Microbix Biosystems Inc.

18 July 2023

MBX-T: $0.35, MBXBF-OTC: US$0.26

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Price	$0.35	Market Cap	$47,697
Target Price	$1.00	Debt	$6,543
Projected Return	190%	Cash	-$11,722
52 Week Range	0.55/0.3	EV ($000s)	$42,519
Basic Shares (000's)	138,253		
FD Shares (000's)*	183,356		
Insiders	13.0%		

Y/E September	2021	2022	2023E	2024E
Revenues ($000s)	18,593	19,076	18,492	32,458
EBITDA ($000s)	5,659	3,647	2,985	13,880
Adj. EBITDA** ($000s)			1,635	9,880
FDEPS	0.02	0.01	0.01	0.07
EV/EBITDA	7.5x	11.7x	14.2x	3.1x

*=Assumes conversion of CD

**=Adj EBITDA excludes impact of Sequel progress payments

Profile

Microbix Biosystems Inc. (MBX-T) is a Canada-based life science company and manufacturer of viral and bacterial antigens and cell culture-based biological products and technologies such as test controls and sample collection media. MBX's catalogue of antigens covers +30 bacterial and viral pathogens implicated in maternal, pediatric, childhood, respiratory, sexually transmitted and insect-borne diseases. MBX is now focusing on a higher growth opportunity: its QAPs™ product line, targeting quality controls within accreditation organizations, IVD equipment manufacturers and clinical laboratories. Partners are being sought for its development asset, Kinlytic Urokinase, a biologic thrombolytic drug used to treat blood clots.

Disclosure

Please refer to important disclosures on page 34.

KINLYTIC® UROKINASE: TARGETING THE CATHETER CLEARANCE (CC) MARKET, RETURN OF THE FORMER MARKET LEADER WILL MAKE FOR A STRONG DUOPOLY

- **Agreement**. On 16 May 2023, MBX announced a commercialization agreement with Sequel Pharma LLC to reintroduce Kinlytic® urokinase (KU) to the catheter clearance (CC) market. It represents the culmination of MBX's stated intention to re-commercialize KU. KU, formerly Abbokinase®, is owned 100% by MBX and approved for multiple indications. While originally targeted massive pulmonary embolism, it became the market leader for CC.
- **Terms**. MBX will receive US$5.0m in pre-commercialization payments (3 payments of US$1.0m-$2.0m each) centered around closing and regulatory approval, then US$30m in sales-based progress payments and a double-digit royalty on net sales. We believe that Sequel will commence selling KU in 2028. Sequel will fund all development costs.
- **CC market:** CC is the return of flow to a central venous catheter (CVC) clogged with a blood clot - around 25% of CVCs become clogged. The US CC market is currently a monopoly with Roche Genentech's Cathflo® Activase® at 100% market share driving sales of US$342m in 2021, having grown 6.5% p.a. over the past 11 years. Principal drivers of this growth include growth in the CVAC market due to aging population and sedentary lifestyles.
- **Limited competition**: both Cathflo® Activase® (t-PA) and KU (off-patent, low molecular weight urokinase, LMW-UK) have molecular and formulation complexities which complicates copying and difficult to make. Also, no biosimilar t-PA or LMW-UK products have been approved in the past ~20 years. The return of KU would see the CC market evolve into a strong duopoly with limited opportunity for other entrants.
- **Competitive advantage.** KU has a well-established safety and efficacy history, dosing advantages (e.g., no refrigeration required), and limited potential for biosimilars. It is expected to be priced at a discount to the incumbent.
- **FDA pathway:** In a 2017 FDA meeting, the FDA agreed that MBX's steps for reintroduction were a "reasonable path". These included proposed plans for manufacturing (process, testing, materials), comparability (analytical, pre-clinical and clinical) and a 2-year regulatory path to filing a supplement to the approved NDA (sBLA). Clinical comparability requires only a simple, low risk, low cost bridging strategy.
- **Valuation.** We believe that the successful reintroduction of KU could add $1.10 to our valuation based on after-tax discounted cash flows. We have historically applied a notional $10m to our valuation for the KU opportunity and will continue to do so until the regulatory risk is ameliorated.

Executive Summary

In the context of this report, LMW or low molecular weight urokinase, Abbokinase® and Kinlytic® urokinase (KU) are used interchangeably as they refer to the same product active ingredient, simply rebranded.

KU is approved for multiple indications in North America, however, it is being positioned with catheter clearance (CC) as its lead opportunity. It will require ~US$30.0m investment by Sequel for capex/launch costs and ~3 years to complete the sBLA filing and to bring to commercialization.

While working to develop a biosimilar approach for an in-house version of LMW urokinase, as early as 2000, MBX described its remaining, key milestones necessary to bring the product to market, which will all now be assumed by Sequel:

- Commission a GMP biologics manufacturing facility (now to be manufactured using an external CMO),
- Confirmation regulatory application approach with the US FDA,
- Gain overall funding from a marketing / development partner.

Two of these milestones are equally applicable to the commercialization of Kinlytic® urokinase today, with the funding in place. On this basis, MBX has a well identified reintroduction strategy for Kinlytic® urokinase which, at a high level, is outlined as follows:

- **Reintroduce the Gold Standard**. Urokinase was the standard of care for the clearance of blocked biomedical catheters, including catheters placed deep within the body (Central Venous Catheters or CVCs).
- **Re-establish safety and efficacy on the reintroduced product**. Urokinase has treated over 4 million patients during its over 20-year history in the clinic.
- **Address a growing market.** Various market studies show that the global CVC market is forecast to grow at between 2.8%-5.4% p.a. Within in this context, the US CC market has grown at 6.5% p.a. over the past 11 years.
- **Convert a market monopoly to a duopoly.** Genentech's Cathflo® Activase® is the 100% market leader. Reintroduction of Kinlytic® urokinase is expected to result in a strong duopoly.
- **Benefit from a de-risked regulatory pathway.** Kinlytic® urokinase is a novel biologic (there is not a biosimilar in play). It has existing FDA and Health Canada approvals for both pulmonary embolism and catheter clearance clinical indications. The FDA has agreed in principle that it is open to the reintroduction of Kinlytic® urokinase subject to a straightforward regulatory process.

Market sizes. The global catheter market was estimated at US$45.3bn in 2020, while the global Central Venous Catheter (CVC) market in 2020 was estimated at US$1.1bn, with the US accounting for 34.2% of the global market, or US$388.2m. The US CC market grew to US$342m in 2021. At its peak in 1998, Abbokinase® commanded ~100% market share of the CC market while currently Cathflo® Activase® has ~100% of the CC market. Kinlytic® urokinase was the gold standard for CC and its return to the US market is expected to result in a duopoly.

Capital investment. MBX has all the necessary scientific, technical and manufacturing expertise needed to bring this product back to market. However, it acknowledged that it did not have the capital or marketing background to reintroduce KU to the market on its own. Hence, the Sequel agreement which will fund all

development costs, and will provide the ~US$30.0m capital required to fund comparability tests, resumption of production, a Phase III bridging trial and to build out manufacturing and sales teams within a 3-year timeframe.

Market research. MBX undertook market research in both 2007 and 2018 and both studies confirmed the need for CC competition, given Roche Genentech's 100% (monopoly) market share with its Cathflo® Activase® (t-PA). Essentially, there has been no new market entrant for nearly two decades and Abbokinase® (now Kinlytic® urokinase) was the gold standard. Also, Kinlytic® urokinase has a 20-year history of safe and predicable results.

Federal regulators. The FDA has responded positively to the potential return of Kinlytic® urokinase to the US market. To reintroduce Kinlytic® urokinase via a supplement to the existing regulatory file (originally an NDA, now designated a BLA), a 6-month bridging study and approval is required of a new manufacturing site and process updates.

Impact on MBX share price. Using a 2-stage discounted cash flow (Figure 7), we believe that the successful reintroduction of KU by Sequel could add ~$1.10 to our target price. High level assumptions include Sequel commencing sales of KU in 2028 and achieving a 25% market share by 2033 and our assumption of a net sales royalty rate to MBX of 10%. This approach is supported by an undiscounted, back of envelope potential valuation of $1.20/share in 2033 (Figure 8) also based on a 10% net sales royalty. Historically, we have applied a notional $10m to our MBX valuation to account for the KU opportunity; and believe that the Sequel agreement validates this approach. We will adjust our valuation of KU once the sBLA is received.

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KU commercialization Agreement - Sequel Pharma LLC

On 16 May 2023, MBX announced that it had executed a commercialization agreement with Sequel Pharma LLC to reintroduce KU to the catheter clearance (CC) market. This Agreement represents the culmination of MBX's stated intention to recommercialize KU.

Terms of the agreement disclosed include:

- Initially targeting the CC market in the US. Expansion into Canada and Europe is expected later.
- To be followed by other geographies and clinical indications.
- Sequel will fund and undertake the necessary work to enable FDA clearance.
- Financial terms of the deal include:
    - Pre-commercialization milestone payments of US$5.0m:
        - US$2.0m paid to MBX upon closing of the Agreement. US$1.0m is repayable if the FDA consultation is negative.
        - US$2.0m to be paid to MBX upon satisfactory FDA consultation.
        - US1.0m to be paid to MBX upon US reapproval via a supplemental Biologics Licensing Application (sBLA).
    - Sales threshold driven milestone payments of US$30.0m and ongoing lower double-digit royalties on net sales.

Expected milestone timelines are estimated in Figure 1:

Figure 1: MBX/Sequel anticipated timelines

Milestone	Anticipated Timing
Closing/receipt of first payment	June 2023
FDA consultation/second payment	Late 2023
Receipt of sBLA/third payment	2027
First revenues	2028
$30m sales driven milestone payments	2029+
Cost of reintroduction	US$20m
Pre-marketing/relaunch costs	US$10m

Source: MBX, KRC Insights

MBX management estimated that the cost of reintroduction of KU would be around US$30m[1] comprising US$20m in support of regulatory filings, drug manufacturing/packaging, new drug comparability studies, Phase 3 bridging trial and US$10m for product pre-launch and relaunch costs (Figure 1). These costs are pre-funded and will be borne by Sequel.

As for the accounting treatment of the Agreement:

- The US$5.0m in pre-commercialization milestone payments will be treated as revenues in the periods when realized.

[1] Q2 2023 conference call 16 May 2023

- The Kinlytic asset was written off in F2020 with MBX recording a charge of $3.1m. The asset will now be written back up to its former book value upon FDA reconsultation and go-ahead by Sequel that it is proceeding. We expect that this could occur in FQ1/24. Included in the write-up will be fees associated with the agreement.

To provide context for the Sequel agreement and MBX's history with KU, this report covers an overview of blood clots/therapies, market size, where KU fits in, MBX's history with KU, its previously stated reintroduction strategy and potential financial impact to MBX.

Overview of blood clot therapies

The formation of a blood clot is a natural process by which blood thickens and coagulates into a mass of blood cells, platelets and strands of fibrin. This a natural process that is essential to repair of damaged tissues. Pathological thrombosis occurs when a blood clot, or thrombus, begins to block a blood vessel or an in-dwelling biomedical catheter, which is a conduit to administer therapeutics.

MBX's Kinlytic™ urokinase is being applied in catheter clearance (CC). Thrombosis is the most common cause of occlusion in biomedical catheters and hence initial treatment is directed at dissolving the occluding clots. While this can be accomplished by replacing the device, restoring its patency without removing the line is the preferred approach, from both health and cost-effectiveness perspectives, and it allows for the preservation of the access site for as long as possible.

Clot formation

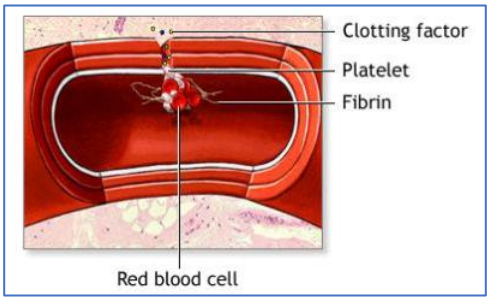
Formation of a clot is the body's primary mechanism for curtailing bleeding from wounds or other injuries to blood vessels. Blood clots can also be caused by a variety of factors other than injury or trauma (such as the rupture of vulnerable plaque in a vessel), arise in connection with surgical and other medical procedures (such as catheter-based administration of dialysis or other treatments), which can lead to clotting around the site of an incision or within a penetrated blood vessel. Sometimes, however, clots form on the inside of vessels without an obvious injury or do not dissolve naturally. These situations can be dangerous and require diagnosis and appropriate treatment.

An example of how a blood clot could develop would be when a blood vessel is ruptured (Figure 2). The injured blood vessel would constrict limiting the blood flow and clotting can start. At the same time, the accumulating pool of blood outside the blood vessel (a hematoma) presses against the vessel, helping prevent further bleeding.

As soon as a blood vessel wall is damaged, a cascade of enzymatic reactions activates circulating blood platelets such that they adhere to the injured area. The "glue" that holds platelets to the blood vessel wall is known as von Willebrand factor, a large protein produced by the cells of the vessel wall. The proteins collagen and thrombin also act at the site of the injury to induce platelets to stick together. As platelets accumulate at the site, they form a mesh that plugs the injury. The platelets change shape from smooth discoid to more spherical and spinier, and they release proteins and other substances that entrap more platelets and clotting proteins in the enlarging plug that becomes a blood clot.

Blood clots can be stationary (thrombosis) and block local blood flow or break loose in circulation (embolism) and travel to various parts of the body, including, very seriously, to the lungs. Blood clots can be life-threatening depending on their location and severity.

Figure 2: Blood clot formation



Source: https://medlineplus.gov/ency/imagepages/19462.htm

Formation of a clot also involves activation of a sequence of blood clotting factors, which are proteins produced mainly by the liver. Other proteins offset extra clotting factor proteins, so the clot doesn't spread farther than it needs to. There are over a dozen blood clotting factors, which interact in a complicated series of chemical reactions that ultimately generate thrombin. Thrombin converts fibrinogen, a blood clotting factor that is normally dissolved in blood, into long strands of fibrin that radiate from the clumped platelets and form a net that entraps more platelets and blood cells. The fibrin strands add bulk to the developing clot and help hold it in place to keep the vessel wall plugged.

Fibrin is an insoluble protein that is produced in response to bleeding and is the major component of the blood clot. Fibrin is a tough protein substance that is arranged in long fibrous chains; it is formed from fibrinogen, a soluble protein that is produced by the liver and found in blood plasma. When tissue damage results in bleeding, fibrinogen is converted at the wound into fibrin by the action of thrombin, a clotting enzyme. Fibrin molecules then combine to form long fibrin threads that entangle platelets, building up a spongy mass that gradually hardens and contracts to form the blood clot[2].

Blood clot treatments

Different treatments exist for the prevention and treatment of blood clots:

- **Prevention**. Aspirin and other anti-platelet agents, as well as heparin and other anticoagulants, are commonly used to prevent or reduce the incidence of blood clots, but have no effect in eliminating such blood clots once they have formed.
- **Treatment**. Once blood clots have formed, there are therapeutic approaches for dissolving or otherwise eradicating blood clots before they cause serious medical consequences or death. In turn, these fall into two categories:
    - clot-dissolving drugs, or thrombolytics, and
    - mechanical devices and procedures.

[2] https://www.britannica.com/science/fibrin

Here we focus on thrombolytics.

Thrombolytics

Broadly speaking, thrombolytic enzymes dissolve blood clots by breaking down fibrin protein lattices within those clots. Thrombolytic enzymes are also known as fibrinolytics. Currently, the most widely used thrombolytic today is a form of tissue plasminogen activator, commonly referred to as t-PA. t-PA is marketed in several different formulations that are approved for a variety of specific vascular disorders, such as: **alteplase** for acute ischemic stroke, acute massive pulmonary embolism, central venous CC and acute myocardial infarction; while **reteplase** and **tenecteplase** (both not t-PA) for acute myocardial infarction, and reteplase is not widely used. Other thrombolytic agents include **urokinase**, which is approved for treatment of acute massive pulmonary embolism and CC; and **streptokinase**, which was approved for treatment of acute massive pulmonary embolism, acute myocardial infarction and deep vein thrombosis. Streptokinase was used as a potential replacement for urokinase; however, it was not FDA-approved for CC and in December 1999, AstraZeneca (manufacturer) issued warnings regarding the risk of life-threatening anaphylaxis when used for treating occluded catheters. Streptokinase is highly immunoreactive due to its bacterial origins.

Systemic use of thrombolytics can generate a variety of risks and potential side effects that can limit their usefulness:

- **Risk of Bleeding**— Thrombolytics dissolve blood clots, including those formed naturally as a protective response to vessel injury, which can result in bleeding. The risk of bleeding increases relative to the dosage and duration of treatment and differs among the various thrombolytics. Patients who are already taking other medications to prevent formation of clots, such as anticoagulants or antiplatelet agents, also may not be good candidates for the use of thrombolytics, due to the increased difficulty of controlling bleeding. As such, thrombolytics approved by the FDA are subject to strict limitations on when, how long and in what dosages they can be administered. Urokinase is known to cause less systemic bleeding than t-PA by virtue, in part, of its lower specific affinity for fibrin.
- **Time Window for Administration**— Due in part to the risk of bleeding, which increases over time, t-PA is only approved for administration to ischemic stroke patients within three hours after the onset of stroke symptoms. This three-hour window is considered to be one of the primary limiting factors in treating ischemic stroke. Approximately 23% of ischemic stroke patients in the U.S. recognize their symptoms and reach an emergency room within the three-hour window, however, due to this and other limitations, only between 10.4% to 18.8% of these patients ultimately receive treatment with a thrombolytic.
- **Possible Immune Response**— Some patients experience an immune response due to the continued administration of thrombolytics. However, this is only significant with streptokinase, which is produced using streptococcus bacteria and is highly immunogenic. Urokinase has been described as non-immunogenic as it is a native human enzyme.

Mechanical Devices and Procedures

There are several mechanical means for removing or destroying blood clots:

- **Thrombectomy**, or surgical clot removal, is used to treat patients with occluded dialysis grafts or some clots in the peripheral vascular system. These procedures are invasive and entail delays, costs and risks

that accompany any major surgery. Although these procedures are less suitable for removing blood clots from the brain, there are devices approved for these procedures.

- **Mechanical devices** that can be introduced through a catheter-based delivery system to mechanically break up a blood clot, or to ensnare and retract a clot through the vascular system and out of the body. These mechanical devices are generally not found outside of major medical centers, as they require a catheter laboratory and skilled personnel to administer the therapy. While they do not cause the same bleeding risk as thrombolytics, these mechanical interventions pose some risk of damaging other tissues during treatment, as well as a risk of breaking off a piece of the clot that can itself become the cause of a stroke or embolism in some other part of the body.

Types of occlusions[3]

Central venous access devices (CVADs) or central venous catheters (CVCs) are devices that are inserted into the body through a vein to enable the administration of fluids, blood products, medication and other therapies to the bloodstream. Catheter occlusions are common and well researched given ~25% of CVADs become occluded. There are multiple risk factors associated with development of a CVC occlusion, including location of the tip of the CVC, number and size of the catheter lumens, and the type of CVC.

These occlusions can occur soon after insertion of a device or develop at any time and may classified as:

- Thrombotic, or
- Non thrombotic.

Thrombotic occlusions (58%)

These result from the formation of a thrombus within, surrounding, or at the tip of the catheter. When introduced into the body, all catheters begin to accumulate fibrin - the body's natural attempt to protect itself against a foreign body. The fibrin starts to form a layer around the outside of the catheter within minutes of insertion, beginning at either the line entry site or where the tip contacts the vein.

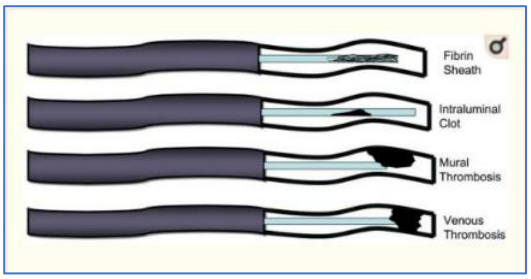
Types of thrombotic occlusions include:

- Fibrin tail/flaps – these extend from the catheter tip but are drawn inward, blocking the opening of the catheter lumen on aspiration attempts resulting in an ability to infuse fluids but an inability to withdraw blood.
- Intraluminal thrombus – occurs when blood refluxes inside the catheter lumen typically after coughing, inadequate flushing after blood draws or after checking for blood return, or improper use of flush syringes.
- Mural thrombus – forms where the catheter touches or "rubs" the vein wall typically at the entry site, anywhere along the catheter path, and the catheter tip.
- Fibrin sheath – forms when fibrin adheres to the external catheter surface, which may include the entry site, and may encase all or part of the catheter like a sock and may completely cover the opening of the catheter tip.

[3] All information in this section sourced from https://www.cathflo.com/catheter-management/types-catheter-occlusions.html and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342964/

Graphically, the above can be shown in Figure 3.

Figure 3: Types of thrombotic occlusions



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2814365/

Non thrombotic occlusions (42%)

Non thrombotic occlusions include:

- Precipitates – can form as a result of drug crystallization, drug-drug incompatibilities, or drug-solution incompatibilities.
- Mechanical obstructions – may occur from malpositioning the catheter during insertion, coughing, sneezing arm movements etc.
- Consequences of malpositioning in general.

How and why CC agents are administered[4]

While the formalized procedures detailed below pertain to Canada, they provide context for their application worldwide.

The Journal of the Canadian Vascular Access Association (Volume 7, Supplement 1 – 2013) issued its "Occlusion Management Guideline for Central Venous Access Devices (CVADs)".

Included in the document was the rationale for the management of occlusions vs catheter replacement:

Catheter salvage is the preferred approach to the management of CVAD occlusions.[14,24,26–28,46] Restoring patency to the CVAD (rather than device removal) is less time consuming, is more convenient, and ensures limited interruption of therapy, reduced trauma and psychological stress to the patient, reduced risk of complications, and decreased costs.[24,26,28] A CVAD remains in situ as long as the device is functional and required. Restoration of catheter patency supports the longevity of the device's lifespan, as many CVADs can have a lifespan of multiple years.[28] The cost of device replacement can be an estimated $200 to $1,500[5] and far exceeds the cost of thrombolysis (which has a drug cost of approximately $65) as well having higher costs of supplies, nursing time, and clinic time.[28,47] (please refer to the original document for the sources references in this text)

[4] http://www.improvepicc.com/uploads/5/6/5/0/56503399/omg_2013_final_revised.pdf

[5] MDsave quotes the cost of a Tunneled Central Venous Catheter (CVC) ranging from US$4,011 to US$6,558. Source: https://www.mdsave.com/procedures/tunneled-central-venous-catheter-cvc/d480f8cb . These prices exclude the cost of the replacement procedure.

As background for the guideline: In 2012, the Canadian Vascular Access Association (CVAA) recognized a lack of standardized practice across the country for managing occlusions of CVADs not specifically used for hemodialysis.

Consequently, a national task force of nurses in Canada was brought together to create a guideline, based on current evidence and clinical expert recommendations…to define the recommended strategies for safely and effectively managing CVAD occlusions in patients in Canada.

Health care professionals to whom the practices were targeted include but are not limited to the following:

- Nurses
- Physicians
- Radiology technicians and technologists
- Respiratory therapists
- Pharmacists

The document detailed the following steps pertaining to the successful restoration of catheter patency:

1. Assessment of CVAD patency
2. Assessment and Management of Mechanical Occlusion
3. Assessment and Management of Thrombotic Occlusion (details provided in Appendix II: Occlusion Management Guideline for CVADs)
4. Assessment and Management of Chemical Occlusion
5. Prevention of CVAD Occlusion

What is a catheter?

A catheter is a thin, flexible tube that can put fluids into your body or take them out. Catheters are used extensively to administer treatments to patients for such purposes as dialysis, nutrition, antibiotic treatment and cancer treatment.

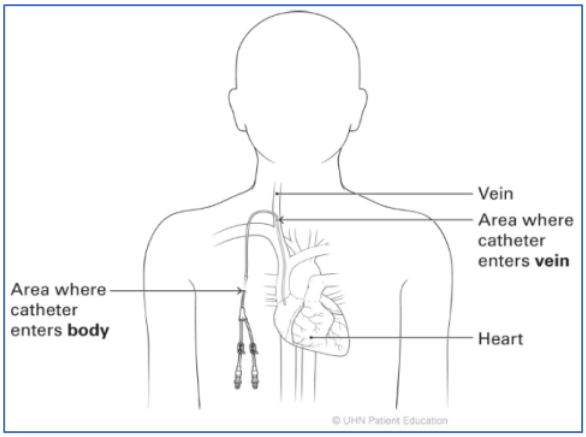
Central venous catheters (CVCs) are one of the most commonly use interventions for a critically ill patient. CVC-related thrombosis (CRT) is the most common non-infectious complication of CVCs insertion. There are various kinds of catheters (Figure 5), however, for this report we focus on CVCs in the US, as MBX's initial target market for the relaunch of Kinlytic® urokinase is catheter clearance (CC). CVCs facilitate the consistent and timely infusion of antineoplastic agents, antimicrobial agents, blood products, and total parenteral nutrition as well the acquisition of blood samples for testing.

A CVC, also known as a central line, is long, soft, thin, hollow tube that is placed into a large vein (blood vessel). CVCs are inserted percutaneously (through the skin) and the most common insertion sites are: subclavian (upper chest), jugular (neck) or femoral (groin). This type of catheter has special benefits in that it can deliver fluids into a larger vein, and that it can stay in the body for a longer period than a usual, shorter IV.

Many CVCs are multi-lumen catheters – a single catheter with more than one internal channel (called a lumen). A different intravenous infusion can be connected to each lumen, and the fluid will usually exit at a slightly

different point along the catheter. A double lumen catheter has 2 lumens. In Figure 4, an example of a tunnelled 2-lumen CVC is shown.

Figure 4: Central Venous Catheter (CVC)



Source: UHN Patient Education

A CVC differs from an intravenous (IV) catheter, which is placed in the hand or arm (also called a "peripheral IV"). The Peripherally Inserted Central Catheter (PICC) is another type of CVC. A PICC line is an IV that is inserted peripherally, usually in the bend of the arm. This catheter is very long and thin, and is advanced until the tip of the catheter is located in a large central vein. They are typically inserted into longer stay patients if it becomes difficult to find a suitable IV site.

There are reusable and single-use CVC insertion kits[6].

The evolution of vascular access within the medical field was described in an Association for Vascular Access Position Paper (September 2019) as:

Over the past 2 plus decades, vascular access has grown into a recognized clinical specialty, requiring specialized knowledge, training, skill development and experience. The combination of this experience and knowledge establishes a high quality of vascular access holistic care, providing greater opportunities for improved device and patient outcomes, minimize the risk of complications and impact on the patient experience.

Market size

Here, we focus on the:

- Macro perspective, the global catheter market; and from a
- Micro perspective, the CC market.

Bear in mind that the Sequel Agreement's initial target market is for CC in the US market.

[6] https://pubmed.ncbi.nlm.nih.gov/22492185/

Global catheter and central venous catheter (CVC) markets

The global catheter market was estimated at US$45.26bn in 2020 and was forecast to grow at 6.4% p.a. from 2021-2028[7]. The types of catheters covered in the report are listed in Figure 5.

Figure 5: Types of catheters

Cardiovascular	Urology	Intravenous (inc. CVC) (1)
Neurovascular	Specialty	

Source: https://www.grandviewresearch.com/industry-analysis/catheters-market-analysis

(1)- The four main types of central venous access devices (CVADs) are: peripherally inserted central catheters (PICCs), nontunnelled CVADs, tunnelled CVADs, and implanted vascular access devices (IVADs).

Kinlytic® urokinase is targeted at the intravenous catheter market. In 2020, various studies estimated this subset of the *global* catheter market at:

- US$1.1bn growing to US$1.5bn by 2026 (5.4% p.a.)[8], with the US currently accounting for 34.17% of the global market, or US$375.8m;
- US$763m growing to US$860m by 2026 (~2.0% p.a.)[9], with over 27m CVC insertion procedures performed annually;
- US$889.9m in 2019 growing to US$992.9m in 2025 (2.8% p.a.)[10]

Catheter clearance market for Thrombolytics

Around 7-8 million catheters are placed annually in the US market. CVCs/CVADs are a subset of that market, and ~25% become occluded and require lytic therapy. This represents the initial CC market and is described by the monopoly sales of Cathflo® Activase® in Figure 6 below.

Figure 6: Cathflo® Activase® sales (US$m's)

Source: MBX presentation

During the 11-year review period, Cathflo® Activase is the market leader and its sales have grown at 6.5% p.a. from US$172m in 2010 to $342m in 2021.

[7] https://www.grandviewresearch.com/industry-analysis/catheters-market-analysis
[8] https://www.reportlinker.com/p05899197/Global-Central-Venous-Catheters-CVCs-Industry.html?utm_source=GNW
[9] https://idataresearch.com/product/central-venous-catheter-market/
[10] https://www.marketwatch.com/press-release/central-venous-catheter-market-analysis-size-share-trend-growth-and-forecast-2025-2021-12-15

MBX's analysis of the Kinlytic market opportunity

To provide context for the evolution of the CC market, here we provide a summary of the history of CC market from MBX's perspective with a more detailed history in Appendix I: History of Abbokinase®/Kinlytic® urokinase.

From 2000 to 2014, MBX quantified its urokinase opportunity as a US$300m opportunity as follows:

- In 1998, Abbott Laboratories' urokinase products represented half the total market for thrombolytic drugs in the United States. Abbott's product Abbokinase® was the leading product used in hospitals to treat patients with peripheral clots (Peripheral Occlusive Disease) with 93% of the sales in the category at US$206m[11].
- Abbott's product Abbokinase® Open-Cath® held 100% of the CC market with sales of US$68m. Abbokinase® and Open-Cath® sales totalled US$274m. This suggests that the CC market has increased ~5.0x from 1998 to 2020 (US$68m to US$345m)
- The other main thrombolytics, Genentech's Activase® (t-PA) and Centocor's Reteplase® occupied the other half of the market in the coronary category where products are used for treatment of heart conditions (AMI). Streptokinase products occupied less than 1% of the market. Sales of all non-urokinase thrombolytics totalled US$273m in that year.
- Abbott responded to the FDA citing of cGMP violations at its urokinase manufacturing facility by ceasing production of the drug while selling its remaining product inventory into early 1999. Abbott's urokinase was not available to clinicians until the company re-launched the product in late 2002. During this period Activase, Reteplase and a similar new drug, Tenecteplase shared the thrombolytics market. Combined sales of all products fell 40% in 1999 to US$332m in the absence of urokinase. Sales of other thrombolytics did increase, but did not replace the void left by urokinase. Patients that would have been treated with urokinase were treated through surgical procedures.

Abbott re-launched its therapeutic product, Abbokinase®, in October 2002 with only one indication (Pulmonary Embolism). Abbott did not return to the CC market, consequently, it generated sales of US$28m during its first full year back on the market in 2003, US$32m in 2004 and sales were trending towards US$80m in 2005 even though Abbott withdrew sales and marketing support of Abbokinase as it divested its hospital products division at that time.

In the absence of Abbott's Open-Cath®, Genentech introduced its reformulated tissue plasminogen activator (t-PA) product for CC which now holds 100% of that market.

What is urokinase?

Prior to 1998, urokinase was the only FDA-approved medication used to treat thrombotic catheter occlusions.

At a high level, urokinase is a thrombolytic drug, a "clot-busting" drug, as it helps your body produce a substance that dissolves unwanted blood clots. Urokinase breaks up blood clots by converting plasminogen, an inactive precursor, into the enzyme plasmin, which in turn degrades fibrin protein strands that are essential to the structural integrity of a clot.

[11] From IMS

Kinlytic® urokinase (formerly Abbokinase®) is therefore described as a plasminogen activator[12] (PA, another name for urokinase is urinary-type plasminogen activator, or u-PA, to distinguish it from the tissue-type plasminogen activator, t-PA). All plasminogen activators catalyze the production of plasmin, the primary enzyme involved in dissolving blood clots.

While there are commonalities in the mode of action for urokinase and t-PA, urokinase has some advantages for treatment of peripheral clots (Pulmonary Embolism, Deep Vein Thrombosis, Peripheral arterial occlusive disease) [13].

Despite this, t-PA in the form of Roche Genentech's Cathflo® Activase® is currently a market monopoly for CC and the balance of this report focuses on urokinase, in the form of Kinlytic® urokinase, and its planned reintroduction to the specific CC market.

Urokinase is a plasminogen activator (u-PA) when found *in vivo* and is normally involved in intracellular signaling pathways and cell proliferation, adhesion, and migration[14]. It is an enzyme (protein) produced in the kidney (and found in the urine) that can also stimulate the body's natural clot dissolving processes. It is short-lived in blood circulation, and it is rapidly cleared by the liver. Its primary substrate of this enzyme in thrombolysis is plasminogen, which is an inactive form (zymogen) of the serine protease plasmin. Activation of plasminogen to plasmin by a plasminogen activator triggers a proteolytic cascade that, depending on the physiological environment, participates in thrombolysis or extracellular matrix degradation[15].

Due to its short half-life of less than 15 minutes, re-thrombosis may occur within 15–30 min of therapy cessation. Hence, heparin is commonly used during and after urokinase administration to minimize this risk.

There are two forms of urokinase, which differ in molecular weight but have similar clinical effects. Urokinase is a serine protease[16]. In cells, urokinase is produced as an inactive zymogen form, single chain urokinase or pro-urokinase, that is cleaved by plasmin to produce the active form of urokinase, also known as two-chain urokinase type plasminogen activator or uPA. Two molecular forms of active two-chain urokinase are known. These are High Molecular Weight Urokinase (HMW-UK) and Low Molecular Weight Urokinase (LMW-UK).

Upon further proteolysis, the A-chain of HMW-UK is degraded to a small polypeptide to form LMW-UK (Kinlytic drug substance), with a total molecular weight of 33,000 Da.

HMW-UK, at 55kDa molecular weight, is made up of an A-chain and a B-chain that have very different functions. The B-chain contains the catalytic domain, the serine protease that is responsible for urokinase's thrombolytic activity.

The A-chain contains a receptor binding/growth factor domain and a structural Kringle domain, which perform other non-therapeutic functions. It is the A-chain and its associated functions that may differentially impact the safety/bioavailability/biodistribution of the HMW-UK molecule.

[12] Plasminogen activators lead to the breakdown of the fibrin lattice structure in blood clots
[13] https://www.wikidoc.org/index.php/Urokinase
[14] https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/urokinase
[15] https://www.wikidoc.org/index.php/Urokinase
[16] Serine proteases are enzymes that cleave peptide bonds in proteins

Microbix' Kinlytic LMW-UK does not contain the A-chain and, therefore, does not include the receptor binding/growth factor domain. The key difference between two molecules is that the HMW-UK form has the receptor-binding/growth factor domain. This domain binds the urine-derived Plasminogen Activator Receptor (uPAR), which is present on the surface of a number of cell types. HMW-UK/uPAR binding causes cellular signaling cascades that cannot be activated with LMW-UK.

HMW-UK/uPAR binding to the A-chain is well-known to initiate a cascade of events leading to general proteolysis[17], degradation of the extracellular matrix (ECM), cell migration, cell invasion, metastasis[1819], and angiogenesis[20]. Further, the HMW-UK/uPAR system has been shown to play a role in the spread of solid tumors. Higher levels of HMW-UK and uPAR correlate with clinical outcome in a variety of malignancies, the upregulation of the uPA system being associated with poor prognosis.

With a receptor binding function in place for HMW-UK, biodistribution could also be altered relative to LMW-UK. One of LMW-UK's best features for safety is its complete and rapid elimination from peripheral circulation, whereas HMW-UK could be locally retained and, in the worst case, cause uncontrolled effects upon binding to uPAR. There are therefore good reasons to predict that LMK-UK should be superior to HMW-UK in terms of product safety and ease of sufficient characterization.

MBX is planning to market its LMW urokinase as Kinlytic® urokinase and will compete with recombinant t-PA (e.g., alteplase) as a thrombolytic drug.

How urokinase is made

The manufacturing process used to make Kinlytic® urokinase (LMW-UK) involves taking donated human kidney cells and putting them in a cell culture medium in a controlled environment. Urokinase is given off by these cells as they grow and metabolise. Many European drug manufacturers make urokinase (but only HMK-UK) from vast amounts of human urine (e.g., 1,500 L for one dose), but the proprietary method originally developed by Abbott Laboratories is faster and cheaper[21]. These production processes use donated human neonatal kidney cells (HNK) from donors who died from non-infectious causes.

Neonatal kidney cells can be cultured to secrete large quantities of urokinase by propagating small seeding quantities of donated human kidney cells into greater numbers of urokinase-excreting cells using roller-bottle mono-layer cultures. HNK cells behave as a normal adherent cell line in cell culture processes, no different to the standard MRC-5 or 293 cell lines.

Note that absolutely no fetal tissue is used in the production of Kinlytic™. Kidney donations are obtained exclusively in the United States from neonates (birth to 28 days) for whom death has not been attributed to

[17] Danø K., et al. *Adv. Cancer Res.* (1985) **44**:139–266.

[18] Andreasen P. A., et al. *Int. J. Cancer* (1997) **72**:1–22.

[19] Laufs, S., et al. *Cell Cycle* (2006) **5**:1760–71.

[20] Mazar A. P., et al. *Angiogenesis* (1999) **3**:15–32.

[21] https://sst.semiconductor-digest.com/1999/03/contamination-threat-prompts-fda-to-add-warning-to-urokinase-shipments/

infectious causes and that have exhibited no evidence of an infectious disease based, before analytical testing, on an examination of the maternal and neonatal donor medical records.

It's worth bearing in mind that each tissue donation provides for up to 5 years of production and MBX already has ~10 years of production in its existing cell banks.

During the manufacturing process, cells are tested at multiple stages to confirm the absence of viruses using *in vitro* and *in vivo* tests that can detect a wide range of such viruses. The manufacturing process used for this product has been validated in laboratory studies to inactivate and/or remove a diverse panel of spiked model enveloped and nonenveloped viruses and includes purification steps and a heat treatment step (10 hours at 60°C in saline solution). A single vial of Kinlytic™ contains urokinase produced using cells derived from no more than one or two donors.[22]

The finished product (powder) can be kept at room temperature for the CC indication.

MBX's CC reintroduction strategy

MBX had a well-identified reintroduction strategy for Kinlytic® urokinase which, at a high level, is outlined as follows:

- **Reintroduce the Gold Standard**. Urokinase was the standard of care for the clearance of blocked biomedical catheters, including catheters placed deep within the body (Central Venous Catheters or CVCs).
- **Re-establish safety and efficacy on the reintroduced product**. Urokinase has treated over 4 million patients during its over 20-year history in the clinic.
- **Address a growing market.** Various market studies show that the global CVC market is forecast to grow at between 2.8%-5.4% p.a. Within in this context, the US CC market has grown at 6.5% p.a. over the past 11 years.
- **Convert a market monopoly to a duopoly.** Genentech's Cathflo® Activase® is the 100% market leader. Reintroduction of Kinlytic® urokinase is expected to result in a strong duopoly.
- **Benefit from a de-risked regulatory pathway.** Kinlytic® urokinase is a novel biologic (there is not a biosimilar in play). It has existing FDA and Health Canada approvals for both pulmonary embolism and catheter clearance clinical indications. The FDA has agreed in principle that it is open to the reintroduction of Kinlytic® urokinase for CC subject to a straightforward regulatory process.

We believe that this strategy will be assumed by Sequel.

Below, we provide details as to MBX's introductory strategy within the contexts of:

- Market research driven penetration strategy
- Barriers to entry
- Project economics
- Regulatory pathway

[22] https://www.rxlist.com/kinlytic-drug.htm

Kinlytic® urokinase market penetration strategy

MBX undertook two independent market research studies to determine market acceptance of the return of Kinlytic® urokinase to the market. Both found the return of urokinase would be welcomed.

The first, in 2007, was conducted by Kendall Gay Consulting. It comprised thirty (30) telephone interviews with a variety of specialists (interventional radiologists, nephrologists and dialysis and oncology nurses). The results found that:

- Doctors and nurses were both somewhat satisfied with t-PA for CC as it could be more effective, but also too expensive and somewhat inconvenient
- Nurses found t-PA requires refrigeration, potential for mixing errors and wait times up to 120 min
- Decision making factors include: Doctors – predictability and safety; Nurses – speed of lysis and safety
- Key wants/needs: Doctors – safety, nurses – increased convenience, Both – cost decrease
- Reason for urokinase withdrawal from the market was unclear to them, but molecule is acceptable
- Urokinase dosage format is an attractive improvement, adding to safety and convenience

The second market study was conducted in 2018 by a group of US based marketing consultants. Forty (40) hospital staff involved in decision making or performing CC were interviewed comprising 18 nurses, 12 hospital/clinic administrators and 10 doctors. The primary results included:

- Safety/Side effects/Bleeding risk – important to 92.5%
- Efficacy/Outcomes/Predictable – important to 90%
- Cost savings/Price/DRG economics – important to 87.5%
- Ease of use/Convenience – important to 85%
- Company support/Knowledgeable reps – important to 72.5%
- Speed/Time to clear/Fast lysis – important to 57.5%
- Use with other agents – important to 35%
- Contracting/Volume-tiered to Drive use – important to 17.5%

Consequently, the study confirmed:

- The US CC market is open to an alternative thrombolytic i.e. wants an alternative to Cathflo® Activase®
- Kinlytic® urokinase has properties that will enable to take market share from Cathflo® Activase®:

Cathflo® Activase® is owned by Roche Holdings Ag, a CHF300.8bn/USD314.7bn market cap company that generated revenues of CHF62.8bn/US$65.7bn in 2021. Within this context, Cathflo® Activase® is a US$345m revenue stream, hardly enough to influence total revenues. Accordingly, MBX has suggested positioning Kinlytic® urokinase vis a vis Cathflo® Activase® with:

- Price discount of ~20%
- Improved efficacy over shorter periods
- Similar safety profile
- Stored at room temperature with longer stability (longer expiration)
- Alternative source as disruptions with Cathflo® Activase® have occurred
- Dosage kit easier to administer (Kinlytic® urokinase comes with WFI[23] syringe and urokinase vial, vs Cathflo® Activase® which requires refrigeration, a WFI vial, syringe and transfer set)

[23] WFI syringe is prefilled with diluent for the reconstitution of the drug

Hence, MBX's go-to-market strategy to reinstate Kinlytic® urokinase as the proven safe thrombolytic of choice for CC includes:

- Educate key hospital/clinical decision makers, foster and leverage thought leader relationships and promote FDA approved indication(s)
- Simultaneously re-establish brand awareness and promote availability through consultive selling and support
- Target the following groups with targeted messaging:
    - Nurses – Ease of use, convenience, predictable outcomes, speed/fast lysis
    - Administrators – Safety (mitigate clinical liabilities); cost savings; contracting (volume-tiered to Drive use); product support (access to specialists)
    - Physicians – predictable outcomes/Proven efficacy; Safety/Side effects; Cost/Savings/Price; Support (knowledgeable reps)
- Given Cathflo® Activase's ® size vs total Roche revenues, it is not expected to be given any priority with regards to growing market share.

We believe that the CC market is open to an alternative to Cathflo® Activase®. In this regard, Kinlytic® urokinase has an established track record, it will be marketed as a cheaper, more convenient alternative, and on this basis should achieve a targeted 40% market penetration.

Barriers to entry

Kinlytic® urokinase is a biologic. USA Biosimilar Regulations require significant cost and effort in analytical, preclinical and clinical studies. If a monopoly were to evolve into a duopoly by the re-introduction of Kinlytic® urokinase, additional parties wishing to enter the market would find it increasingly difficult to penetrate such a market.

In addition, no biosimilar LMW-urokinase or t-PA products have been approved in other major markets, such as Europe or China. We are not aware of any new thrombolytic approvals in the past decade.

Despite coming off patent in 1993, LMW urokinase still has no competition. One of the reasons includes the technical hurdles to manufacture LMW urokinase:

- It is a two-chain glycoprotein and, like t-PA, has complex post translational secondary and tertiary structure
- Urokinase in particular is difficult to manufacture by recombinant means. MBX is one of the only companies that possess the roller-bottle and cell culturing expertise to facilitate production.
- Proprietary reagents and cell banks would have to be developed (refer to roller bottle comment above)
- Analytic comparability is confounded by Kinlytic® urokinase excipients

We believe that development of a biosimilar version of Kinlytic® urokinase will not begin until it has been re-established in the market, suggesting the earliest biosimilar approval is 7-10 years away, if it ever happens.

Project economics for CC

MBX sought a financial partner to return Kinlytic® urokinase to the CC market. We believe that its objectives were satisfied in whole and in principle by the Sequel agreement.

Primary considerations in this regard, included:

- Cost to commercialization were estimated at US$18.2m
- Sequel will file the sNDA submission estimated to take 36 months
- A single Phase 3 bridging trial is required to support sNDA at a cost of US$1.7m (incl. in US$18.2m) and should take 6 months. The randomized, double-blind, placebo-controlled multicentre trial will support analytical and non-clinical comparability, with efficacy endpoint being one or two doses of urokinase at 90 or 180 minutes. In short, **we estimate that Sequel will record first sales around 2028**.

Project specific estimates include:

- Cumulative 10 year CC sales of $1.6bn
- Projected CC product margin of >70% (using contract manufacturers)
- IRR >80% for CC use, in the US
- Modelling CC sales in year 5 of US$183m and year 10 of US$240m
- In perpetuity CC sales growth of ~5.6% p.a.

All costs and timelines were validated by 3rd parties. Also, the FDA has already provided input that it is amenable to the return of Kinlytic® urokinase to the market (see below).

However, we note that we have made our own assumptions in our discounted cash flow model (Figure 7).

Regulatory pathway for US re-introduction

Kinlytic® urokinase is already FDA-approved – its former NDA was deemed to be a BLA on 23/3/20[24]. A focus of the supplemental NDA (sNDA, now sBLA) is therefore simple qualification of a new manufacturing site and updated production process for the approved product.

MBX held a meeting with the FDA in April 2017 to discuss the potential to reintroduce Kinlytic® urokinase. MBX provided proposed plans to the FDA on:

- Manufacturing (process, testing materials):
    - Existing, and validated as viable, cell bank inventory to be used with updated testing. ~10 years' worth cell inventory for CC is currently stored in liquid nitrogen at a 3rd party site.
    - Drug substance purification will use modern methods thereby minimizing impurities
    - Animal products use in culture will be reduced (but not removed entirely)
    - No change in drug product manufacture (standard lyophilisation per the approved and marketed product)
- Comparability (analytical, pre-clinical and clinical)
- Phase 3 bridging study (discussed above), and
- Regulatory mechanism.

[24] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021846

The FDA agreed in principle it was open to the reintroduction of Kinlytic® urokinase subject to the usual regulatory steps, which include:

- Implement manufacturing and testing upgrades as discussed with the FDA
- Install the process in manufacturing facilities and prepare drug substance and drug product
- Perform comparability tests as discussed with the FDA, including a small confirmatory human clinical trail for the CC indication, and
- File a supplement to the approved BLA (sBLA)

The FDA agreed that the "Microbix plan, as modified by FDA input, is a reasonable path forward for urokinase for catheter clearance return to market". The FDA suggested improvements to the drug product testing and additions to the planned characterization strategy for the proposed new reference standard and the final new product. These suggestions are incorporated into the project plans. The FDA also agreed that two studies (analytical and non-clinical) would support comparability and made suggestions for protocol improvement which will be incorporated into the final protocols.

Valuation and Conclusion.

As detailed in Figure 1, several seminal events must occur prior to unlocking the full value inherent in KU. At a high level, the FDA meeting authorizing the commencement of comparability studies and Phase 3 bridging trial at a cost of ~$20m (~3.5 years to complete), culminating in the issue of the sBLA and then eventual penetration of a monopolistic market suggest that initial sales royalties to MBX could start ~2028.

Our analysis suggests that MBX/Sequel are well positioned to penetrate a monopoly. However, the reaction of Genentech/Roche to its monopoly position being penetrated remains a significant unknown.

Given MBX's strategy to partner with a third party who is bearing the regulatory/reintroduction/marketing costs, with MBX receiving a royalty off net top-line sales, the reintroduction of Kinlytic® urokinase is not expected to have any negative impact on MBX's core business.

Nevertheless, from an MBX shareholder perspective, the Sequel deal is a tangible first step in unlocking this value. We have historically attributed a $10m notional valuation to the KU asset and believe that this approach is now validated with the Sequel deal.

We will continue to use this approach but note that our KU valuation methodology will change as the KU product commercialization is derisked.

We believe that the successful reintroduction of Kinlytic® urokinase to the market could add around $1.10/share on a discounted cash flow basis (Figure 7), using the following assumptions:

Figure 7: Kinlytic® urokinase Discounted cash flow valuation (US$)

Factor	Input	Detail
Commencement	2028	
Urokinase revenues to Sequel	US$4.5m	TAM US$340m in 2020, growing to US$566m (6.5% p.a. to 2028). Market share 1% in year 1, KU priced at 20% discount
Tax rate	30%	
High growth period revenues	2028-2033	US$4.5m-US$155.1m (2033 achieves 25% market share)
Stable growth	2034-in perpetuity	3.0% (with KU growing to 40% market share by 2035)
Discount rate	30% (high growth) 8% (maturity)	
FD number shares	177m	
Royalty to MBX	10% of net sales**	NPV – C$1.10/share*

Source: KRC Insights *=rounded to nearest 10c, includes milestone and progress payments **=KRC Insights estimate

Alternatively, using a more simplistic approach: based on the assumption of what investors might pay for the KU opportunity in 2033, when Sequel is anticipated to achieve 25% market share, we drive an undiscounted $1.20/share in 2033 (Figure 8):

Figure 8: KU back of envelope valuation

		Input
2033 US catheter clearance market	US$ms	775 (growing at 6.5% p.a.)
Sequel KU market share		25%
KU revenues to Sequel	US$ms	155.1 (after 20% discount)
Royalty to MBX		10%
Royalty revenue to MBX		US$15.5m/C$20.7m
After tax (30%)	C$ms	14.5m
Per MBX share		0.08
Multiple		15x
Value in 2033		C$1.20

Source: KRC Insights

Given management's historical efforts to commercialize the KU asset, we ascribed a notional $10m value towards this asset. The Sequel agreement validates this approach, and we will continue to apply this notional valuation until FDA authorization.

At that stage, given mitigation of regulatory risk and the shorter time to market, we will move to one of the above-mentioned valuation methodologies to more fully reflect the value creation to MBX shareholders.

Appendix I: History of Abbokinase®/Kinlytic® urokinase

MBX has had a long history with urokinase. Initially, commencing in 1997 with the development of its own Thromoboclear™ and CathClear™. These projects were canceled in 1998 when MBX acquired Kinlytic® urokinase from IMRX.

Below are the histories of:

- Abbokinase®/Urokinase®
- ImaRX Therapeutics (IMRX-delisted)
- Genentech's Cathflo® Activase® (t-PA)

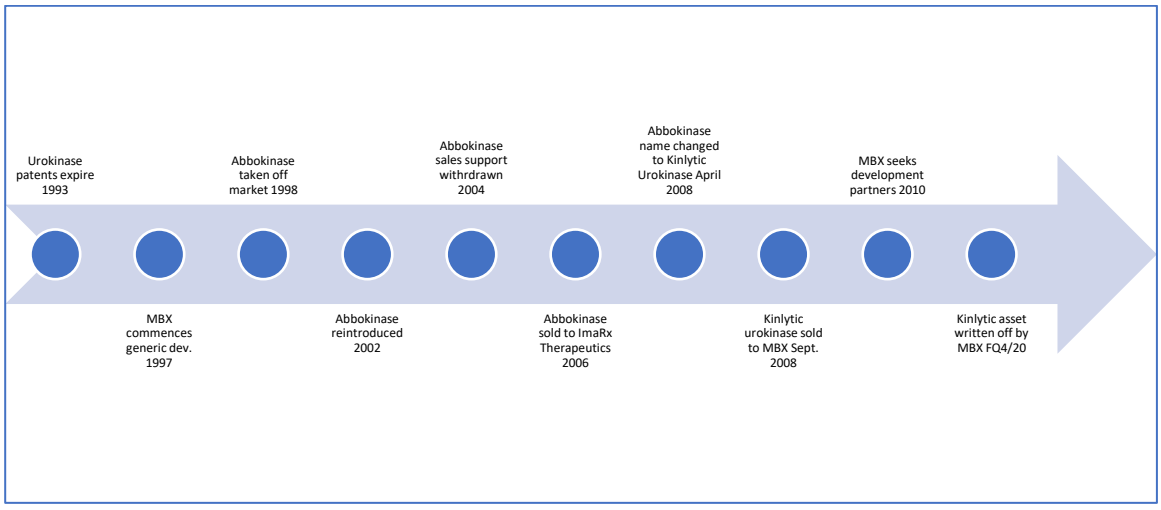
Abbokinase®/Urokinase®

Urokinase was discovered in 1947 and initially approved by the FDA in 1978. Prior to 1998, urokinase was the only FDA-approved medication used to treat thrombotic catheter occlusions[25]. It was withdrawn from the market in 1998. In 2002, at the time of its reintroduction, Abbott Laboratories estimated that Abbokinase® had treated over 4 million patients[26] . This was within the context of Abbokinase® being a thrombolytic therapy used to dissolve blood clots i.e. not just CC.

Hence, despite it being off the market for ~20 years, its 20 years as the market leader points to its well-established record of efficacy and safety.

Figure 9 shows a high-level overview of the history of urokinase.

Figure 9: Abbokinase/Kinlytic urokinase - high level overview



Source: KRC Insights

While below, we provide a detailed chronological overview of select events as they pertain to urokinase's history:

[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342964/
[26] https://www.biopharminternational.com/view/abbott-laboratories-receives-fda-approval-reintroduce-abbokinaser-urokinase

- **1978**: Abbott Laboratories' UK was approved as Abbokinase® by the FDA initially for massive pulmonary embolism but subsequently expanded for catheter occlusion clearance and acute myocardial infarction.
- **1991**: Urokinase was approved for use in clearing blood clots in biomedical catheters (Open-Cath®).
- **1993:** Key patents expired on urokinase.
- **1997:** MBX embarks on a strategy to develop a generic version of Abbokinase®, Abbott Laboratories' urokinase by raising $6.75m for the development and bulk manufacture of Thromboclear, a generic alternative to urokinase. Gensia Laboratories was appointed MBX's marketing partner for ThromboClear.
- **1998:** Abbokinase® was withdrawn from the market in December 1998 due to concerns over the *manufacturing process* (not the product), including failure to screen donors and test materials for infectious disease, and inadequate storage and handling of materials to prevent contamination with infectious agents. In short, the FDA observed "significant deviations from current good manufacturing practices (cGMP)". MBX completed pilot batches of ThromboClear, a generic form of urokinase for injection, under FDA GMP on schedule. It intended to capture approximately one-third of the US$250m urokinase market in the first three years of sales**.**
- **1999**: Abbott was allowed to resume shipping on 26 January 1999 after the FDA distributed an "Important Drug Warning Letter" on January 25, 1999, alerting physicians to a number of problems related to the *manufacture* of Abbokinase®, outlined the risks associated with Abbokinase® and encouraged users to consider alternative sources. Abbott was ordered to put this warning in the labeling for the drug. By mid-January 1999, many clinics and hospitals were out of the drug. Peak sales in 2008 were ~US$300m. In the last half of fiscal 1999, MBX scaled back its generic thrombolytic (urokinase) development operations (as an alternative to Abbott Laboratories' Abbokinase®) due to legal issues between Abbott/BioWhittaker and MBX. This resulted in delays to its urokinase commercialization efforts.
- **2000**: The legal dispute between Abbott and MBX was resolved definitively. Any doubt about the ownership of MBX's urokinase technology was removed as the US District Court for the District of Maryland granted MBX's motion to dismiss Abbott's lawsuit against Microbix. Abbott subsequently gave up its right of appeal.
- **2001**: MBX was in late-stage discussions with potential marketing partners and looked forward to concluding an agreement in 2001.
- **2002:** After revising its manufacturing processes to the FDA's satisfaction, in October 2002 Abbott Laboratories obtained FDA approval to resume commercial sales of Abbokinase®, but with fewer indications than before. According to the product's new labelling, urokinase was now indicated for the lysis of acute massive pulmonary emboli and pulmonary emboli accompanied by unstable hemodynamics. Previously approved labelling included lysis of pulmonary and coronary emboli and for the clearance of IV catheters. The narrower indication was to speed up the approval process. *However, we note that FDA and Health Canada approval remains valid for the original indications, which includes clearance of IV catheters*. In November 2002, MBX's ThromboClear™ was licensed to Genpharm Inc. of Toronto, a division of Merck Generics. MBX established a cGMP supply of cells that would support ongoing manufacturing. Genpharm's drug substance manufacturing site was renovated to support product launch.
- **2003:** Despite not returning to the CC market, Abbott generated sales of US$28m during its first full year back on the market in 2003. Sales reached US$32m in 2004 even though Abbott withdrew sales and marketing support of Abbokinase as they divested their hospital products division.

- **2004**: Genentech halted its sales and marketing effort in 2004 when it decided to divest its thrombolytic assets. The FDA's approval of Abbokinase® was not withdrawn or suspended in 2004 and has not been withdrawn or suspended at any time since then.
- **2005**: In September 2005, IMRX acquired Prolyse and Open-Cath® assets from Abbott Laboratories for US$24.0m. Both were in advanced stages of development and the purchase included related Phase 3 clinical data. It was unsure at that time if further clinical trials were required. Open-Cath® showed in two Phase 3 multinational clinical trials to be generally well tolerated and active as a treatment for clearing blocked intravascular catheters. Between 1990 and 2002, Abbott Laboratories evaluated Open-Cath® in 11 clinical trials involving 1,941 patients. Five of these clinical trials primarily evaluated the ability of Open-Cath® to clear blood clots from central venous catheters, including two Phase 3 clinical trials for CC. Methods of production patents expired in 2014/2015.
- **2006**: In January 2006, MBX assumed the costs to commercialize urokinase as Genpharm was sold by Merck to Mylan Inc. and the rights to the ThromboClear® and CathClear® urokinase products were returned to MBX along with the new urokinase manufacturing facility (Skyway). This transaction released MBX from any further obligations to Genpharm. Genpharm transferred certain inventory, equipment and leaseholds to MBX in exchange for a $2.0m contingent payment to be made 120 days following the first commercial sale of the generic Urokinase, ThromboClear. This obligation was voided upon the 2008 acquisition of the Kinlytic® assets because MBX abandoned the development of the generic version of urokinase. In April 2006, MBX took steps toward commercializing urokinase with an exclusive collaboration agreement with Angiogen LLC, the owner of the patent estate for use of urokinase cancer therapy, to finance Phase I and II clinical trials. In April 2006, Abbott Laboratories exited the business when IMRX acquired from Abbott Laboratories the assets related to Abbokinase®, refer to ImaRx Therapeutics, Inc section below.
- **2007**: The MBX/Angiogen agreement expired in 2007.
- **2008:** Several developments occurred:
  - On 30 January 2008, IMRX announced that it was emphasizing growing the market for urokinase vs its primary strategy of developing SonoLysis. This move included substantial layoffs.
  - On 7 April 2008, ImaRx Therapeutics, Inc. (IMRX-N) announced that it had received approval from the FDA to change the brand name of Abbokinase® (urokinase) to Kinlytic™ (urokinase for injection). Its NDC changed from 24430-1001-01 to 24430-1003-1. It was approved for the following indications in adults:
    - Lysis of acute massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments.
    - Lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.
  - On 17 April 2008, IMRX announced that the US$15.0m promissory note payable to Abbott Laboratories for Abbokinase® was satisfied in full by way of US$5.2m cash payment. The Note was cancelled and full title re-vested with IMRX.
  - On 6 May 2008, IMRX entered into a Letter of Intent (LOI) with respect to the acquisition by MBX of ImaRx Therapeutics' urokinase inventory and related assets for US$17 million in cash. On 10 June 2008, IMRX and MBX terminated the LOI due to MBX's inability to raise funds. Also, IMRX was to terminate all staff except for the President/CEO.
  - On 24th September 2008, MBX acquired all of the assets relating to the approval and sale of Abbokinase® rebranded as Kinlytic™ in the United States, including the New Drug Application (NDA 21-846) filed with the U.S. Food and Drug Administration (FDA) from ImaRx Therapeutics, Inc. of

Tucson, Arizona, (IMRX-Q) for US$2.0m cash. Upon receiving FDA release of the Urokinase inventory subject to a May 2008 Approval Letter, a further US$2.5m bonus was to be paid to ImaRx. The acquired inventory had a retail value of more than US$35m once released by the FDA. Sales for 2007 were over US$10m. Pursuant to the Agreement Microbix also assumed all regulatory and commercial responsibilities for urokinase as of September 23, 2008. Per NDA 21-846, Kinlytic™ is indicated in adults:

- For the lysis of acute massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiples segments.
- For the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

MBX positioned itself as the only company with the technical know-how and expertise to manufacture the Urokinase and was expecting to expand its manufacturing capacity to supply ~$70m-$100m in retail value of Urokinase. The Kinlytic® inventory was to be sold to existing hospitals in the US, and product manufactured in Toronto was expected to be launched in 3 years. MBX intended to then expand the market to its former market size of $300m. Further, two new indications were to be launched for biomedical catheters and a third indication for treatment of solid tumors will be developed.

Sales of Kinlytic® were expected to make MBX cash flow positive in the near term thereby providing funding for the installation of the Kinlytic process into the Skyway urokinase manufacturing facility and for the ongoing development of the product to expand its approved indications into Catheter Management, Oncology and Ophthalmology. MBX expected to enter reintroduce urokinase to the market for CC with minimal regulatory risk as it was previously approved by the FDA for CC. At the time of acquisition, the PE and CC market was estimated at $120m p.a.

- **2009**: MBX signed a marketing and supply agreement with Riso Pharma granting exclusive rights to market Kinlytic® urokinase throughout the Middle East. Riso agreed to buy not less than 50,000 Kinlytic® urokinase vials over the next three years. Purchased urokinase inventory expired in 2009.
- **2010**: MBX received marketing approval for Kinlytic® in the first fiscal quarter 2010 from Health Canada. MBX awaited Health Canada's authorization to distribute LMW-Urokinase production lots in inventory, so that clinical trials could be funded and sales could begin in Canada. Extensive discussions were held with several interested companies regarding a potential partnership for the development of Urokinase. A potential US$200k bonus was to be paid to IMRX upon FDA release on acquired inventory no longer applied as the date of sale of acquired inventory had passed. MBX stated that its leased Skyway manufacturing facility in Toronto could supply up to $70m of Kinlytic® urokinase in retail value
- **2011**: In the year, extensive discussions were held with several interested companies regarding a potential partnership for the development of urokinase. MBX was progressing with commercialization plans, but noted that the product will require 36 months for market release following arrangement of financing from a marketing partner. In addition to the existing indication of thrombolytics, three new potential indications were identified: two for catheters and the last being for treatment of solid tumours.
- **2012**: MBX partnered with Zydus Cadila, an Indian company, by way of a licensing agreement. MBX provided an exclusive license to the intellectual property and manufacturing methodology for development and manufacture of urokinase in India for sale into the US and other countries. Future

growth of the (thrombolytic) market was envisioned with the possibility of launching two new indications related to biomedical catheters. Regulatory approval was expected in 2014.

- **2013**: In December 2013, Zydus Cadila terminated the license agreement as "….further investment…would not (be) commensurate with the return we might expect"[27]. MBX believes that this was driven by major forex rate changes in 2013. MBX reduced its overhead by closing its urokinase manufacturing facility in favour of manufacturing by its commercial partners.
- **2017**: In April 2017, MBX conducted a formal consultation with the FDA about plans to refocus on CC. MBX interpreted the meetings as supporting of its refocusing strategy. Consequently, using third party quotations, it repositioned Kinlytic as follows: for an investment of US$30m over a period of three years, an investor could achieve annual North American sales of US$200m in the CC market. On 24 July 2017, Cameron Groome was appointed CEO and President.
- **2018**: MBX determined that an investment of US$20m would allow access to the $200m p.a. CC market. In April 2018, MBX engaged Torreya Partners LLC of New York to find investment partners for Kinlytic® urokinase. Partnering was needed to fund validation of new manufacturing. Outreach was undertaken to secure project funding from development partners.
- **2019**: MBX progressed toward an alliance to fund the re-introduction of Kinlytic® urokinase "clot buster" for its CC sub-indication. Confidential discussions continue with multiple qualified parties. MBX actively worked with a U.S. agent on outreaches to potential out-licensing and development partners, principally with companies focused on hospital-oriented drugs.
- **2020**: The former Abbokinase® NDA was deemed to be a BLA on 23/3/20. Due to lack of progress with regards to finding an investment partner, in FQ4/20, MBX wrote off its Kinlytic® urokinase asset resulting in a $3.1m charge. The COVID-19 pandemic also impacted partnering efforts by disrupting sales of hospital-oriented specialty pharma companies.

ImaRx Therapeutics, Inc. (IMRX-Q, delisted)

In this section, we provide detail on IMRX's acquisition of Abbokinase® as some of the requirements and obligations carried over to MBX when it acquired the Kinlytic® urokinase assets.

On April 10, 2006, IMRX entered into an asset purchase agreement with Abbott Laboratories to acquire its entire remaining finished-product inventory of Abbokinase®, all regulatory and clinical documentation, validated cell lines, and intellectual property rights, including trade secrets and know-how relating to the manufacture of urokinase using the tissue culture method. The consideration consisted of US$5.0m in cash and a 6% non-recourse promissory note for US$15.0m that matured on December 31, 2007. The note was secured by the acquired inventories and related assets and an escrow of 50% of proceeds from the sales of such inventories in excess of US$5.0m, up to a maximum escrow of US$15.0m, and was subject to certain offsets in the event of a failure to transfer certain related distribution contracts.

The acquired indication was for Acute Massive Pulmonary Embolism. There were no patent rights associated with Abbokinase®. To sell Abbokinase® for the treatment of acute massive pulmonary embolism, IMRX was required to continue an ongoing 200 patient immunogenicity clinical trial that commenced in 2003. IMRX was planning a catheter occlusion prophylaxis indication for Abbokinase® or Open-Cath®. Abbokinase® was shown

[27] Cadila Healthcare Limited Q1FY15 Post Results Conference Call transcript 30/7/14

in a Phase 3 clinical trial to be generally well tolerated and has demonstrated activity in preventing catheter occlusions when compared to heparin.

As part of this arrangement IMRX entered into a trademark license agreement with Abbott Laboratories in which it granted to IMRX an exclusive, non-transferable license, without any sublicense rights, to use the Abbokinase® trademark. IMRX must adhere to certain quality control standards when marketing and selling the Abbokinase® inventory under the trademark. This trademark license automatically terminates on the earlier to occur of the completion of IMRX's sale of the acquired Abbokinase inventory or the expiration date for all such Abbokinase inventory as of the date it was transferred to IMRX.

As part of the acquisition of Abbokinase®, IMRX acquired the cell banks that could be used to manufacture urokinase. If IMRX decided to sell urokinase beyond the existing acquired Abbokinase inventory, IMRX would need to undertake manufacturing and to demonstrate that its manufactured material is comparable to the urokinase IMRX purchased from Abbott Laboratories. To demonstrate this, IMRX would need to have its manufacturing process validated by the FDA and may be required to conduct additional preclinical studies, and possibly additional clinical trials, to demonstrate its safety and efficacy.

The Abbokinase product had no patent protection and IMRX had a one-half interest in a patent related to the manufacturing process for Abbokinase[28].

IMRX's agreement with Abbott Laboratories prohibited it from marketing urokinase under the Abbokinase® trade name beyond the expiration date of the inventory at the time it was acquired. In May 2007 IMRX obtained FDA approval to market urokinase under the trade name Kinlytic® and it began efforts to rebrand the product under the trade name Kinlytic®.

In January 2008, IMRX entered into a letter of intent with MBX which provided for manufacture of a long term urokinase supply. MBX was responsible for securing the necessary capital resources and obtaining approval from Abbott Laboratories. MBX did not have a facility at which it could manufacture urokinase[29], and would therefore need to obtain adequate funding to develop such a facility. The FDA would then determine whether compliance was satisfactory at facilities that manufacture Kinlytic® products.

On September 23, 2008, IMRX divested its urokinase business to MBX. Under the terms of the agreement, MBX acquired the remaining urokinase inventory and related assets and assumed full responsibility for ongoing commercial and regulatory activities associated with the product. MBX paid IMRX an upfront payment of US$2.0m and assumed up to US$0.5m in chargeback and other liabilities for commercial product that was currently in the distribution channel. An additional US$2.5m payment from MBX was contingent upon release by the FDA of three lots of urokinase that were subject to a May 2008 FDA Approval Letter.

On June 15, 2009, IMRX entered into the First Amendment to the Asset Purchase Agreement with Microbix which reduced the size of the contingent payment from US$2.5m to US$0.2m contingent upon receipt by MBX of written authorization from the FDA for the release of the urokinase lots on or before September 1, 2010. As of the date of this report, the FDA has not released the three urokinase lots, which are now long past their original expiry dates.

[28] As per S1 19/7/07 filing p18
[29] imARX Therapeutics Inc. 2007 10K p15

Genentech's Cathflo® Activase® (t-PA)

CC market leader, Genentech's Activase (alteplase) is a recombinant tissue plasminogen activator (t-PA) used for unclogging central venous access catheters (CVAC). Alteplase is approved for use in the restoration of function to occluded central venous access devices (CVADs). Alteplase causes the breakdown of a clot by inducing fibrinolysis.

It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator (t-PA) obtained from an established human cell line. The manufacturing process involves secretion of the enzyme Alteplase into the culture medium by an established mammalian cell line (Chinese hamster ovary cells) into which the cDNA for Alteplase has been genetically inserted.

Alteplase is an enzyme (serine protease) that has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. Alteplase binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, thereby initiating local fibrinolysis.[30]

An article described alteplase vs urokinase as follows[31] (references updated):

As early as 1990, investigators reported that doses of 2 mg/2cc of alteplase were effective in the treatment of occluded central venous catheters that failed treatment with urokinase……Although it has long been recognized that alteplase is an effective treatment for occluded catheters, it never became universally popular because of the impracticalities associated with using it. Alteplase requires refrigerated storage, and it must be reconstituted prior to use.

MBX management and the experts it has consulted believe that the two products have largely equivalent efficacy in CC (Figure 10).

Because of Abbokinase®'s removal from the market, clinicians re-examined the existing data about the use of alteplase and came up with a new way of using it[32]. In July 1999, two pivotal FDA label-enabling phase III trials were initiated to determine the efficacy and safety of using up to two sequential 2-mg doses of TPA as an alternative to urokinase for CVC function restoration..

Considering the favorable results from this trial and the temporary removal of urokinase from the market, alteplase was investigated further as an alternative method for catheter clearance. A pivotal study was the COOL (Cardiovascular thrombolytic used to Open Occluded Lines) trial which demonstrated resolution of CVC obstruction in 74% of treatment patients versus only 17% of placebo after 120 min (P<0.0001). Additional studies demonstrated an overall catheter clearance rate of 87%, with 52% being cleared after the first 30 min and even higher rates in treated peripherally inserted central catheters (PICC) line.

The high efficacy and low risk of alteplase for treating CVC occlusions in adults prompted studies in children. Several trials found that alteplase administered for 1–4 h produced catheter clearance rates of 85–95%. In a

[30] https://www.gene.com/download/pdf/cathflo_prescribing.pdf
[31] https://oley.org/page/NewOptions_CathOcclu
[32] https://oley.org/page/NewOptions_CathOcclu

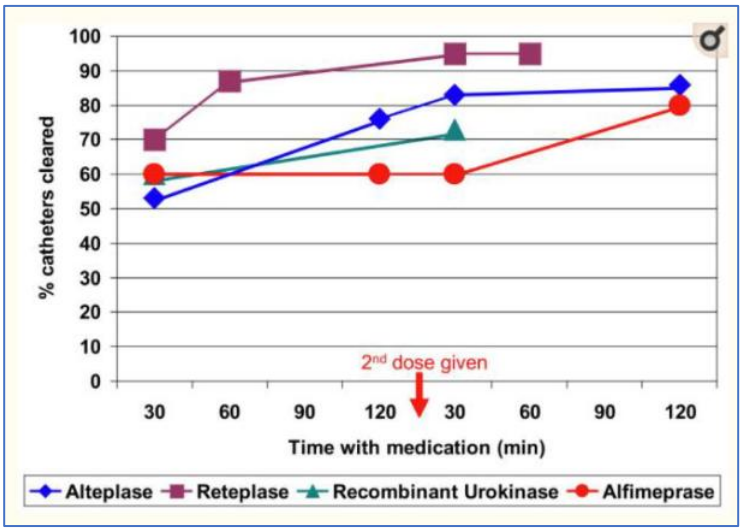
subset analysis of pediatric patients in the COOL trials and a multicenter trial using a dosing regimen and dwell times identical to those in the COOL trials, alteplase was confirmed to be safe and effective with overall catheter clearance rates of 83–87% and no adverse outcomes documented. [33]

A subsequent Phase III trial, COOL-2, targeting 1,000 patients was successfully concluded in 2001 showing flow successfully restored in 52% and 78% of CVCs at 30 and 120 minutes after one dose, and 84% and 87% at 30 and 120 minutes after a second dose, respectively. Estimated 30-day catheter patency was 74%.[34]

In 2000, Genentech filed a supplemental Biologics Application (sBLA) with the FDA seeking expanded labelling for Activase® (alteplase) for use in CC, It stated at that time, ~5m catheters were placed each year in the US.

Results of a study showed that when compared with the average clearance rate of 53% for alteplase, recombinant urokinase appears to have greater efficacy within the first 30 minutes, with an average clearance rate of 60% (Figure 10).

Figure 10: Cumulative incidence of catheter clearance after administering a thrombolytic agent



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2814365/

In other words, recombinant urokinase (Kinlytic® urokinase) is more effective than alteplase at early time points but less so after two doses.

In a 2003 study, comparing the efficacy of alteplase versus urokinase in re-establishing adequate blood flow in partially or completely occluded hemodialysis vascular catheters, alteplase was generally more effective than urokinase in restoring blood flow through catheters, especially those that were completely occluded[35].

However, specialists consulted by MBX consider t-PA and Kinlytic® urokinase to equivalent in CC with differences in efficacy considered "noise". We believe that Kinlytic® urokinase's ease of use and improved efficacy in the early stages are competitive advantages.

[33] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342964/
[34] https://www.cathflo.com/occluded-catheter/clinical-trials.html
[35] https://pubmed.ncbi.nlm.nih.gov/12503929/

Appendix II: Occlusion Management Guideline for CVADs

As per the Journal of the Canadian Vascular Access Association (Volume 7, Supplement 1 – 2013) "Occlusion Management Guideline for Central Venous Access Devices (CVADs)". Once a mechanical obstruction has been ruled out, further assessment should be done to determine if the obstruction is the result of a thrombotic occlusion.[24,28,53]

3.0 Assessment and Management of Thrombotic Occlusion

3.0 Recommendations
3.1 Assess the catheter occlusion to identify if the occlusion is caused by a thrombotic obstruction. [IB]
3.1.1 Assess for visible blood in catheter or add-on devices. [IC]
3.1.2 If no blood return on aspiration, may alternate gently drawing back and then gently infusing small amounts of saline.[64] [IIB]
3.1.3 Consider using a small-barrel syringe to aspirate blood if no blood return obtained but able to flush catheter. A smaller-barrel syringe exerts less negative pressure when withdrawing blood and may result in more success. Do NOT flush with smallbarrel syringe (i.e., 1 mL or 3 mL syringe) because of high pressures generated.[48] [IIB]
3.2 Manage as thrombotic occlusion if unable to determine type of occlusion.[14,24,28,29,46,48] [IB]
3.3 Promptly administer thrombolytic agent approved for restoring central venous access device (CVAD) patency in catheter lumens that are suspected to be occluded by blood/fibrin.[14,24,28,29,46,48] [IB]
3.3.1 Follow hospital policy, medical directive, or prescriber's orders. [IIC]
3.3.2 Discuss risks and benefits of these agents with the licensed prescriber and patient/family, and obtain order from licensed prescriber for thrombolytic agent.[6,7,36] [IB]
3.3.3 Ensure that the health care professionals (HCPs) administering a thrombolytic agent have knowledge of the agent, dosage, contraindications, adverse effects, administration methods, potential complications, and patient/caregiver education. Validation of competency is recommended.[6,7] [IB]
3.3.4 Administer thrombolytic agent as soon as signs of thrombotic occlusion are identified to increase the efficacy of thrombolysis and thereby avoid or at least delay the need for catheter replacement.[14,28,29,31,46,48,65] [IB]
3.3.5 Treat occlusions of unknown onset in the absence of other signs of complications.[49] [IC]
3.3.6 Instill thrombolytic agent into occluded lumens of CVADs, including tunnelled, peripherally inserted central catheters (PICCs) and implanted vascular access devices (IVADs). [1B] Instill thrombolytic agent into occluded lumens on non-tunnelled, short-term, single, and multi-lumen CVADs. [1C]
3.3.7 Use the direct instillation method when the CVAD can be flushed (partial or withdrawal occlusions).[26,28] [IB]
3.3.8 Use negative pressure technique, with either a single syringe or three-way stopcock method, for complete occlusions.[6,7,26,28,66] [IB]
3.3.9 Use a syringe no smaller than 10 mL for administration of thrombolytic agent.[6,7] [IB]
3.3.10 Perform a risk and benefit analysis for treatment of double- and triple-lumen catheters when all lumens are occluded. Instillation of alteplase may exceed the recommended maximum dose of 4 mg. Understand that risks may be mitigated by the safety profile of the thrombolytic. [IIC]
3.3.11 Treat all catheter lumens with partial, withdrawal, or complete occlusion. Do not leave an occluded lumen untreated because another lumen is functional.[24] [IB] Instillation of thrombolytic agent into a patent lumen of a multilumen catheter where other lumens are occluded is an unresolved issue.

3.3.12 Stop all infusions if possible (particularly if treating a suspected fibrin tail/sheath) for optimal thrombolysis during dwell time and to facilitate maximum contact between thrombolytic and the thrombus/fibrin on the internal and external surface of the catheter. [IIC]
3.3.13 Let thrombolytic dwell for 30– 120 minutes. [IB] Consider extending dwell to 24–72 hours to permit longer contact time of thrombolytic with the fibrin in the catheter or around the catheter tip in the case of a fibrin sheath or mural thrombus. [IC]
3.4 Consider alternative methods to deal with persistent/recurring CVAD occlusions not resolved by direct-instillation method of previous doses of thrombolytic:
• Push method over 30 minutes [IB]
• Low-dose infusion over 30 minutes to 3 hours [IB]
3.4.1 Consider low-dose thrombolytic infusion for treatment of a large fibrin tail/sheath that is confirmed by dye study or other radiographic studies and is causing persistent catheter occlusion not responsive to thrombolytic by direct instillation and a dwell time of 24–72 hours. [IIC]
3.5 Consider instillation of thrombolytic (using single-syringe or negative pressure technique) for CVAD occlusions in community and long-term care settings.[14,67] [IB]
3.6 If catheter patency is not restored, notify the licensed prescriber. Consider alternative actions such as radiography (to rule out catheter tip malposition) and/or a referral to interventional radiology (for dye study). Catheter removal may be necessary, with an alternative plan for vascular access.[6,7,26] [IB]
3.7 Document assessment findings, related interventions, and response to intervention. [IC]
3.8 Amend the patient's care plan to reflect any occlusion preventative strategies to ensure catheter patency, considering the causative factors of catheter occlusion. [IC]

Appendix III: Terminology

Embolism. An embolism occurs if all or part of a blood clot breaks away and lodges in another part of the body. When a blood clot blocks normal blood flow within the body, it can have a variety of undesirable effects, such as causing pain and swelling, ischemia or tissue damage, stroke, or even death.

Plasminogen activators: lead to the breakdown of the fibrin lattice structure in blood clots

Roller bottle: Cylindrical in shape, a roller bottle is used to grow and store cell cultures. Placed on a roller, roller bottles are slowly rotated and bathe cells that are attached to the inner surface of the bottle. Roller bottles are typically made of single-use plastic or autoclavable glass.

sBLA: A Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into US interstate commerce. A BLA includes: Applicant information, Product/Manufacturing information, Pre-clinical studies, Clinical studies and Labeling. The supplemental BLA (SBLA) means the equivalent successor filing with the FDA, and any supplements or amendments to the original filing.

sNDA: To change a label, market a new dosage or strength of a drug, or change the way it manufactures a drug, a company must submit a supplemental new drug application (sNDA).

Tissue plasminogen activator (t-PA): is classified as a serine protease (enzymes that cleave peptide bonds in proteins). It is thus one of the essential components of the dissolution of blood clots. Its primary function includes catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in dissolving blood clots.

Disclosure

- 2622632 Ontario Inc. is doing business as KRC Insights.
- KRC Insights/2622632 Ontario Inc. undertakes paid research and was paid by Microbix Biosystems Inc. (MBX-T) for this report.
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