Zacks Small-Cap Research

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DiaMedica Therapeutics (V.DMA-TSX, DMCAF-OTC)

V.DMA: Zacks Company Report

DMA: Positive data reported for lead candidate DM199; will enter into Phase II study for acute ischemic stroke and diabetic kidney disease.

Current Price (06/09/17)	$0.27
Valuation	**$**0.80

OUTLOOK

DiaMedica is a clinical stage biopharmaceutical Company. The Company's lead candidate DM199 is a recombinant human tissue kallikrein (KLK1) targeting acute ischemic stroke (AIS) and diabetic kidney disease (DKD). The company has reported positive results from a Phase I study. The company plans to use the Phase Ib data to guide Phase II trials of DM199 to be initiated in 2017.

We are optimistic about the prospects of the Company and hold a fair value of $0.80/share.

SUMMARY DATA

52-Week High	**$0.35**
52-Week Low	**$0.15**
One-Year Return (%)	**N/A**
Beta	**2.11**
Average Daily Volume (sh)	**101,408**
Shares Outstanding (mil)	**110**
Market Capitalization ($mil)	**$18**
Short Interest Ratio (days)	**0.02**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med Products**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of C$)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2016	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2017	0.00 A	0.00 E	0.00 E	0.00 E	0.00 E
2018					0.00 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.01 A	-$0.01 A	-$0.00 A	-$0.01 A	-$0.02 A
2016	-$0.01 A	-$0.01 A	-$0.01 A	-$0.00 A	-$0.02 A
2017	-$0.01 A	-$0.01 E	-$0.01 E	-$0.01 E	-$0.05 E
2018					-$0.05 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

New Financing Boosts Balance Sheet

On Apr 18, 2017, DiaMedica Therapeutics (DMA) announce that it completed a non-brokered private placement with a prominent U.S. investor.

DiaMedica issued 10,526,315 units to the investor at an issue price of USD$0.19 (CAD$0.25) per unit. Gross proceeds from the financing were approximately USD$2 million. In the news release, the company indicated that the proceeds will be used by the Company to advance its research and development program, including DM199 for the treatment of neurological and kidney diseases, and for general corporate purposes.

Each Unit consisted of one common share and one-half of one common share purchase warrant, with each whole warrant entitling the holder thereof to acquire one additional common share at an exercise price of USD$0.23 (CAD$0.31) per share until 5:00 p.m. (Central Time) on the date that is: (i) twenty-four months after the date of issuance, or (ii) if on any date (the "Accelerated Exercised Date") (a) the volume-weighted average closing trading price of the common shares on any recognized Canadian stock exchange equals or exceeds USD$0.30 for a period of 10 consecutive trading days, then, at the Company's sole discretion and upon the Company sending the holder written notice of such Accelerated Exercise Date and issuing a news release announcing such Accelerated Exercise Date, the day that is 21 days following the later of: (i) the date on which such Notice is sent to the holder; and (ii) the date on which the News Release is issued.

The common shares and warrants are subject to restrictions on resale in accordance with applicable securities laws and the policies of the TSX Venture Exchange. These restrictions will expire four months and a day following the issuance of the Units.

We welcome this financing. It not only boosts the company's balance sheet, but also validates the company's technology and clinical programs. Per the news release, the U.S. based life science investor has numerous academic, national, and international awards for leadership and contributions to the biopharmaceutical industry. Also, the investor has a deep understanding of recombinant proteins, and has rich experience and understanding of the biopharmaceutical industry in the U.S., Europe, and Asia. We think the investment in DiaMedica is an excellent strategic fit for the company and will help accelerate the company's clinical programs, especially for DM199.

As of March 31, 2017, DiaMedica held $0.94 million in cash. The current cash plus the proceeds from the new financing will be able to fund the company's operations into the end of 2017.

Positive DM199 Phase Ib Data Reported

On March 13, 2017, DiaMedica (DMA) reported positive results from its **Phase Ib bridging trial.** The study was designed to compare the profile of DM199 to the approved urinary KLK1 product (trade name Kailikang®) on the market in Asia for acute ischemic stroke (AIS). The reference drug (Kailikang) is administered intravenously and has a very short half-life.

Background of the Phase Ib Trial

The goal of the **Phase I bridge clinical study** of DM199 is to determine the **safety, optimal dose & delivery.**

The **Phase I** controlled trial was an open-label single ascending study, where healthy volunteers received one of four single doses of DM199 **(n=36),** administered as a 30-minute intravenous **(IV)** or a single

subcutaneous **(SQ)** infusion. Plasma DM199 concentration, biomarker concentrations, and other safety and pharmacokinetic parameters were measured in the trial.

In **December 2016**, the company reported positive results from intravenous **(IV)** part of the clinical trial. The study results demonstrated the dose dependent levels of DM199 and identified a dose of DM199 via intravenous **(IV)** administration that produced pharmacokinetic and pharmacodynamic activity that were comparable to those produced by the reference drug, human urinary KLK1 (trade name Kailikang®) approved in Asia.

This clinical study also provided clinically relevant safety data via intravenous delivery of DM199 for the first time at dose levels comparable to the currently approved human urinary KLK1 product.

No treatment limiting adverse events were reported in any dose group. A few patients experienced mild orthostatic hypotension which is consistent with the mechanism of action and demonstrated drug activity. The Company plans to publish the full results of the study in a peer reviewed journal.

The Updated Result from the SC Part of the Phase Ib Trial

Today the Company is reporting an improved **subcutaneous (SC) dose** of DM199 producing sustained plasma levels **superior to** the reference drug.

The DM199 SC delivery provides sustained levels of the KLK1 protein, offering a potentially superior profile to the reference drug, which has a very short exposure window. The dosing of DM199 will be significantly more convenient and potentially provide improved efficacy to the short half-life of the reference drug. DM199 has the same amino acid sequence as the reference drug, identical biochemical activity, and demonstrated similar physiological effects.

No treatment-limiting adverse events were reported in any dose group. The Company plans to publish the full results of the study in a peer reviewed journal.

The Implications

- **More frequent delivery could improve efficacy:**
  - Kailikang® has very short half-life potentially limiting efficacy;
    - Administered 1 times/day 50-minute slow infusion;
    - KLK1 levels decline quickly after infusion;
    - 1 times/day IV dosing may not be enough KLK1 in system for optimal efficacy;
    - **1 vs. 3 times/day dosing** IV urinary KLK1 clinical trial study recently initiated;

- **IV DM199 delivery**
  - DM199's very low manufacturing cost will support economics of increased dosing frequency

- **SQ DM199 delivery**
  - Significantly longer half-life vs. IV Kailikang®
  - Promote elevated KLK1 levels throughout the day, not just after infusion
  - Support full 21-day treatment regimen at home – delivery every 1 to 3 days
  - Today, many patients in China do not come back to hospital for daily 50-minute slow infusion affecting efficacy and sales.

The Phase Ib trial has now identified the optimal dosing of DM199, **both IV and SQ** compared to the Kailikang (urinary KLK1). Kailikang is administered via IV for 50 minutes daily for 21 days. The challenge is that within minutes of stopping the slow infusion, KLK1 drops right off. A single SQ dose of DM199 maintains KLK1 levels for 3 days thus supporting less frequent dosing and more importantly anticipated increased efficacy by having KLK1 levels elevated for the full day instead of just during the infusion period and minutes after stopping the infusion with Kailikang.

The company is also leveraging the existing efficacy and understanding of Kailikang by over 300,000 patients who have received treatment to date. Thus, efficacy can be improved by using the company's long acting SQ delivery, targeting patients with greatest likelihood to respond, targeting patients with lower KLK1 levels and shortening the treatment window from the 48 hours approved by Kailikang while still capturing more stroke patients.

What's Next?

DiaMedica intends to seek **worldwide** approval for DM199 as a novel therapy for **acute ischemic stroke (AIS).** The company will also position DM199 in **China** as an improved product over the urine-sourced KLK1 protein currently used there. With the potential that effective treatment can be initiated up to 48 hours after the first sign of symptoms, DM199 may fill a large unmet need for stroke patients who cannot receive tPA, benefiting millions of people around the world who currently have limited treatment options.

DiaMedica intends to initiate a **Phase II** study of DM199 for AIS in 2017. The Phase II trial will enroll approximately 100 AIS patients and start treatment within 24 hours of stroke over 21 days. The primary end points include:

- Safety and tolerability
- Biomarkers - blood flow and inflammation
- Modified Rankin Scale (mRS)
- National Institute of Health Stroke Scale (NIHSS)
- Activities of Daily Living on Barthel Index (BI)

The Company plans to use the results of this Phase Ib study to guide Phase II dosing in upcoming clinical trials.

Valuation Attractive

We maintain our optimism of DMA's long term prospect and keep our fair valuation for the company at $0.80/share. Our call is based on the Company's relatively strong fundamentals.

DiaMedica is a clinical-stage biopharmaceutical company with a current focus on acute ischemic stroke **(AIS)** and diabetic kidney disease **(DKD).** The company's lead candidate is **DM199**, a recombinant human tissue kallikrein (KLK1). DiaMedica is developing DM199 for the treatment of AIS and DKD, two large markets with huge unmet medical needs.

The only **FDA approved** treatment for acute ischemic strokes **(AIS)** is tissue plasminogen activator (**tPA**, also known as IV rtPA). tPA works by dissolving the clot and improving blood flow to the part of the brain being deprived of blood flow. If administered within 3 hours (and up to 4.5 hours in certain eligible patients), tPA may improve the chances of recovering from a stroke. However, a significant number of stroke victims don't get the chance to go to the hospital in time for tPA treatment. As a result, only 5-7% patients have the chance to receive tPA treatment.

DiaMedica's **DM199** has the potential to treat AIS patients up to 48 hours post AIS attack due to its unique mechanism of action. DM199 restores blood flow to the ischemic brain region by generating additional bradykinin to activate BK-B2 receptors. Activation of this pair of receptors triggers several important physiological responses that could be beneficial following AIS.

For diabetic kidney disease **(DKD),** there are no formally approved agents in the US and the EU. Two blood pressure medications angiotensin converting enzyme inhibitors (**ACEi**) and/or angiotensin receptor blockers **(ARBs**) are widely used and are considered the standard of care. However, both drugs can cause hyperkalemia and angioedema, which leads to only 25% of patients receiving optimal treatment.

DiaMedica is developing DM199 as a **biobetter product** to replace approved Kailikang and porcine KLK1 in Asia and as a **new product** to enter into the US & markets in rest of the world for both AIS and DKD. Since DM199 is recombinant KLK1, which eliminates the side effects of both Kailikang and porcine KLK1. In addition, since DM199 is synthetic, it has unlimited supply and can be manufactured at a very low cost.

We estimate DM199 could be approved in China in 2020 and in the US in 2021. If approved, worldwide peak sales of DM199 for AIS and DKD combined could potentially surpass **$1 billion.**

With respect to valuation, we agree that it's always difficult to exactly value a development stage biotech Company like DiaMedica. We don't think a discounted cash flow (DCF) model is appropriate for the valuation of DiaMedica since the Company's lead candidate DM199 is still a few years away from reaching the market. Instead, one better way is to use relative value metrics to reach fair value for DiaMedica. According to our experience and current market conditions, most small cap biotech companies are valued at from $50 million to $2 billion in market cap based on how advanced the Company's pipeline is and the market potential of the Company's drug candidates. Other factors affecting a small cap biotech valuation include cash balance, burn rate and management expertise and experience.

We think the current market price does not reflect the Company's true value. Currently, the Company's shares are trading at about CAD$0.30 per share, which values the Company at CAD$38 million in market capitalization based on 120 million outstanding shares. This is a discount compared to its peers. Based on our above discussions, DM199 will be approved in 2020 in China and in the US in 2021 for acute ischemic stroke. We assign a probability of 50% for DM199 stroke and 50% for DM199 diabetic nephropathy for approval at this time. Based on our financial model, DiaMedica will become cash flow positive in 2020 with an EPS of $0.01 based on revenue of $15 million. EPS will grow to $0.24 in fiscal 2022 based on total revenue of $75 million. A 25x P/E multiple and 30% discount rate are used to arrive at our fair value of $0.80 per share. Our price target values the company at $100 million in market cap, which is still conservative in our view.

We believe data is the ultimate driving force to grow a biotech Company. When more positive data are generated from the Company's lead candidate, DM199, and from other early stage candidates, value will be generated for the Company and its shareholders. In this regard, we will keep a close eye on the Company's development plan and update investors on any new data (either clinical or preclinical) generated from its drug candidates.

But keep in mind **the risks**. As we discussed, DiaMedica is still a clinical stage biopharmaceutical company. Our valuation assumes the final approval of its lead candidate DM199 and other candidates. In order for the candidates to reach the market, the Company still needs to overcome both clinical and regulatory hurdles which have proven to be high.

Cash burn is another concern. When DM199 enters into Phase II trials, we expect R&D expenses will also increase. Current cash in hand plus proceeds from recent financing can only support the Company's operations into the end of 2017 according to our financial model. We expect the Company needs to tap the capital market for new funding soon. We reminder investors that equity financing will dilute the existing shareholder base, and could cause the share price to fall.

But generally speaking, we think the stock has a typical high risk/high return profile, which could be part of a portfolio for investors with a high-risk tolerance and relatively long investment horizon.

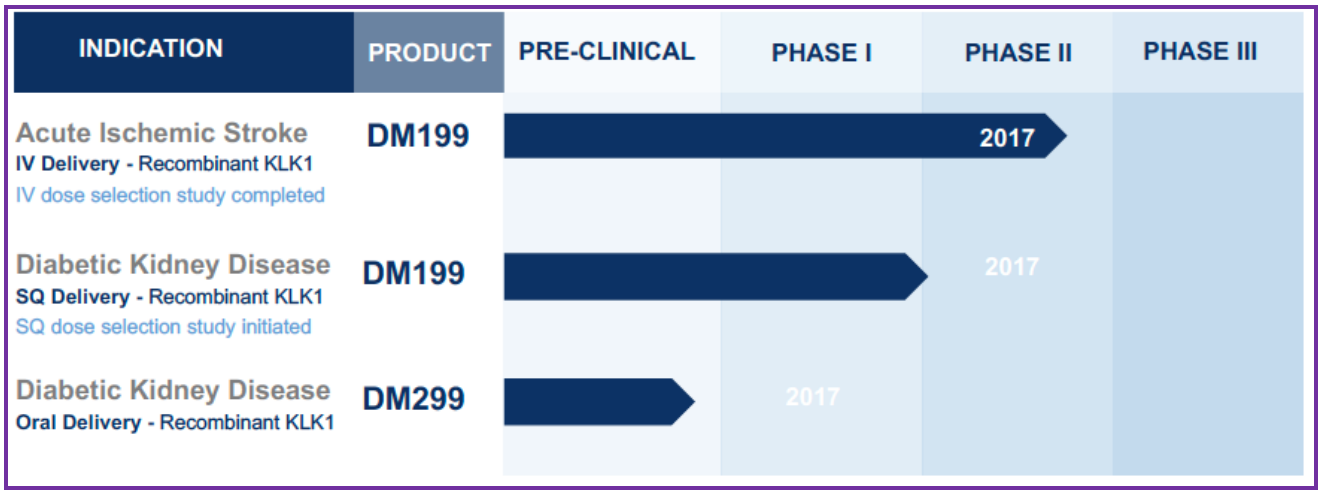
OVERVIEW

DiaMedica Therapeutics Inc. (TSXV: DMA, OTC: DMCAF) is a **clinical stage** biopharmaceutical company focused on the discovery and development of novel approaches to treat patients with unmet medical needs.

The company's lead drug candidate is **DM199**, a recombinant (synthetic) human tissue kallikrein **(KLK1).** DiaMedica is developing DM199 for patients suffering from neurological and kidney diseases. DM199 has undergone clinical testing that demonstrates its exceptional safety as a potential treatment for a variety of disorders. The Company is positing DM199 for the treatment of **diabetic kidney disease (DKD)** and post-insult treatment for **acute ischemic stroke (AIS).** There are no approved FDA therapeutic treatments for DKD and the only FDA approved drug treatment for AIS is **tissue plasminogen activator (tPA)**, which is limited to only 3-4 hours after a stroke.

DM199 has composition of matter **patent** protection until 2033. Several other biotechnology and pharmaceutical companies have unsuccessfully attempted to manufacture the recombinant KLK1 protein. DiaMedica has been able to secure composition of matter patent protection, numerous other patents have been filed while also keeping portions of the manufacturing know-how as trade secret.

So far, five clinical trials in over 100 patients have been conducted with DM199. These studies were designed primarily to establish the safety and tolerability of DM199 and characterize the pharmacokinetics after subcutaneous and intravenous dosing. Importantly, the studies also included regular monitoring of blood pressure. Measurable decreases in blood pressure and/or postural hypotension as the dose-limiting tolerability were observed at doses that generated plasma concentrations of DM199 and consistent with the mechanism of action.



DiaMedica is currently conducting a **Phase Ib clinical trial** designed to identify a dose of DM199 that is comparable to the human urinary and porcine approved versions in Asia. The results of this study will guide dosing for Phase II and III clinical trials.

DiaMedica shares are publicly traded on the TSX Venture Exchange in Canada under the symbol “DMA” and the OTCQB in the U.S. under the symbol “DMCAF”. DiaMedica is a Canadian Company. Its corporate office is at Two Carlson Parkway, Suite 165, Minneapolis, Minnesota 55447.

INVESTMENT THESES

DM199 for Acute Ischemic Stroke (AIS)

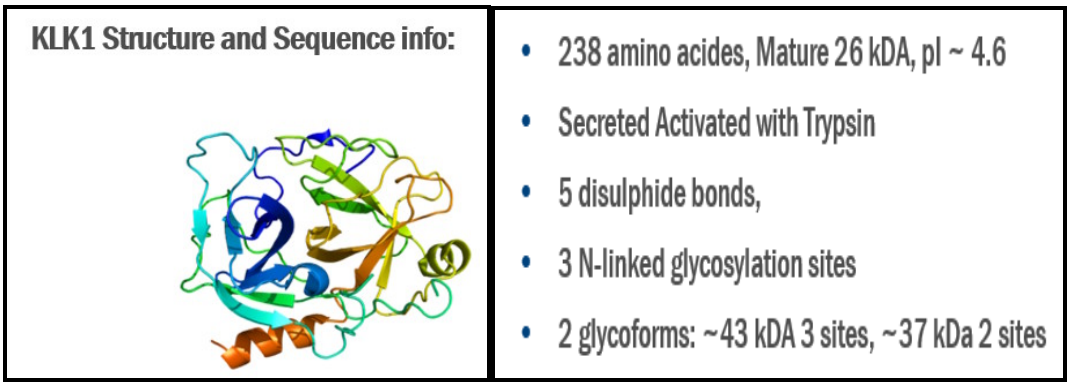
DiaMedica’s lead drug candidate DM199 is a human recombinant tissue kallikrien (rhKLK1) protein.

Background of KLK1

Kallikreins (KLK) are a subgroup of serine **proteases** having diverse physiological functions. The proteins arise from a family of 15 genes. DiaMedica is developing human **tissue kallikrein (KLK1)** to distinguish itself from an unrelated protease called **plasma kallikrein**. KLK1 differs from plasma kallikrein in substrate specificity, types of kinins released, localization, and regulatory mechanisms. Other members of this family include the protein commonly known as prostate specific antigen (PSA) or KLK3.

KLK1 possesses protease activity with a substrate specificity similar to that of trypsin or chymotrypsin. The most well-characterized activity of KLK1 is its enzymatic cleavage of **kininogen** to produce bradykinin (BK) like peptides, collectively known as **kinins**, which activate both subtypes of bradykinin receptors (BK-B1, BK-B2). Activation of BK receptors by kinins promote blood flow by inducing an immediate vasodilation followed by longer term angiogenic actions. By this mechanism KLK1-mediated release of kinins has been shown to increase blood flow in a variety of tissues including brain, kidney and heart. This is likely the **primary mode** by which kallikrein treatment addresses brain pathologies caused by acute ischemic stroke (**AIS**).

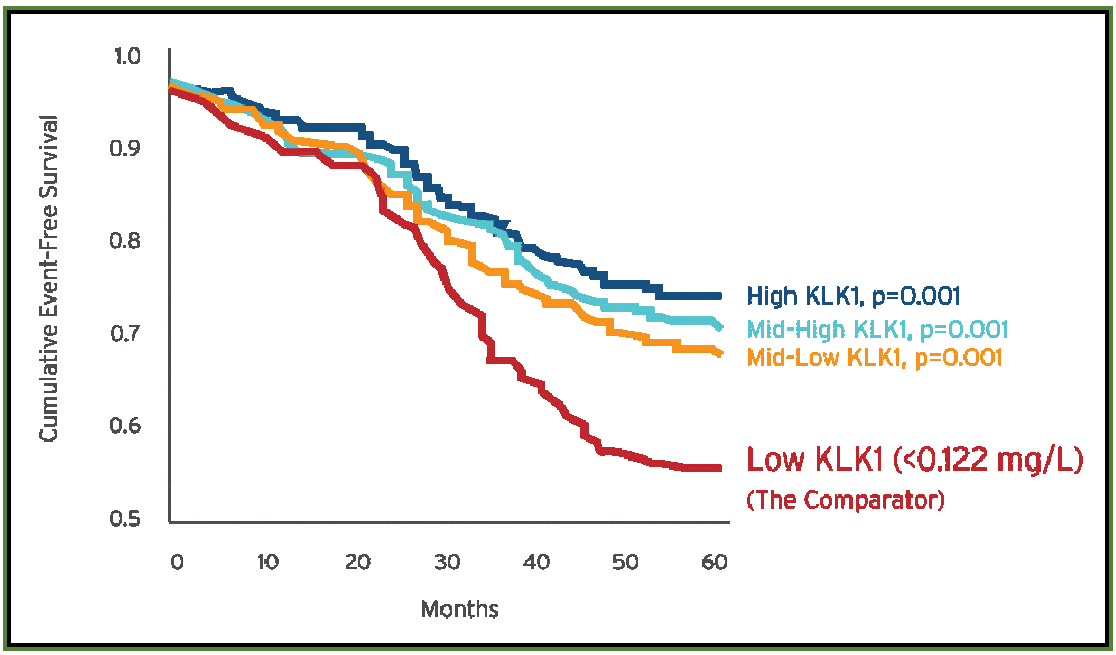
Kinins have a short half-life *in vivo* as they are rapidly degraded by ubiquitous enzymes, most notable are the angiotensin converting enzymes (ACE). KLK1 activity also is tightly regulated by inhibitor proteins found throughout the body. Because of these multilayered regulatory systems, it is plausible that levels of bradykinin drop below optimum levels in pathological conditions such as AIS and DKD. Treatments that provide additional supplies of active KLK1 can serve to maintain sufficient bradykinin levels and thereby promote BK-B2 receptor activation.



KLK1 and Stroke

Lower level of the **protein tissue KLK1** in the blood and urine has been independently associated with first-ever stroke and lower long term survival and is an independent predictor of recurrence after an initial stroke.

In a 2,478 patient case-controlled clinical study of KLK1 levels in stroke patients, higher KLK1 activity is predictive of fewer stroke recurrences and longer event-free survival time. Event free survival functions were measured using Kaplan-Meier survival curves.



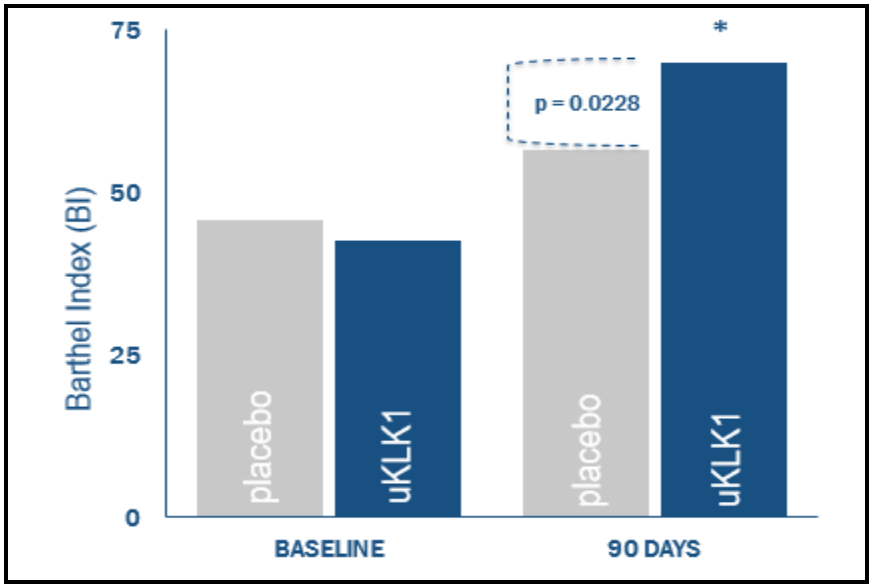
Zhang, Q., et al. *Annals of Neurology*. 2011 Aug; 70(2): 265-273.

Published preclinical and clinical research with a naturally occurring KLK1 protein has demonstrated reduced blood pressure, cell death, and inflammation and increased angiogenesis (creation of new blood vessels) and neurogenesis. In a preclinical study, DM199 has also demonstrated significant increase in blood flow in the brain after a single dose.

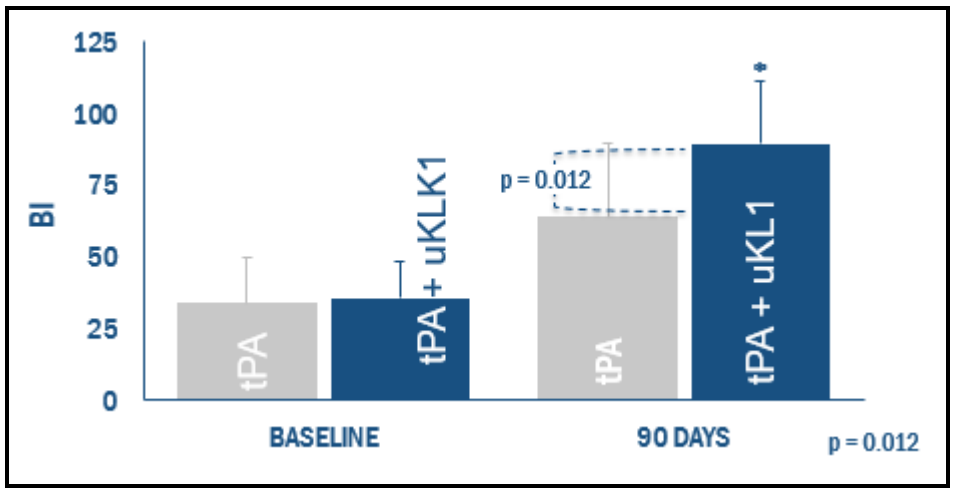
In the **People's Republic of China**, a human urine-extracted version of KLK1 (uKLK1) is currently being used to treat AIS. The product is isolated from human urine and marketed by Techpool Bio-Pharma Inc. under the brand name **Kailikang®**. Kailikang® is prescribed to stroke patients up to 48 hours after an AIS and is given by intravenous administration.

More than 40 published clinical studies have shown a beneficial effect of Kailikang® treatment in AIS, including a meta-analysis covering 24 clinical studies involving 2,433 patients.

In a double-blinded, placebo-controlled, **Phase III** trial of 446 patients treated with uKLK1 or placebo up to 48 hours after a stroke, significant differences were found in the European Stroke Scale and Activities of Daily Living at three weeks of treatment and at three months using the Barthel Index with uKLK1 treated vs placebo.



In a 200-patient Phase II study, human urine KLK1 in combination with tPA, the only FDA approved agent for AIS, significantly improves stroke function using Barthel Index (BI) measure.



The conclusion: KLK1 is highly correlated with stroke and treatment of stroke patients with KLK1 products may improve outcome.

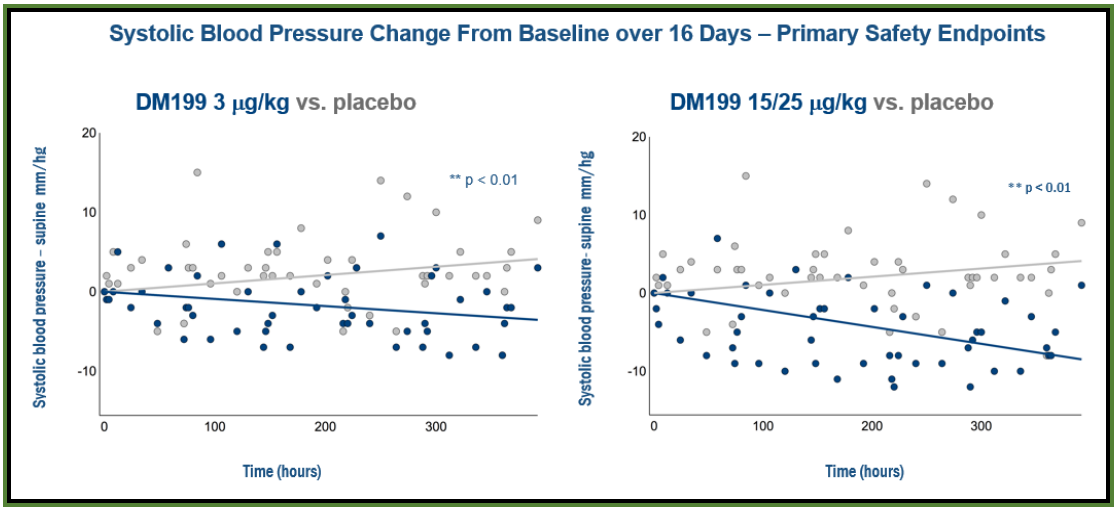
DM199 Has the Potential to Treat AIS

Like uKLK1, we believe DM199 has the potential to preserve “at risk” brain tissue by establishing better collateral circulation, decreasing inflammation, reducing apoptosis, and helping generate collateral circulation by initiating angiogenesis and neurogenesis.

Studies have shown that DM199 and other KLK1 products increases blood flow in a variety of tissues including kidney, heart and brain. This is believed the primary mode DM199 use to preserve brain tissue after an AIS attack.

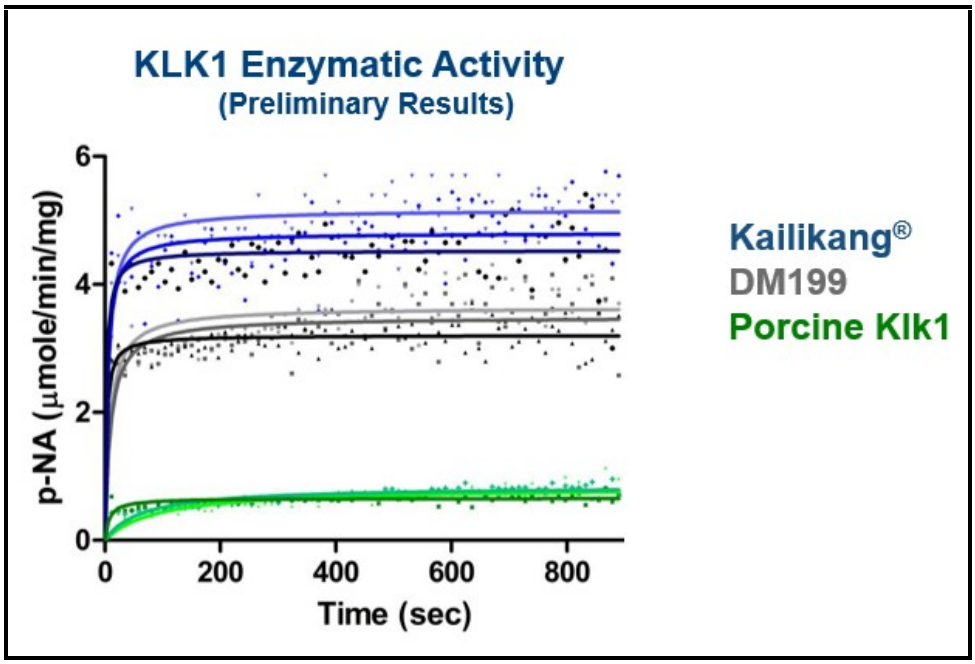
Five clinical studies have been completed for DM199, which include single ascending, multiple ascending, PK, 28 day & bridging studies. These studies have demonstrated the safety and efficacy of DM199 for the treatment of AIS.

In a **Phase I** study, DM199 demonstrated statistically significant decrease from baseline **systolic blood pressure** that was not observed in the placebo group. Since hypertension is the most common modifiable risk factor for stroke, with blood pressure reduction being associated with a reduced rate of stroke recurrence, the effect of DM199 on blood pressure indicates activity in patients.



In all five studies, DM199 has been well tolerated and has demonstrated excellent safety profile with clean safety profile at anticipated dosing levels.

In another comparable study, DM199 demonstrated similar enzymatic activity to two approved KLK1 products in Asia.

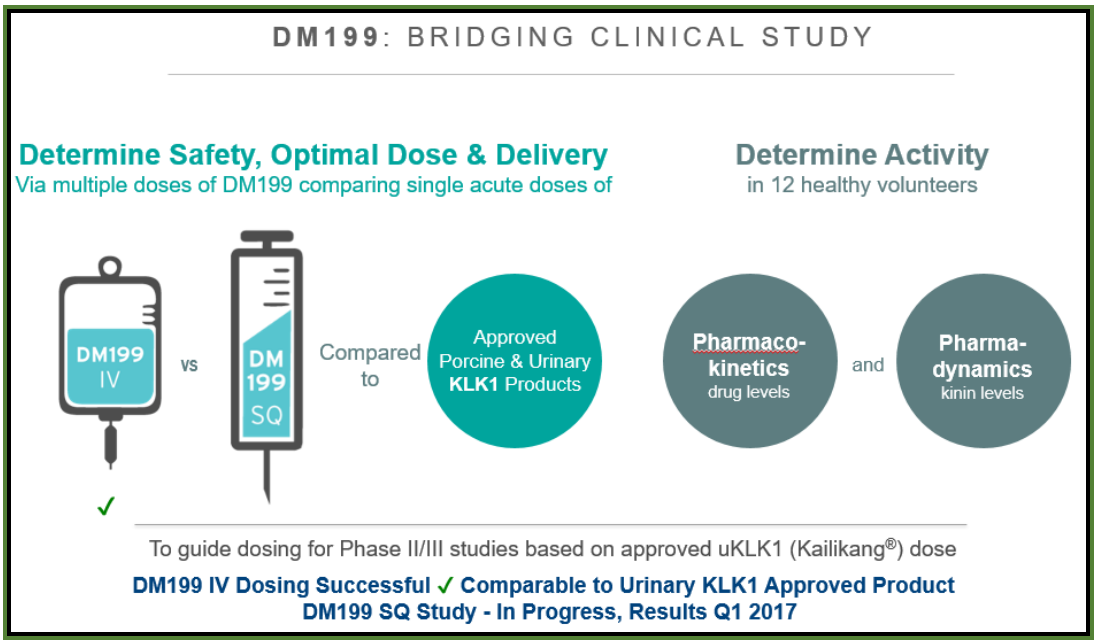


Kailikang® (human urine KLK1) has been approved in China for acute ischemic stroke, while **porcine KLK1** has been approved in China, Japan and Korean for treatment of diabetic kidney disease, hypertension and retinopathy.

Development Plan for DM199 for AIS

DiaMedica is conducting a **Phase I bridge clinical study** of DM199 to determine the **safety, optimal dose & delivery.**

The **Phase I** controlled trial was an open-label single ascending study, where healthy volunteers received one of four single doses of DM199 **(n=36),** administered as a 30-minute intravenous (IV) or subcutaneous (SQ) infusion. Plasma DM199 concentration, biomarker concentrations, and other safety and pharmacokinetic parameters were measured in the trial.



In December 2016, the company reported positive results from the clinical trial. The study results demonstrated the dose dependent levels of DM199 and identified a dose of DM199 via intravenous **(IV)** administration that produced pharmacokinetic and pharmacodynamic activity that were comparable to those produced by the reference drug, human urinary KLK1 (trade name Kailikang®) approved in Asia.

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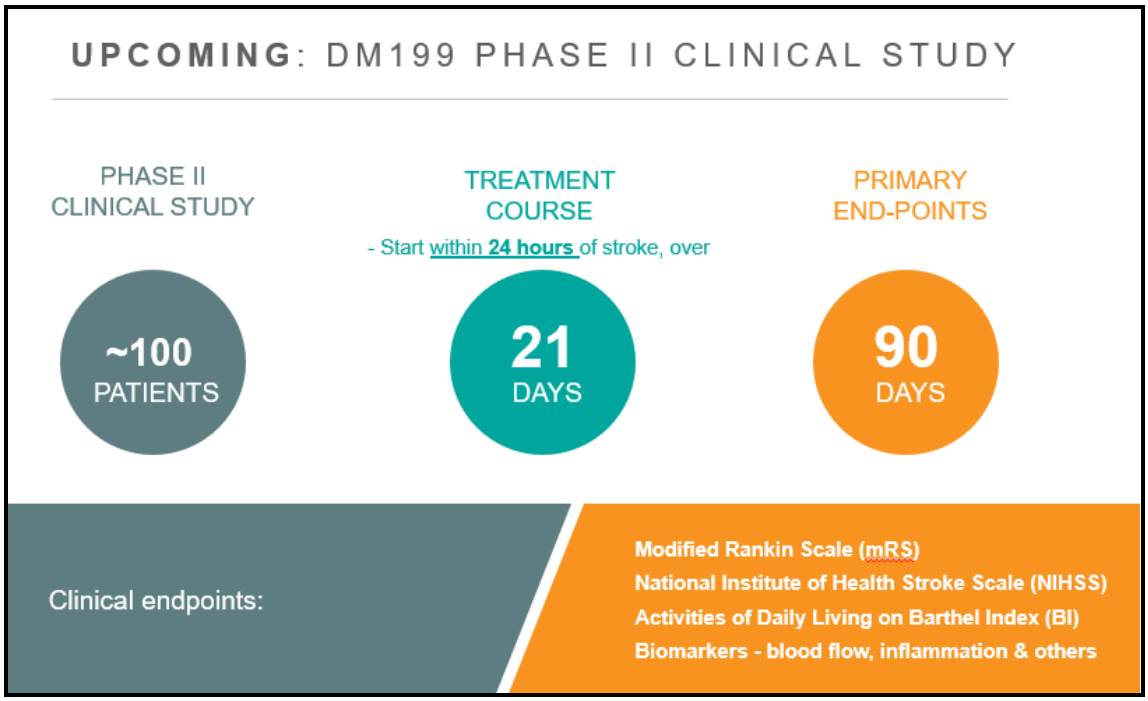
No treatment limiting adverse events were reported in any dose group. A few patients experienced mild orthostatic hypotension which is consistent with the mechanism of action and demonstrated drug activity. The Company plans to publish the full results of the study in a peer reviewed journal.

The company has initiated the second part of the clinical trial to include **subcutaneous** (under the skin) delivery of DM199. The objective of this phase is to further refine and identify an optimal dosing of the intravenous and subcutaneous forms of DM199, possibly superior to the human urinary and porcine derived KLK1 products approved in Asia for acute ischemic stroke and diabetic kidney disease.

DiaMedica intends to seek **worldwide** approval for DM199 as a novel therapy for **acute ischemic stroke (AIS).** The company will also position DM199 in **China** as an improved product over the urine-sourced KLK1 protein currently used there. The company also intends to seek **worldwide** approval for DM199 as a novel therapy for **acute ischemic stroke**. With the potential that effective treatment can be initiated up to 48 hours after the first sign of symptoms, DM199 may fill a large unmet need for stroke patients who cannot receive tPA, benefiting millions of people around the world who currently have limited treatment options.

DiaMedica intends to initiate a **Phase II** study of DM199 for AIS in 2017. The Phase II trial will enroll approximately 100 AIS patients and start treatment within 24 hours of stroke over 21 days. The primary end points include:

- Safety and tolerability
- Biomarkers - blood flow and inflammation
- Modified Rankin Scale (mRS)
- National Institute of Health Stroke Scale (NIHSS)
- Activities of Daily Living on Barthel Index (BI)



A Huge Market of AIS for DM199

A **stroke** is the rapidly developing loss of brain function due to disturbance in the blood supply to the brain. As a result, the affected area of the brain becomes inactive and eventually dies. Strokes can be classified into two major categories: **acute ischemic stroke (AIS)** and **hemorrhagic stroke**. AIS are those that are caused by interruption of the blood supply by a blood clot (ischemia), while hemorrhagic strokes result from rupture of a blood vessel or an abnormal vascular structure. About **87%** of strokes are acute ischemic strokes, with the remainder classified as hemorrhagic and 1 in 6 people will have a stroke in their lifetime according to the World Stroke Organization.

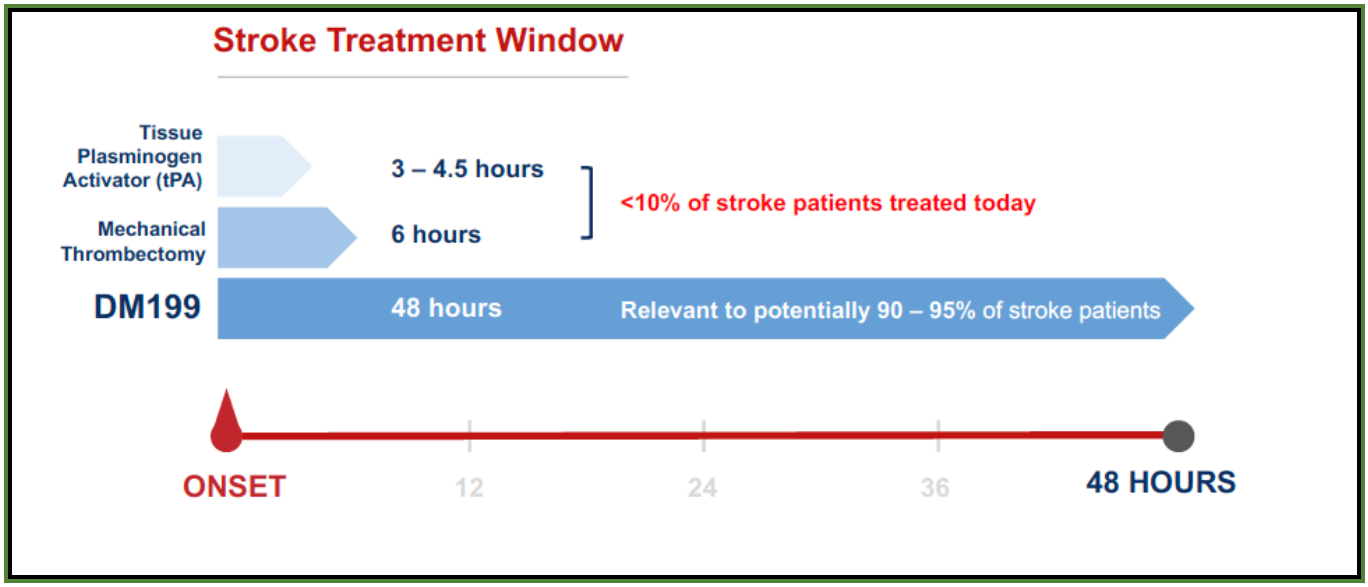
According to the World Heart Federation (WHF), each year approximately **15 million** people **worldwide** suffer a stroke of which 6 million will die and 5 million will be permanently disabled. Worldwide, stroke is the leading cause of adult disability and the second leading cause of death in developed countries.

Each year **in the US**, approximately 800,000 people experience a new or recurrent stroke (ischemic or hemorrhagic). Approximately 610,000 of these are first events and 185,000 are recurrent stroke events.

Stroke represents an area of tremendous unmet medical need.

Currently, the only FDA approved therapeutic-based treatment is **tissue plasminogen activator (tPA**, also known as Activase® and Altapase), a protein involved in the breakdown of blood clots (thrombolysis)

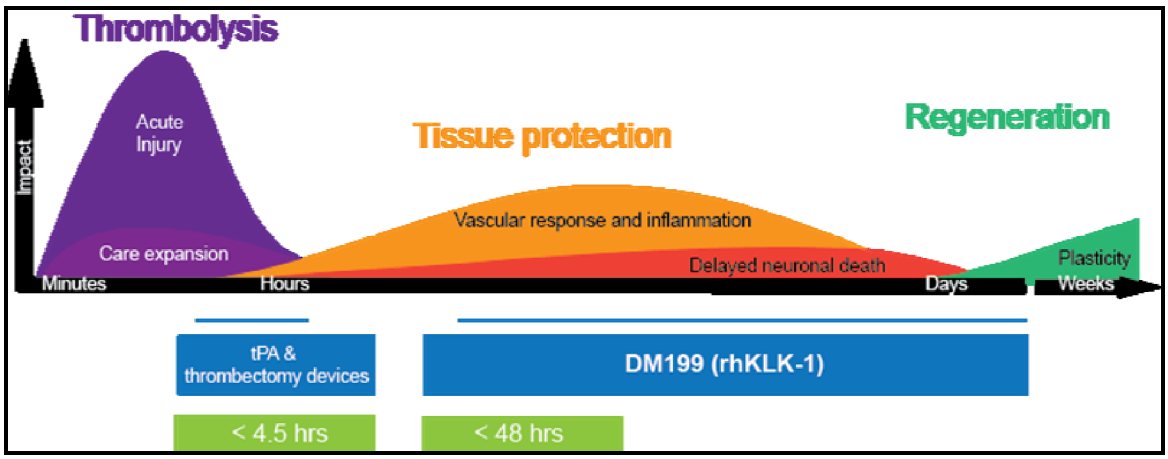
to re-establish normal blood flow (recanalization). However, tPA is only effective if administered within 3-4.5 hours (preferably closer to within the 3 hour timepoint) of an acute ischemic stroke, as outside this therapeutic window tPA is not only ineffective but its use leads to a greater risk of hemorrhage (bleeding in the brain). As such, only **5-7% of AIS patients** are treated with tPA.



Therefore, a clear unmet therapeutic need exists for the vast majority of stroke patients who do not receive tPA. New therapeutic options in development include tissue protection focused therapies (hours to days after the stroke) that preserve and protect brain cells beyond the tPA therapeutic window, and are especially targeted toward preserving viable cells in the penumbra hours after a stroke. This represents a potential **$10+ billion** market opportunity for a drug that is able to successfully obtain approval of a therapy outside of the tPA **4.5-hour therapeutic window**.

DM199 May Be Administered up to 48 hours post-AIS

From the characteristics and unique mechanism of action for AIS, we believe DM199, as a recombinant KLK1 protein, has the potential to preserve brain tissue after AIS attack. In addition, clinical trials with a human urinary KLK1 suggest DM199 may be administered up to 48 hours post-AIS.



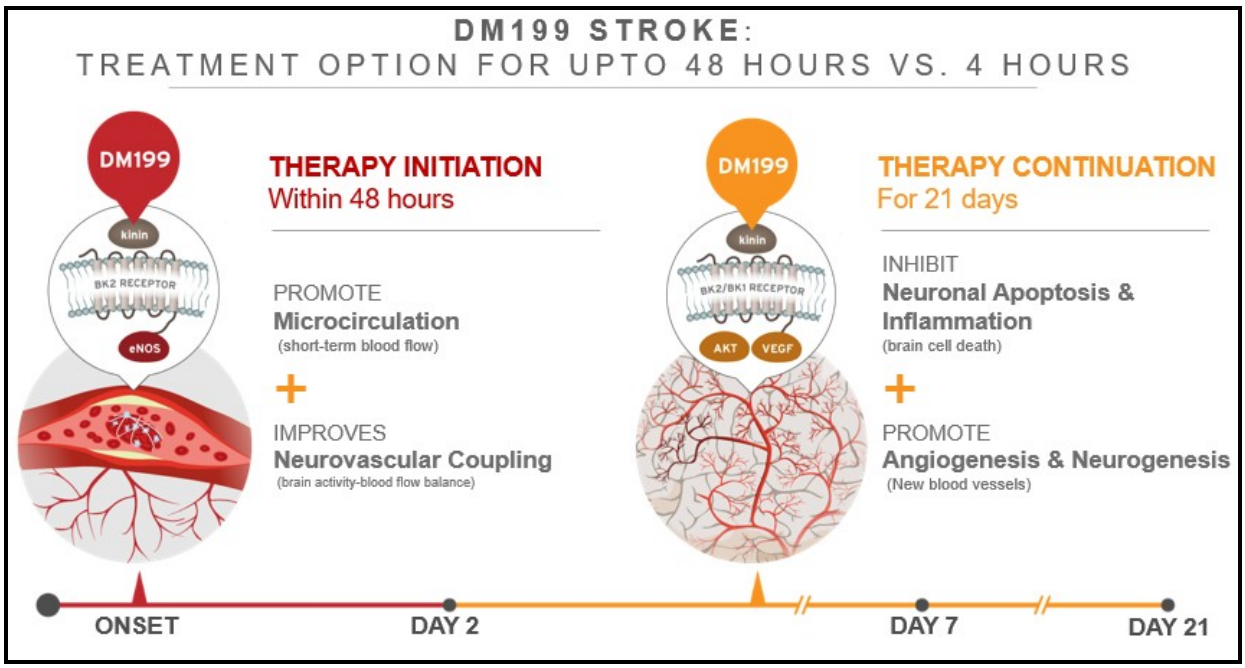
Adapted from (Sinden and Muir, 2012)

As demonstrated by the beneficial effect of timely tPA treatment, restoring blood flow to the ischemic brain region is among the most critical factors for successful recovery from AIS. **DM199** does this by

generating additional bradykinin to activate BK-B2 receptors. Activation of this pair of receptors triggers several important physiological responses that could be beneficial following AIS.

First, activation of the BK2 receptor activates the endothelial nitric oxide synthetase enzyme **(eNOS)** to produce nitric oxide (NO), which relaxes blood vessels and improves blood flow. NO has been known to play a complex role in cerebral ischemia. Ischemia can activate **neuronal** NO synthase (NOS), resulting in production of NO that is toxic to surrounding neurons. Inducible NOS, which is not normally present in healthy tissues, is induced shortly after ischemia and contributes to secondary damage. However, NO generated from **endothelial** eNOS is critical in maintaining cerebral blood flow and reducing infarct volume. Its up-regulation is neuroprotective against cerebral ischemia. Overall these results suggest that the tissue KLK1, through activation of eNOS and subsequent NO production, might modulate endothelial function and promote cell survival and could have protective effects on the brain in the setting of ischemic stroke.

Second, activation of both the BK-B1 and BK-B2 receptors can increase **angiogenesis** (creation of new blood vessels). Activation of the BK-B1 receptor leads to an increase in basic fibroblast growth factor, which is known to improve both angiogenesis and neurogenesis in animal models of stroke. Activation of the BK-B2 receptor leads to transactivation of the VEGF receptor and release of **VEGF** itself. VEGF is a potent growth factor that triggers angiogenesis and could improve collateral perfusion in stroke.



DM199 is Developed as a Biobetter in Asia

Currently, two KLK1 products are approved in Asia. uKLK1 (**Kailikang®)** is derived from human urine (human urine KLK1) and is approved in **China** for the treatment of acute ischemic stroke. Another KLK1 product is derived from pig (**porcine KLK1, trade name Kallidinogenase**) and is approved in Japan, China and Korea for diabetic kidney disease and hypertension.

Both approved KLK1 products faces the issues of endotoxin risk, impurity and antibody formation, which limit the utilization. For Kailikang®, there is also an issue of limited supply since manufacturing requires very large quantities of human urine at what the Company believes has a high cost of goods sold.

DM199 is recombinant KLK1, which eliminates the side effects of both human urine and porcine KLK1. DiaMedica has mastered the complicated manufacturing process for DM199 with high expression and

stability. The company can produce commercial scale of DM199 (up to 200 Liter) under cGMP with very low costs.

DiaMedica is developing DM199 as a new product **worldwide** use and in Asia as a **biobetter product** to replace approved uKLK1 and porcine KLK1 in China & Japan.

If approved, we estimate the worldwide peak sales of DM199 for AIS could surpass **$1 billion**.

TWO APPROVED FORMS OF KLK1 PROTEIN IN ASIA

PRODUCT	CARNACULIN & KALLIDINOGENASE	KAILIKANG®	DM199
Source	Porcine KLK1	Human Urine KLK1	Recombinant KLK1
Company	Sanwa Kagaku Kenkyusho, Changzhou Qianhong & others	Techpool: Takeda & Shanghai Pharma J.V.	DiaMedica
Pro's/Con's	Risk of endotoxins, antibody formation & impurities	Supply limitations, risk of endotoxins, impurities & antibody formation	Synthetic, very low cost, unlimited supply
indications	Diabetic kidney disease, retinopathy & hypertension	Acute ischemic stroke	Diabetic kidney disease & acute ischemic stroke
Markets	Japan, China & Korea	China	Worldwide
Sales/stage	**$150M+ USD** Est. (IMS Health)	**$50M+ USD Est.** (IMS Health)	Clinical stage

DM199 for Diabetic Kidney Disease

In addition to AIS, DiaMedica is also developing DM199 for the treatment of **diabetic kidney disease (DKD).**

Background on Diabetic Kidney Disease

Diabetic kidney disease (DKD) or Diabetic nephropathy (DN) is one of the most common complications of late stage diabetes.

DKD is a form of chronic kidney disease (CKD) characterized by a gradual loss of kidney function. **Diabetes & high blood pressure** are main causes. Clinically, DKD causes a progressive increase in urine albumin/albuminuria and a decrease in glomerular filtration rate (GFR) or hyperfiltration. In the healthy individual, the kidney has millions of capillaries with tiny pores that act as filters located in the glomerular basement membrane. Waste products pass through these filters and become urine while useful products, such as proteins and red blood cells, are too large to filter and stay in the blood stream. In DKD impaired glomerular membrane filtration leads to the abnormal release of protein into the tubules and urine (proteinuria). In normal healthy kidneys only a tiny amount of albumin is found in the urine. A raised level of albumin in the urine is the typical first sign that the kidneys have become damaged by diabetes.

Diabetic kidney disease is divided into two main categories, depending on how much albumin is lost through the kidneys:

Microalbuminuria: in this condition, the amount of albumin that leaks into the urine is between 30 and 300 mg per day. It is sometimes called incipient nephropathy.

Proteinuria: in this condition the amount of albumin that leaks into the urine is more than 300 mg per day. It is sometimes called macroalbuminuria or overt nephropathy.

At the final stages of DKD, the kidneys completely fail and dialysis or a kidney transplant is needed.

Treatment Options for DKD

There are no formally approved treatment strategies for **DKD** in the US and other Western countries. Current treatment strategies for DKD include the strict control of **high blood pressure** and **high blood sugar.**

Blood pressure medications including angiotensin converting enzyme inhibitors (ACEi: Ramipril®) and/or angiotensin receptor blockers (ARBs: Banicar®) are widely used and are considered the **standard of care for** DKD**.**

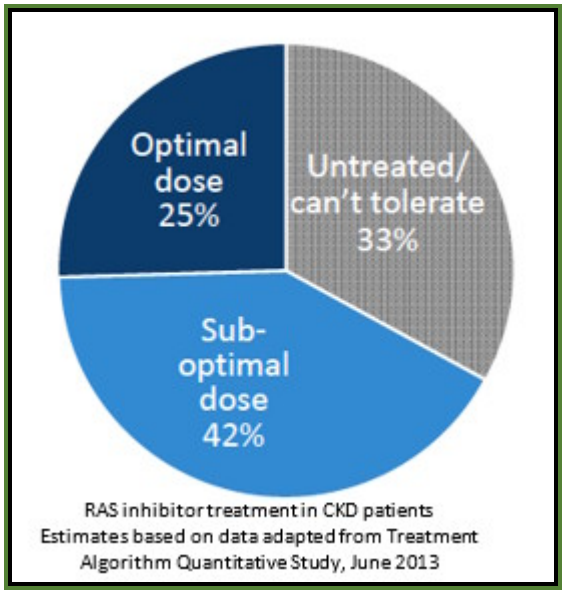
Both ACEi and ARBs work primarily in the renin-angiotensin system (RAS) of the kidney through the angiotensin receptors 1 (AT_1) and 2 (AT_2). These therapies act predominantly by blocking both receptor subtypes and thus suppressing **aldosterone**, and **improve blood flow** within the capillaries thereby decreasing kidney pressure.

However, both ACEi and ARBs can lead to increased level of blood potassium **(hyperkalemia).** The primary factor regulating potassium in the renal system is aldosterone, which modulates the potassium transport across the nephron. However, as the aldosterone systems fails or AT-receptors are blocked (i.e. ACEi and ARBs), high potassium levels can lead to cardiac complications including rapid decreases in resting membrane potential, increased cardiac depolarization and muscle excitability. KLK1 protects against hyperkalemia after consumption of potassium.

Studies have shown that people diagnosed with chronic kidney disease, regardless of treatment status, are more likely to develop hyperkalemia. This risk of hyperkalemia in DKD can result in suboptimal dosing of ACEi and ARBs. In fact, it is estimated that 42% of people with DKD are not receiving optimal dose regimens and 33% are not treated because they cannot tolerate the regimens.

A component of ACEi efficacy appears to involve increasing bradykinin levels by blocking bradykinin breakdown. Thus ACEi's increase bradykinin in an unregulated, global fashion and will have less benefit if bradykinin production is already insufficient. Importantly, ACEi appear to lose efficacy in animals that lack a functional KLK1 enzyme. DM199 restores healthy levels of KLK1, which is the primary enzyme that produces bradykinin, likely focusing on cells and organs where bradykinin is needed to maintain normal function. This suggests that DM199 treatment can improve kidney function beyond what can be achieved with ACEi drugs.

Another complication that can arise from ACEi and ARB treatment is **angioedema**. Angioedema (AE) is a nonpitting edema (swelling) of the dermis and subcutaneous layers. ACEi block the degradation of kinins, which leads to a significant increase in plasma and tissue BK and substance P. The increase in BKB2 receptor activation leads to increased vascular permeability at the post capillary venules which causes the edema. DM199 could potentially be combined with an ARB with significantly lower risk of hyperkalemia and angioedema.

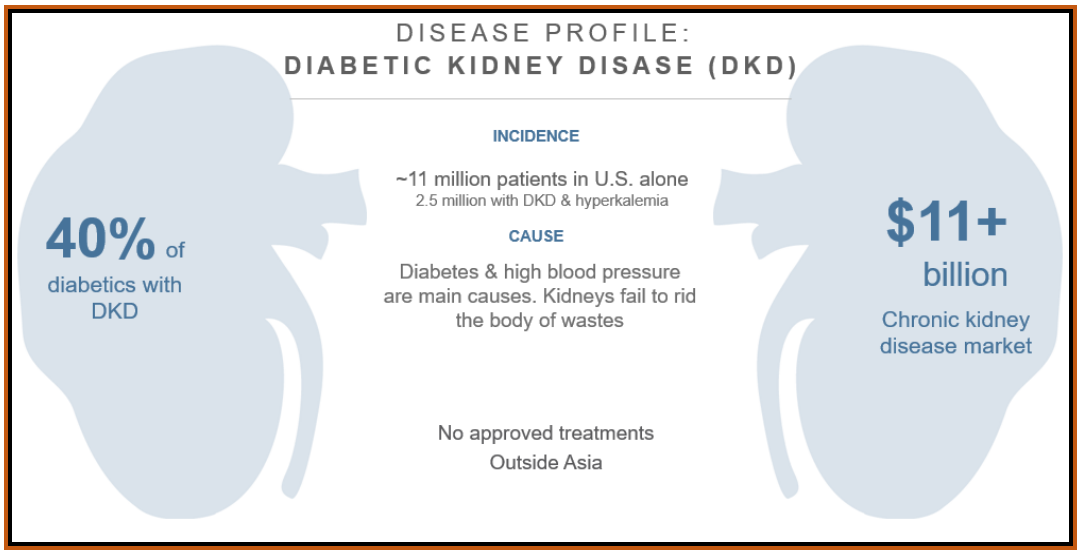


Another Huge Market of DKD for DM199

Diabetes is a worldwide heath issue for millions of people with billions of dollars spent for dealing with this epidemic. According to the World Health Organization (WHO) the number of people diagnosed with diabetes worldwide has risen to 422 million in 2014. The prevalence of diabetes mellitus has grown significantly, primarily due to the increased incidence of Type 2 diabetes.

Diabetic kidney disease (DKD) is one of the most common complications of both Type 1 and Type 2 diabetes occurring in **20-40% of all patients** diagnosed with Type 2 diabetes. Additionally, people with **hypertension** or a familial history of DKD are at an even greater risk. DKD is the leading cause of end-stage renal disease (ESRD) accounting for approximately 50% of cases in the developed world.

In the United States, there are approximately 11 million people diagnosed with DKD currently and among them 2.5 million with both DKD and hyperkalemia. The cost of caring for DKD patients accounts for 90% of the direct and indirect costs of diabetes care. In China, approximately 119.5 million people are diagnosed with DKD with an overall prevalence of 10.8%. With these demographics, there is a potential $11.7 billion market for treatments of chronic kidney disease.



DKD Products in Development

In the clinic, along with DM199, there are approximately five other drugs in development to treat DKD, all with aldosterone-independent mechanisms of action. Most of these drugs are being developed to be combined with an ACEi or ARB.

Finerenone (BAY94-8862) is a non-steroidal mineralocorticoid receptor antagonist (MRA) currently in an active **Phase III** clinical trial. In a Phase II trial, Finerenone reduced urine albumin-to-creatinine ratio (UACR) at day 90 post treatment in a dose-dependent manner when combined with a low dose ACEi. However, approximately 1.8% of patients were discontinued from the study because of hyperkalemia.

Pentoxifylline, Atrasentan, Canagliflozin, and Liraglutide, marketed drugs that are used to treat other complications of diabetes, also are being tested for efficacy in DKD. For all these drugs, long-term efficacy and safety data is needed to completely elucidate the effects on DKD and the prevalence of side effects or serious adverse reactions.

DM199 Advantages for DKD

As we discussed above, blood pressure medications including angiotensin converting enzyme inhibitors (ACEi: Ramipril®) and/or angiotensin receptor blockers (ARBs: Banicar®) are widely used and are considered the **standard of care** for DKD**.** However, both ACEi and ARBs can lead to hyperkalemia and angioedema, which can cause severe **cardiac complications**.

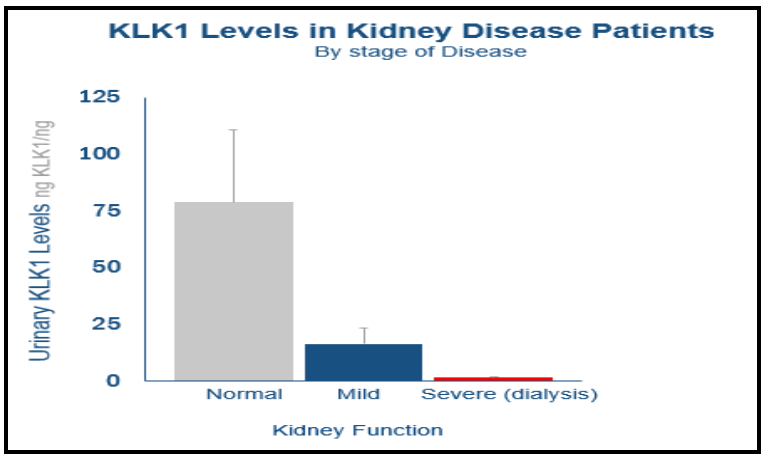
DM199 is a recombinant human tissue kallikrien (KLK1), which has demonstrated excellent safety profile in animal models and in human studies. DM199 is in development as a replacement therapy for DKD patients to restore KLK1 levels to natural levels. Due to its unique mechanism of action, DM199 is believed to improve kidney function without risk of hyperkalemia and other side effects of compounds like ACEi. DM199 could potentially be combined with ARB or new treatments such as Finerenone if approved to further improve kidney function.

Kallidinogenase (porcine KLK1), a similar product of DM199 have been approved in Asia for the treatment of acute ischemic stroke (AIS), DKD and hypertension. We believe DM199 has a high probability to get approved by health authorities once its efficacy and safety have been established in clinical trials.

Worldwide peak sales of DM199 for DKD could potentially also surpass **$1 billion**. With combined sales from AIS, DM199 could become a blockbuster for DiaMedica.

Clinical Evidence of DM199 for the Treatment of DKD

Studies have shown that lower KLK1 level is associated with worsening kidney function.



The most compelling evidence for developing DM199 as an effective treatment for DKD lies in the therapeutic effect of porcine derived KLK1 in DKD patients in China. **Porcine KLK1** (kallidinogenase) has been approved in China for the treatment DKD and hypertension.

In a 2015 study, 200 patients with diabetes were treated for 60 days with porcine KLK1 or dipyridamole (blood thinner) tables. The urinary albuminuria excretion of the KLK1 group decreased significantly from baseline and from the control group. When the treatment group was divided into participants that displayed microalbuminuria (UAE 30-300mg/24hrs) or clinical albuminuria (UAE >300mg/24hrs), participants with microalbuminuria showed more robust treatment effects of porcine KLK1 than the clinical albuminuria group. This suggests that during early stages of DKD (microalbuminuria) kidney damage is more easily reversed. However, as DKD evolves into clinical albuminuria, the disease might enter into an irreversible stage.

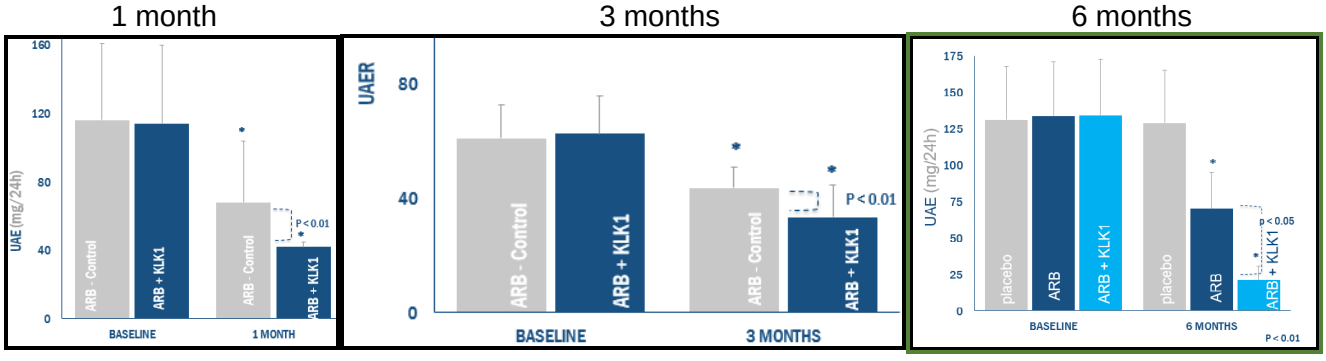
There have been several studies that have investigated the effects of ARBs and **ARB + KLK1** in patients with DKD. Notably, studies have shown lasting effects of KLK1 plus ARB significantly reducing urinary albumin excretion (UAE) rate after 1, 3 and 6 months of dosing.

In a study of 68 patients with early DKD treated with either an ARB alone or an ARB + KLK1, after one month of treatment participants receiving the combination of ARBs and KLK1 had significantly lower levels of urinary albumin excretion rate (UAER) from baseline before treatment, and from participants who were treated with just an ARB alone **(Left Panel).**

In another study following 58 participants with daily dosing of ARB or ARB + KLK1 showed a significant reduction in UAER in the combination group. Levels were significantly lower than their own baseline and from the ARB alone treated group after 3 months of treatment (**Middle Panel**).

Similar effects were seen in participants treated for 6 months with either an ARB alone or a combination of ARB + KLK1 (**Right Panel**). Again, participants who were treated with a combination of medications showed significantly lower UAER (84.3% reduction) and β2-microglobulin (β2-MG; 56.9% reduction), a marker of reduced glomerular filtration rate, compared to their own baseline and to the placebo group and ARB alone group after 6 months of treatment. Notably, after 6 months of daily dosing, the KLK1 + ARB group UAER levels were brought from 129 mg/24 hr to 21 mg/24hr, which is lower than the clinical diagnosis for DKD (urine albumin >30 mg/24hrs).

Porcine KLK1 (Kallidinogenase) Treatment for DKD



Similar clinical studies have investigated the effects of **KLK1 with ACEi** in DKD patients. These studies have shown that participants treated with the combination therapy showed significantly lower urinary protein excretion and lower UAER compared to treatment with ACEi alone. Additionally, the combination treatment group showed decreased whole blood and plasma viscosity, decreased hematocrit and

decreased fibrinogen. Each of these hemorheology measurements are correlated with cardiovascular disease, which can be comorbid with diabetes.

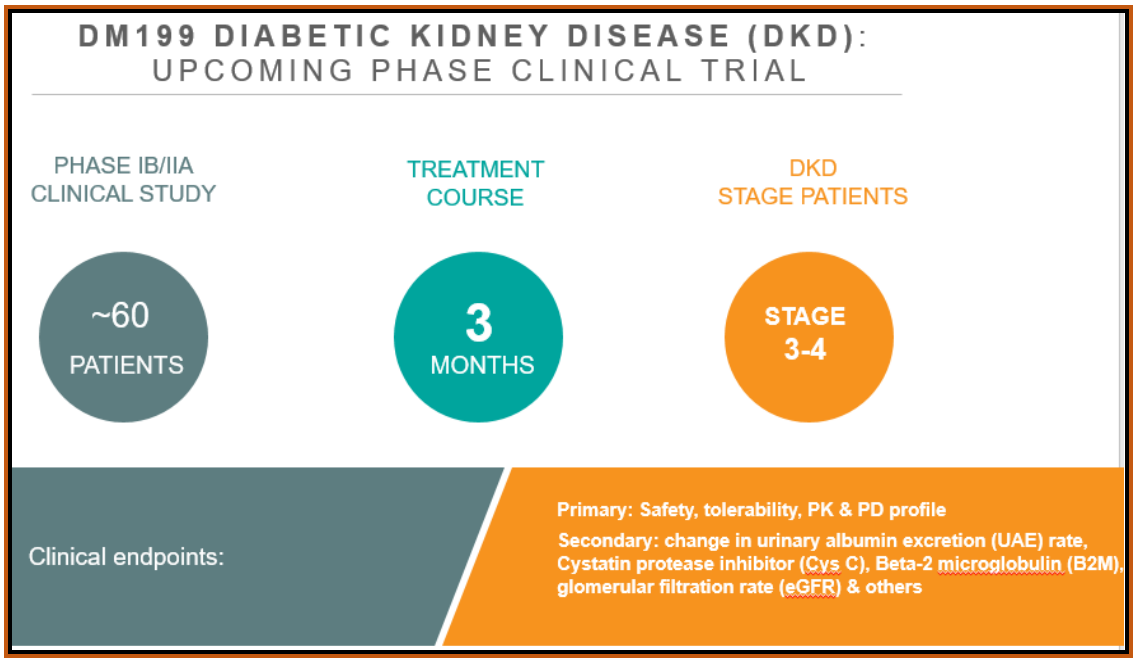
All these data from the clinical studies suggest that KLK1 treatment could greatly compliment the use of ARBs or ACEi in the treatment of DKD. Although a great deal of work has been published, it is worth noting that several clinical studies in China are not well-controlled and additional properly controlled trials designed according to Western standards are needed to confirm the Chinese publications.

Development Plan for DM199 for the treatment of DKD

As we discussed above, DiaMedica is conducting a **Phase I** bridge clinical trial to determine the safety, optimal dose & delivery. The trial has completed the first part of IV dosing and has identified a IV dose comparable to approved KLK1 products. The **subcutaneous** dosing is continuing.

The company plans to use the results of this study to guide the upcoming **Phase II** clinical trial. The planned Phase II clinical trial intends to enroll about **60 patients** with stage 3-4 DKD disease. The primary endpoints include safety, tolerability, PK & PD profile. Secondary endpoints will include change in urinary albumin excretion (UAE) rate, cysteine protease inhibitor (Cys C), Beta-2 microglobulin (B2M), glomerular filtration rate (eGFR) & others. The patients will be treated and followed up for 3 months.

We expect the Phase II trial to begin in 2017 and that data from the trial will be available in 2018.



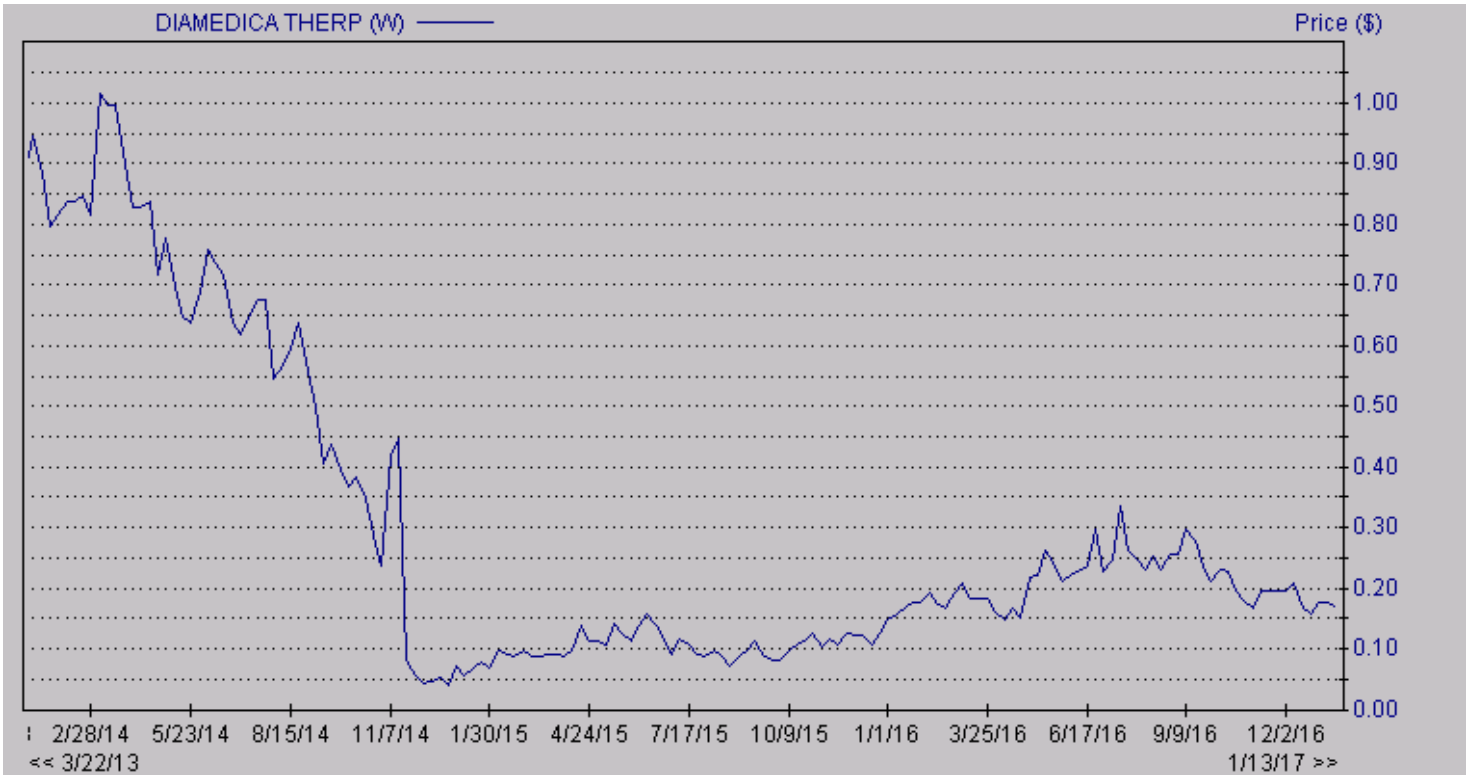
INCOME STATEMENT

	2016A (Dec)					2017E (Dec)					2018E (Dec)	2019E (Dec)	2020E (Dec)	2021E (Dec)	2022E (Dec)
$CND in million except per share data	Q1	Q2	Q3	Q4	FYA	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE	FYE
R&D revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Product Revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$15.00	$45.00	$75.00
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$15.00**	**$45.00**	**$75.00**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	200.0%	66.7%
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.25	6.75	11.25
Gross Income	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$12.75**	**$38.25**	**$63.75**
Gross Margin	-	-	-	-	-	-	-	-	-	-	-	-	85.0%	85.0%	85.0%
R&D	$0.31	$0.48	$0.97	$0.00	$1.76	$1.16	$1.18	$1.20	$1.25	$4.79	$5.00	$6.00	$7.50	$9.00	$12.00
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	50.0%	20.0%	16.0%
SG&A	$0.17	$0.24	$0.29	$0.02	$0.72	$0.14	$0.20	$0.25	$0.35	$0.94	$1.50	$2.50	$4.00	$5.00	$9.00
%SG&A	-	-	-	-	-	-	-	-	-	-	-	-	27%	11%	12%
Operating Income	**($0.5)**	**($0.7)**	**($1.3)**	**($0.0)**	**($2.5)**	**($1.3)**	**($1.4)**	**($1.5)**	**($1.6)**	**($5.7)**	**($6.5)**	**($8.5)**	**$1.3**	**$24.3**	**$42.8**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	54%	57%
Other Net	$0.0	$0.0	$0.0	$0.2	$0.3	($0.0)	$0.0	$0.0	$0.0	($0.0)	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	**($0.5)**	**($0.7)**	**($1.2)**	**$0.2**	**($2.2)**	**($1.3)**	**($1.4)**	**($1.5)**	**($1.6)**	**($5.7)**	**($6.5)**	**($8.5)**	**$1.3**	**$24.3**	**$42.8**
Income taxes(benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$6.4
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15.0%
Reported Net Income	**($0.5)**	**($0.7)**	**($1.2)**	**$0.2**	**($2.2)**	**($1.3)**	**($1.4)**	**($1.5)**	**($1.6)**	**($5.7)**	**($6.5)**	**($8.5)**	**$1.3**	**$24.3**	**$36.3**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49.8%
Net Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	53.9%	48.5%
Diluted Shares Out	87.3	90.3	110.3	154.1	110.5	110.6	120.0	122.0	125.0	119.4	130.0	135.0	140.0	145.0	150.0
Reported EPS	**($0.01)**	**($0.01)**	**($0.01)**	**$0.00**	**($0.02)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.05)**	**($0.05)**	**($0.06)**	**$0.01**	**$0.17**	**$0.24**
One time charge	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($0.5)**	**($0.7)**	**($1.2)**	**$0.2**	**($2.2)**	**($1.3)**	**($1.4)**	**($1.5)**	**($1.6)**	**($5.7)**	**($6.5)**	**($8.5)**	**$1.3**	**$24.3**	**$36.3**
Non GAAP EPS	**($0.01)**	**($0.01)**	**($0.01)**	**$0.00**	**($0.02)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.05)**	**($0.05)**	**($0.06)**	**$0.01**	**$0.17**	**$0.24**

Source: Company filings and Zacks estimates

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HISTORICAL ZACKS RECOMMENDATIONS



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