4 May 2021

Botanix update on BTX 1801 clinical development

Key highlights

- **Recent Phase 2a study data demonstrated BTX 1801 was safe, well tolerated, clinically effective and successful at achieving decolonisation of Staph aureus in the nose**
- **Botanix has launched the next phase of BTX 1801 development, targeting the nasal decolonisation of Staph aureus in haemodialysis patients to prevent bloodstream infections**
- **Limited current preventative measures mean there is an urgent need and significant market opportunity for novel approaches to prevent bloodstream infections in haemodialysis patients**
- **Botanix's approach enables a rapid clinical development pathway, with the opportunity to apply for key FDA incentives to accelerate development and increase exclusivity**
- **Plans for a Phase 2b clinical study are well advanced and fully funded with existing capital reserves**

Philadelphia PA and Perth Australia, 4 May 2021: Clinical dermatology and antimicrobial company, Botanix Pharmaceuticals Limited (ASX:BOT, "Botanix" or "the Company"), is pleased to announce a clinical development update of its antimicrobial platform with the identification of a new indication, targeting the prevention of bloodstream infections in haemodialysis patients. A presentation providing key takeaways of the recent positive Phase 2a study data, summary of the target indication identified, significant market opportunity and clinical development plan is attached to this release.

Vince Ippolito, President and Executive Chairman, commented: *"We are very excited to announce the clinical development update for our BTX 1801 antimicrobial platform. Our assessment indicates that haemodialysis patients with central venous catheters are at considerable risk of bloodstream infections, with no currently approved treatments.*

BTX 1801's novel mechanism of action has been shown to rapidly kill Staph aureus and MRSA without generating resistance, and the recent positive Phase 2a study data demonstrated the clinical utility of BTX 1801 as a nasal decolonisation agent. This represents a potential novel approach for removing sources of bacteria to prevent bloodstream infections in haemodialysis patients, representing a valuable market opportunity to significantly lower the health system impact of haemodialysis infections."

Clinical data generated to date by Botanix indicates that synthetic cannabidiol has a unique bactericidal mechanism of action that rapidly kills *Staphylococcus aureus* (Staph aureus) and drug-resistant Staph aureus (MRSA) without generating antimicrobial resistance. In addition, Botanix recently announced positive top-line data from its BTX 1801 Phase 2a study, with efficacy of BTX 1801 demonstrated by nasal decolonisation of Staph aureus.

In the BTX 1801 Phase 2a study, the bacterial killing effect was demonstrated to be sustained in a proportion of patients without further treatment for up to 3 weeks and none of the analysed bacteria developed resistance to BTX 1801 during the 28-day study period. In addition, data generated to date

has shown that BTX 1801 is safe and generally well tolerated, providing Botanix the confidence that BTX 1801 has the potential to be used as a nasal decolonisation agent for prolonged periods to prevent recolonisation (from other parts of the subject's body) over time.

Following an extensive assessment of clinical data generated to date with key opinion leaders and after a thorough review of potential market opportunities, Botanix has identified its target indication for next phase of clinical development for BTX 1801 – nasal decolonisation of Staph aureus in patients undergoing haemodialysis treatment in order to reduce the incidence of life-threatening bloodstream infections.

Dialysis largely replicates the functions of the kidneys in patients with chronic kidney failure, with dialysis taking over the key functions of the kidneys (including filtering and removing waste materials from the body). Haemodialysis patients undergoing ongoing dialysis regularly (e.g. three to five times per week), are at a high risk of bloodstream infections, due to their treatment requiring frequent use of catheters which in the first year are routinely central lines with direct access to the heart. As a result, infection is a leading cause of death in haemodialysis patients with 20% to 40% of patients eventually dying from an infection[i]. Despite the significant health risks, the treatment to prevent bloodstream infections are essentially limited to the application of antiseptics at the catheter site[ii,iii]. Other issues with the use of antiseptics including the potential degradation of the catheter's plastic construction and potential to cause patient toxicities[iii] (especially if antiseptics enters the opening of the catheter). No topical antibiotic creams or gels are recommended for catheter sites, primarily due to fungal growth and antimicrobial resistance concerns[iv].

The potential benefit of BTX 1801 in haemodialysis patients to prevent bloodstream infection is supported by previous studies using mupirocin. These studies indicated that mupirocin was able to reduce Staph aureus bloodstream infections by as much as 60% to 70% among patients undergoing haemodialysis[v]. However, despite these successful studies, mupirocin was never approved and is not expected to be a suitable long-term solution for haemodialysis patients, given the level of resistance to mupirocin (e.g. up to 95% in some hospitals[vi]) and the fact that mupirocin is now generic (so there is no economic motivation to develop it for this indication).

The health system impact of haemodialysis infections is significant – with the estimated annual cost of treating bacteraemia in haemodialysis patients with central venous catheters to be approximately US$1bn[vii] and approximately 60% of staph aureus-related hospital admissions occurring within the first year of the initiation of dialysis therapy[viii].

Botanix intends to leverage a range of existing US Food and Drug Administration (FDA) programs (e.g. Qualified Infection Disease Product, Fast Track and Limited Population Pathway for Antimicrobial and Antifungal Drugs status) to accelerate BTX 1801 clinical development, reduce clinical costs and increase the exclusivity period. Botanix is finalizing plans to progress BTX 1801 into a Phase 2b study to assess how effective BTX 1801 is at killing Staph aureus over a 3 month treatment period, with three times weekly treatment of the nose. Planning is well advanced to optimise the study design and the Company plans to initiate this Phase 2b study in 4Q CY2021.

Release authorised by

Vince Ippolito
President and Executive Chairman

About Botanix Pharmaceuticals

Botanix Pharmaceuticals Limited (ASX:BOT) is a dermatology focused company based in Perth (Australia) and Philadelphia (USA) committed to the development of pharmaceutical products that are underpinned by science and supported by well-controlled randomised clinical trials. The Company has two separate development platforms, dermatology and antimicrobial products, both of which currently leverage the unique anti-inflammatory, immune modulating and antimicrobial properties of cannabinoids, particularly synthetic cannabidiol. Botanix has an exclusive license to use a proprietary drug delivery system (Permetrex™) for direct skin delivery of active pharmaceuticals in all skin diseases, which it utilises in its existing development programs and is being explored with a number of other product opportunities.

The Company is developing a pipeline of product candidates with recent positive data from its BTX 1801 Phase 2a antimicrobial study and plans for an upcoming Phase 2b study. For the dermatology platform, the Company has received ethics approval to commence its Phase 1b rosacea study and following a successful meeting with the FDA, the Company has confirmed a drug development plan for the BTX 1503 acne program to support registration. To learn more please visit: https://www.botanixpharma.com/

For more information, please contact:

General enquiries	**Investor enquiries**	**Media enquiries**
Corporate Communications	Joel Seah	Haley Chartres
Botanix Pharmaceuticals	Vesparum Capital	H^CK
P: +61 8 6555 2945	P: +61 3 8582 4800	P: +61 423 139 163
investors@botanixpharma.com	botanixpharma@vesparum.com	haley@hck.digital

Cautionary Note on Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for the Company, the Company's strategy, future operations, and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the Company's ability to successfully develop its product candidates and timely complete its planned clinical programs and the Company's ability to obtain marketing approvals for is product candidates. In addition, the forward-looking statements included in this press release represent the Company's views as of the date hereof. The

Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date hereof.

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[i] 'Mortality in dialysis patients: analysis of the causes of death', Mailloux LU, Bellucci AG, Wilkes BM, Napolitano B, Mossey RT, Lesser M, Bluestone PA. AJKD. 1991 Sep;18(3):326-35

[ii] CDC recommends the use of antiseptics greater than 0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine.

[iii] 'Hemodialysis Central Venous Catheter Scrub-the-Hub Protocol', CDC, 2016, https://www.cdc.gov/dialysis/prevention-tools/scrub-protocols.html

[iv] O'Grady NP, Alexander M, Burns LM, et al. Guideline for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011; 52:e162-e193. CDC Guidelines for Central Venous Catheters, updated 2017

[v] 'Mupirocin Prophylaxis to Prevent Staphylococcus aureus Infection in Patients Undergoing Dialysis: A Meta-analysis' (2003) Tacconnelli, E. et al Clinical Infectious Diseases, Volume 37, Issue 12, 15 December 2003, Pages 1629–1638

[vi] Preventing Surgical-Site Infections in Nasal Carriers of Staphylococcus aureus Jan 2010, Bode et al N Engl J Med 2010; 362:9-17

[vii] 'Following CDC Protocols Cuts Dialysis Bloodstream Infection in Half', CDC, May 2013, https://www.cdc.gov/media/releases/2013/p0513-dialysis-infections.html

[viii] 'Clinical and Economic Outcomes of Staphylococcus aureus Septicemia in ESRD Patients Receiving Hemodialysis', Nissenson A et al, American Journal of Kidney Diseases, Vol 46, No 2 (August), 2005: pp 301-308

Unlocking the potential of synthetic cannabinoids

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BTX 1801
Development Update
May 2021

Executive summary

New generation antimicrobial	Synthetic cannabidiol (CBD) with a **novel mechanism of action rapidly kills** *Staphylococcus aureus* (Staph aureus) and drug-resistant Staph aureus (MRSA) **without generating resistance**
Demonstrated clinical efficacy	BTX 1801 demonstrated in recent Phase 2a study to **effectively and safely achieve bacterial decolonisation of Staph aureus in the nose**
Target indication identified	Nasal decolonisation of Staph aureus in patients undergoing haemodialysis treatment to prevent life threatening bloodstream infections
Significant market opportunity	Hospitalisations due to **bloodstream infections among haemodialysis patients with central venous catheters cost the US health system ~US$1bn p.a.**[2]
Efficient clinical development	Targeting haemodialysis patients as the first indication, **allows a streamlined pathway to FDA approval in an attractive market**, with the opportunity to efficiently expand into other infection types

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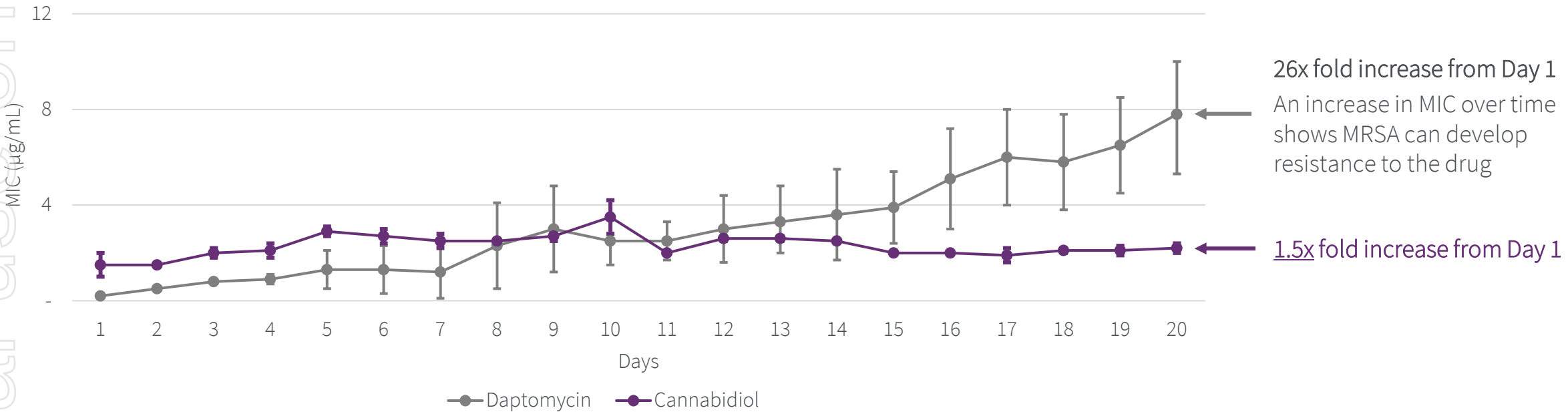
1. 'Prevention of Bloodstream Infections in Patients Undergoing Hemodialysis', Fisher, M. Golestaneh, L. Allon, M. Abreo, K. and Mokrzycki, MH. CJASN January 2020, 15 (1) 132-151
2. 'Following CDC Protocols Cuts Dialysis Bloodstream Infection in Half', CDC, May 2013, https://www.cdc.gov/media/releases/2013/p0513-dialysis-infections.html

BTX 1801 has remarkable activity against bacteria without inducing resistance

MIC daily variability[1]



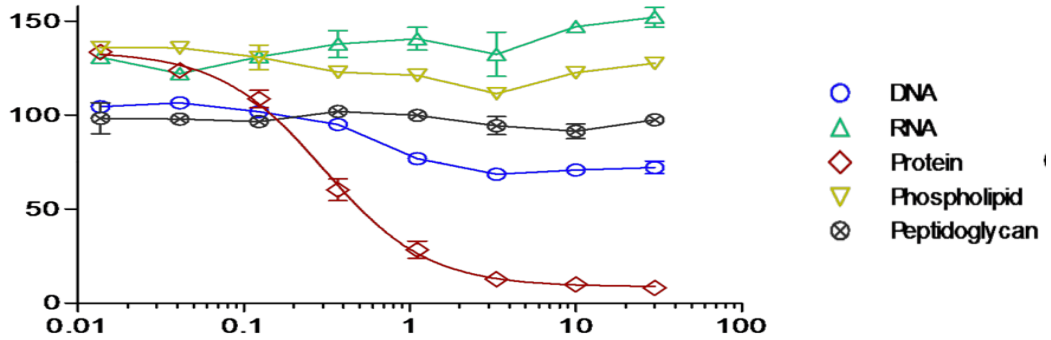
Repeat challenge experiments demonstrate that MRSA bacteria develop resistance to commonly-used antibiotics such as daptomycin, but not easily to synthetic CBD

1. The Antimicrobial Potential of Cannabidiol, Communications Biology 4, Article number: 7 (2021) Blaskovich, M et al

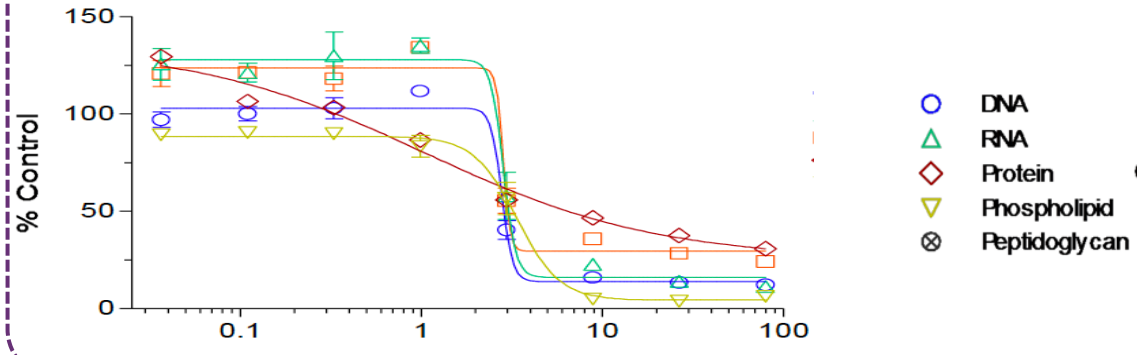
Unique mechanism of action – bactericidal

CBD rapidly kills MRSA bacteria by targeting all 5 macromolecular pathways

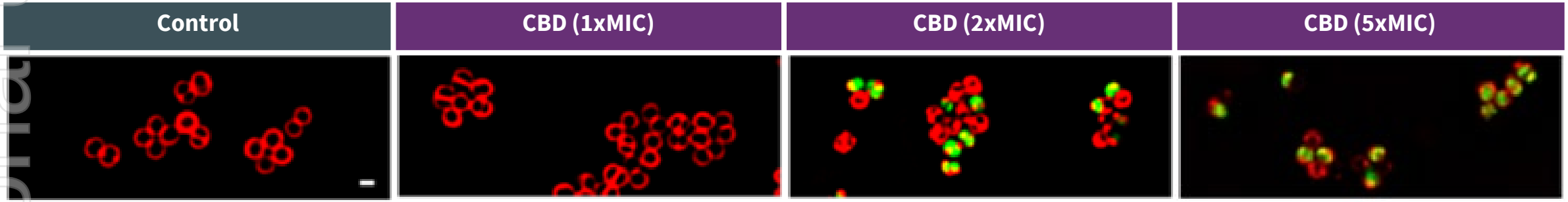
Mupirocin – targets only protein synthesis[1]



CBD – affects all macromolecular pathways[1]



CBD – MRSA bacteria dead within 10 minutes[2]



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1. Based on testing conducted by HD Biosciences – BOT data on file
2. Based on testing conducted by Linnaeus Bioscience – BOT data on file

Efficacy of BTX 1801 demonstrated by nasal decolonisation of Staph aureus in Phase 2a study

- Double-blind, vehicle-controlled, Phase 2a clinical study
- **4 dose groups:** 66 healthy volunteers:
  - BTX 1801 Formulation A
  - BTX 1801 Formulation B
  - Vehicle A
  - Vehicle B
- **Sites:** single Australian centre
- **Patients:** adults: 18 ≥years with positive nasal Staph aureus
- **Treatment:** twice daily for 5-days
- **Primary endpoints:** safety and local tolerability, proportion of volunteers with Staph aureus/ MRSA carriage at Day 12

Safety & tolerability

- ✓ Safe and generally well tolerated at doses of active drug up to 20%
- ✓ All 66 participants successfully completed the BTX 1801 study
- ✓ No severe adverse events reported[1]

Efficacy

- ✓ Efficacy of ointment and gel formulations demonstrated for primary endpoint at Day 12
- ✓ Eradication rates as high as 76.2% at Day 7, with eradication effects extending through to Day 28, despite no treatment after Day 5

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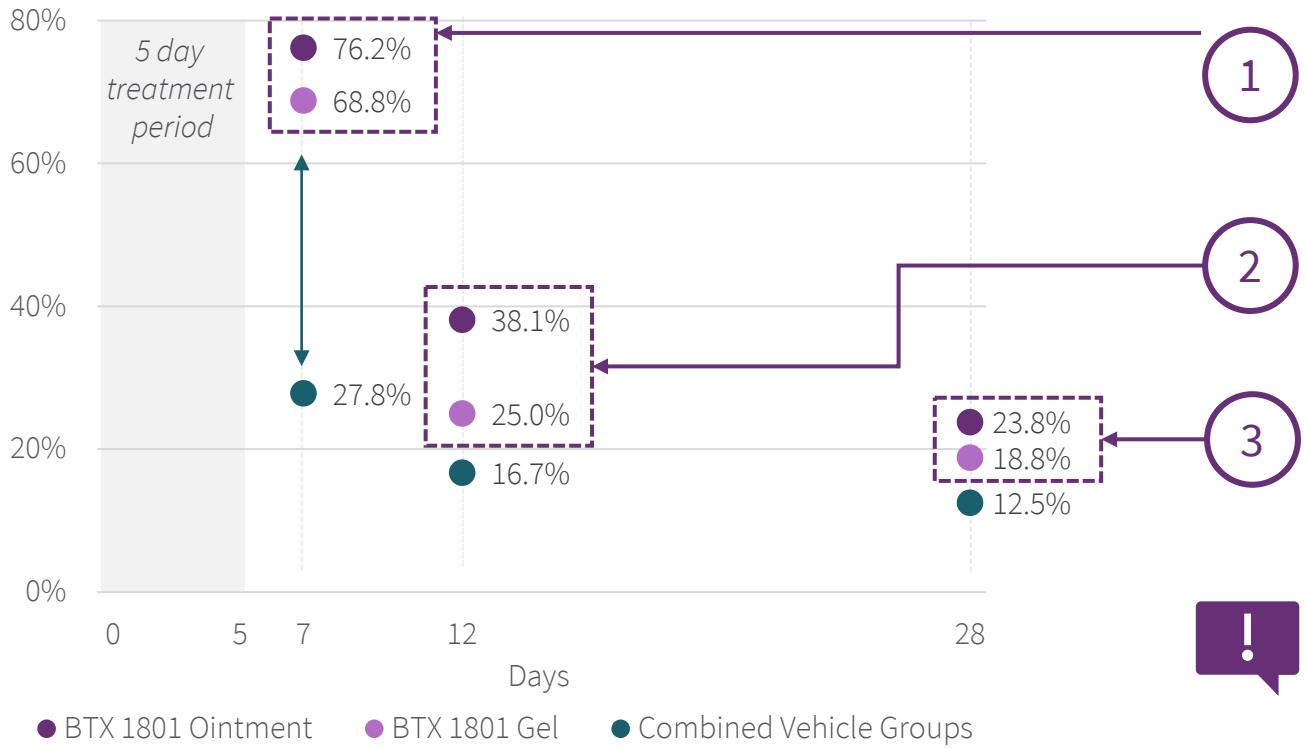
1. BTX 1801 Phase 2a Clinical Study - BOT data on file
2. The incidence of adverse events was low, mild in severity and occurred at similar rates across the different treatment groups with no severe events reported

Phase 2a study data: Staph aureus eradication

BTX 1801: Staph aureus eradication rates (% of participants)[1]



Study observations

- ✓ Significant eradication of Staph aureus 2 days after completion of treatment period
- ✓ Large difference between active groups / vehicle control
- ✓ After 7 days of no treatment with BTX 1801 – significant % of subjects maintained eradication of Staph aureus
- ✓ After 23 days of no treatment with BTX 1801 – significant % of subjects maintained eradication of Staph aureus

- *The BTX 1801 Phase 2a study did not include a full body chlorhexidine wash, that has been used in other clinical studies to remove bacterial reservoirs in other parts of the body (that recolonize the nose)*
- *Bacterial detection was with high accuracy PCR testing rather than less accurate culture methods*

First human data demonstrating clinical utility of synthetic CBD as an antimicrobial agent

1. BTX 1801 Phase 2a Clinical Study Data announced 3 February 2021

BTX 1801 for nasal decolonisation: key takeaways

- ✓ BTX 1801 is safe and generally well tolerated
- ✓ BTX 1801 kills Staph aureus
- ✓ The bacterial killing effect can be sustained in a proportion of patients without further treatment for up to 3 weeks
- ✓ None of the analysed bacteria developed resistance to BTX 1801 during the 28 day study period
- ✓ BTX 1801 has the potential to be used as a nasal decolonisation agent for prolonged periods to prevent recolonisation over time
- ✓ Very low systemic blood levels of active drug – provides a targeted and localised effect

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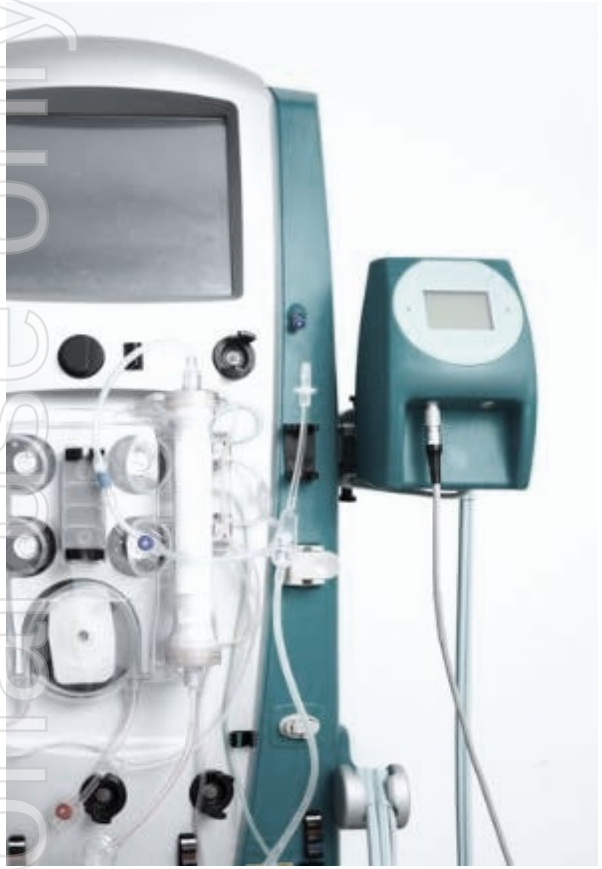
Note: BTX 1801 Phase 2a Clinical Study BOT data on file.

Haemodialysis patients
with central venous catheters at risk of bloodstream infections



Disease overview

- Dialysis largely replicates the functions of the kidneys in patients with chronic kidney failure – haemodialysis takes over the key tasks of the kidneys, removing waste materials from the body
- Patients undergoing dialysis 3 times per week are at a high risk for bloodstream infections due to the frequent use of catheters to access the blood stream
- Infection is a leading cause of death in haemodialysis patients
- 20% to 40% of haemodialysis patients will eventually die from an infection[1]

Significant health risks

- There are more than 468k[2] patients in the US currently receiving dialysis with more than 100,000 new patients added annually[3]
- 80% of patients start haemodialysis with a central venous catheter which is generally replaced after 12 months, by a 'fistula' or graft access port in the arm[4]
- Some studies have found that risks for central venous catheter-related complications were as high as 30% and 38%, at 1 and 2 years respectively[5]
- The central venous catheter population (approx. 160,000 patients) is responsible for more than 70% of blood infections in the total dialysis population[4]

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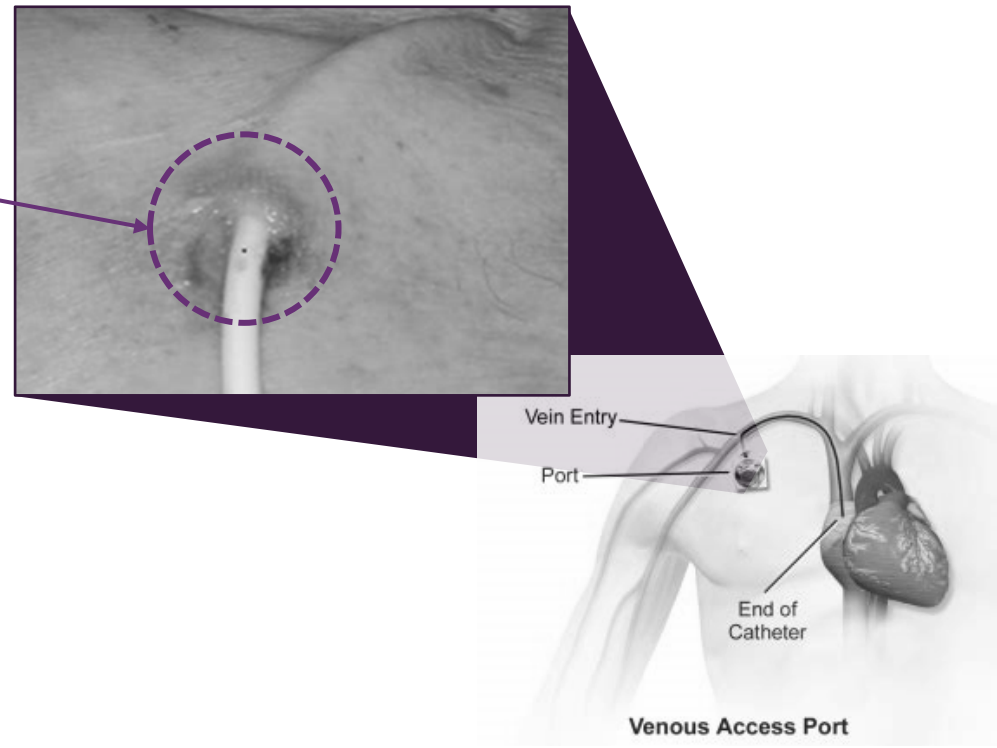
1. 'Mortality in dialysis patients: analysis of the causes of death', Mailloux LU, Bellucci AG, Wilkes BM, Napolitano B, Mossey RT, Lesser M, Bluestone PA. AJKD. 1991 Sep;18(3):326-35
2. United States Renal Data Service 2019 Annual Data Report, https://www.usrds.org/media/2371/2019-executive-summary.pdf
3. 'Kidney Disease Statistics for the United States', NIH, 29 April 2020, https://www.niddk.nih.gov/health information/health-statistics/kidney-disease
4. 'Prevention of Bloodstream Infections in Patients Undergoing Hemodialysis Fisher', M. Golestaneh, L. Allon, M. Abreo, K. and Mokrzycki, MH. CJASN January 2020, 15 (1) 132-151
5. 'Complications From Tunneled Hemodialysis Catheters: A Canadian Observational Cohort Study', (2019) Poinen, K. et al AJKD Volume 73 Issue 4 Pages 467-475

Limited preventative measure: nasal decolonisation is not widely utilised

CDC currently focuses on the catheter site

- CDC only recommends disinfecting the catheter hub with appropriate antiseptics prior to accessing it[1,2]
- These antiseptics can degrade the plastic of catheters and are not widely used[3]
- No topical antibiotic creams or gels are recommended for catheter sites due to fungal growth and antimicrobial resistance concerns[3]
- If antiseptics enters the lumen (opening) of the catheter, they can potentially cause toxicities to the patient[2]



Multiple publications suggest the utility of addressing nasal decolonisation to prevent bloodstream infections

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1. CDC recommends the use of antiseptics greater than 0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine.
2. 'Hemodialysis Central Venous Catheter Scrub-the-Hub Protocol', CDC, 2016, https://www.cdc.gov/dialysis/prevention-tools/scrub-protocols.html
3. O'Grady NP, Alexander M, Burns LM, et al. Guideline for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011; 52:e162-e193. CDC Guidelines for Central Venous Catheters, updated 2017

Potential benefits of BTX 1801 in haemodialysis: supported by previous studies using mupirocin (but never approved)

Overview

- Mupirocin was evaluated in clinical studies in the 1990s as a potential nasal decolonisation therapy in haemodialysis patients
- Studies indicate that mupirocin was able to reduce Staph aureus bloodstream infections by as much as 60% to 70% among patients undergoing haemodialysis[1]
- Despite these successful studies, mupirocin was never pursued for FDA approval for use in haemodialysis patients (and is now generic - so no incentive to try)
- In addition, mupirocin is not a suitable long-term solution for haemodialysis patients considering the levels of bacterial resistance to mupirocin (up to 95% in some hospitals[2])

Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011

"Several studies have demonstrated a reduced risk of [catheter related bloodstream infections] when mupirocin ointment was applied nasally…However, enthusiasm for this measure has been dampened by the rapid emergence of mupirocin resistance observed at some centers and the potential degrading effect that mupirocin has on polyurethane catheters."

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1. 'Mupirocin Prophylaxis to Prevent Staphylococcus aureus Infection in Patients Undergoing Dialysis: A Meta-analysis' (2003) Tacconnelli, E. et al Clinical Infectious Diseases, Volume 37, Issue 12, 15 December 2003, Pages 1629–1638
2. Preventing Surgical-Site Infections in Nasal Carriers of Staphylococcus aureus Jan 2010, Bode et al N Engl J Med 2010; 362:9-17

Haemodialysis: population characteristics and risks of infection

Weakened immune system

- An estimated 40% to 60% of haemodialysis patients have diabetes
- Diabetes is a known risk factor for developing infections, due to compromised circulation and immune systems

High hospitalisation rates

- Patient population is hospitalised on average once per year with a serious bloodstream infection

100x More likely…

- …to get a bloodstream infection from a common resistant bacteria, such as MRSA, than other people[1]

8x Higher risk of…

- catheter access related bloodstream infections for patients with a central venous catheter compared with a fistula or graft access port[2]

New approaches for removing sources of bacteria are urgently required

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1. ''Following CDC Protocols Cuts Dialysis Bloodstream Infection in Half', CDC, May 2013, https://www.cdc.gov/media/releases/2013/p0513-dialysis-infections.html
2. 'Prevention of Bloodstream Infections in Patients Undergoing Hemodialysis' Fisher, M. Golestaneh, L. Allon, M. Abreo, K. and Mokrzycki, MH. CJASN January 2020, 15 (1) 132-151

Health system impact of haemodialysis infections

~60%
of Staph aureus–related hospital admissions occur within the first year of the initiation of dialysis therapy[1]

~US$32k
Mean cost (per episode) of treating Staph aureus bloodstream infections, including re-admissions and outpatient costs[1]

US$1bn
Estimated annual cost of treating bacteraemia in haemodialysis patients with central venous catheters[2]

13 days
Average length of stay for the index admission[1]

11.8%
of patients were readmitted within 12 weeks of hospitalisation related to Staph aureus infections[1]

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1. 'Clinical and Economic Outcomes of Staphylococcus aureus Septicemia in ESRD Patients Receiving Hemodialysis', Nissenson A et al, American Journal of Kidney Diseases, Vol 46, No 2 (August), 2005: pp 301-308
2. 'Following CDC Protocols Cuts Dialysis Bloodstream Infection in Half', CDC, May 2013, https://www.cdc.gov/media/releases/2013/p0513-dialysis-infections.html

Significant market with further upside potential

Market for nasal decolonisation of haemodialysis patients with central venous catheters

Market benchmarked against **GSK Bactroban Nasal** where the total cost of 1 Year of treatment course costs ~$5,184[2]

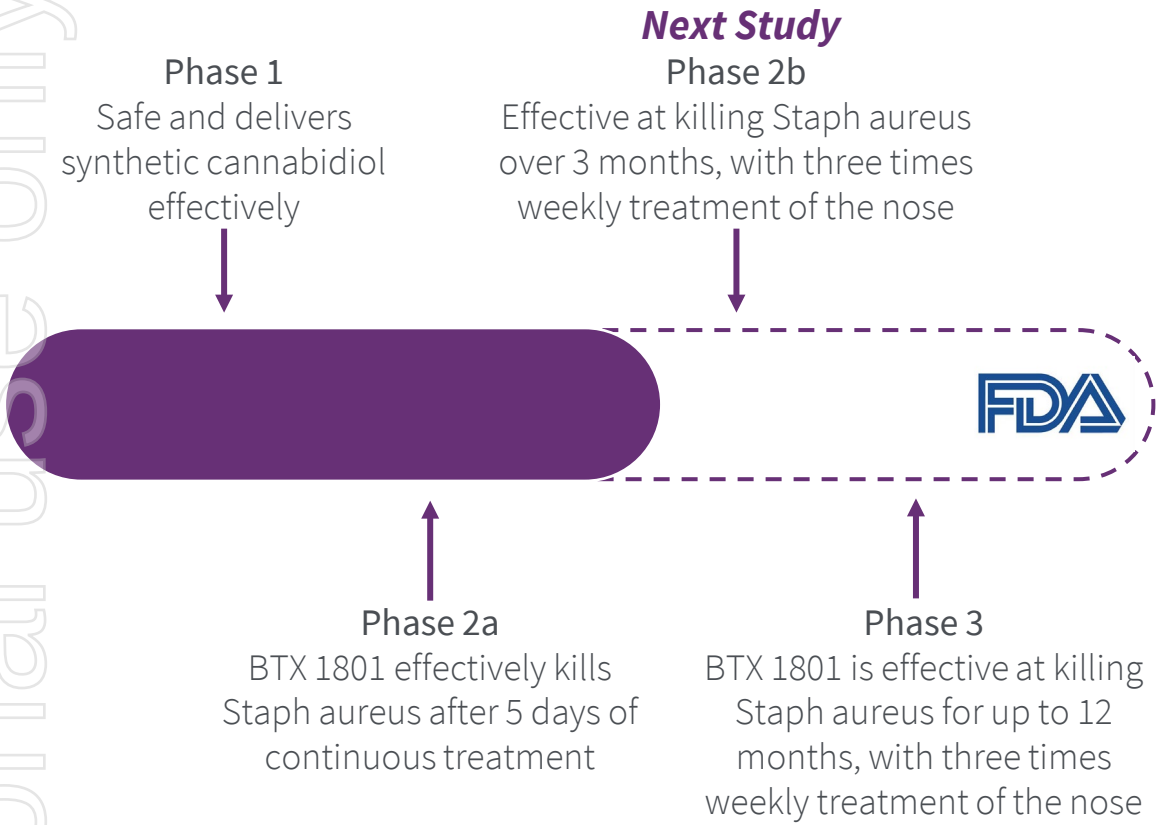
Potential to expand into other vascular access methods

An estimated **~15% to ~25% of haemodialysis patients** continue to remain with central venous catheter usage after the first year

Represents an additional revenue opportunity of **~US$78m to US$130m**[1]

1. Using GSK Bactroban Nasal Pricing/BTX 1801 pricing to be developed following analyses of potential impact on healthcare system; assumes 5% YOY pricing following product approval/launch in 2025
2. https://www.goodrx.com/bactroban-nasal

BTX 1801: rapid clinical development



FDA incentives provide accelerated development and increase exclusivity

QIDP[1] status	❖ Extra 5 years (total of 8 years) exclusivity from generic competition ❖ Attractive economic benefits from FDA approval
Fast track status	❖ Following IND submission, allows increased consultation with FDA ❖ De-risks clinical trials and accelerates development pathway
LPAD[2] status	❖ Allows smaller, fewer and / or shorter clinical trials for FDA approval

Botanix plans to apply for all three programs to accelerate development, reduce clinical costs and increase exclusivity

1. QIDP: Qualified Infections Disease Product
2. LPAD: Limited Population Pathway for Antimicrobial and Antifungal Drugs

Summary

New generation antimicrobial

Novel mechanism of action rapidly kills without resistance

Demonstrated efficacy

Effectively and safely achieves bacterial decolonisation

Target indication identified

New indication with significant morbidity and mortality

Significant market opportunity

Large market with significant financial burden on healthcare system

Efficient clinical development

Streamlined pathway to FDA approval with ability to expand to other infection types

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General enquiries

Botanix Pharmaceuticals
Corporate communications
+61 8 6555 2945
investors@botanixpharma.com