*] Van T. Hoang, [1,*] Hope E. Burks, [1,*] Jacqueline La, [1,*] Steven Elliott, [1] Courtney Brock, [1] Douglas B. Rusch, [2] Aaron Buechlein, [3] Kenneth P. Nephew, [3] Akshita Bhatt, [4] Jane E. Cavanaugh, [4] Patrick T. Flaherty, [5] Bridgette M. Collins-Burow, [1,6] and Matthew E. Burow [1]

Cancer Letters

Inhibition of MEK5/ERK5 signaling overcomes acquired resistance to the third generation EGFR inhibitor, osimertinib, via enhancing Bim-dependent apoptosis

So far no approved products are available

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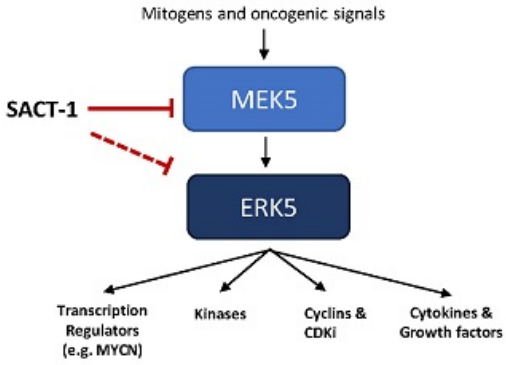
- **MEK5-ERK5 pathway is reported to regulate MYCN oncogene expression** (Kang et al., 2006; Umapathy et al., 2014; van Hoang et al., 2017) which is known to contribute to the poor prognosis of patients with neuroblastoma
- Aptorum discovered **SACT-1 has a K_D of 150 nM against MEK5**, well below the C_{SS} in humans (290 nM to 1.5 µM at 25 mg to 150 mg QD), we proposed its use in modulation of the MEK5-ERK5 pathway
- To the best of our knowledge, SACT-1 is the **only potential drug candidate already in the market to downregulate MYCN expression through modulation of MEK5-ERK5 pathway**, thus the reproposed drug programme for relapsed/refractory neuroblastoma.



Roles in cancer

- Tumour cell proliferation and survival
- EMT and metastasis
- CSC-like traits
- Therapy resistance
- Immunosuppression
- Angiogenesis

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Targeted product profile

Preclinical Toxicology	Not relevant as this is a repurposed drug
PK/PD Model	To be determined in Phase 1b/2a trial
CM&C	Oral suspension with low complexity for production
Dose/dose schedule	RP2D will be determined in Phase 1b
Half-life	To be determined in Phase 1b/2a Trial
Adverse Event Profile	None of the subjects were discontinued from the study because of an adverse event. None of the adverse events experienced by subjects was judged as serious
Other AE Profile	None
Efficacy Profile	To be determined in Phase 1b/2a Trial
Health Outcome	Improve progression free, and overall, survival in high-risk neuroblastoma patients
Pharmacology	SACT-1 is proposed to modulate MEK5-ERK5 pathway subsequently reducing the poor prognosis factor MYCN

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Neuroblastoma - market overview

MARKET SIZE

PREVALENCE	• ~700 cases of high-risk neuroblastoma patients each year in the US[3] and we estimated EU has 1.5x this number of cases, c. 1050 high risk neuroblastoma patients per year • Accounts for ~15% of all cancer-related deaths in the pediatric population[4]
ORPHAN DRUG DESIGNATION[5]	• SACT-1 has gained FDA Orphan Drug Designation for the treatment of neuroblastoma in 2022. • Designated orphan drugs receive 7 years of market exclusivity in US and 10 years of marketing exclusivity in EU • Patents on new indication and reformulation of SACT-1, if granted, will provide up to 20 years of patent exclusivity from the application date in parallel to the market exclusivity

1. Pediatr Rev. 2018 Feb;39(2):57-67; 2. "Pediatric Neuroblastoma Treatment Market size 2022: Sales, Price, Revenue, Gross Margin, News Product Launches, Upcoming Trend Analysis and Forecast 2027" (2022). Market Watch. 3. Curr Oncol Rep. 2009 Nov;11(6):431-8 4. Paediatr Drugs. 2011 Aug 1;13(4):245-55 5. https://www.fda.gov/about-fda/office-special-medical-programs/office-orphan-products-development

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Standard of care for high-risk neuroblastoma

- Surgery
- Chemotherapy
- Radiotherapy
- Immunotherapy (anti-GD2 monoclonal antibodies)
  - **Dinutuximab beta (Qarziba)**
  - **Dinutuximab (Unituxin)**
  - **Naxitamab (Danyelza)**

SACT-1 uses a unique mechanism and works in combination with other therapies rather than competing or replacing the current therapy

SACT-1 works in combination with standard of care chemotherapy and / or new therapies for neuroblastoma. It downregulates MYCN expression through the MEK5-ERK5 pathway and is proposed to enhance anti-tumor effect and reduce occurrence of drug resistance.

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In vitro

- SACT-1 demonstrated inhibition of all tested neuroblastoma cell lines (IMR-32, SK-N-BE(2), SK-N-SH, SH-SY5Y)
- In combination with standard chemotherapy for neuroblastoma, SACT-1 in general provides additive to synergistic efficacy[1]

In vivo

- Aptorum conducted mouse xenograft studies with a primary objective of assessing the efficacy of SACT-1 alone, and with other chemotherapeutic agents:

Combination Treatment		Enhanced tumour shrinkage compared to monotherapy
SACT-1 + Cisplatin	SOC First-line Treatment	**Yes**
SACT-1 + Carboplatin	SOC First-line Treatment	**Yes**
SACT-1 + Vincristine	SOC First-line Treatment	**Yes**
SACT-1 + Irinotecan	SOC for relapse	**Yes**

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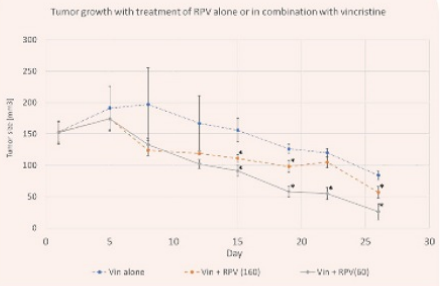
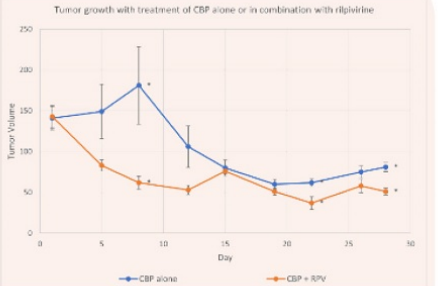
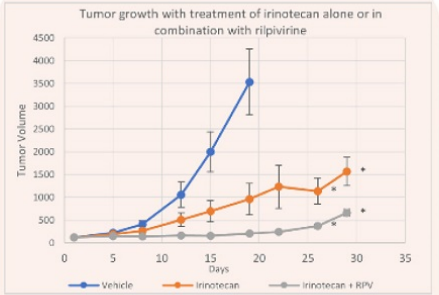


SACT-1 (RPV) dosed at 60 and 160 mg/kg (PO; daily x 21) potentiates the antitumor effects of vincristine (IP; QWK x3) in the neuroblastoma xenograft model



The addition of SACT-1 (RPV) (160 mg/kg; PO; daily x 21) demonstrated greater tumor volume reduction compared to carboplatin (80mg/ kg; IP; QWK x3) alone in the neuroblastoma xenograft model



The addition of SACT-1 (RPV) (80 mg/kg; PO; daily x 21) demonstrated greater tumor volume reduction compared to irinotecan (80mg/ kg; IP; QWK x3) alone in the neuroblastoma xenograft model

IP = Intraperitoneal; PO = oral; QWK = weekly; RPV = SACT-1; Vin = vincristine; CBP = carboplatin; * P < 0.05

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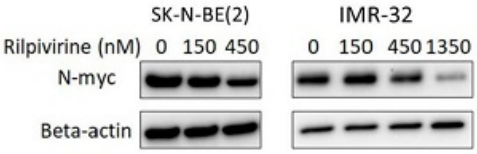
- MYCN is involved in regulating various biological activities, such as apoptosis, proliferation, and angiogenesis in neuroblastoma (Huang and Weiss, 2013) and contributing to drug response
- SACT-1 at 150 to 1350 nM reduced MYCN protein levels in MYCN overexpressed neuroblastoma cell lines SK-N-BE(2) and IMR-32

Decrease of MYCN Expression



The effects of SACT-1 on MYCN expression.
Representative western blot analysis images of MYCN expression in response to SACT-1 at 150 to 1350 nM for 2 and 24 hours in SK-N-BE(2) and IMR-32 cells, respectively.

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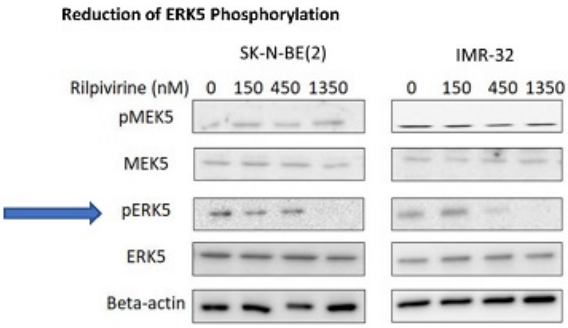
- SACT-1 was found to have a binding constant (K_D) of 150 nM against MEK5 in a previous study by employing KdELECT Kinase Assay Panel
- Expectedly, ERK5 phosphorylation in IMR-32 and SK-N-BE(2) cells was decreased after SACT-1 treatment for 2 hours at 150 nM to 1350 nM



The effects of SACT-1 on ERK5 phosphorylation. Representative western blot analysis images of phospho-MEK5, MEK5, phospho-ERK5, and ERK5 expressions in response to SACT-1 at 150 to 1350 nM for 2 hours in MYCN overexpressed SK-N-BE(2) and IMR-32 cells.

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Relative Bioavailability

- Comparative bioavailability analysis between administration of SACT-1 under fasted condition vs. fed condition and between SACT-1 vs. Edurant® tablets (both under fed conditions).
- SACT-1 fed dosing resulted in 90% increased AUC and 100% increased C_{max} with respect to SACT-1 fasted
- Results of SACT-1 vs Edurant® showed ~40% higher exposure for AUC and 20% higher C_{max} for SACT-1

Safety

- The study treatments in Phase 1 (administration of SACT-1 under fasted and fed condition) were **well tolerated:**
  - All reported **adverse events were considered grade 1 or "mild"** and had an outcome of "resolved"
  - **No subjects were discontinued** from study participation **because of adverse events**
  - **No serious adverse events** were reported during the study.
- The effect of study drug on the QTc interval is mild and remains within clinically acceptable limits

PK of SACT-1 administered under fed and fasting condition; Least-squares means for test to reference and associated variability

PK parameter	Fed condition (ref; n=14)	Fasting condition (n=14)
$AUC_{0\text{-}tlast}$ (ISCV)	-	189.87% (15.4%)
$AUC_{0\text{-}\infty}$ (ISCV)	-	189.43% (17.5%)
C_{max} (ISCV)	-	205.25% (25.3%)

PK of SACT-1 vs Edurant® tablets administered under fed condition; Least-squares means for test to reference and associated variability

PK parameter	SACT-1 (ref; n=14)	Edurant® tablets (n=14)
$AUC_{0\text{-}tlast}$ (ISCV)	-	139.01% (20.5%)
$AUC_{0\text{-}\infty}$ (ISCV)	-	137.28% (21.8%)
C_{max} (ISCV)	-	119.52% (29.1%)

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- Phase 1: Open-label, Randomized, 3 period, 3- sequence, Single-dose Crossover Bioavailability and Food Effect Study of SACT-1 and Edurant® Tablets in Healthy Adult Volunteers (NCT05358756)

- Phase 1b/ 2a: A Multiple Ascending Dose Trial to Determine the Safety, Pharmacokinetic, and Activity of SACT-1 as Adjunctive Therapy in Children with High-risk or Relapsed Neuroblastoma
  - Target engagement & modulation to be determined in this study
  - Location: US or other countries

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Phase 1b/2a trial: Proposed Primary and Secondary Objectives

Phase 1b	
Primary Objective	• Evaluate the safety and tolerability of SACT-1 in combination with chemotherapy • Determine recommended Phase 2 dose (RP2D) of SACT-1
Secondary Objective	• Characterize the pharmacokinetic (PK) profile of SACT-1
Exploratory Objective	• Evaluate preliminary activity of SACT-1

Phase 2a	
Primary Objective	• Evaluate antitumor activity of SACT-1 in combination with chemotherapy as measured by objective response rate (ORR). • Evaluate the safety and tolerability of the RP2D of SACT-1 in combination with chemotherapy
Secondary Objective	• Evaluate antitumor activity of SACT-1 in combination with chemotherapy as measured by other parameters • Determine the PK characteristics of SACT-1 when given in combination with chemotherapy
Exploratory Objective	• Evaluate biomarkers of response (MYCN) in participants treated with SACT-1

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Title	Country	Application Date	Expiration date	Status
Composition Including SACT-1 and Method for Treating Tumors or Cancer	US	27 Nov 2020	27 Nov 2040	**Granted**
Composition Including SACT-1 and Method for Treating Tumors or Cancer	US	5 Oct 2021	n/a	**Pending**
Composition Including SACT-1 and Use for Treating Tumors or Cancer	PCT	27 Nov 2020	n/a	**Pending**

- For PCT, national phase applications have been filed in Australia, Canada, China, EU, Indonesia, Japan, Korea, Malaysia and Singapore

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