Tyme Technologies, Inc. (TYME)
Flash Alert
Rating: Strong Sell
Long-term Price Target: $0
Date: March 1st, 2018

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Tyme Technologies, Inc. (TYME)

We are initiating a *Flash Alert* on TYME with a *STRONG SELL* rating and a $0 long-term target.

➢ Several million shares may be owned by two individuals affiliated with “pump & dump” schemes

➢ The company’s single drug candidate, SM-88 has an extremely controversial history and weak clinical data

➢ The principal investigator on SM-88’s most important study to date, the IRB study, quit and accused the head of the IRB that approved the study of stealing money paid by TYME

➢ Amid the controversy and due to conflicts of interest the head of the IRB was fired, and an FDA investigation ensued

➢ The Chief Medical Officer of the hospital where the SM-88 IRB trial was conducted stated that all trials affiliated with the head of the IRB were “tainted”

➢ SM-88 started as a breast cancer drug but the company has unexpectedly pivoted to clinical development in prostate and pancreatic cancer and has deemphasized development in breast cancer

➢ TYME’s press releases continue to tout great breast cancer results despite the pivot away from breast cancer

➢ SM-88 is a four-component drug cocktail with compounds that either *cause* cancer, or have shown little efficacy in treating cancer

➢ TYME’s founders appear to have no background in pharmaceuticals or oncology and have recently started selling stock

➢ TYME is actively accessing a dilutive at-the-money facility and has just announced another dilutive 12mil share equity offering that could further pressure shares lower
Not This Tyme

Overview:

Tyme Technologies (TYME) was formerly known as Luminant Biosciences and came public via a reverse merger in March of 2015. TYME is a clinical-stage biopharmaceutical company that looks to develop and commercialize cancer therapies that address a broad range of cancers. Their sole candidate is SM-88, a “drug cocktail” that combines three generic drugs and a naturopathic supplement. The three drugs are administered at 25% (or less) of their recommended therapeutic dosing levels. At least one of the drugs could be a carcinogenic (cancer causing). To date the company has only completed an Institutional Review Board (IRB) clinical trial akin to a Phase 1 trial, and a follow-on study. They are currently enrolling patients in a Phase 2 trial for a small subset indication in prostate cancer and intend to conduct Phase 2 trials in pancreatic cancer.

This Story Just Gottbetter:

Before we get started with TYME’s current state of business, we believe it’s worth discussing the background of some of the individuals involved with the company due to the egregious nature of their actions. TYME merged into an OTC listed defunct Florida-based liquor shell company called Global Group Enterprises and later uplisted to Nasdaq in 2017. We have several concerns with individuals affiliated with the shell who we believe may own shares of TYME and were in de facto control of the shell at the time of the merger. To be clear, we have no reason to believe these individuals are currently connected to TYME management, but they may own shares.

The individuals in question are the shells former auditor Peter Messineo of DKM and attorney Adam S. Gottbetter of Gottbetter & Partners. Messineo has been affiliated with several “pump and dump” schemes and was listed as auditor on several shell companies with no operations. According to the SEC, he retained ownership in two companies that were audited by DKM after he had merged his own practice into DKM. Messineo was permanently barred from practicing as an accountant for any SEC regulated entity. DKM was suspended by the SEC in late 2015 for falsifying documents and other misconduct. The SEC stated that the “accountants and their firms showed a complete disregard for the basic rules of their profession. As a result, they are now barred from working on any SEC related matters.”

In May of 2015, just two months after Global Group completed the reverse merger with TYME, Mr. Gottbetter was sentenced to 18 months in prison and was hit with a $4.6mil fine for orchestrating a microcap stock manipulation scheme. According to the Department of Justice, Mr. Gottbetter “marketed himself as an expert in taking companies public through a reverse merger process.” He also was the owner of a registered broker-dealer called Gottbetter Capital Group Inc. As you can see here, Global Group announced Gottbetter Capital’s intention to purchase shares of Global Group Enterprises at the same time they announced that a “private investment fund” planned to purchase 50% of the company. We believe this transaction was the first step in the reverse merger into Tyme Technologies.
The private investment fund purchased 6mil shares from then CEO Andrew Keck who owned 9mil of 12mil shares outstanding. The holders of the other 3mil shares were never disclosed.

The IRB First Human Study:

TYME’s first human proof-of-concept trial was an IRB study conducted by the New York Downtown Hospital (NYDH) in 2012. At this time the company was still known as Luminant Biosciences and SM-88 was known as SMK. Although the study took place nearly 6 years ago, it is the trial the company most actively refers to when discussing meaningful clinical results. We can’t overstate the importance of this trial to TYME. The company consistently touts results from this study in press release after press release, consistently finding ways to slice and dice the data as if it is new when in reality it is the same nearly six year old data with a slight update. To the right is a recent example of a press release from November of 2017, based on a study conducted in 2012!

Without strong results from this trial we believe the company would not have moved forward with SM-88 into Phase 2 trials. Their most recent presentation from January 2018 dedicates five full slides (slides 8-12) to the study’s results and it is the first study they discuss in detail. This study has been fraught with drama that led to a $30mil lawsuit, and we have our doubts that what unfolded has not impacted results.
Let the Drama Begin:

The IRB first human study began in 2011 when TYME entered an agreement with doctor Leonard A. Farber, M.D. to develop a clinical trial to test SM-88 on cancer patients. He was tasked with designing the study protocol but was having difficulty. Farber asked colleague Dr. Jeanetta Malanowska-Stega, M.D. (Stega) to assist.

Dr. Stega worked for NYDH and was Chairperson of the hospital’s institutional review board (IRB) at that time. Dr. Stega met with TYME management and was paid $50k to complete the protocol and a patent application. This payment was made directly to Dr. Stega and was deposited in the “Stega Research Group” bank account. Stega claims she received permission for the payment and to conduct the work from senior staff and compliance of NYDH. Once the protocol had been established by Dr. Stega, Dr. Farber applied for IRB approval from NYDH in November 2011. Since Dr. Stega was the Chairperson of the IRB, she recused herself from the vote, but she attended the meeting. As you may have guessed, the study was approved.

In late 2011 around the time the IRB trial began Dr. Farber, principal investigator of TYME’s IRB trial, apparently ran into financial difficulties related to his medical practice. We were able to find two cases against Dr. Farber and his medical practice “The Farber Center.” In each case the plaintiffs were seeking monies owed. One of the cases involved personal loans amounting to $170k that he allegedly did not repay to a colleague. In the other case Dr. Farber was able to file bankruptcy to avoid making good on a promissory note.

When Dr. Farber discovered that Dr. Stega had received a $50k payment from TYME he was apparently upset. He complained that he was not receiving enough money from TYME to conduct the study and felt that the $50k payment to Stega was rightfully his. This led Dr. Farber to resign from the study. At this point Dr. Stega and TYME requested NYDH to take over the study.

In January of 2012 Dr. Farber changed his mind and tried to resume his role as principal investigator but was informed by Dr. Stega that he was no longer part of the study. Dr. Farber reported to NYDH that Dr. Stega had “stolen the study from him and taken money he should have received.” This led to an investigation of Dr. Stega by NYDH. Ultimately the hospital determined that Dr. Stega “had a conflict of interest with respect to the Luminant (TYME) study and had improperly taken money from study sponsors and the Hospital.” Dr. Stega, the Chairperson of the NYDH IRB and the designer of TYME’s IRB trial protocol, was fired on February 2nd, 2012. IRB Vice Chairperson Dr. Wesley Tzall who had been on the IRB since 1992, had been employed by NYDH for 28 years, and who also likely voted on TYME’s trial approval was also fired.

Dr. Stega sent letters to the NYDH Board of Trustees alleging that the NYDH had “violated confidentiality laws in accessing records of patients in clinical trials,” and that “the Hospital’s legal counsel had tried to force her to reveal confidential information pertaining to the Luminant (TYME) study and improperly went through study records and protocols not belonging to the Hospital.” Dr. Stega and Dr. Tzall both filed a complaint to the FDA, which launched an investigation.
The FDA spoke with NYDH Chief Medical Officer Stephen Friedman on May 22, 2012 and he told the investigator that Stega “demanded that because she was the IRB, Farber include a patient in the Luminant (TYME) study, whom Farber thought would not be approved by the IRB.” Friedman went on to say that all the IRB trial approvals while Dr. Stega was Chairperson were “tainted.”

Below is a photo of Dr. Stega with Dr. Giuseppe Del Priore at NYDH. Dr. Del Priore is currently TYME’s Chief Medical Officer.

Source: The Berkshire Eagle

The extent of the drama related to the IRB trial causes us to question results. **To reiterate, the IRB trial in our opinion is the most significant trial completed on SM-88 to date.** It is the trial TYME management most often points to when discussing the safety and efficacy of SM-88, their only drug in development. Now that we’ve shed light on the drama filled atmosphere in which this study took place, we’ll discuss the trial data and why we believe the results should not be relied upon.

**Clinical Trials:**

**The IRB Trial – First Human Study:**

Typically, in the drug industry a company will conduct toxicity testing on hundreds, perhaps thousands of compounds and conduct several studies on animals before moving ahead to trials involving humans. **TYME is attempting a very unorthodox route to market for SM-88.** As far as we can tell, the founders simply came up with a “drug cocktail” they thought might work for cancer patients and, with approval, started testing it on humans.
“Unlike most cancer treatments, which are developed by trained medical researchers and tested in animal models, SM-88 was developed by an engineer – Steve Hoffman (TYME’s current CEO)...

He scoured the medical literature in a way that was different from the approach typically taken by classically trained cancer investigators... Also unusual was the conscious decision to eschew the use of any preclinical models to test the underlying assumptions in animals. Rather, based upon extensive reading and an effective understanding of the medical literature, a theoretical approach was developed to attack and kill tumor cells selectively while sparing normal cells; and this was then tested in people.”

“Zacks analyst David Bautz

This IRB trial was a single-center, open-label trial intended to determine the safety, tolerability and efficacy of SM-88. Additional exploratory endpoints included assessment of progression free survival (PFS), overall survival, duration of response, quality-of-life assessments and others. TYME evaluated 30 patients with several types of metastatic (stage IV) cancer. These patients had failed or declined available anti-cancer treatments. 14 (47%) of the patients had breast cancer, 4 (13%) had non-small cell lung cancer, 3 (10%) had pancreatic cancer, 2 (7%) had prostate cancer and the rest had a different version of other types of cancer.

The patients were administered SM-88 five days per week over a six-week cycle. Several of the patients received several cycles with some patients receiving up to 10 cycles of treatment. SM-88 was administered orally as 3 capsules and via subcutaneous injection. Median overall survival was 29.8 months with 90% of patients experiencing clinical benefit. According to TYME’s presentation, 4 patients had a complete response (CR), 6 had a partial response (PR) and 17 had stable disease (SD). We note that 3 patients had progressive disease (PD) indicating a worsening condition while on SM-88, but TYME chose not to highlight this in the presentation. No drug-related serious adverse events (SAE’s) were reported.
On the surface the results seem compelling, but we have several concerns with this study. For one, the trial was an open-label study. Since it was not a blinded study, the patients knew they were receiving treatment which opens-up the possibility of a strong placebo effect. The study was also non-controlled, single-arm study, so we have no way to compare results of patients who received treatment with those who did not. And although the patients were diagnosed with metastatic cancer, it is not clear exactly how sick they were at the time of treatment.

When interpreting these results, it’s important to understand how the stages of cancer are defined. Often a metastatic cancer patient is referred to as a “stage IV” cancer patient. But the stage that is assigned to a cancer patient is the stage of the cancer when the initial diagnosis is made, and it does not change (except in extremely rare cases). For example, consider a patient that is initially diagnosed with stage II breast cancer that goes into remission after treatment. If the cancer comes back and spreads to the bone they are still considered a stage II patient. The diagnosis is simply updated as stage II cancer with bone metastasis. A patient who is diagnosed with “stage IV” cancer has cancer that has metastasized, and it is considered incurable. Even if these patients go into remission with no signs of cancer they are not considered “cured.” From a medical perspective they are still stage IV patients. The IRB trial revealed that the patient’s cancer had metastasized, but we have no way of knowing exactly how sick each patient was at the time of treatment.

According to TYME, the average Eastern Cooperative Oncology Group (ECOG) score prior to treatment was 1.6. The ECOG Scale of Performance Status is used to determine the “patient’s level of functioning
in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.).

Patients are given scores ranging from 0 to 5 with 0 being the best. Since all the patients had cancer that is commonly referred to as “stage IV,” you might think these patients were on their “death bed,” but they quite literally were not.

**Average ECOG score was 1.6 and 26/30 patients scored 2 or less. Patients were not on their “death bed.”**

**FHS: ECOG Performance Status Improvement**

<table>
<thead>
<tr>
<th>Score</th>
<th>ECOG Definition ¹</th>
<th>Patients</th>
<th>Median OS (months)</th>
<th>Mean ECOG PS after 6 Weeks</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
<td>2 (7%)</td>
<td>29</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>Able to perform light work</td>
<td>14 (47%)</td>
<td>44</td>
<td>0.1</td>
<td>-0.9</td>
</tr>
<tr>
<td>2</td>
<td>Unable to perform any work</td>
<td>10 (33%)</td>
<td>38</td>
<td>1.1</td>
<td>-0.9</td>
</tr>
<tr>
<td>3</td>
<td>Only limited self-care</td>
<td>3 (10%)</td>
<td>7</td>
<td>1.3</td>
<td>-1.7</td>
</tr>
<tr>
<td>4</td>
<td>Bedridden</td>
<td>1 (3%)</td>
<td>11</td>
<td>1</td>
<td>-3.0</td>
</tr>
<tr>
<td>1.6</td>
<td>Average</td>
<td>26/30</td>
<td>-0.6</td>
<td>-1.0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Tyme Technologies, JP Morgan Healthcare Conference, Slide 12 & Cliffside Research

It’s also worth noting that a score of 2 is defined by ECOG as “ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours,” which to us sounds relatively active (see appendix for full ECOG definitions). Our takeaway is that the patients in the study were clearly sick, but most were in relatively decent condition at the start of the trial. Even without the drama that unfolded at NYDH, we feel little can be determined from this study based on the studies questionable protocol.

**The Compassionate Use Study:**

Following the IRB trial, TYME conducted a follow-on compassionate use expanded access program for select cancer patients. To date 76 patients have been included in this study and TYME presented analysis on the first 57 patient in 2016. We found it odd that TYME has not released the complete data on the other 19 patients. The first thing that stands out to us is that these results don’t seem as compelling as the IRB study that only included 30 patients, which we feel is telling.

This point is further emphasized by what we consider to be particularly disappointing results in breast cancer for the compassionate use program. Breast cancer was the top category in both the IRB trial (14/30) and the follow-on expanded access study (11/57). Overall breast cancer patients accounted for...
29% of the patients in both trials (25/87). The results in the expanded access program do not appear to be as encouraging for breast cancer, the number one category in both studies.

### SM-88: Compassionate Use Expanded Access Program

**Analysis of first 57 patients conducted in 2016**

<table>
<thead>
<tr>
<th>Primary Disease</th>
<th>Number of Patients</th>
<th>Complete Response (CR)</th>
<th>%</th>
<th>Partial Response (PR)</th>
<th>%</th>
<th>Stable Disease (SD)</th>
<th>%</th>
<th>Progressive Disease (PD)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>11</td>
<td>1</td>
<td>9%</td>
<td>4</td>
<td>36%</td>
<td>2</td>
<td>18%</td>
<td>4</td>
<td>36%</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>10</td>
<td>1</td>
<td>10%</td>
<td>2</td>
<td>20%</td>
<td>5</td>
<td>50%</td>
<td>2</td>
<td>20%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>4</td>
<td>2</td>
<td>50%</td>
<td>1</td>
<td>25%</td>
<td>1</td>
<td>25%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>3</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>67%</td>
<td>1</td>
<td>33%</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>4</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>25%</td>
<td>1</td>
<td>25%</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Glioma</td>
<td>5</td>
<td>0</td>
<td>0%</td>
<td>5</td>
<td>100%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4</td>
<td>1</td>
<td>25%</td>
<td>2</td>
<td>50%</td>
<td>1</td>
<td>25%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>4</td>
<td>0</td>
<td>0%</td>
<td>3</td>
<td>75%</td>
<td>1</td>
<td>25%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Bile Duct Cancer</td>
<td>4</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>25%</td>
<td>1</td>
<td>25%</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
<td>3</td>
<td>38%</td>
<td>0</td>
<td>0%</td>
<td>4</td>
<td>50%</td>
<td>1</td>
<td>13%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>57</td>
<td>8</td>
<td>14%</td>
<td>19</td>
<td>33%</td>
<td>18</td>
<td>32%</td>
<td>12</td>
<td>21%</td>
</tr>
</tbody>
</table>

*8 other types

Source: TYME & Cliffside Research

### Cancer Pivot:

We find these results particularly interesting when considering TYME’s go-to-market strategy for SM-88. When TYME initially came public it was largely assumed that the company would seek FDA approval for SM-88 in breast cancer. We can clearly see this in a report titled “FDA accepts IND for SM-88; set to initiate phase 2 trial in breast cancer patients” by Zacks analyst Jason Nopadano (who later pled guilty to insider trading of biotech stocks). In TYME’s own press release announcing the FDA’s acceptance of their IND application of SM-88, they refer to the drug as their “breast cancer candidate.” The company makes no mention of other specific cancers in the press release.

“In October of 2015, the FDA accepted the IND and concluded that we may proceed with a clinical investigation of SM-88 for breast cancer. We are currently preparing protocols for a phase II breast cancer clinical trial, as well as other phase II trials to be initiated in 2016.”

~TYME 2015 10-K, pg. 2

As we can see below, they have by far more data on breast cancer patients than any other patient type, so it seems to make sense that they would seek approval for a breast cancer indication. Yet for some reason that in our opinion has not been well explained, the company decided to pivot to prostate cancer for their first Phase 2 study. The first two studies combined have data on only 6 prostate cancer patients.
We find that as time passes, they are discussing moving forward in breast cancer less and less. We find this concerning since breast cancer is the top patient category in the two major studies to date. The fact that they continue to promote impressive results in breast cancer in press releases make this shift even stranger. If the results were so great for breast cancer, why pivot? As you can see below, after getting the go-ahead from the FDA in October of 2015 to move to Phase 2 for their “breast cancer drug” SM-88, that indication is lumped into third place behind pancreatic and prostate cancer by December 2016.
By 2018 breast cancer no longer makes the pipeline discussion for SM-88 and falls further down the list for a future transdermal application that is Pre-IND. Again, recall that when the FDA reviewed and accepted their IND for SM-88, the company implied this was for their “breast cancer drug.” Now they consider that indication to be Pre-IND even though they have more data on breast cancer patients than any other patient type.
Phase 2:

TYME is currently enrolling patients in a Phase 1b/2 trial for prostate cancer patients treated with SM-88. Like their earlier trials, this is another open-label (non-blinded) study without control (single-arm). Unlike earlier trials where patients received SM-88 both orally and via subcutaneous injection, Phase 2 patients are only dosed orally. Phase 1b was a dose escalation phase in 4 patients that was completed in January 2017. That is currently being followed by a Phase 2 dose expansion in 30 patients with a 460mg dose of tyrosine. As recently as September of 2017 TYME expected Phase 2 results by the 1st half of 2018, but they have since quietly moved results to the 2nd half of 2018 (see pg. S-2). It’s also worth noting that the trial is on biomarker-recurrent, non-metastatic prostate cancer patients which is a small subset of the overall prostate cancer market. Preliminary results have been positive, as they often are at this stage for many drugs. Following the Phase 2 trial in prostate cancer, TYME is planning a Phase 2 trial in pancreatic cancer.
How Does It Work?

SM-88 is a “drug cocktail” of generic drugs that include rapamycin, phenytoin and methoxsalen, but the real “secret sauce” in SM-88 is their tyrosine derivative. It’s worth noting that the three generic drugs in the cocktail are at concentrations of 25% or less of therapeutic recommendation. How they arrived at this level is unclear but determining dosing levels can be tricky enough with a single compound, let alone a quadruple combination therapy.

When combined, TYME believes these three generic drugs and tyrosine can lead to cancer cell death, but how? We’ll briefly review these drugs and how TYME hopes they will work to kill cancer cells. Then we’ll review two other drugs that tried a similar path and ultimately failed in the later stages of drug development.

TYME’s SM-88 Quadruple Drug Cocktail Components

Rapamycin:
According to TYME, rapamycin “enhances tyrosine uptake.” Rapamycin, also known as Sirolimus, is a very powerful mTOR inhibitor that is typically used to prevent kidney transplant rejection. It has also been extensively studied as a cancer treatment, but according to this 2016 study, rapamycin has been ineffective as an anti-cancer therapy.

Phenytoin:
Phenytoin is an anticonvulsant used in the treatment of epilepsy. It’s role in cancer treatment is not well established. There is some evidence that it might actually cause cancer, but the topic is largely open to debate. TYME believes it “stimulates production of reactive lipid species, which are associated with apoptosis.”

Methoxsalen:
Methoxsalen belongs to a group of medicines called psoralens. It is combined with UV light to treat skin conditions like psoriasis and vitiligo. Methoxsalen’s black box warning indicates it can cause skin cancer. TYME believes it “promotes toxic electron transfer and enhances reactive oxygen species (ROS).”

Tyrosine Derivative – The “Secret Sauce”:
Tyrosine is one of 20 standard amino acids used by cells to synthesize proteins. The human body makes tyrosine and it is found in common foods like meats, eggs and wheat. It is also commonly sold as a naturopathic supplement.

TYME’s version of tyrosine is a dysfunctional tyrosine derivative. Cancer cells use amino acids like tyrosine to build proteins. One form of protein that cancer cells create is mucin. Mucin acts as a protective barrier around the cancer cell. TYME believes they can “break the metabolic circuit of cancer” by inducing uptake of this dysfunctional tyrosine derivative. Once inside the cell they believe protein synthesis will fail, compromising the protective mucin layer. Once this has occurred, apoptosis (programmed cell death) can occur due to increased oxidative stress. They believe the other three drugs (rapamycin, phenytoin & methoxsalen) will assist this process.
Does This Sound Familiar?

We believe the key to TYME’s “drug cocktail” is the increase in oxidative cell stress caused by elevated reactive oxygen species (ROS), commonly referred to as “free radicals.” This is not a novel approach to cancer treatment. Scientists have been trying to induce generation of ROS in cancer cells since the 1950’s. It is the same approach utilized by chemotherapy and radiation therapy. Once ROS reaches an excessive level within the cancer cell, cell death occurs (apoptosis). But the level of ROS is extremely important. At levels that are less than excessive, ROS can facilitate cancer cell survival. The type of ROS, dosage, duration, and site of ROS production all play critical roles. ROS levels within cancer cells are also influenced by cell type. To what degree SM-88 influences ROS levels within specific cell types is unclear. Below we provide two examples of drugs similar to SM-88 that failed late stage trials.

Xcytrin (Motexafin Gadolinium):

You may be familiar with the story of Pharmacyclics and their wildly successful drug ibrutinib, but do you know the story about the ROS cancer drug that almost destroyed Pharmacyclics? Like SM-88, Pharmacyclics drug xcytrin was intended to treat a wide range of cancers by inducing oxidative stress within the cancer cell via elevated ROS levels, leading to cancer cell apoptosis. Also like SM-88, xcytrin preferentially accumulates in cancer cells due to their increased rate of metabolism.

Early on the clinical results looked promising. In 2003 Pharmacyclics announced positive Phase 1 data for xcytrin for head and neck cancer. In combination with chemoradiation 8 out of 9 patients had CR, and 7 out of 9 were in remission after nine months. Xcytrin also had positive Phase 2 data in metastatic non-small cell lung cancer. But Phase 3 results didn’t meet primary endpoints and the stock cratered by over 60%. Pharmacyclics tried to move ahead and eventually filed an NDA but the FDA rejected the drug.

Elesclomol (STA-4783):

Elesclomol was developed by Synta Pharmaceuticals and GlaxoSmithKline. Like SM-88 and xcytrin, elesclomol was supposed to induce oxidative stress by provoking a buildup of ROS within a broad range of cancer cell types (including prostate cancer) leading to cancer cell apoptosis. Elesclomol also had the potential advantage of “fast track” and “orphan drug” designation that can lower the approval hurdles and expedite approval in some cases. Currently SM-88 does not have these designations.

Once again, early clinical results looked promising for elesclomol. A Phase 2 study on 53 metastatic melanoma patients showed statistically significant doubling of median progression free survival (PFS). We also note this study was a randomized, controlled, double-blinded study which is generally considered far more rigorous than TYME’s non-randomized, non-controlled, non-blinded studies to date.

Unfortunately, early in the Phase 3 study of metastatic melanoma it was discovered that patients receiving elesclomol were dying faster than those that did not. This is a far cry from the positive PFS
data in Phase 2. The Phase 3 trial and all other ongoing trials, including the prostate cancer trial, were immediately shut down. **Synta’s shares plunged 72% on the results.**

We could go on, but we feel we’ve made our point. Positive early clinical trial results often provide very poor insight on FDA approval. The risk of failure is further increased when the studies conducted are not the randomized, controlled, double-blinded studies that are considered the gold standard of clinical results. We readily admit that these other drugs are different from SM-88 in many ways, but they do have some similarities to SM-88. Both were oncology drugs, and both were attempting to increase oxidative stress to induce (cancer) cell apoptosis.

**Management:**

TYME was founded by current **CEO & Chief Science Officer Steve Hoffman** and current **COO Michael Demurjian. As of the most recent quarter they own nearly 60% of the company combined.** Because of their majority ownership in the company, the CEO and COO also control the board and as a result the company has weak corporate governance. They have worked closely together in prior endeavors. While both have extensive business experience and are well educated, **we found no biopharmaceutical industry experience prior to TYME** for either gentleman.

Prior to co-founding an oncology focused biopharmaceutical company, COO **Michael Demurjian** was President and CEO of Kitchen Concepts from 2007-2008. Kitchen Concepts was a foodservice industry company that developed kitchen equipment. Prior to that he was Director of Marketing & Business Development at Mikronite from 1998-2008. Mikronite provided **surface treatments** for various industrial parts to reduce friction. The process was often applied to auto parts like gears and cam shafts. His **biography** on TYME’s website also mentions that he led operations at Mikronite.

TYME co-founder and CEO **Steve Hoffman** was the owner of Kitchen Concepts Inc. from 2006 – 2013. From 1995 - 2009 he was co-founder and Chief Technology Officer at Mikronite Technologies Group, Inc. After acquiring Crane Cams in 2006 **Mikronite ran into financial difficulty and disappeared around 2009.**

Mr. Hoffman’s **biography** on TYME’s website makes no specific mention of Kitchen Concepts or Mikronite and instead focuses heavily on his background in biochemistry, physics and science in general. While it appears that he has a strong scientific background, it is not clear how this background would lead him or Mr. Demurjian to oncology drug discovery.
Recently Hoffman and Demurjian have started to sell stock.

Recently Hoffman and Demurjian have started to sell stock.

**Conclusion:**

We found it surprising that the company had **zero cash**, liabilities of $96,528 and paid-in capital of $38,300 when they completed the reverse merger in 2015 even though the company was founded in 2011! The company didn’t even have their own office and were “operating in space provided at no expense by a shareholder of ours.” In our opinion, **this implies they were unable to raise any significant amount of capital privately and are instead relying on the public markets for funding.**

Last quarter they had **$7.5mil** on the books and will need much more than that to move forward into Phase 3 with SM-88. **They are going to need a lot more cash.** While writing this report the company has indeed announced plans to raise more cash with a **12 million share** round of dilutive equity. We’ve been expecting a big dilutive equity raise and this is exactly what they are doing. We doubt it will be the last.
Post the quarter, TYME had already raised an additional $5mil via an at-the-market (ATM) facility issuing 1.2mil shares on December 5th. **The ATM facility provides the option to dilute shareholders by an additional $25mil as needed.** That would be on top of the 12mil share offering just announced. TYME stated in a press release that they **would not be announcing the timing of future ATM sales.** We fully expect the company will be quietly issuing stock to raise funds in the coming years.

Recent studies indicate that the average cost of research and drug development is **$2.6bil per drug.** If they can get the funding, we believe the company will burn through at least 10’s and possibly 100’s of millions of dollars seeking FDA approval, but the likelihood of approval (LOA) is very, very low. The LOA overall for drugs from Phase 1 is approximately 9.6% and oncology drugs have the lowest LOA at **5.1%**.

![Likelihood of Approval from Phase I](image)

Source: [BIO](#), Clinical Development Success Rates 2006 – 2015

TYME started with human trials, and then later worked backwards to test for toxicity in animals. We note that this is highly unusual. The only trials TYME has completed to date are the IRB trial and the compassionate use study, which was a follow-on study conducted by the same hospital. These two trials were completed before TYME filed an IND application with the FDA and therefore were not FDA registered trials. We do not find these trials compelling because they are non-randomized, non-controlled, non-blinded studies. **According to TYME’s filings these trials do not meet the rigors of an official FDA approved trial** *(10-k, pg. 34)*. Yet the company repeatedly touts their results in what we feel are highly promotional press releases.

The IRB trial was surrounded by extensive drama and accusations of impropriety by individuals directly involved in the trial, including a $50k payment by TYME to the Chairperson of the IRB. When the hospital discovered these conflicts of interest, **the Chairperson was fired**. A $30mil lawsuit and an FDA investigation followed. These events increase our doubt regarding the validity of trial results for SM-88.
We’re also concerned by TYME’s Phase 2 trial pivot from breast cancer to prostate cancer. TYME was approved by the FDA to test SM-88 on breast cancer patients, but unexpectedly switched to prostate cancer. The IRB and compassionate use study had at least 25 breast cancer patients. This is by far more patients than any other cancer type. We could only find 6 prostate cancer patients that had been tested with SM-88 before TYME decided to move forward with a Phase 2 in prostate cancer. As they move forward, TYME appears to be deemphasizing their focus on breast cancer.

We believe that TYME is at extremely high risk of failure for SM-88, which is the only drug in their pipeline. We found examples of other companies that tried a similar approach, and had convincing early clinical results, but failed miserably in Phase 3. The founders do not appear to have a background in oncology or in pharmaceuticals and lack experience in obtaining FDA approval (10-K, pg. 44). This likely further increases the level of risk to investors in TYME. We applaud their efforts to find treatment for a horrendous affliction, but based on our analysis, we do not believe they will be successful.

According to the 424B5 filed on February 26th, they have 90.8mil shares outstanding and have issued another 1.5mil shares via the ATM facility. Including another 5.6mil in-the-money warrants and the 12mil shares from the new equity offering they will have 109.9mil shares outstanding. Based on 109.9mil shares the company’s market cap is approximately $373mil. This value excludes another 5.2mil out-of-the-money options, 5.4mil shares set aside for executives, and 1.8mil underwriter options related to the raise. Even accounting for cash post the raise the company is likely valued well north of $300mil. We believe this is extremely excessive for an early stage, single candidate company with unproven management and highly questionable clinical results.

Since we do not believe in the likelihood of success for SM-88, we believe long-term investors will experience a total loss on their investment.

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Appendix

Below we provide the official ECOG Performance Status grades to get a better understanding of a grade 0-2 patient in comparison to a 3 or 4.

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ECOG PERFORMANCE STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Source: ECOG-ACRIN Cancer Research Group
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