



THE GREEN FUND

BOTANIX PHARMA
BTX1503 PHASE II
TOP LINE DATA

O C T O B E R 2 0 1 9

BOT BTX1503 PHASE II

Yesterday, [Botanix Pharma \(ASX:BOT\)](#), released top line data from their Phase 2 study evaluating the safety and efficacy of their drug in patients with moderate to severe acne. The drug - BTX1503 - is targeting the \$6 billion global acne market. A market that has not seen a new acne drug released in over 20 years.

Acne is one of the most common dermatological disorders. It affects 9.4% of people worldwide, and approximately 50m people in the US alone. So, as you can expect, there was much anticipation surrounding these results. When the release finally came out at 7pm on Tuesday night, it read like this:

For the primary endpoint, all dose groups of BTX 1503 reduced the number of inflammatory lesions from baseline with the highest efficacy obtained for the 5% BTX 1503 QD group (-11.8 lesions). This corresponds to an average percent reduction of 40.54%. The combined vehicle group result was -11.3 lesions or an average percent reduction of 40.15%.

For the non-inflammatory lesions, all dose groups of BTX 1503 reduced the number of non-inflammatory lesions from baseline with the highest efficacy observed again for the 5% BTX 1503 QD group. The number of non-inflammatory lesions with this dose of BTX 1503 was reduced by -17.3 compared to -8.3 lesions in patients in the combined vehicle group ($p=0.006$), or an average percent reduction of 34.99% compared to 19.08% ($p=0.007$).

The primary endpoint of reduction in inflammatory lesions did not achieve statistical significance, but the secondary endpoint of reduction in non-inflammatory endpoints, was statistically significant.

Like what the actual f***?

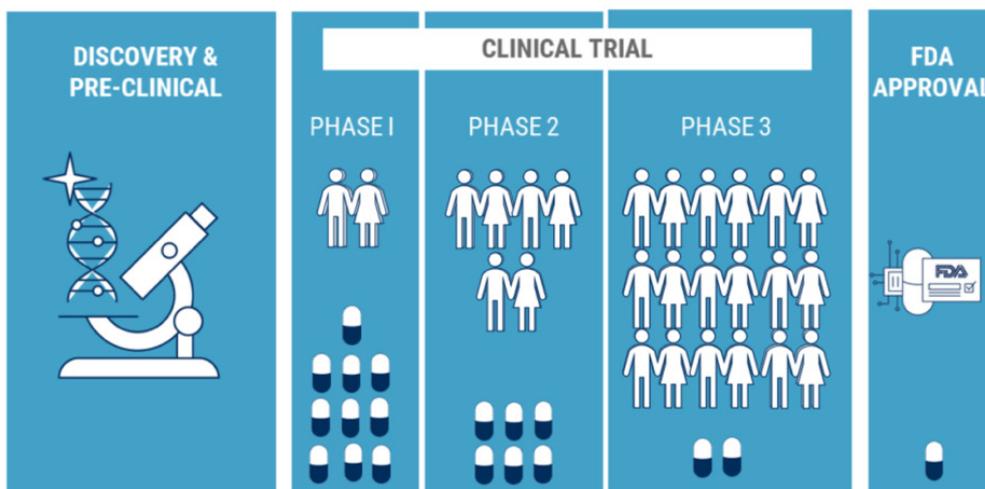
And herein lies the first problem. It's far, far, far, far too complicated. Not many people we spoke with actually understood it, and at the same time we were trying to make heads or tails of it, we got bombarded by our readers, asking us to explain it to them. The skeptics (and there are always going to be the naysayers) immediately jumped on board with the argument that it was that technical for a reason. And the reason - they were trying to cover up bad results.

So were the results bad?

And therein lies the second problem. They did not go on to clearly articulate what the results actually meant. Were they good? Were they bad? And retail investors, fickle at the best of times, fled for the hills. Hot Copper was alit with atomic-bomb comments like “not achieving statistical significance = death sentence for biotechs”. People were confused, confounded, and concerned. The result...a meltdown. BOT lost over 50% in just one day.

So, we sat down with senior management and asked the hard questions. We pushed for answers and we got them. The outcome...we're buying the dip, big time, and here's why.

For those of you averse in clinical trial terminology, feel free to skip forward. However, for the vast majority of us, in order to make head or tail of the results, we're going to need to understand clinical trials as a whole. Starting with the terminology.



Phase I

Phase I studies are designed to determine the safety of a drug or device. Typically Phase I studies will take several months to complete, and will look into how the drug is absorbed, metabolised, and excreted while investigating potential side effects as dosage increases. Roughly 70% of experimental drugs pass this phase of testing.

Phase II

Phase II studies are designed to test the efficacy of a drug or device. Phase II testing can last much longer than Phase I, from several months up to years, and can involve several hundred patients. Most studies in Phase II are "randomised" trials in which one group of patients receives the developmental drug, while a second "control" group receives a placebo, or vehicle.

A "double-blind" study is one where neither the patients nor those carrying out the research are aware of who has received the developmental drug.

Phase III

Phase III studies are randomised and double-blind, however, these will often involve several hundred to several thousand patients, and can take many years. Phase III trials show legislators the risks and benefits associated with the developmental drug, and upon completion, means that drug developers can apply for approval by a regulatory agency such as the FDA or TGA.

Now, back to the study

Botanix Pharma's Phase 2 study was run in Australia (11 sites) and the US (25 sites) for 12 weeks, and was a randomised, double-blind, vehicle-controlled study with 368 patients, of which 50% were under the age of 18 (this is important).

There were 5 dose groups, who were split accordingly:

- 92 subjects were given 5% BTX1503 twice-a-day
- 92 subjects were given 5% BTX1503 once-a-day
- 92 subjects were given 2.5% BTX1503 once-a-day
- 46 subjects were given the Vehicle twice-a-day
- 46 subjects were given the Vehicle once-a-day (so 92 subjects in total)

Endpoint

A clinical trial endpoint is fairly self-explanatory and is often a primary set of metrics that determine the efficacy of the drug. Endpoints can then be split into being either primary or secondary. For example, if you are creating a drug that is designed to improve cancer survival rates, your primary endpoint is to look at survival rates. Your secondary endpoint is an additional point of interest from using the drug that perhaps wasn't even intended, such as reduced seizures or tumour size.

What is the vehicle? Is that the placebo?

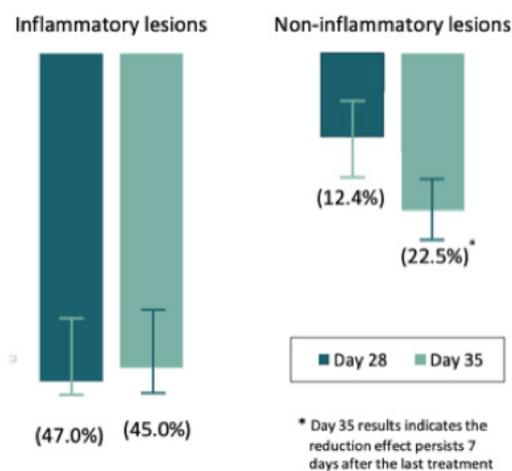
Yes, and no. A placebo is normally referred to when conducting oral studies, as it normally takes the form of a sugar-pill. This is a dermatological study, and BTX1503 is a topical cream containing synthetic CBD that is delivered to the skin via a “vehicle” or delivery mechanism. In this case, that vehicle is Permatrex. The 5% and 2.5% doses both contain synthetic CBD and the vehicle. However, the vehicle dose group is BTX1503 without any synthetic CBD (so just the cream and Permatrex).

In this case, the trials were testing for both a primary endpoint and a couple of secondary ones.

The primary endpoint was the absolute change (by number) from Baseline to Week 12 in inflammatory lesion count. In other words, how many less inflammatory lesions were there on the subjects at the end of the 12 week trial. The higher the number, the better the results.

The secondary endpoints (note plural) included how many less non-inflammatory lesions there were on the subjects at the end of the 12 week trial, and also, what was the absolute % change in inflammatory and non-inflammatory lesions there were, again, over the 12 week period.

Lesion Count Reduction in Phase 1b Trial



Source: Botanix Investor Presentation 05/02/18

But, there was a hidden gem in the results. The company noticed the fact that for 7 days post the completion of the 28-day study, patients continued to see an improvement in the non-inflammatory lesions. Whilst only having a 5% impact on non-inflammatory lesions in the first 28 days, that number jumped almost four times after the period extended another 7 days.

The initial results from these clinical trials suggested that BOT's acne drug could deliver on par efficacy-based results as the incumbents, but with a statistically significant improvement in the safety profile. Same results, less side effects.

Now, on to the Phase 2 results.

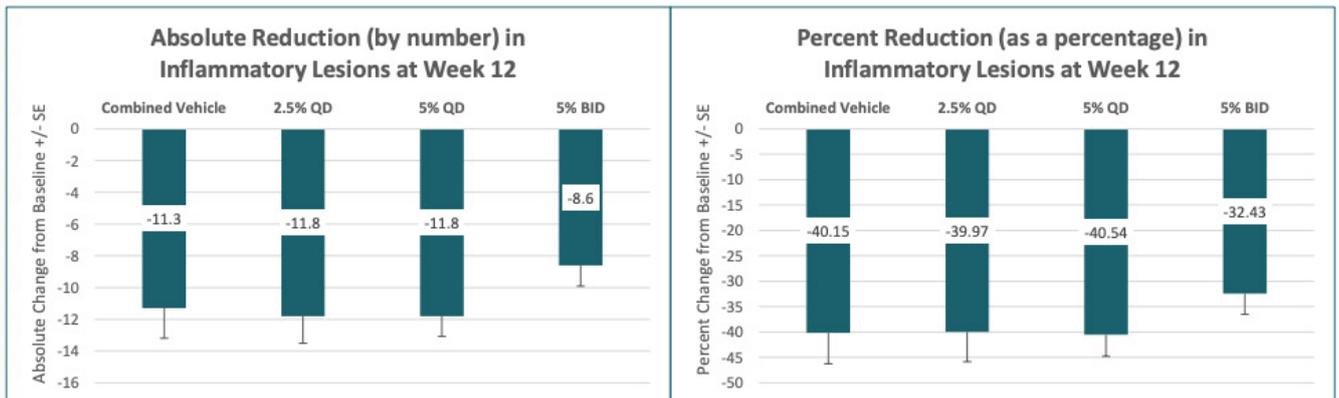
Before we go into the Phase 2 results, and to offer a first pass at understanding the results, let's consider the Phase 1b study results.

The BTX 1503 Phase 1b study that was completed in 2018, enrolled 21 patients and ran over a 4 week period. The key data from the study was:

- The drug reduced inflammatory lesions by 47% and non-inflammatory lesions by 5.4%; This compares with reductions of 42% and 38% respectively for the two leading existing acne treatments: Epiduo and Aczone (which together have approximately \$1 billion in annual sales); and
- There were no adverse safety effects associated with BTX1503

The Phase 2 study - Primary Endpoint

The first thing to note is that the dose group - BTX1503 5% once-a-day (QD) - was the best performing active dose.



As you can see, it reduced the actual number of inflammatory lesions by around 11.8, which in percentage terms (the graph on the right) equates to a reduction in inflammatory lesions of 40.5%. This compares with reductions of 42% and 38% respectively for the two leading existing acne treatments; Epiduo and Aczone

Following on from the results of the Phase 1b study, all doses of BTX 1503 were very safe. There were no serious adverse events or treatment related discontinuations. The most common adverse event was upper respiratory infection (common cold) which was not related to the treatment. Of the 368 subjects that took part, only 3 of them withdrew from the study.

One was from the vehicle arm, and the 2 from the BTX1503 arms were not from the 5% QD arm that the company intends to take to Phase 3 trials.

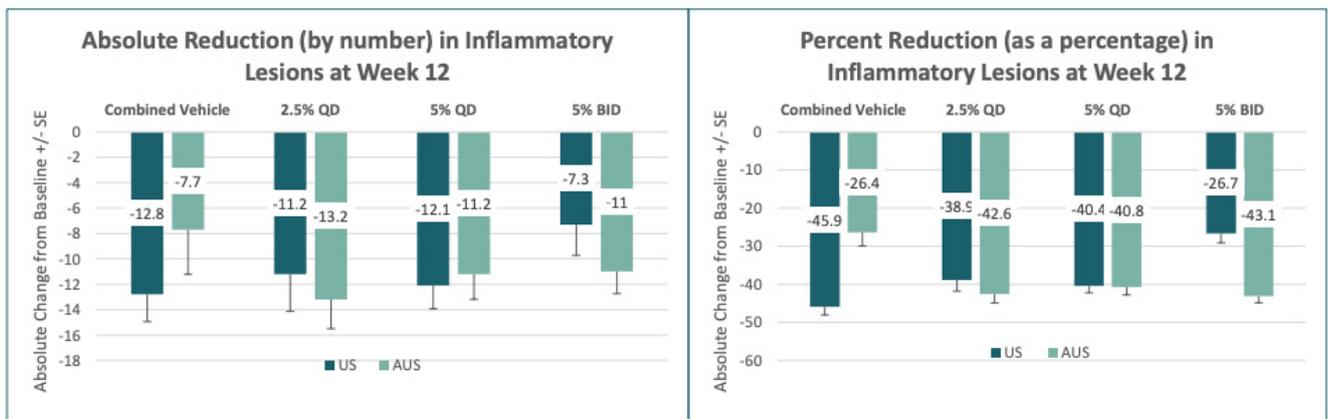
"The safety profile of the drug was super clean and we expected that because of the body of literature that sits around CBD today and its safety profile. But the the drug performed even better than we expected. There were no severe adverse events out of 368 patients that were studied, and there were no treatment related withdrawals in that 5% once a day group, which is what we'll go through and carry on to Phase 3"

- Vince Ippolito, President & Executive Chairman of Botanix Pharma

So what's the problem?

The problem is that the Combined Vehicle shows a 40% reduction in inflammatory lesions which, against the 40.54% reduction in inflammatory lesions BTX1503 5% (QD) achieved, meant there was almost no difference between the two.

However, there was a significant difference between the US and Australian results. The US results show almost no separation from vehicle, while the Australian results show a clear separation between the vehicle and active doses.



In the Australian market, the combined vehicle (ie both once-a-day and twice-a-day vehicle only subjects) saw a 26.4% reduction in lesions compared to their US version which saw a whopping 45.9% reduction in lesions. And herein lies the problem.

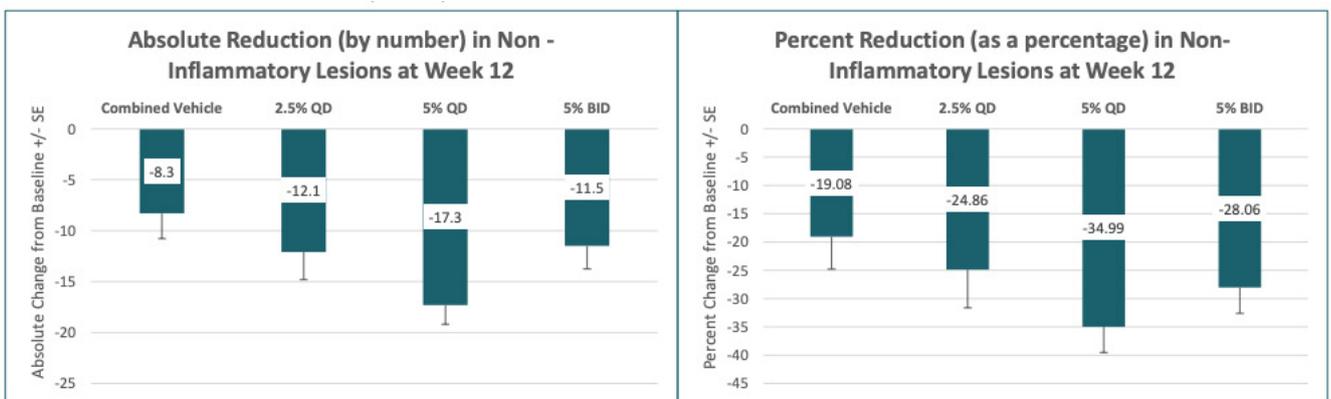
BTX1503 does work, and on average achieves a 40% reduction in lesions (on par with global best in class incumbent products). It has delivered the same levels of efficacy, and safety profile, in both the US and Australian trials, but for some reason the vehicle group response in the US was almost twice the response seen in Australia.

Understand something - this makes the vehicle group product, one of the world's BEST topical treatments for moderate to severe acne on the planet. The US subject group was much larger than the Australian group, and hence the final results yielded an endpoint that did not achieve statistical significance. Before we get to the "WTF happened there" part, let's first consider the Secondary Endpoints

The Secondary Endpoints

Just to recap, the secondary endpoints were how many less non-inflammatory lesions were there on the subjects at the end of the 12 week trial, and also, what was the absolute % change in inflammatory and non-inflammatory lesions over the 12 week period.

“We chose to put non-inflammatory lesions in our secondary endpoint because it’s a harder endpoint to meet in acne because these are the pimples that sit below the skin. They’re harder to reach and it’s harder to treat,” said Vince Ippolito, President & Executive Chairman of Botanix Pharma.

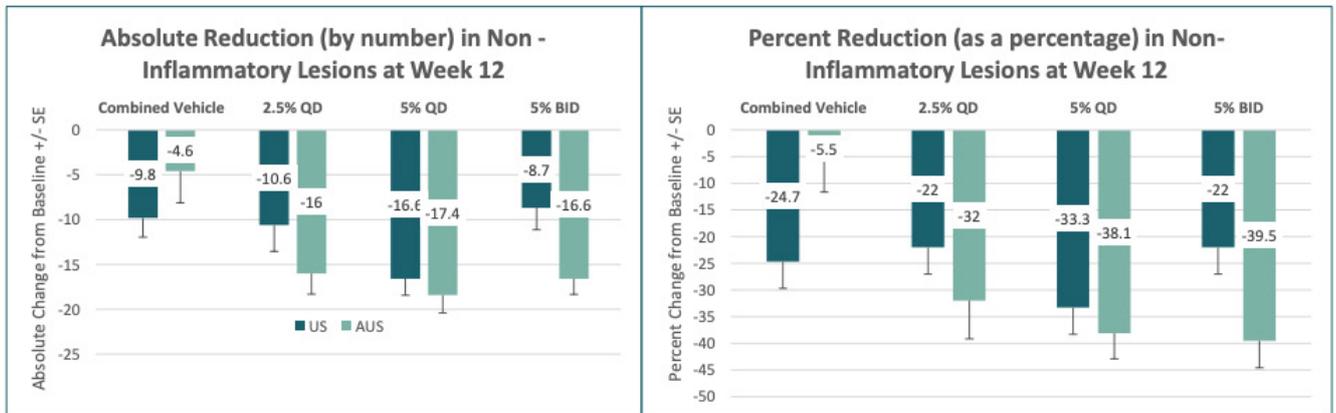


Once again, BTX1503 5% once-a-day (QD) was the best performing active dose, but this time, the results were statistically significant. BTX 1503 5% once-a-day (QD) showed a 34.99% reduction in non-inflammatory lesions versus the vehicle at 19.08% ($p=0.007$).

The “p” value is simply the probability that the “drug” will not have a meaningful impact. Thus, the higher the “p” value the worse the result. In this case, $p=1/7$ th of a percent - meaning that the drug has shown to have a significant impact on the disease. Once again, we must highlight the fact that efficacy is in line with leading topical acne prescription products.

“I think the more important thing is the FDA are going to like the fact that the drug actually treats both inflammatory and non-inflammatory really well, because the agency knows oftentimes it’s a few drugs that a doctor’s prescribing and that’s additional cost to the healthcare system and can lead to noncompliance. I think we checked the box there on that.”

- Vince Ippolito, President & Executive Chairman of Botanix Pharma



However, once again, the US vehicle arm displayed very weird results. If you consider the image above, it clearly shows that the US vehicle group response was almost four times the response seen in Australia (24.7% in the USA vs 5.5% in Australia). This makes no sense, and once again brings into question the validity of the US vehicle arm.

If one considers the inputs that make up the trial, they could be summarised as; the subject base, the test (process, formulations etc.) and the supply of product for the trial. Having spoken with management on this, we can confirm that there was no significant differences in the profile and demographic makeup of the subjects across both territories. The tests and formulations and execution of the study protocol was consistent across geographies and within geographies.

The only difference between the two geographies was the manufacturing process and drug supply. Because Cannabis is still illegal at the Federal Level in the US, the DEA would not allow Botanix to import their formulations and drugs, for the Phase 2 study, into the US. Hence they had to produce their formulations on US soil for the very first time, using brand new providers for each and every part of the supply chain.

“Everything that we did here in the U.S. was for the first time. There was nobody developing a synthetic CBD that would contract manufacturer here and we had to do 11 batches of material in order to produce enough drug supply for this clinical trial. That's a lot of batches. That's a lot of variability going into making drug supply”, said Vince Ippolito, President & Executive Chairman of Botanix Pharma.

Just a few days back the company announced a supply agreement with Purisys, for the manufacturing and supply of synthetic CBD. Our initial read on this was that it was announced to show that the company could now handle the scale for the demand that was coming post the successful outcome of Phase 2. Clearly, it was to alleviate the concerns surrounding their manufacturing process.

“We're looking at the efficacy and the safety of the drug and we're saying this is commercially viable. We're looking at Australia and saying that's a home run. So we're looking at one arm within the study here, which is the vehicle arm in the U.S. and saying we've got an abnormality here. But our manufacturing process and protocols have advanced over the last two years, and hence how we're producing the drug today is totally different than how we did it two years ago.”

While we're going to look to figure out what potentially went wrong, I think more importantly for us, and the part that that resonated with the U.S. Investor community, is that our process has evolved over the last two years.

“Our AD drug (BTX1204 targeting Atopic Dermatitis) wasn't produced this way (as it was in Phase 2), and Phase 3 (for BTX1503) won't be produced this way. So the event that occurred is now in the past and we don't believe it will occur again. Now that we have the supply agreement with the world's largest CBD supplier, we're going to make everything for the Phase 3 study out of our facility. And we will control it. I will produce it, test it, test it some more, and then test it again, making sure it's ready for the study,” said Vince Ippolito, President & Executive Chairman of Botanix Pharma.

The Bottom Line

If we break this into three parts, it becomes a little clearer. First off, the unique selling proposition for BTX1503 has always been its safety profile. BTX1503 is targeting an industry where the majority of diseases are found in teenagers, and the incumbent drugs all produce significant and horrific side effects.

And it did not disappoint in this area. Less than 1% of the subjects experienced an adverse event, and not one of these 3 subjects (out of 368) who exited the study, were from the BTX1503 5% once-a-day (QD) dose group.

“The FDA's primary concern is safety, and we nailed the safety profile on this trial. They let us go down to 12 years of age, which is unheard of for clinical trials in the US. They're going to love what they see in that cohort of patients under the age of 18, and as low as 12, so I'm going to check the safety box here.”

- Vince Ippolito, President & Executive Chairman of Botanix Pharma

Secondly, the drug works. Simple as that. In both the Australian and US geographies, BTX1503 produced efficacy results that are on par with (and in some cases better than) the leading, multi-billion dollar, acne drugs in market today. Read that again.

And now for the third part, the dodgy US vehicle arm. While we understand what has been explained to us, we do feel there has been incompetence in the production and manufacture of the US vehicle doses.

There are many theories being thrown around various investor forums right now, including the fact that perhaps there was a labelling, distribution or packing issue that caused some of the actual BTX1503 dose to be given under the guise of being a “vehicle only” dose. To be clear, the company is saying this did NOT happen, and have put the manufacturing issue down to two key facts:

- They had to produce the doses in the US (as the DEA forbid them importing the Australian doses) and had to “start from scratch”
- Given that no one had the experience or scale to produce enough synthetic CBD and Permatrex formulations, they could not outsource to just one provider, and had to outsource to various suppliers, with the end result being 11 different batches produced for the purposes of the US study.

While we completely understand, we are also not entirely satisfied with this response. There are some very, very smart people driving this bus (it’s one of the primary reasons we have been so bullish on BOT), and make no mistake, we have the utmost faith in Vince, Matt and the team, but on this one we have to score them very low.

To make matters worse, the way in which the release was put out (late in the evening and about as technical as we have ever read) simply did not help the matter. There are stark lessons to be learnt from this, and we are comfortable that management have taken this experience on board and have learnt from it.

The drug works, and although the statistical endpoint was missed, it will not impact the next steps for BTX1503 which include a meeting with the FDA to run through the results from the Phase 2 trial and to prepare for the Phase 3 trial. The company stated that the strength and statistical significance of the Australian data combined with the overall efficacy and safety from the Phase 2 Study provides them with enough confidence to proceed with preparation for Phase 3 clinical studies.

The Australian sites - 11 sites covering 111 subjects - displayed solid performance on inflammatory, and non-inflammatory lesions, and produced a clear separation from the vehicle. That's what we expected to see in the US too.

- Vince Ippolito, President & Executive Chairman of Botanix Pharma

Let’s be clear on this. This was not a perfectly run trial and although we’re not entirely satisfied with the reasons for the manufacture/production failure, having spoken with management, we honestly believe that they have taken steps to address the manufacturing and supply issues that impacted the vehicle in this study.

Our view, and investing thesis, has not changed. The drug is efficacious and safe, and is targeting a significant addressable market. We are still firmly behind the management team and company, and believe the current share price offers an unbelievably attractive opportunity for investors looking to initiate a position, or to dollar average down their existing position.

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