



AMULET
PHARMACEUTICALS

EXECUTIVE SUMMARY

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1. EXECUTIVE SUMMARY

High value therapeutics through nitric oxide

Amulet Pharmaceuticals, Inc is an early stage biotechnology company developing clinically differentiated new chemical entities for unmet medical needs serving large, rapidly growing markets. Amulet minimizes development risk, shortens development time and improves drug safety through the combination of our NORTECH™ technology and FDA approved commercially successful therapeutics.

- By integrating proprietary nitric oxide donors into FDA approved, commercially successful therapeutics with known safety and efficacy liabilities, these known liabilities are directly addressed and an NCE is created with a differentiated clinical advantage.

Our first application of the technology is the unmet medical need of gastroparesis, a gastrointestinal indication, where there is no safe effective treatment for up to 3 Million sufferers in the US. The goal is to complete a Phase 2 Human Proof of Concept Clinical study on our lead compound AMU-301 by the first half of 2011. Our strong early stage pipeline is in Gastrointestinal diseases (GI) and Osteoarthritis (Pain).

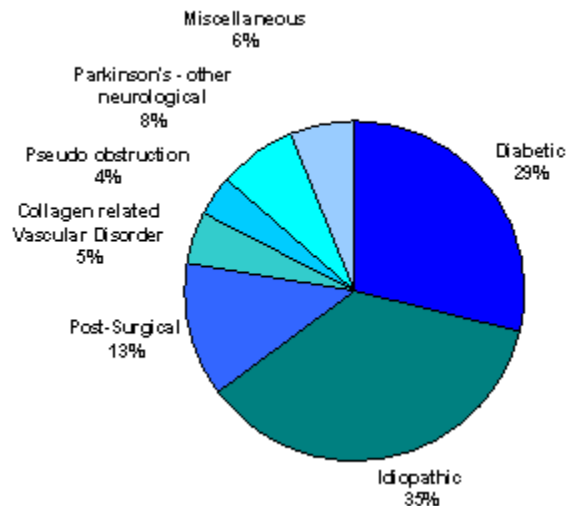
Amulet Pharmaceuticals Inc's therapeutic technology, NORTECH™, is innovative, proprietary and superior to other nitric oxide technologies.

- Amulet Pharmaceuticals, Inc novel therapeutic (AMU-301) based on NORTECH™ technology is designed to treat diabetic gastroparesis and related motility disorders of the GI tract; all of which are considered significant unmet medical needs.
 - The primary problems with current treatments are that they are either effective with serious and treatment limiting side effects (e.g. metoclopramide, cisapride) or have fewer side effects but limited efficacy (e.g. domperidone, erythromycin).
- AMU-301 treats the root cause of the disease not just the symptoms
 - Gastric motility disorders are caused by the loss of the neurotransmitter, nitric oxide.
 - The loss of the nitric oxide neurotransmitter was newly discovered in 2006 and 2007 to be the central pathophysiological finding in gastric motility disorders.
 - In 2007 and 2008, several critical papers established that the loss of the nitric oxide neurotransmitter for gastric smooth muscle relaxation and a survival factor for gastric pace maker cells (Interstitial Cells of Cajal (ICC)) leads to the development of gastroparesis and other GI motility disorders and a therapeutic opportunity for exogenous nitric oxide.
- AMU-301 is the best value on the GI market today for in-licensing or acquisition
 - AMU-301 Composition of matter PCT protection with long patent life to 2024
 - Rapid development to Registration Phase II completed by H12011 NDA by 2013
 - Few competitive compounds in development and all have potential liabilities that increase regulatory timelines and risk.
 - Treats root cause of disease not symptoms - Safe and efficacious - Novel mode of action
- AMU-301 is the only technology on the market that controllably delivers physiologically active nitric oxide (●NO) without metabolic activation, making AMU-301 a first-in-class drug that delivers ●NO nitric oxide topically to the gut wall.
 - AMU-301 is a therapeutic polymer built on a proven safe polymer backbone

2. GASTROPARESIS MARKET OPPORTUNITY

In 2004, there were estimated to be over 5 Million gastroparesis (GP) patients in the U.S.: 29% with diabetic and 35% with idiopathic gastroparesisⁱ. Up to 5-10%ⁱⁱ of the overall US diabetic population (~1.5 Million) suffers from gastroparesis. About the same number suffers from gastroparesis from no known cause (idiopathic) for an overall US market size of about 3 Million in our target markets of diabetic and idiopathic gastroparesis. This is expected to grow at 5% per year in line with the increased incidence of diabetes across the population (ADA). The market is likely to reach 4 Million patients by 2012. Amulet's market opportunity for gastroparesis based on a conservative patient population of 3.5 Million is over \$1 Billion in revenue by 2015.

Gastroparesis is characterized by early fullness, abdominal bloating and fullness, nausea and vomiting, and delayed gastric emptying leading to erratic blood glucose levels and malnutrition. The symptoms can lead to extreme distress and medical emergencies requiring repeated hospitalizations. There are currently no good treatment options and the disease is considered an unmet medical need. A recent and extensive review of animal models and human examples of GP concluded "In the context of gastroparesis, it is, therefore, unsurprising that neuronal nitric oxide and the enzyme responsible for its synthesis, neuronal Nitric Oxide Synthase (nNOS), have emerged as the molecules of greatest interest in studies of the condition"ⁱⁱⁱ. There is strong evidence that in both diabetic and idiopathic gastroparesis, the loss of neuronal Nitric Oxide Synthase (nNOS) containing neurons and the nitric oxide mediated loss of Interstitial Cells of Cajal (ICC) in the stomach is the root cause of the disease in humans and animal models^{iv}.



Food normally moves through the stomach in a highly coordinated manner. In healthy individuals, two systems work to relax and contract the Smooth Muscle Cells (SMC) of the stomach through specialized "pacemaker" cells known as the Interstitial Cells of Cajal (ICC). The nitrenergic system uses nitric oxide made by the enzyme nNOS to cause the SMC to relax, and the cholinergic system uses acetylcholine (ACh) to signal a contraction. The ICC act to coordinate the two incoming signals.^v ^{vi} Diabetes and many other diseases such as autoimmune disease cause the loss of nNOS, resulting ultimately in the degeneration of nitrenergic neurons in the stomach, leading to a reduction in the amount of ICC in the stomach^{vii}. In the development of gastroparesis, the loss of the nitric oxide message has two profound effects: first, there is a loss of the ability of the stomach muscle to relax, leading to hypercontractility and second, a decrease in the number of ICC leading to disorganized motor function.^{viii} The combined pathologies can lead to a hypercontractile, non-coordinated state in the SMC, resulting in 1) decreased accommodation in the stomach and associated symptoms of fullness, pain, bloating, nausea, and vomiting, 2) loss of muscular coordination in the stomach leading to poor distribution of food within the stomach, and 3) an inability of the pylorus to relax. The combined result of these effects is delayed gastric emptying and gastroparesis.

Nitric oxide is a survival factor for the ICC where loss of the nitric oxide signal leads directly to a reduction in the number and volume of the ICC.^{ix} Conversely, increased nitric oxide levels leads to an increase in the ICC, indicating that treatment with nitric oxide may both relieve symptoms of gastroparesis through stimulating the ICC and direct relaxation of smooth muscle, and prevent the progression of the disease and possibly even reverse the symptoms with chronic administration.

3. THERAPEUTIC USE OF NITRIC OXIDE IN GASTROPARESIS

- Nitric oxide is a key inhibitory neurotransmitter in the GI tract and many nitric oxide-related GI disorders can be treated with AMU-301, including gastroparesis, functional dyspepsia and IBS. In addition, AMU-301 could enhance the effectiveness of enteral feeding in the critical care setting.
- NORTECH™ and AMU-301 deliver nitric oxide through a carbon-based (C-based) NONOate (Diazeniumdiolate) group, greatly increasing the safety profile of the drug.
- NORTECH™ and AMU-301 does not require metabolic activation unlike the organic nitrates, and repeated treatment with NORTECH™ does not result in the development of tolerance.
- Exogenous nitric oxide relaxes the stomach and empties the stomach in advanced disease where both nitrergic nerves and the ICC are lost.
- Exogenous nitric oxide acts via the ICC to coordinate gastric motility (ICC are more sensitive to nitric oxide than smooth muscle) in disease states where the ICC are present but reduced.
- Exogenous nitric oxide can prevent progression of the disease and possibly reverse the disease in early stages of the neuropathy by increasing the survival of the ICC.

4. DIFFERENTIATING CLINICAL ADVANTAGES OF AMU-301

- Insoluble polymer based on a proven safe backbone (Cholestyramine USP) ensures localized topical delivery of nitric oxide to the stomach – minimizes systemic side effects.
- Delivers a sustained release of pharmacologically active nitric oxide in stomach acid over the course of impaired gastric emptying.
- Insoluble polymers have a long record of patient safety and short IND filing-to-approval times.

5. LICENSING/ACQUISITION OPPORTUNITY

- AMU-301 is an NCE with a novel mode of action for gastroparesis, functional dyspepsia and IBS
- AMU-301 is the only therapeutic in development for gastric motility disorders that is non-systemic and therefore far less likely to have systemic side effects than any other drug available for licensing
- AMU-301 is the only therapeutic for gastric motility disorders available for licensing or acquisition that does not have demonstrated cardiac liabilities or have cardiac liabilities associated with a drug class such as the 5HT₄ agonists and D₂ antagonists
 - It is likely that AMU-301 will not be required to be tested for cardiac safety because the FDA has already agreed that no cardiac safety study is required by NicOx AG with an orally delivered nitric oxide naproxen derivative.
 - Any risk of cardiac safety will heighten FDA scrutiny thereby lengthening regulatory timelines and risk.

6. PRE- CLINICAL (*IN-VIVO*) RESULTS TO DATE

Amulet Pharmaceuticals Inc in collaboration with Georgetown University Medical Center has shown, in diabetic rat models that exogenous sources of nitric oxide can restore gastric emptying to pre-disease levels.

- Gastric emptying was restored to normal with doses of 10 and 20 mg/kg AMU-301 consistently in all studies using diabetic rats models conducted to date by **Amulet Pharmaceuticals Inc**.
- Safety studies performed at WIL Research Laboratories demonstrate that AMU-301 up to doses of 30 mg/kg has no effect on small intestine motility in healthy rats
- Safety studies performed at WIL Research Laboratories demonstrate that AMU-301 at doses up to 30 mg/kg had no effect on blood pressure or heart rate in healthy rats.
- Ongoing safety and efficacy studies are being conducted in animals and in excised human tissue at Xenometrics, LLC, Georgetown University Medical Center, Mayo Clinic and the University of Kansas Medical Center.

7. COMPANY PROFILE

Amulet Pharmaceuticals Inc has a deep pipeline, a strong management team and globally protected composition-of-matter intellectual property. Our patent portfolio has a long life and Amulet's patented NORTECH™ nitric oxide delivery technology is the only nitric oxide delivery technology available for licensing that releases safe, physiologic levels of nitric oxide in a predictable and controllable manner with minimal toxicity or tolerance.

Amulet Pharmaceuticals Inc minimizes development risk, shortens development time and enhances safety of gastrointestinal and osteoarthritis drugs with liabilities that can be directly addressed using a nitric oxide donor.

- NORTECH™ addresses gastrointestinal diabetic neuropathies through topical delivery of nitric oxide throughout the GI tract to replace the lost neurotransmitter.
- NORTECH™ addresses gastrointestinal liabilities of GI and osteoarthritis drugs through increased production of protective stomach mucus and increased blood flow.
- NORTECH™ addresses cardiovascular liabilities through reducing blood pressure and reducing platelet mediated clotting as well as anti-inflammation.

Amulet Pharmaceuticals Inc initial lead compound, AMU-301, is a new polymeric chemical entity to treat diabetic and idiopathic gastroparesis that is designed to be safe and has blockbuster potential. Rapid approval can be expected due to the non absorbed polymeric nature of the drug. Additional GI indications, such functional dyspepsia, are available to the AMU-301 family of drugs through pharmacological manipulation of the GI tract using topical delivery of the key neurotransmitter nitric oxide.

Amulet Pharmaceuticals Inc has filed international patent protection on all forms of exogenous nitric oxide delivery to the stomach to treat gastroparesis as well as composition of matter protection on the AMU-301 family of the molecules. The use of exogenous nitric oxide to treat gastroparesis represents a differentiating clinical advantage for AMU-301 and a clear advantage in both safety and efficacy.

Nitric oxide is an important naturally occurring chemical found in the body that promotes the health of the heart, circulatory system, gastrointestinal tract, brain and immune system. Imbalances in nitric oxide are pivotal in the development of gastrointestinal diseases, heart disease and diabetes and nitric oxide has a vast array of therapeutic applications.

Amulet creates value by applying its proprietary nitric oxide delivery technology to unmet medical needs in large, fast growing markets by adding nitric oxide delivery capability to FDA approved therapeutics where nitric oxide provides a differentiating clinical advantage in safety and/or efficacy. Amulet closed on over \$3 Million Series A financing in 2006, has received over \$1.7 Million in grants and contracts. Amulet seeks to create value for investors through licensing and M&A.

NORTECH™ Technology

Amulet Pharmaceuticals Inc's therapeutic technology NORTECH™ brings several innovations to the delivery of nitric oxide in general and to the problem of gastrointestinal disease in particular. Amulet's nitric oxide delivery technology, NORTECH™ and AMU-301 delivers nitric oxide through a carbon-based (C-based) NONOate (Diazeniumdiolate) group in response to neutral and acidic pH. C-based NONOates cannot form carcinogenic breakdown products, unlike the nitrogen-based NONOates, greatly increasing the safety profile of the drug. Furthermore, NORTECH™ therapeutic polymers deliver •NO (physiologically active nitric oxide), a natural free radical produced in the body. NORTECH™ delivery of nitric oxide is triggered by pH only and does not require additional metabolic activation by the body, and unlike the organic nitrates, repeated treatment with NORTECH™ does not result in the development of tolerance.

Our lead compound, AMU-301, has a microporous hydrophobic polymer backbone where the acid-sensitive NONate groups sit deep in the polymer and are protected from the acidity of the stomach. The polymeric nature of AMU-301 allows it to release nitric oxide continuously over the entire duration of the gastric emptying process without being degraded. AMU-301 delivers targeted nitric oxide throughout the GI tract. The polymer scaffold of AMU-301 is identical to the scaffold of the approved drug Cholestyramine USP which has a long history of safe clinical use. The same polymer scaffold is also used as a GRAS (generally regarded as safe by FDA) food additive.

Insoluble, orally delivered polymers such as AMU-301 possess a distinct safety advantage over systemic drugs, as demonstrated by the short IND to approval times for insoluble polymers such as Renagel and WelChol, that progressed from IND to Approval within 3 years.

In addition to Amulet's NORTECH™ therapeutic polymer program, we have a small molecule program with several leads in various stage of development in gastrointestinal diseases and osteoarthritis (pain).

8. COMPETITION

- Weak competition
 - Lack of efficacy (metoclopramide, 5-HT₄ agonists, erythromycin) ^x
 - Dangerous CNS (metoclopramide) and cardiovascular side effects (5-HT₄ agonists, domperidone, erythromycin)
 - Inconvenience and small market - TZP-101 (I.V. only)

- AMU-301 is safe – topical release of nitric oxide in the stomach
 - The polymer is not absorbed into the bloodstream – limits systemic side effects
 - Nitric oxide does not reach the bloodstream
 - Short half-life of nitric oxide – limits systemic side effects
 - Limited diffusion – limits systemic side effects
 - Safety profile of AMU-301 allows expansion of patient population into those mildly affected

- Insoluble drugs have a long history of rapid FDA approval
- AMU-301 replaces lost neurotransmitter
 - Treats the disease (loss of nitric oxide), does not simply counteract the symptoms
- Local release of nitric oxide within the stomach
 - Mimics normal physiological digestion process (*i.e.* fundus to antrum to pylorus to duodenum) without treating the entire patient

Due to the mechanism of action and adverse event profile of current therapies, Amulet does not expect significant competition from these drugs once physicians understand the benefits of AMU-301 for treating gastroparesis.

TZP-101 from **Tranzyme Pharmaceuticals Inc** is in phase 2 clinical trials as an intravenous treatment for gastroparesis. It is efficacious, but it is not orally available and the systemic administration of TZP-101 renders a higher risk for side effects than the localized oral delivery of AMU-301. Tranzyme has a second lead, TZP-102 in phase 1 trials, which is orally available.

ATI-7505 from **Aryx Therapeutics Inc** licensed to **Proctor and Gamble Inc**, is a novel 5-HT4 agonist that targets receptors in the GI and heart. It is prokinetic in the GI by releasing acetylcholine which stimulates motility, but 5-HT4 receptors are also found in the human atrium and ventricle, and atrial 5-HT4 receptor stimulation is proarrhythmic by nature. This means ATI-7505, like all 5-HT4 agonists, has the potential to produce atrial arrhythmias. Published clinical data shows good colonic prokinetic efficacy in humans but poor efficacy on gastric emptying (600 patients). ATI-7505 is currently being evaluated for a FDA mandated thorough cardiovascular evaluation with results due by Q208^{xi}.

9. INTELLECTUAL PROPERTY

Amulet core NORTECH™ technology is protected by international and U.S. Patent applications that provide a rich source of core Intellectual Property to support the company and provide a rich pipeline: PCT Patent Application # PCT/US2005/000174, and # PCT/US2006/046214 nitric oxide-releasing Polymers and US provisional filing 60/924830 Compounds, Polymers and Methods for treating Gastrointestinal Dysfunction. Amulet is responding to office actions on PCT/US2005/000174 and is filing a PCT patent application for 60/924830.

10. AMU-301 DEVELOPMENT PLAN

Amulet Pharmaceuticals Inc has a well-defined development plan in place for AMU-301 through nonclinical studies to completion of human clinical proof-of-principle. These plans include timelines, and budgeted CRO studies as well as proper dependencies to ensure the chemistry is available to conduct studies in a timely and cost effective manner. The major goal of the preclinical studies is to file an IND for AMU-301 in the first half of 2009.

Amulet anticipates that it will require three clinical studies to achieve proof of concept with AMU-301. The first study planned is a Phase 1 single dose study in normal healthy volunteers. The second study planned is a Phase 1 multiple dose study also in normal volunteers. The third study planned is a Phase 2 multiple dose study in diabetic patients with gastroparesis to establish proof of concept with AMU-301. Top line proof of concept data is expected be available in the first half of 2011.

Use of Funds

We are seeking investment to:

- Complete animal proof of concept studies in several models
- Initiate process chemistry optimization of AMU-301
- Produce first GMP kilo scale-up synthesis of AMU-301
- Reach national filing stage in North America, EU, and Asia of composition of matter patents
- Undertake global PCT filing for gastrointestinal application of our composition of matter
- Conduct IND enabling studies
- File IND in first half 2009
- Perform Phase 1 and Phase 2 clinical trials for AMU-301

11. AMULET MANAGEMENT AND ADVISORS

Chairman and Chief Executive Officer – Craig M Liddell, PhD

Dr Liddell is a successful entrepreneur with over 20 years experience in biotech, pharmaceuticals and academia. A former tenured professor, Dr Liddell has served as VP and CSO of Paradigm Genetics Inc, Artesian Therapeutics, Inc. a heart failure drug development company and BioFortis, Inc. a translational medicine software company.

Chief Financial Officer, Secretary and Treasurer – Jonathan Proch, CPA, MBA

Mr. Proch is a seasoned financial veteran whose successful career has spanned 24 years. Mr. Proch's experience includes serving as CFO of Artesian Therapeutics, Inc. a heart failure drug development company, VP Finance for a chain of privately owned hospitals and CFO of a \$35 million electronics company. Mr. Proch has raised substantial capital in these and other capacities.

Chief Operating Officer – Hank Dietz, MBA

Hank Dietz' career has encompassed over 25 years in the Information Technology field spanning all aspects; from operations, application programming, systems programming, network management and design including systems administration and extensive management in both project work and supervision of technical staff. He has extensive laboratory management experience along with major system's design and implementation for three startup biotech companies.

VP, Pharmacology – Robert Rauli, PhD, MSSTC

Dr Rauli is an experienced scientist/entrepreneur and founder of **Amulet Pharmaceuticals Inc**. He also co-founded a spin-out company (NOXILIZER, Inc) to commercialize sterilization technology developed at Amulet.

VP, Chemistry – Ralph Scannell, PhD

Dr. Scannell has more than 20 years of experience in the pharmaceutical/biotechnology industry where he held several leadership roles in drug discovery and development in multiple therapeutic areas.

Senior Director, Product Development - Maria Charest, MBA, PMP

Ms. Charest has amassed over 20 years experience in medical product development, about half of which has been in drug development. Most recently as Director of Project Planning and Management at MGI Pharma, she focused on early stage programs and has aggressively moved a number of lead compounds out of research and into the clinic.

Counsel: Samuel (Sandy) B. Sterrett, Jr., Partner, Foley & Lardner, LLP, Washington, D.C. (www.foley.com).

12. BOARD OF DIRECTORS

- Craig M Liddell, PhD Chairman and Chief Executive Officer
- Robert Raulli, PhD, MSSTC VP and Founder
- Carlos Parajon Managing Partner, Harbor Island Equity Partners, LLC
- Michael Cain Managing Member, Wilmington Investor Network LLC

13. BOARD OF ADVISORS

- Pankaj J. (Jay) Pasricha, MD Chief, Division of Gastroenterology and Hepatology, Stanford University
- Gianrico Farrugia, MD Director of the Enteric Neuroscience Program, Mayo Clinic
- Michael Horowitz, MD Chairman, Medicine University of Adelaide
- Richard Gillis, PhD Professor, Autonomic Pharmacology Georgetown
- Harry Mandeville, PhD CEO, Lipid BioSystems Inc.
- Joseph Verbalis, MD Chief of Medicine, Georgetown University Hospital

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- ⁱ Buckle and McCallum (2003) New Approaches for gastroparesis. *Advanced Studies in Medicine* 3(1):39-44.
- ⁱⁱ Digestive Diseases Interagency Coordinating Committee "Gastroparesis: A Common Disorder" April 2, 2004
- ⁱⁱⁱ Vittal, H, Farrugia, G, Gomez, G and Pasricha, P (2007) Mechanisms of Disease: the pathological basis of gastroparesis – a review of the experimental and clinical studies. *Nature Clinical Practice Gastroenterology and Hepatology* 4(6):336 - 346
- ^{iv} Vittal, H, Farrugia, G, Gomez, G and Pasricha, P (2007) Mechanisms of Disease: the pathological basis of gastroparesis – a review of the experimental and clinical studies. *Nature Clinical Practice Gastroenterology and Hepatology* 4(6):336 - 346
- ^v Ward SM and Sanders KM. Involvement of intramuscular interstitial cells of Cajal in neuroeffector transmission in the gastrointestinal tract. *J Physiol* 576.3: 675-682, 2006.
- ^{vi} Hirst GDs and Edwards FR. Role of Interstitial cells of Cajal in the Control of Gastric Motility. *J Pharmacol Sci* 96:1-10, 2004
- ^{vii} Choi et al *Neurogastro. Motil.* 19:585-595
- ^{viii} Zarate N, Mearin F, Wang X-Y, Hewlett B, Huizinga JD, Malagelada J-R. Severe idiopathic gastroparesis due to neuronal and interstitial cells of Cajal degeneration: pathological findings and management. *Gut* 52:966-970, 2003.
- ^{ix} Choi KM, Gibbons SJ, Roeder JL, Lurken MS, Zhu J, Wouters MM, Miller SM, Szurszewski JH , Farrugia G. Regulation of interstitial cells of Cajal in the mouse gastric body by neuronal nitric oxide. *Neurogastroenterol Motil* 19:585-595, 2007.
- ^x Parkman, HP, Hasler, WL and Fisher, RS (2004) American Gastroenterological Association technical bulletin on the diagnosis and treatment of gastroparesis. *Gastroenterology* 127:1592-1622
- ^{xi} Press Release, Aryx Therapeutics Inc , 20 December 2007