Applied Therapeutics (APLT)

Come take a spin on the Applied Therapeutics Wheel of Red Flags™

Summary

- Applied Therapeutics, Inc. (APLT) is a recent biotech IPO (March 2019) that has seen its stock run from $10 per share to over $40 on the back of 'positive' Phase 2 data for their lead program in galactosemia.

- The Company was founded in January 2016 and to us everything about it looks and feels hastily put together. To us, the lines between oversight and misdirection are blurred.

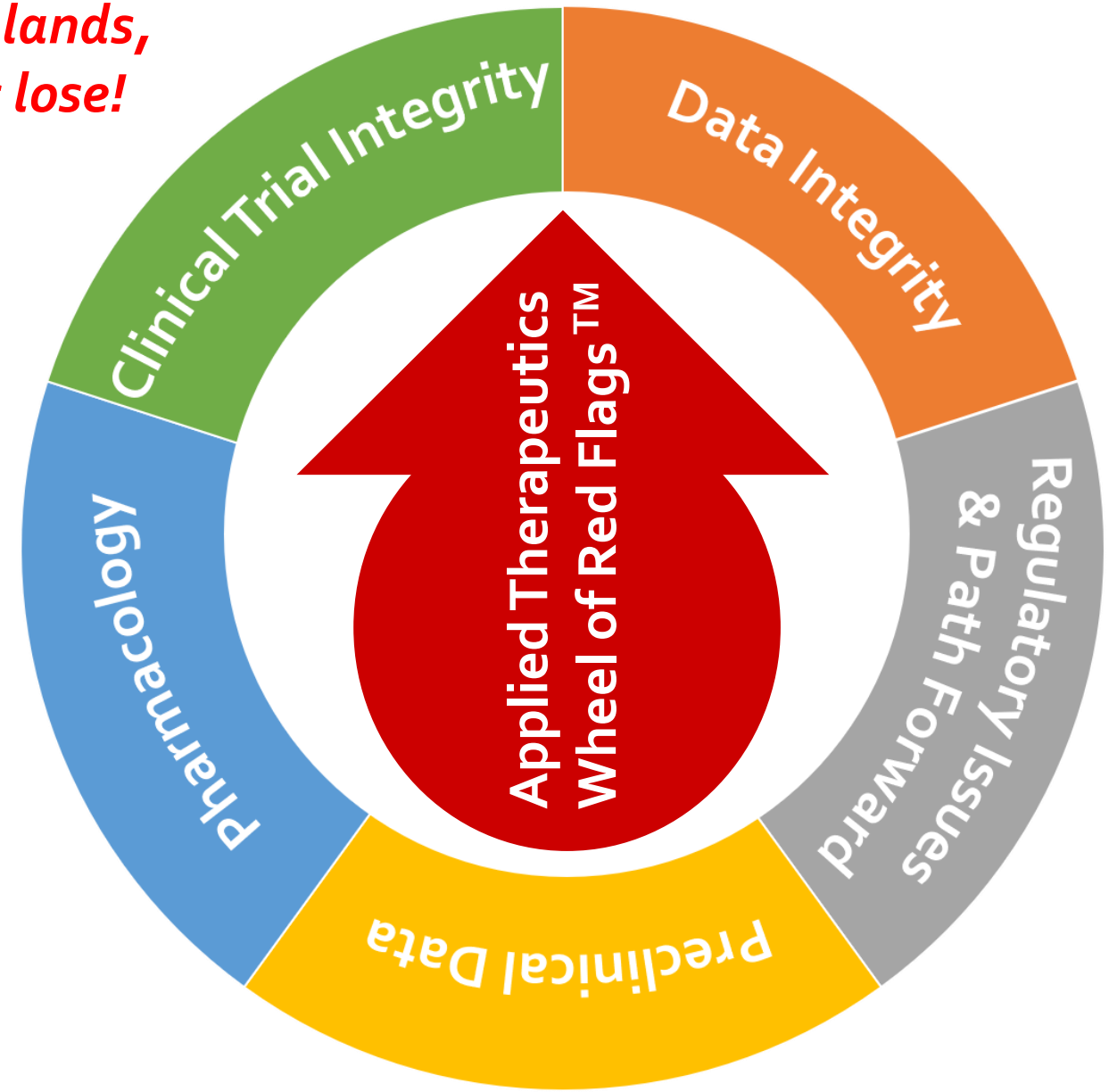
- We have found so many **inconsistencies, errors and incorrect information** when analyzing APLT that we almost don't know where to begin. It remind us of the classic child's toy See 'N Say: you know, the one where you pull the lever, an arrow spins and lands on a random farm animal? **Except in the case of Applied Therapeutics, replace the farm animal with a critical aspect of their business.** And each time it lands, instead of a farm animal sound you get a major red flag.

- **We believe that Applied Therapeutics' stock is wildly overvalued and that its prospects for commercial success of any kind are dim.**

Shall We Take a Spin?

Introducing the Applied Therapeutics Wheel of Red Flags™

No matter where the arrow lands, investors lose!



Spin 1: Clinical Trial Integrity

Clinical Trial Integrity Issues

- Applied Therapeutics' lead program is AT-007 for a rare genetic disease known as Galactosemia. These patients cannot process the sugar galactose normally and must avoid foods such as dairy products.
- Management has been very bullish on the Phase 2 clinical trial data generated to date and even more bullish on how rapidly the Company will be able to commercialize AT-007 on the back of said data.
- In our opinion, the Company is doing more than just leveraging a permissive FDA—we think they are cutting corners.

Issue 1: The current trial size is substantially smaller than originally planned. This, for a disease the Company claims has thousands of sufferers.

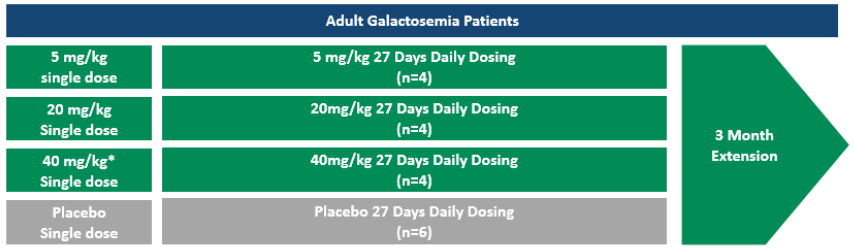
Posting on Clinicaltrials.gov (not updated since original October 2019 filing):

This study consists of 4 parts:

- Part A (SAD) in 32 healthy subjects. Once daily oral escalating dose (6 active, 2 placebo).
- Part B and C (MAD for 7 days) in 36 healthy subjects. Once daily multiple daily dosing (8 active, 2 placebo per each dose cohort).
- Part D (SAD followed by MAD for 27 days) in 18 subjects with Classic Galactosemia. Once daily followed by multiple daily oral dosing (6 active, 2 placebo for each dose cohort).

Clinical Trial Integrity Issues

What was reported instead (from latest Company presentation):



...Four patients per dose cohort (plus two placebo) instead of six (plus two placebo). As we will see later, this decrease is relevant when the Company is touting each and every individual data point.

Issue 2: The Company inexplicably allowed a participant to be in the study **TWICE**. Once in the placebo group and once in the 20 mg/kg group.

Baseline Demographic and Diagnostic Characteristics (n=11*)
Broad Age Range, Multiple Genetic Mutations Represented

Subject	Age	Gender	Ethnicity	BMI	Gene mutation	Urine galactitol (mM/urine creatine mol/L) Baseline	Plasma galactitol (ng/ml) Baseline	GALT enzyme activity (Mmol/h/mg)
2003-101	33	M	Caucasian	24.3	Q188R/Q188R	208	2630	0
2003-102	51	M	Caucasian	21.7	Q188R/Q188R	123	2390	0
2003-104	19	M	Caucasian	21.6	Q188R/Q188R	137	2150	0
2003-105	22	F	Caucasian	22.7	Q188R/Q188R	255	2860	0
2004-001*	37	M	Caucasian	21.3	Q188R/Q188R	152	2700	0
2004-004	40	M	Caucasian	32.7	N314D/ c119-116 deletion	102	2500	0
2004-005	24	F	Caucasian	23.1	Q188R/Q188R	142	2210	0
2002-002	19	F	Caucasian	23.9	K285N/c119-116 deletion	139	2500	0
2004-007	19	F	Caucasian	21.4	Q188R/Q188R	133	2450	0
2004-008	22	M	Caucasian	17.4	Q188R/Q188R	130	1930	0
2004-009	28	M	Caucasian	20.5	Q188R/Q188R	99	2630	0
Summary	28.55 ± 10.5	4F and 7M	Caucasian	22.78 ± 3.8	9 Q118R homozygous and 2 compound heterozygous	147.27 ± 45.8	2450 ± 268.7	0

*One placebo patient in cohort 1 crossed over to active for total of n=12

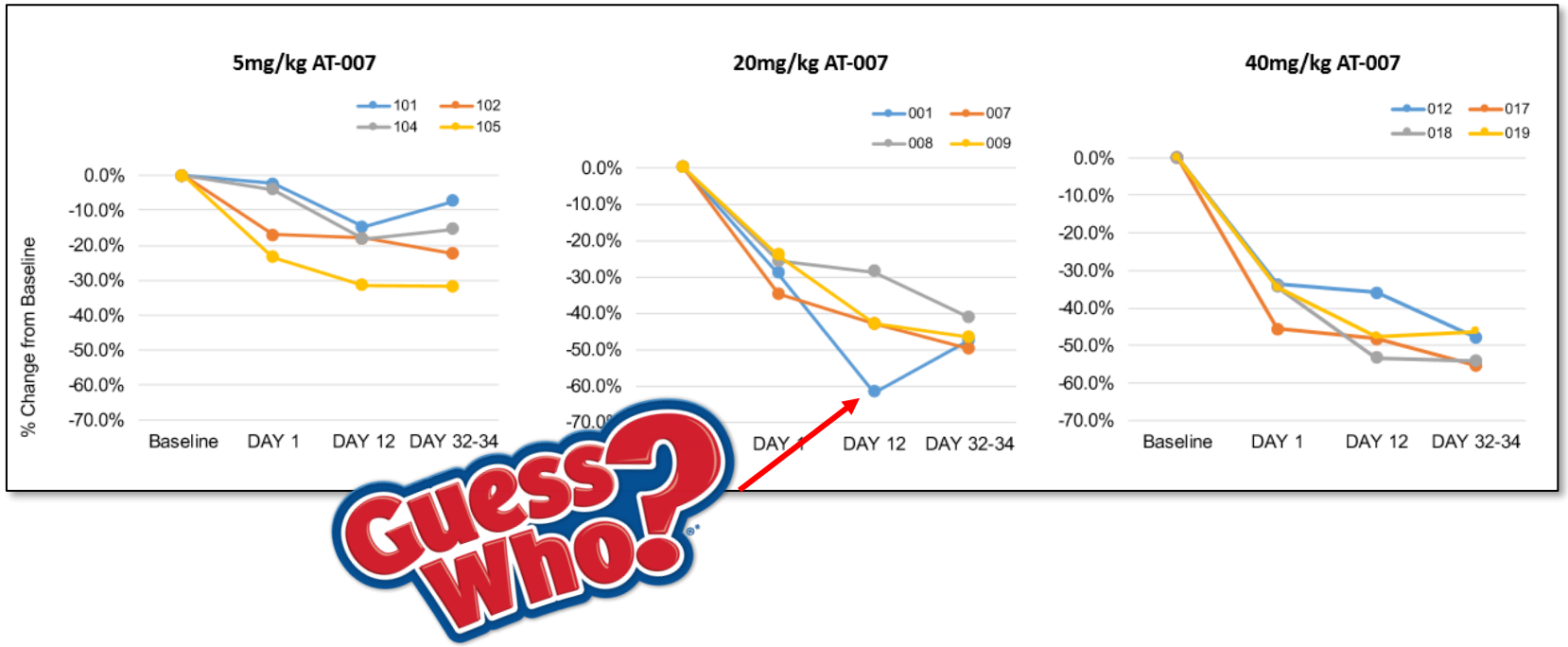
*One placebo patient in cohort 1 crossed over to active for total of n=12

"CROSSED OVER" to ACTIVE?!?

APPLIED THERAPEUTICS

Clinical Trial Integrity Issues

Issue 3: The patient that was enrolled in both the placebo and the 20 mg/kg dose cohort was the best responder in the **entire clinical trial** during their "encore performance" (lower on the graph is 'better'):



One should not enroll the same patient twice in a clinical trial. The entire purpose of randomization is to eliminate patient specific variability. This patient must have known they were originally enrolled in the placebo arm otherwise they would have continued in an open-label extension. Moreover, if most of the change in plasma galactitol is due to dietary modifications made by the patient diet then re-enrolling them can easily skew the results. That is what appears to have happened here as this patient was the single best responder in the trial his second time through.

Clinical Trial Integrity Issues

Issue 4: The patient who participated in the trial twice has a **single** (original) baseline plasma level of galactitol (the key biomarker being measured in the study):

Baseline Demographic and Diagnostic Characteristics (n=11*)
Broad Age Range, Multiple Genetic Mutations Represented

Subject	Age	Gender	Ethnicity	BMI	Gene mutation	Urine galactitol (mM/urine creatine mol/L) Baseline	Plasma galactitol (ng/ml) Baseline	GALT enzyme activity (Mmol/h/mg)
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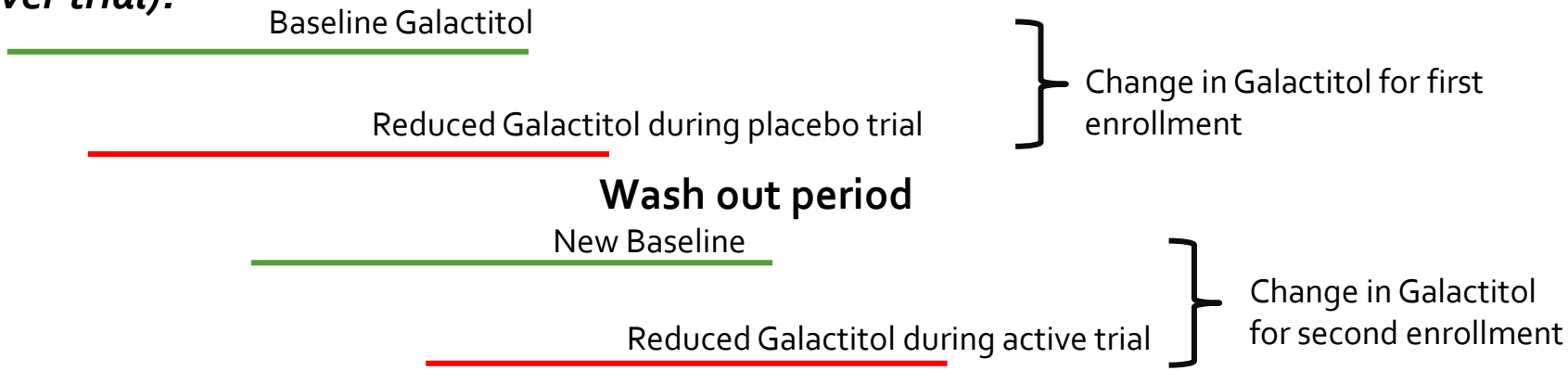
*One placebo patient in cohort 1 crossed over to active for total of n=12

APPLIED THERAPEUTICS

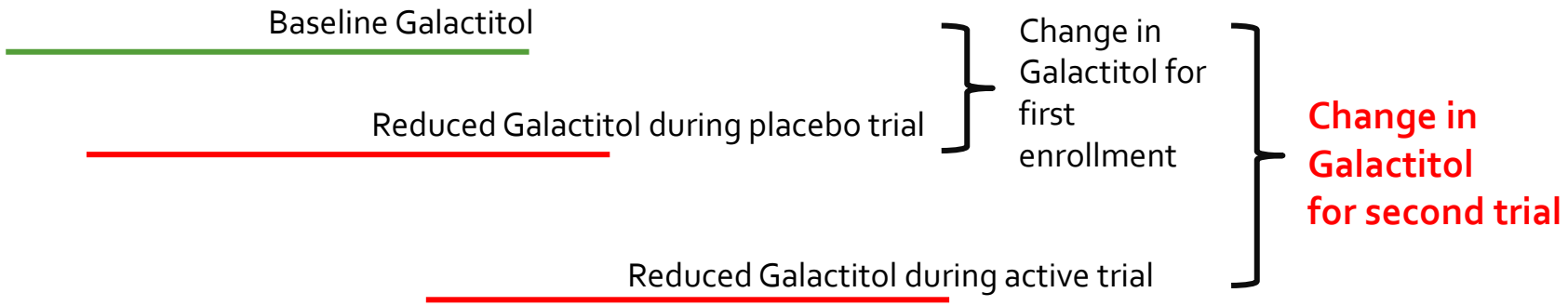
Why does this matter? Even the Company will tell you placebo patients had a substantial drop in plasma galactitol. At the very least patient 101 should have had a second baseline measurement at the time of the cross over to correct for the drop they experienced in the first trial.

Clinical Trial Integrity Issues

Here's what you want to see ***(if you are ok with breaking almost every clinical trial rule in the book to begin with by letting a patient cross over in a non-cross over trial):***



Makes sense, right? Well, here is what you got:



The 'Crossover Patient' is unacceptably poor clinical trial conduct. If there are so few patients that they must be recycled for a 30(ish) day trial is there really a commercial opportunity to be had?

Clinical Trial Integrity Issues

Issue 5: The Company refuses to release urine galactitol data from the AT-007 study and instead provides only plasma galactitol levels. They admit that urine is the established way of measuring galactitol levels. They also go so far as to say there was a 'correlation' between the urine and plasma levels in the study but do not elaborate further. From the May 18, 2020 UBS Conference presentation by APLT management (emphasis ours):

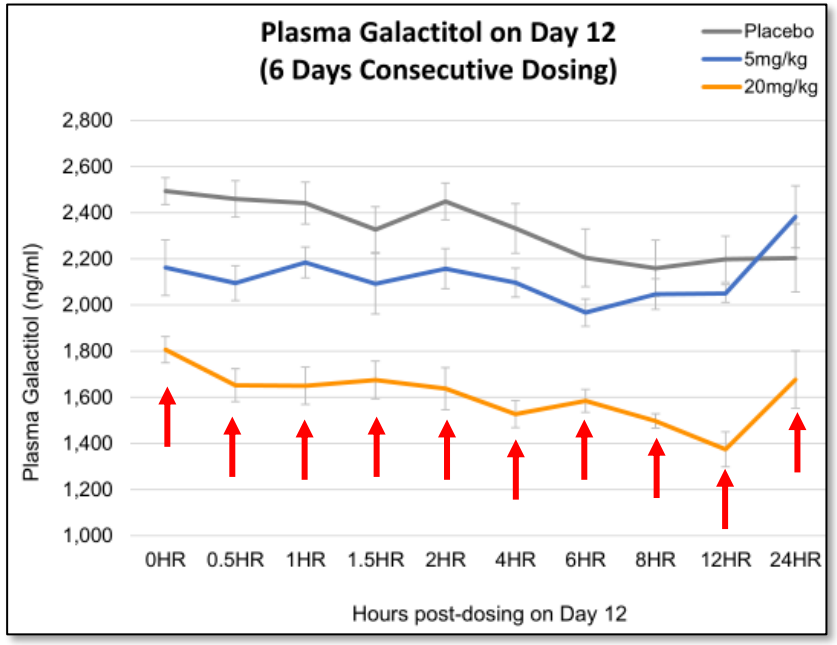
> "… Urine levels is what previously was done in the field… this is what happened more often in the literature and so we felt that it would be important to measure that in our clinical study. It's much more accurate to look at galactitol levels in the blood but we did not know that before we did the experiments and saw that this was the case. We did look at galactitol levels in blood and in urine. Levels of galactitol both in blood and in urine do correlate, it's just little bit technically more difficult to look in urine… it's more annoying than taking the blood sample, so we did it, we thought it would be important to have it … they do correlate.. but I think from this moment on we should focus on galactitol in the blood because we saw that the accuracy was just so much greater…"

More annoying to take a urine sample than draw blood? Nonsense. **Their ability to state there is a correlation means they have the urine galactitol data and refuse to report it. DO YOU THINK THEY ARE HIDING WONDERFUL DATA FROM YOU?**

WHERE IS THE URINE GALACTITOL DATA FROM THE CLINICAL STUDY? Let investors determine if the claimed treatment effect is real.

Clinical Trial Integrity Issues

Issue 6: Beyond the 'urine is more difficult' rhetoric, the Company also claims that they can't get CSF (cerebrospinal fluid) from galactosemia patients in the study. These CSF samples would confirm that their product is indeed penetrating the brain and provide evidence that the levels of galactitol in the brain are lower on drug. The company collected CSF from 40 healthy volunteers in the study. LOOK HOW FREQUENTLY THEY ARE DRAWING BLOOD ON THE GALACTOSEMIA PATIENTS (red arrows):



Spare us the 'urine is difficult' and 'CSF is impossible'. The Company is providing data solely on plasma galactitol…which just so happens to be measured ***using an assay that APLT designed themselves*** *(Source: January 8, 2020 call on Phase 2)*.

Spin 2: Pharmacology

Spin 2: Pharmacology

- Applied Therapeutics' lead compound AT-007 looks pretty good on paper. Given the well-established issues with the drug class, we would say that the drug looks a little TOO good. Here is how the Company describes their oral 'CNS penetrant' aldose reductase inhibitor:

Drug Profile	• Structurally distinct molecule with potent AR inhibition and unique PK profile • Exposure to all Galactosemia target tissues – CNS, nerve and retina penetrant • Oral once-daily dosing (half life 12-18 hrs)

Herein we present some issues related to AT-007's purported pharmacology:

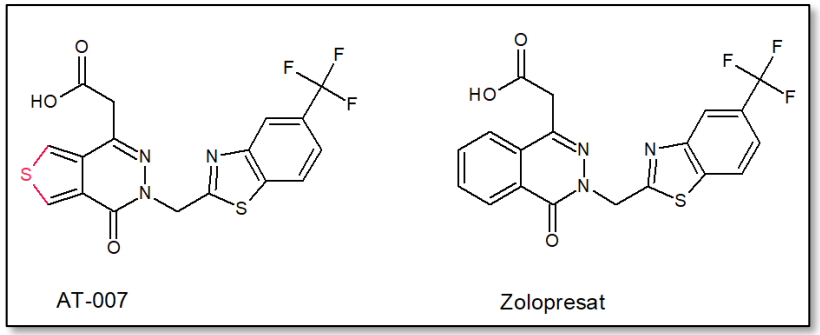
Issue 1: For a drug that is allegedly picomolar potent, the company feels the need to achieve blood levels that are ~4-MILLION FOLD HIGHER at the 20mg dose. At 40 mg/kg patients are consuming almost 3 GRAMS of drug per day! Yet they resort to picking (non placebo-corrected) 'maximum' reductions chosen from multiple data points over multiple days to declare victory. **If AT-007 is as potent as the Company says, there is no need to dose this high.**

Spin 2: Pharmacology

Issue 2: The target (aldose reductase) is an intracellular enzyme and galactitol, once produced, is stuck inside the cell. Because galactitol is an intracellular compound, its reduction in plasma **is not a proxy** on its levels in brain. The galactitol in brain is produced locally by the neurons and thus showing reduction in plasma is not enough. The drug needs to get into the neurons in order to reduce the galactitol locally.

The low levels of brain penetration (~0.05% of plasma concentration) is probably explained by the drug's chemical properties. AT-007 is a carboxylic acid which has a very low penetration through membranes. At physiological pH, the drug will predominantly exist as a charged chemical species that will not cross lipid membranes rapidly.

It has a very similar structure to Zopolrestat and other early AR inhibitors, suggesting it is strongly bound to plasma proteins (>99%), which means that only a very small proportion of AT-007 is available free in the plasma for AR inhibition or for penetrating the BBB.

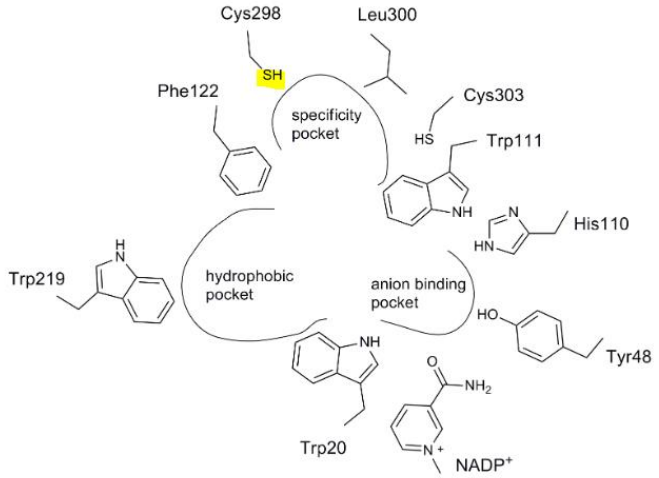


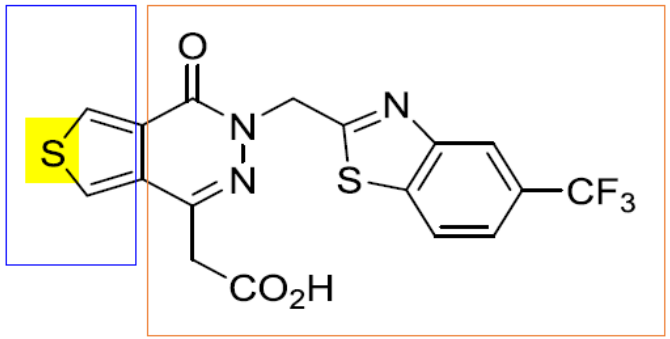
Spin 2: Pharmacology

Issue 3: The compound appears to break the laws of thermodynamics.

The Company claims AT-007 has a highly active AR inhibitor as a result of chemical modifications which enable AT-007 to create a covalent disulfide bond.

We simply do not know what chemical mechanism would allow a thiophene sulfur—connected to two carbons—to produce a covalent bond with a thiol. Negative 3 is not an oxidation state of sulfur but may be fair value for APLT shares.



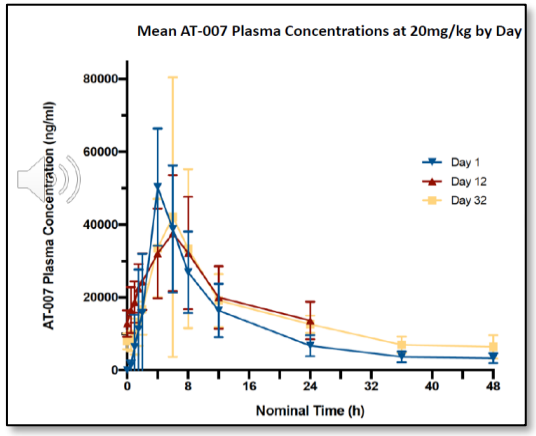


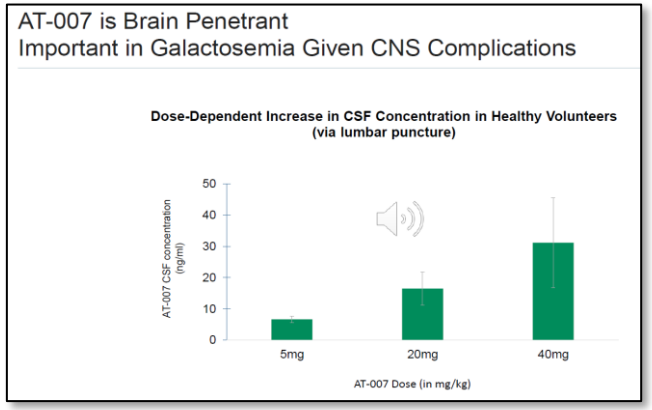
AT-007

Spin 2: Pharmacology

Issue 4: The Company claims their AT-007 compound is 'brain penetrant'. However, the class of drugs it belongs to has poor CNS penetration (approx. 0.05% in humans and approx. 1-2% in rats).

Based on the graphs below provided by APLT in their April 2020 'Trial Results' presentation, the concentration of AT-007 in brain is >2,000 fold less than in plasma, which is evident from the graphs below. At 20mg/kg the maximum concentration of AT-007 in plasma is ~40,000 ng/ml and in brain ~17 ng/ml, which is a difference of 2,350X.





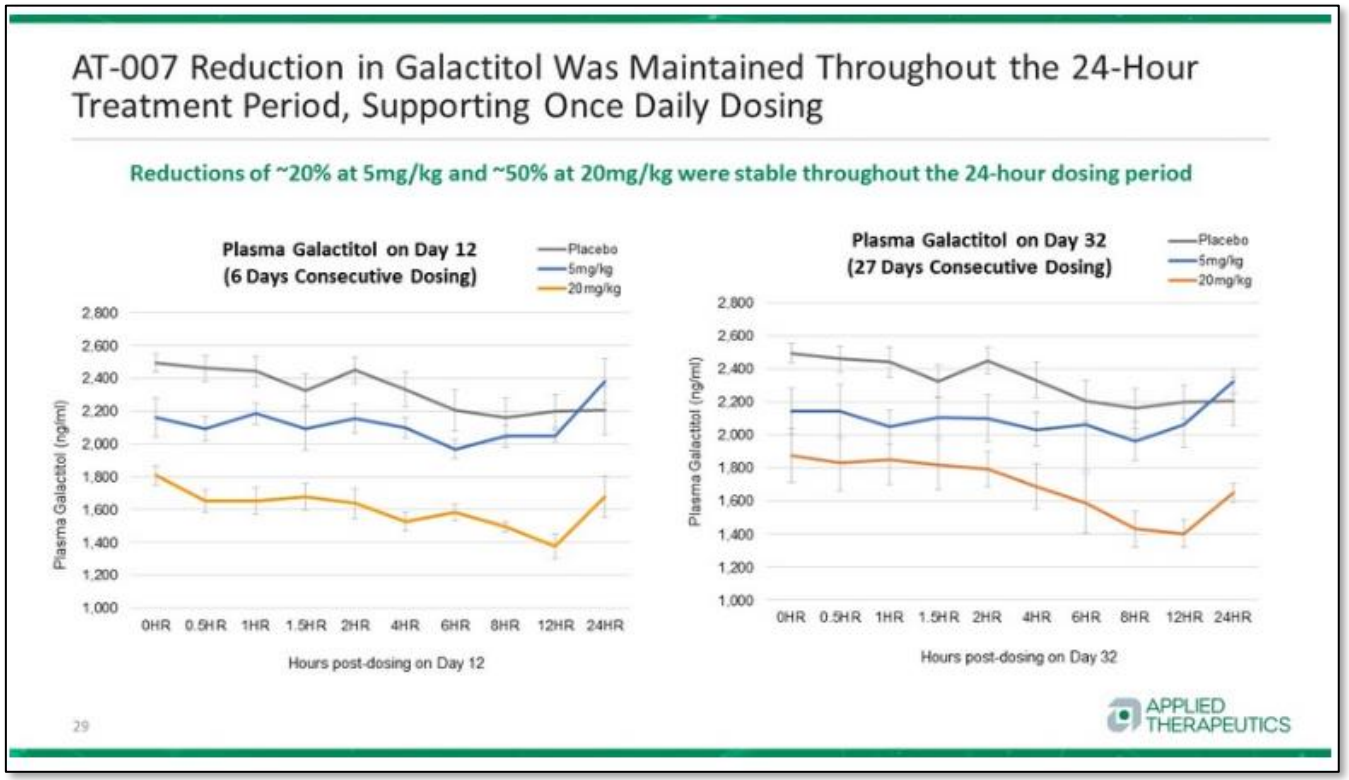
AT-007 is an inhibitor of Aldose Reductase and its activity is characterized by its IC50. There should be a clear correlation between the concentration of the drug in the relevant organ and inhibition of the enzyme. If a drug concentration of ~40,000 ng/ml inhibits the enzyme to reduce galactitol by ~30-35% (our generous estimates when placebo correcting APLT's data), **with 2,350X less concentration in brain (~17 ng/ml) the inhibition and reduction should be negligible.**

Spin 3: Data Integrity

Data Integrity Issues

Issue 1: The Company has presented clinical data that is flat out WRONG. Whether by negligence or deception (or both) we don't think it matters much. This is not the behavior one expects of a Company with a nearly $1 billion market capitalization.

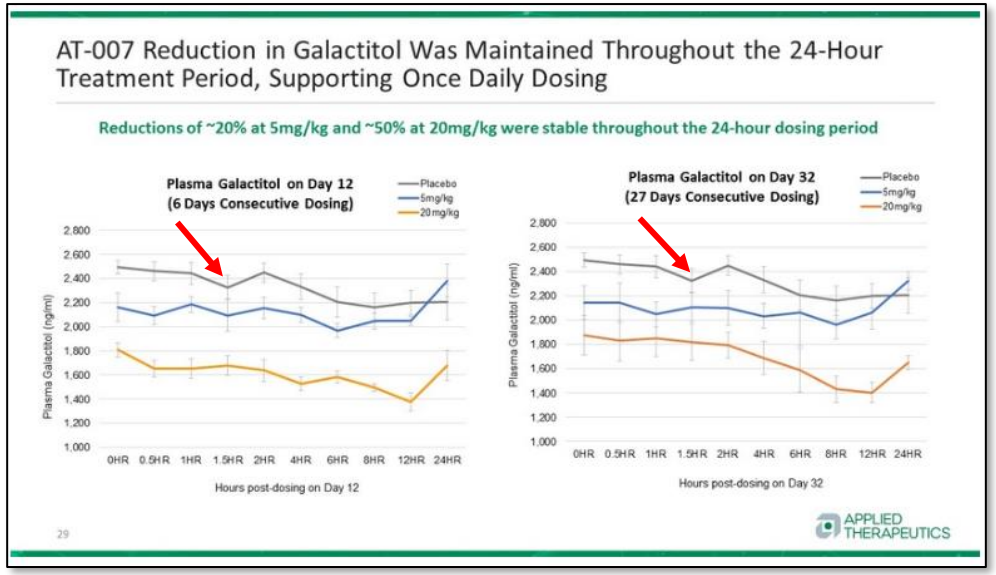
From the Company's April 2020 data presentation (found here) on Slide 29:



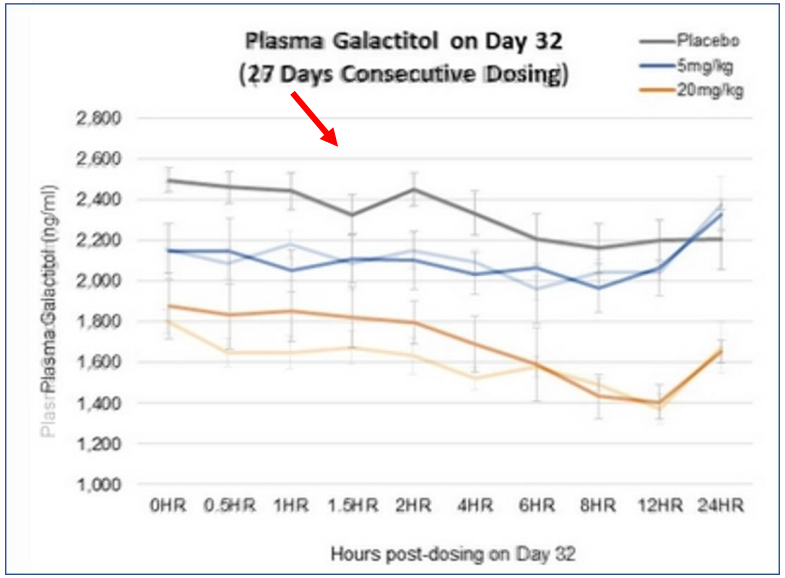
Looks to be data from three different cohorts (placebo, 5 mg/kg and 20 mg/kg on two separate time points (Days 12 and 32). **Right?**

Data Integrity Issues

WRONG…Let's take a closer look at the gray (placebo) lines. Notice anything weird?



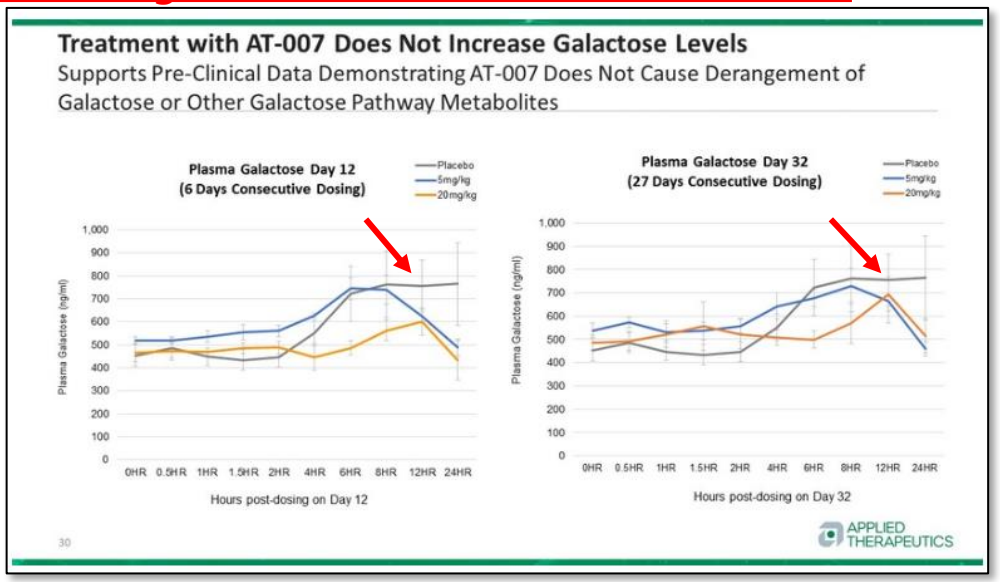
When we overlay the two charts we see that the placebo data is IDENTICAL (including **ERROR BARS**) on both time points:



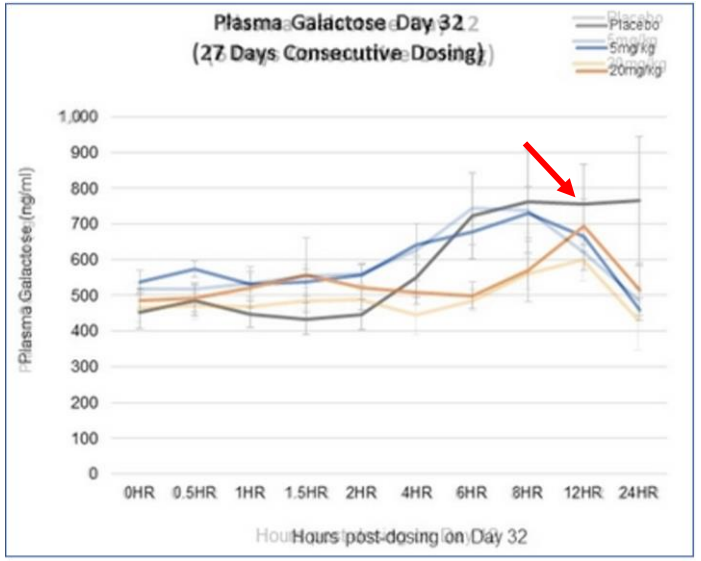
Note that the 5 mg/kg and 20 mg/kg data has separate lines (blue and orange, respectively but the placebo group is a SINGLE LINE WITH IDENTICAL DATA ACROSS TWO TIME POINTS

Data Integrity Issues

And before you say 'well maybe that was just an accident' they do the EXACT SAME THING ON SLIDE 30 with Galactose measurements!



When you overlay the two graphs you see that the Placebo cohort data is (again) IDENTICAL across the two time points:



***Again**, note that the 5 mg/kg and 20 mg/kg data has separate lines (blue and orange, respectively but the placebo group is a SINGLE LINE WITH IDENTICAL DATA ACROSS TWO TIME POINTS*

Data Integrity Issues

A quick summary on the placebo data being identical across *multiple time points* in *multiple analytes*:

- The probability that every data point in the d12 and day 32 placebo arm measurements **is the same** approaches zero

- **All** measurements have some degree of randomness associated with them.
  - If your cholesterol was measured 10 times over the course of a day and 10 times over the course of the next day, the results would presumably be similar **but not identical** owing to a host of vagaries.

- Not only are the day 12 values identical to the day 32 values but the associated error bars **ARE ALSO IDENTICAL**.

- This is not the case for the 5mg and 20mg dose cohorts. They are different between days 12 and 32 begging the question of how it is that the placebo arm data was reproduced while the drug arms were not?

We don't know if this is fraudulent behavior, negligent behavior (or both). But each and every scenario points to this being a BIG PROBLEM for APLT and its shareholders.

Data Integrity Issues

Issue 2: The Company touts a '50 % reduction' (or greater) in plasma galactitol levels. From their most recent PR (6/15/2020):

ACTION-Galactosemia Adult Trial: 40 mg/kg Dose Results

ACTION-Galactosemia is a Phase 1/2 clinical trial of the CNS penetrant Aldose Reductase inhibitor AT-007 in healthy volunteers and adults with Galactosemia. The biomarker-based pivotal study targeted reduction in plasma galactitol, an aberrant toxic metabolite of galactose formed by Aldose Reductase in Galactosemia patients. Accumulation of galactitol causes long-term complications ranging from CNS dysfunction to cataracts. Previously, Applied Therapeutics reported safety and efficacy data demonstrating a rapid and robust reduction in galactitol from baseline (approximately 50% reduction) at 20mg/kg. The reduction in galactitol at 20mg/kg was statistically significant vs. placebo ($p<0.01$) and did not result in any compensatory increase in other galactose metabolites, such as Gal-1p. Because there were no dose-limiting safety issues at 20mg/kg (and no drug-related adverse events overall), a higher dose cohort at 40mg/kg was initiated to fully explore optimal dosing in adults with Galactosemia. Once-daily 40 mg/kg AT-007 resulted in plasma galactitol reduction of 55%, an incremental improvement in efficacy vs. the 20mg/kg dose. Reduction in galactitol was statistically significant vs. placebo ($p<0.01$). All patients on the 40 mg/kg dose demonstrated significant reduction in galactitol from baseline, and reduction in galactitol was rapid and sustained over the 28-day dosing period. 40mg/kg was safe and well-tolerated with no drug-related adverse events reported, and no compensatory increase in galactose or other metabolites, such as Gal-1p.

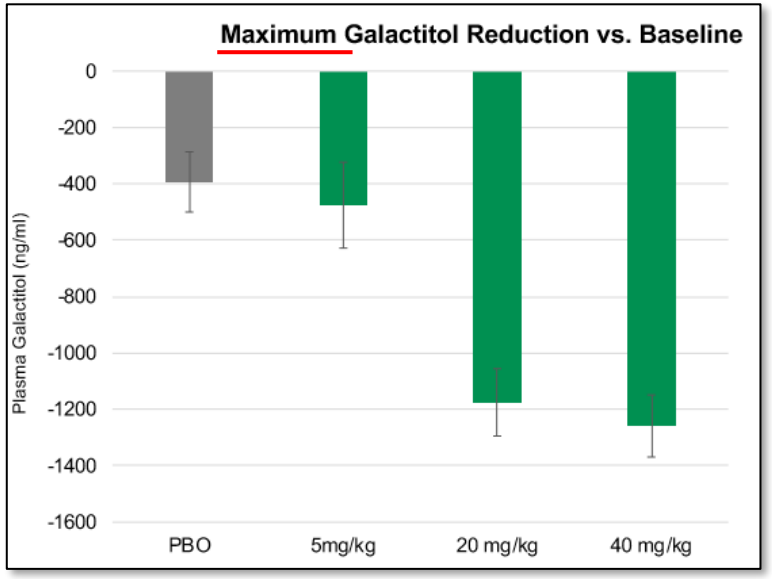
No one knows if a 50% reduction in plasma galactitol will have any impact on the course of the disease, but the Company's use of this metric is highly misleading for the following three reasons:

1) They are reporting a 'MAXIMUM' reduction for each patient.
2) They are not placebo-adjusting this number
3) The variability in the assay over time appears to be equal to the amount of 'benefit' they are showing.

In our view, they are utilizing statistical chicanery by selecting a single maximum data point from a highly variable dataset and calling it 'treatment effect'.

Data Integrity Issues

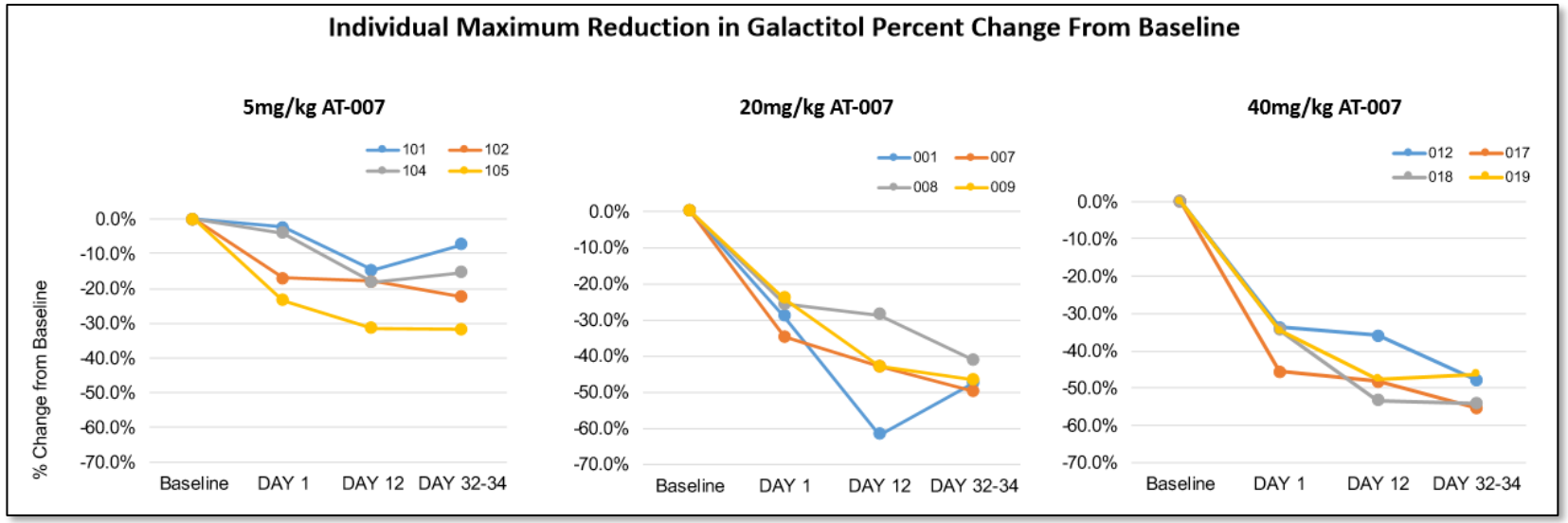
1) They are reporting a 'MAXIMUM' reduction for each patient—from a single time point in the trial—as their summary key data point:



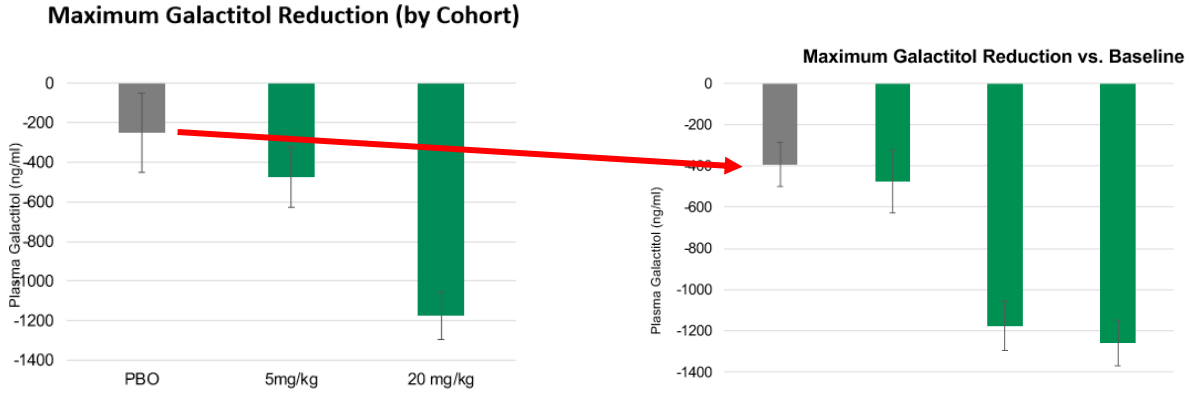
Why does this matter? Chronic diseases, no matter how progressive, rarely follow a monotonically declining course. Selecting the most favorable measurement amongst a panoply of values is THE VERY DEFINITION OF CHERRY PICKING. Imagine if you stated that you were a par golfer because you had a scored par on a single hole *en route* to your 140 stroke game.

Data Integrity Issues

2) The maximum galactitol reduction datapoints are not placebo adjusted. Here is how they summarize AT-007 data:



The company has never produced a similar chart for placebo. There is a reason for this. Look what happened to the placebo 'performance' when just two patients from the 40 mg/kg cohort are added. This data is not robust.



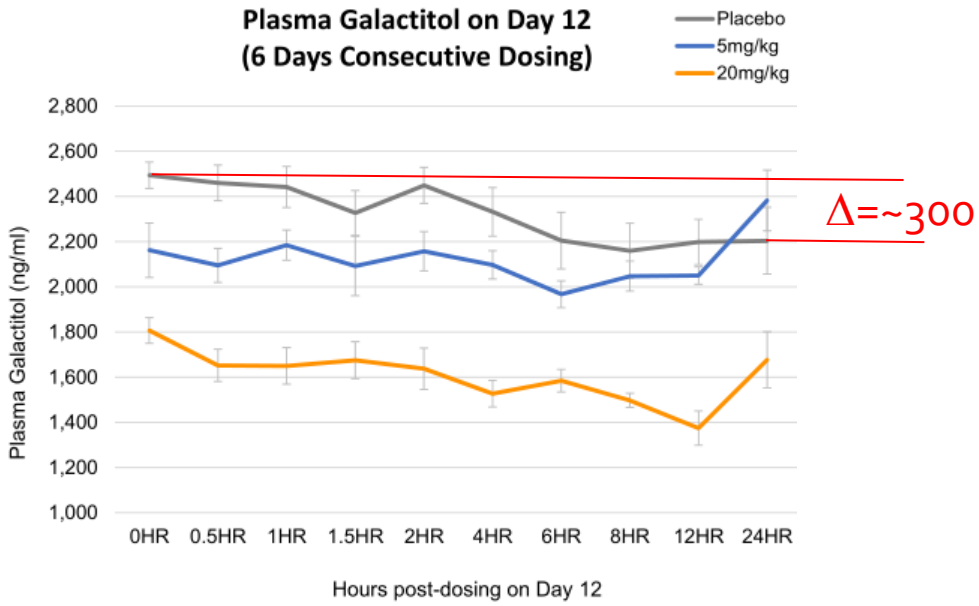
May 2020

June 2020

Data Integrity Issues

Comparing to a patient's own baseline (when done correctly) is fine. But these values then need to be placebo-adjusted.

3) The variability in the plasma galactitol assay appears nearly equal to the amount of 'benefit' the company claims. Let's look at how variable galactitol levels are WITHIN A SINGLE DAY (red added by us):

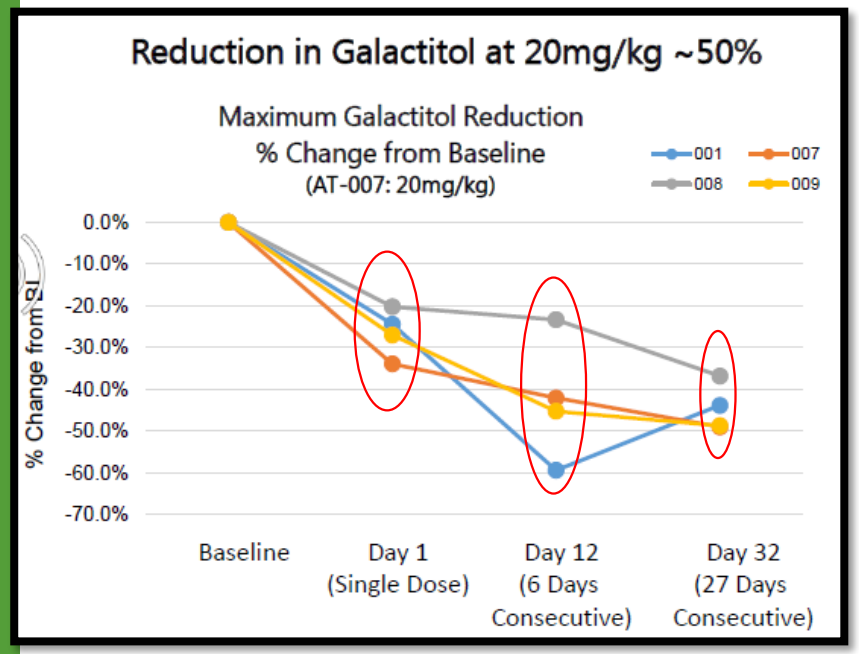


The placebo arm shows AT LEAST a 300 ng/ml fluctuation in plasma galactitol ***in a single day***. 300 ng/ml translates to a >12% reduction in plasma galactitol based on the baseline values given. It is even worse for the 20mg dose cohort which demonstrates a 22% intra-day variation!

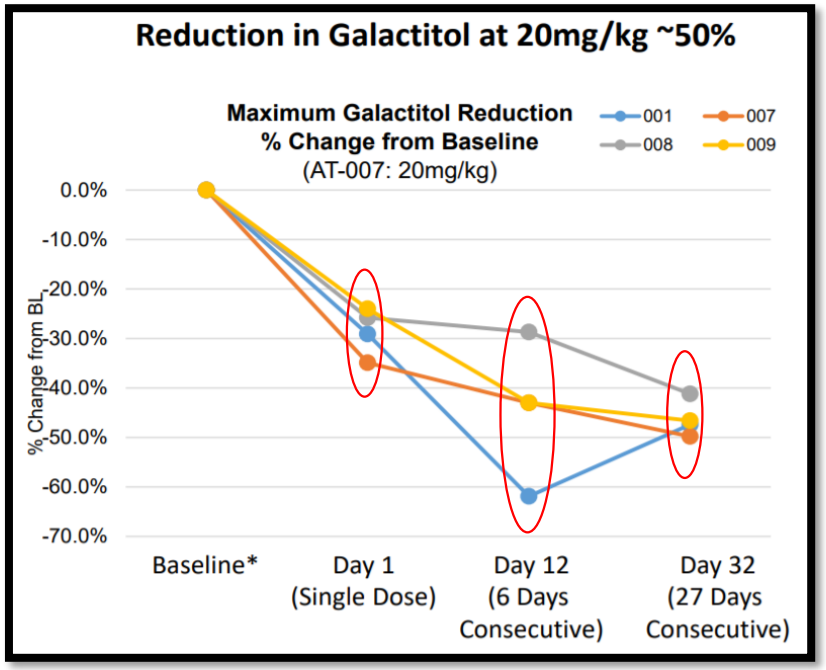
Data Integrity Issues

There are a number of other data integrity issues we have noted. We don't know necessarily that one is any worse the others. Maybe they were oversights…clerical errors…we don't know for sure but find it alarming to find so many. Here are just a few:

- Original (4/21/2020)[1]



- Updated (4/28/2020)[2]



This is the same data set yet the plots are clearly different. <u>This is carelessness at best and rank manipulation at worst.</u>

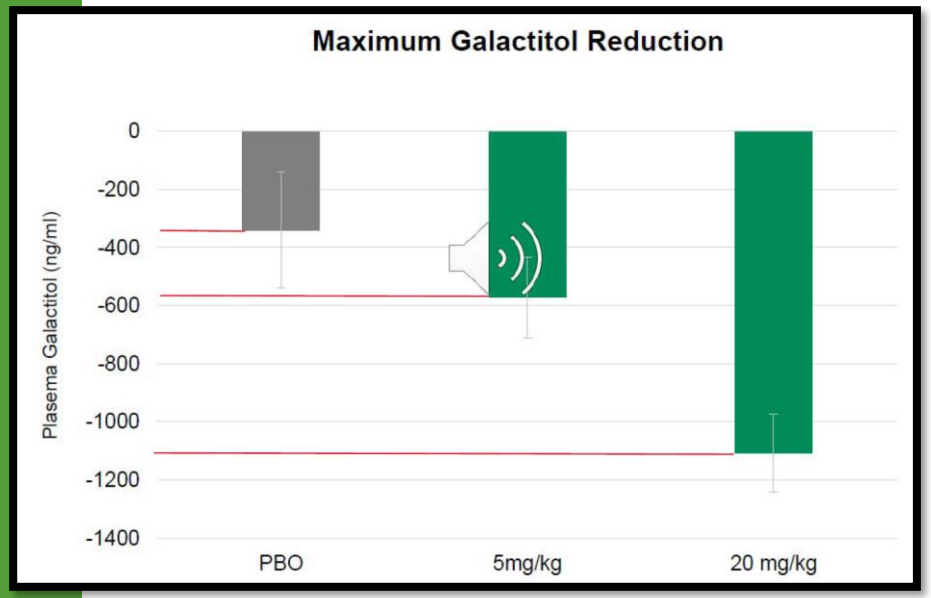
1. Source: ACTION-GALACTOSEMIA Trial Results, Slide 28. Annotations added. **<u>Since deleted from company website</u>**. Used PDF version.
2. Source: Galactosemia Educational Symposium deck, Slide 41. Annotations added. Aaccessed via https://ir.appliedtherapeutics.com/static-files/789078ae-1f21-4a98-992c-901a2bf8d9f4

Data Integrity Issues

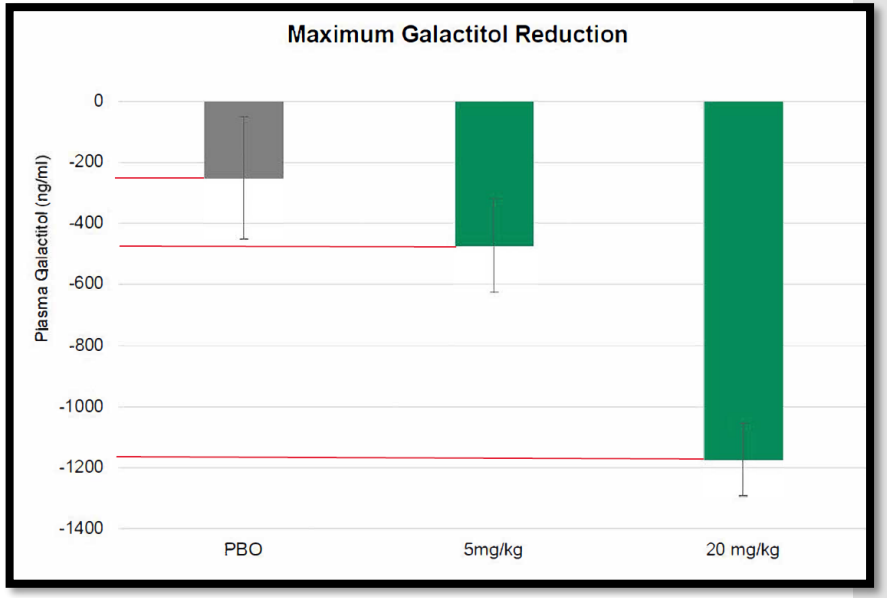
More 'updated' data…

Pick your favorite red line and compare it across updates

- Original (4/21/2020)[1]



- Updated (4/28/2020)[2]



This is the same data set but the charts are different! Carelessness

Or data misrepresentation. We report. You decide!

1. Source: ACTION-GALACTOSEMIA Trial Results, Slide 27. Annotations added. Since deleted from company website. Used PDF version.
2. Source: Galactosemia Educational Symposium deck, Slide 40. Annotations added. Aaccessed via https://ir.appliedtherapeutics.com/static-files/789078ae-1f21-4a98-992c-901a2bf8d9f4

Data Integrity Issues

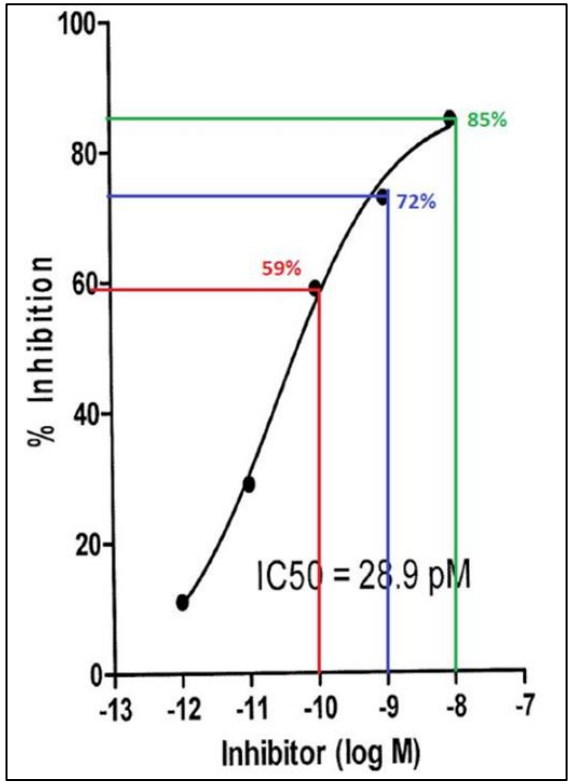
Inconsistencies in the IC50 data

From the Company's patent Wasmuth et al. ALDOSE REDUCTASE INHIBITORS AND USES THEREOF. US 8916563 B2, USPTO, 23 December 2014. Colored annotations ours.

TABLE 2

Aldose Reductase Activity for Zopolrestat and Compound A.

Concentration	% Inhibition (zopolrestat)	% Inhibition (Compound A)
1 pM	11.0	
10 pM	29.0	
0.1 nM	31.7 ± 5.1	69.0 ± 1.3
1 nM	39.3 ± 4.3	79.6 ± 2.4
10 nM	52.2 ± 1.9	80.0 ± 1.8
100 nM	76.7 ± 2.7	89.2 ± 0.7
1 µM	86.3 ± 3.6	93.6 ± 2.8
10 µM	90.1 ± 3.4	95.3 ± 1.1
100 µM	93.2 ± 3.8	96.2 ± 3.3



The data in the table and the data in the chart simply do not match.

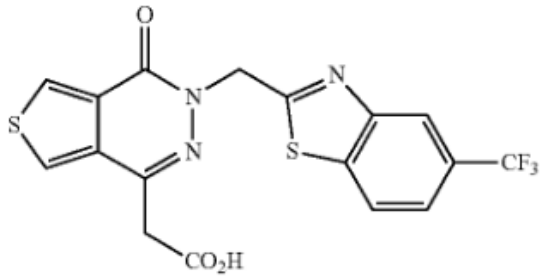
Data Integrity Issues

Inconsistencies in the IC50 data

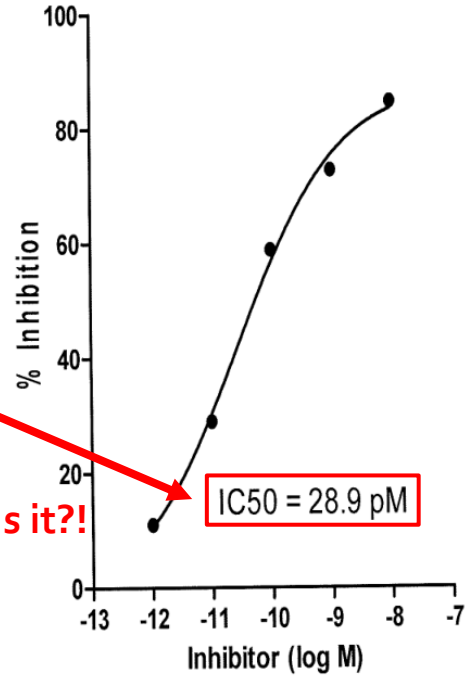
From the Company's patent Wasmuth et al. ALDOSE REDUCTASE INHIBITORS AND USES THEREOF. US 8916563 B2, USPTO, 23 December 2014. Colored annotations ours.

TABLE 1

Physical, Chemical, and Biological Assay Results:

Compound	Structure	Mol. Wt. (AMU)	Solu-bility (mg/mL)	LogD	Aldose Reductase Inhibition (IC50)
XII		425	0.97	−0.09	0.1 nM

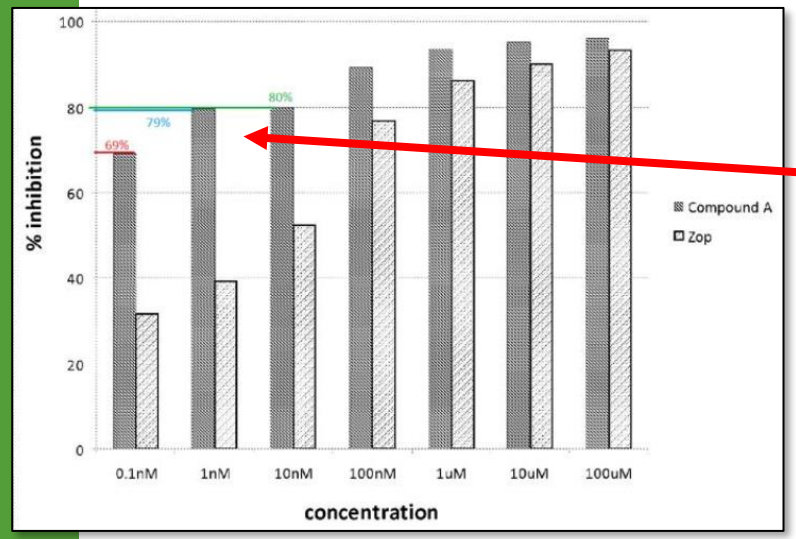
Which is it?!



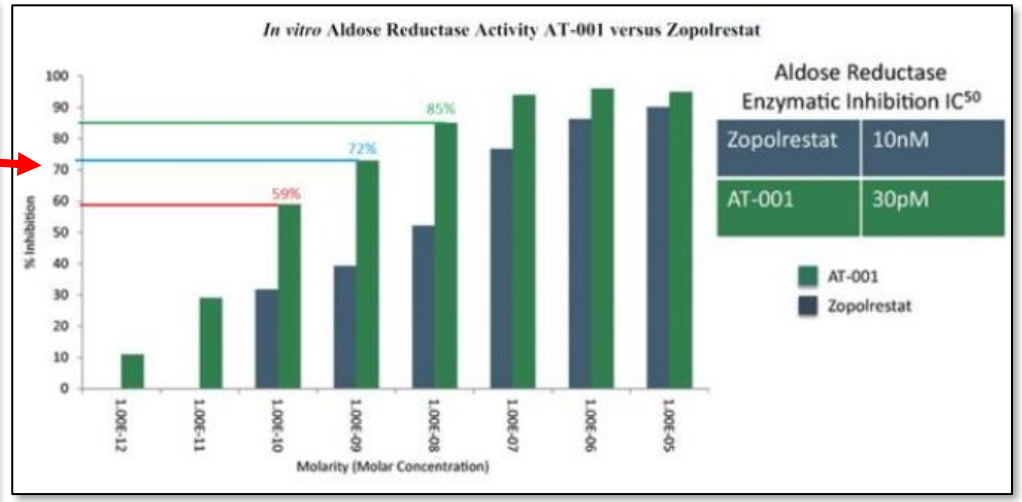
Data Integrity Issues

Inconsistencies between AT-001 Patent and Company's S-1

Note this is for AT-001 which is in the same family as the lead AT-007. Colored annotations ours.



Wasmuth et al. Patent



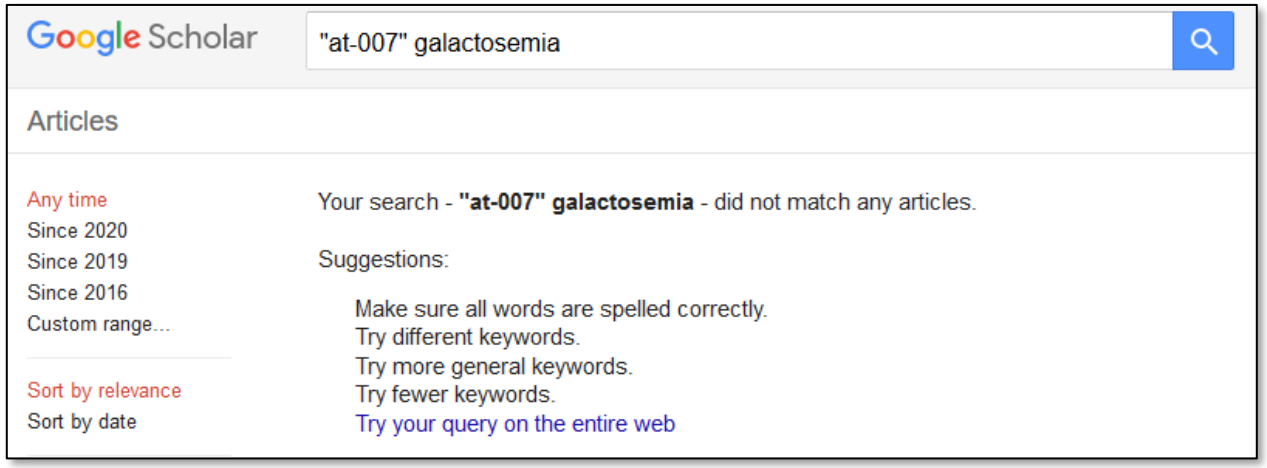
Applied Therapeutics' S-1 Filing from 4/12/2019

There is simply no excuse for the discrepancies in this data. Either the data is flat out WRONG, careless errors were made or a combination of both. Investors in a $1B market capitalization company deserve better.

Spin 4: Preclinical Data

Preclinical Data Issues

Issue 1: Let's start with the elephant in the room. To the best our knowledge, *zero* preclinical data on the lead AT-007 program in Galactosemia has been published in peer reviewed research journals.



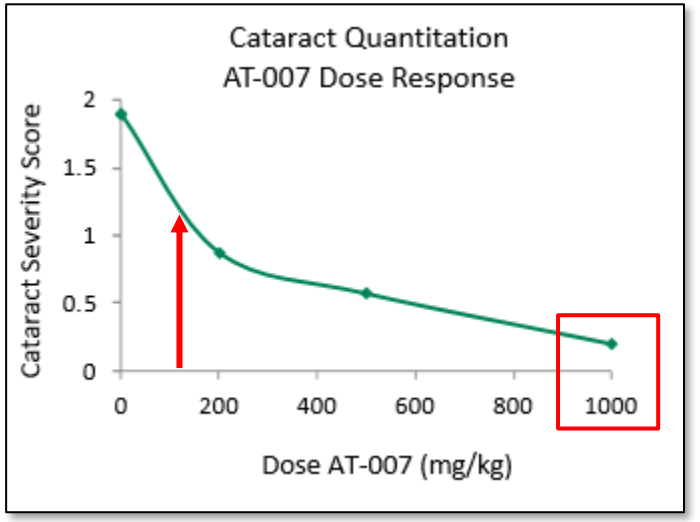
Issue 2: The animal model which APLT management claims validates their program and is a 'game changer' for galactosemia was first published in mid-December 2019. To the best of our knowledge this one publication has not been validated by any other research groups.

Is it possible that a months-old animal model supersedes years of research in galactosemia? Yes. Is it likely? No. Do we think the FDA will agree that this animal model is sufficient for APLT's aggressive regulatory plans? Absolutely not.

Preclinical Data Issues

Issue 3: Besides being extraordinarily new, there appear to be several flaws with the chosen animal model (the GALT-null rat model) including:

1) The effective dose in rats was MUCH higher than what is currently dosed in humans. The 20 mg/kg dose used in humans is equivalent to approximately 124 mg/kg in rats. That dose would appear to have very little impact on cataract formation:



2) The rats are not put on a low galactose diet so it doesn't mirror what happens with a galactosemic patient.

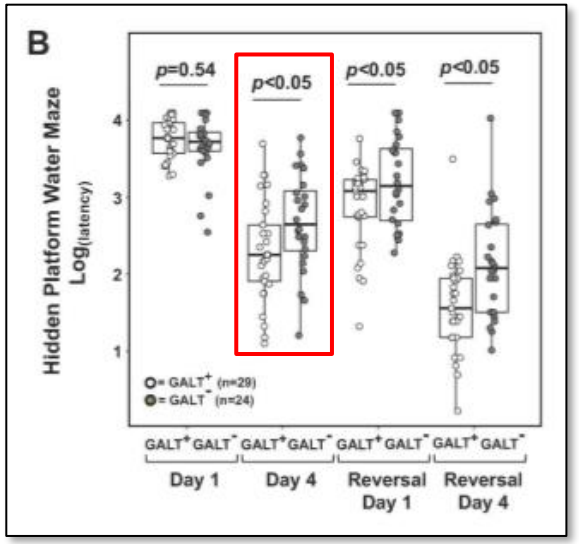
Preclinical Data Issues

3) The rats do not develop the severe acute phenotype at birth like infants do. Why does this matter? It is believed that this initial damage in infants (which can include multiple organ failure) is a major contributor to the problems seen later in life in these patients.

4) The phenomena of cataract formation in *wild type (wt)* rats is different from healthy humans. Rats fed with high galactose diet develop cataracts early in life, while such a phenomena is not observed in humans. This is probably due to differences in Aldose Reductase activity between rats and humans.

5) The published data on the water maze test in the GALT rat model appear highly unconvincing to us. Judge for yourself:

Note: we actually re-analyzed the data in the red box to the right using plotting software and can confirm that the difference between the groups is either not statistically significant or ***barely*** *statistically significant at p<0.5. And this is after the authors made numerous tweaks to the data (log scale, etc.). But the naked eye does a pretty good job of seeing that those groups have significant overlap.*



Preclinical Data Issues

Issue 5: The magnitude of galactitol reduction in the rat study--which the model claims correlates with an effect in GALT rats' CNS symptoms--is MUCH higher than what the company has shown in their clinical trial.

Reduction of galactitol in the brain in the rat model was >80% and was >90% in plasma.

As we have already shown, the AT-007 clinical trial allegedly achieved (on a true placebo-adjusted basis) no more than 30% decrease from baseline. This simply would not translate to CNS improvements according to the rat model.

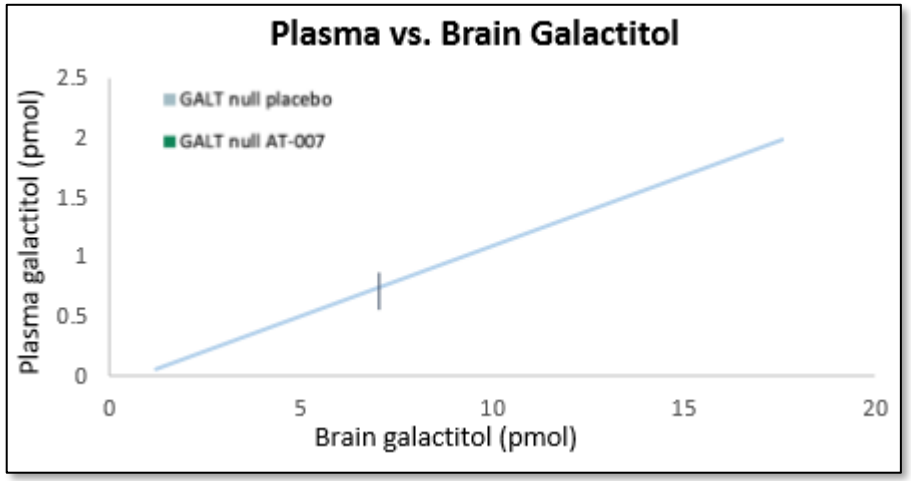
Issue 6: We do not know the PK data of AT-007 in rats or any other animal model because to the best of our knowledge the Company has never shared them.

We don't know the concentrations of the drug in blood and brain, and how those concentrations are correlated, what is the protein binding of AT-007 in rat plasma and how is the AUC in rats compared to humans.

Furthermore, it is not clear if rats can serve as a good model for AT-007 penetration due to differences between rodents and primates BBB penetration.

Preclinical Data Issues

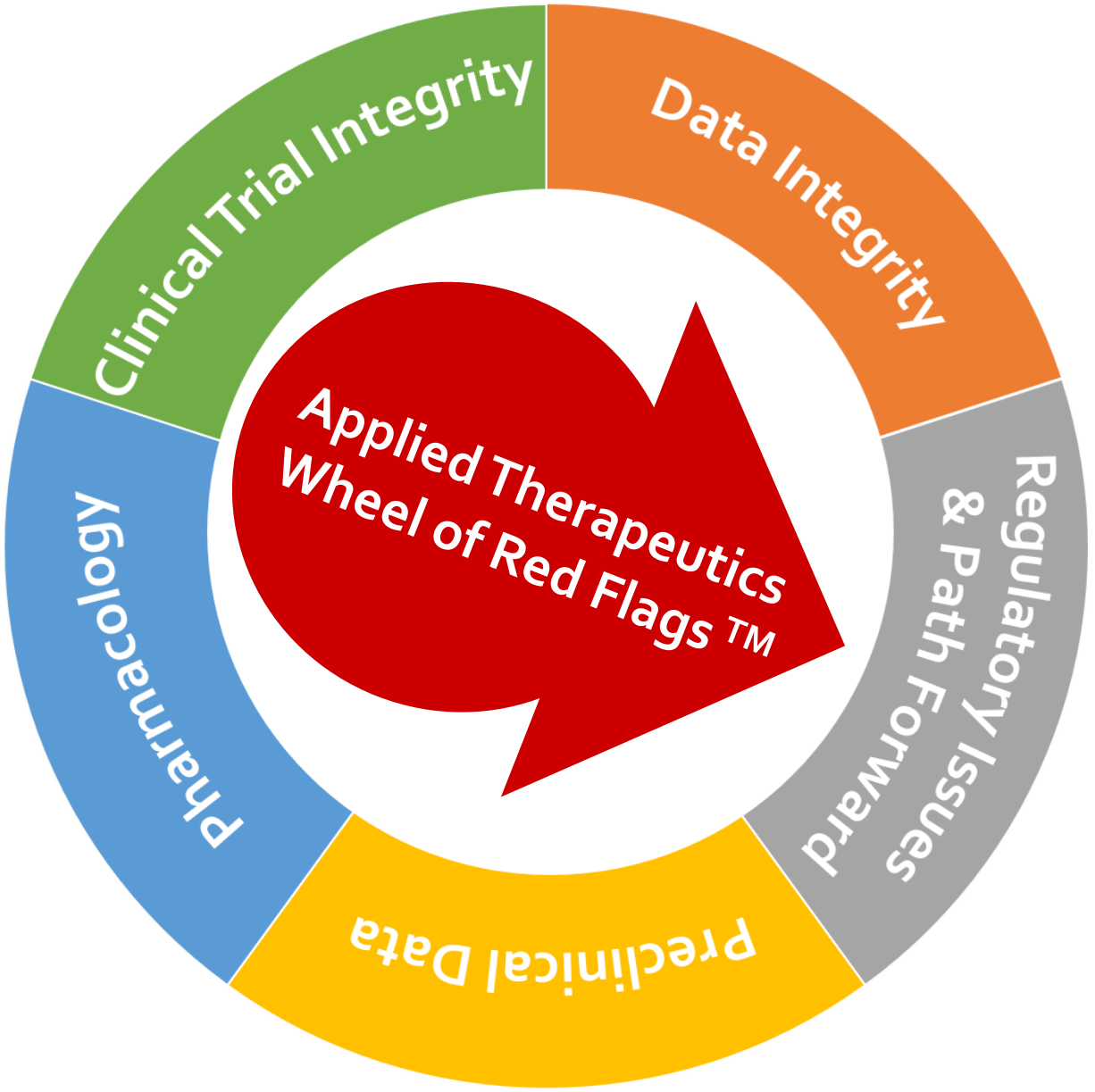
Issue 7: The Company presents 'evidence' of a brain/plasma correlation but the figure they use makes zero sense. From their corporate presentation:



Numerous issues with this 'chart', including:

1) The units on the axes are not clear. 'pmol' is a quantity and not a concentration.
2) There is no data here: no p value, R value or any specific data points
3) There is a random hash mark at ~7.5pmol. The company never makes clear what this is or why it is there.
4) We have already pointed out numerous flaws in the animal model itself compared to the natural human course of the disease, so this 'data' is not likely reliable in extrapolating plasma-brain correlation in rats and humans.
5) ***Where is the corresponding human data?***

Spin 5: Regulatory Issues and Path Forward



Spin 5: Regulatory Issues and Path Forward

- As far as we can tell, the entire bull thesis for APLT stock is that the Company will be able to get AT-007 approved rapidly and that the drug will be a commercial success. In the Company's own words:
  - **Low burden of development due to biomarker-based program under new FDA guidance**
- We do not agree at all with the Company's assessment of the regulatory pathway for AT-007 and believe there is zero chance the FDA or any other similar regulatory body will approve this program with the current data in hand.
- The guidance the Company refers to ("Slowly progressive, low-prevalence rare diseases with substrate deposition…") can be found here.

Issue 1: There is significant debate as to whether galactosemia passes even the first test for coverage by the guidance: "well-characterized pathophysiology".

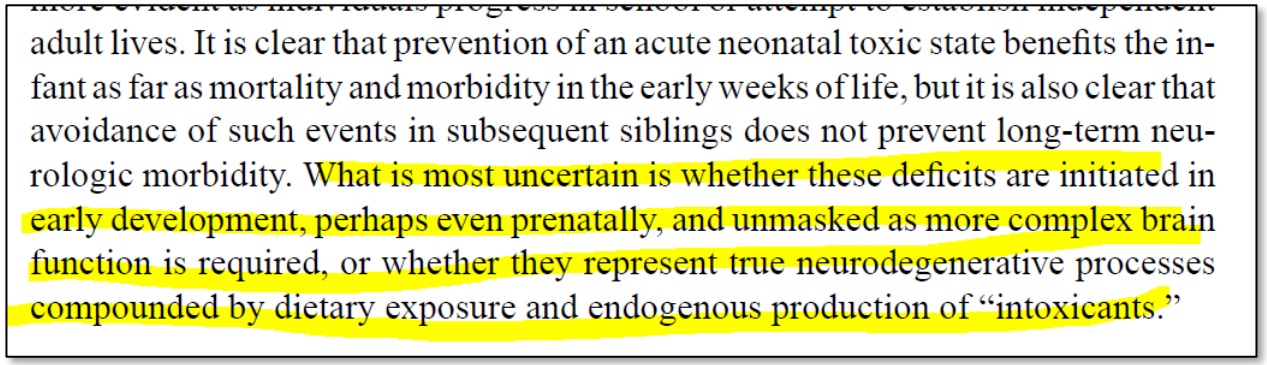
Many peer reviewed publications (here, here and here to name just a few) cite Gal-1P (and not galactitol) as the most relevant biomarker of the disease and the most probably toxic compound in galactosemia. Applied Therapeutics says their therapy has no effect on Gal-1P. This is a massive disconnect in thinking and not one we think the FDA will simply put aside.

No 'gold standard' biomarker, no approval

Spin 5: Regulatory Issues and Path Forward

Issue 2: There is significant debate as to whether galactosemia is even a 'slowly progressive' disease.

Some of the literature (here and here for example) claim that the damage maybe acquired **early** after birth due to late initiation of the restrictive diet, or even before birth due to fetal exposure to galactose metabolites. Furthermore, some believe the CNS phenotype in adult patients is actually the manifestation of the early acquired neurological damage, and not due to a progression of the disease.



adult lives. It is clear that prevention of an acute neonatal toxic state benefits the infant as far as mortality and morbidity in the early weeks of life, but it is also clear that avoidance of such events in subsequent siblings does not prevent long-term neurologic morbidity. What is most uncertain is whether these deficits are initiated in early development, perhaps even prenatally, and unmasked as more complex brain function is required, or whether they represent true neurodegenerative processes compounded by dietary exposure and endogenous production of "intoxicants."

Not clearly a 'slowly progressive disease', no approval

Spin 5: Regulatory Issues and Path Forward

Issue 3: The FDA demands that the assay, which is used to measure the toxic compound **in the relevant tissue**, would be characterized and its variability would be well defined.

> single enzyme defects. This guidance applies only to those low-prevalence rare diseases with well-characterized pathophysiology, and in which changes in substrate deposition can be readily measured in relevant tissue or tissues.

There is no question that plasma galactitol levels do not satisfy the requirement that the toxic compound is measured in the relevant tissue. The Company is angling to mitigate the CNS deficiencies caused by the disease, so it would make the brain the relevant tissue. The Company did not confirm the efficacy of their therapeutic in the CSF, leaving just the HIGHLY variable, non-placebo adjusted plasma galactitol levels to stand (poorly) on their own.

The Company has teased MRS (magnetic resonance spectroscopy) as a way to show they are lowering levels in the brain. We anticipate the data to come out shortly and we believe it will be inconclusive at best. We believe that galactitol levels under MRS in patients under restrictive diets (as is required in the APLT study) will yield no conclusive evidence as to the efficacy of their therapy.

No well-defined assay measuring toxic compound *in the relevant tissue*, no approval

Spin 5: Regulatory Issues and Path Forward

Issue 4: The FDA requests an animal model which will be representative of the human phenotype with well conserved metabolic pathways.

> Some animal models of single-gene human storage disorders display phenotypes that mimic to a large extent the clinical manifestations and overall course of the human disease (e.g., tripeptidyl peptidase null dachshund dog model for tripeptidyl peptidase deficiency) and offer opportunities for evaluating the effect of human enzymes in situations in which there is significant structural and functional conservation of the missing enzyme across species. Animal models can provide opportunities for

As laid out in the 'preclinical data' section of this presentation, we believe the GALT-null rat model in no way shape or form satisfies the FDA's requirements as part of their guidance. In short, the model simply does not mimic the human disease in multiple key areas (no restrictive diet, early vs. late cataract formation, no initial bolus of organ damage after birth, non-lethal model, etc.).

No representative animal model with well conserved metabolic pathways, no approval

Spin 5: Regulatory Issues and Path Forward

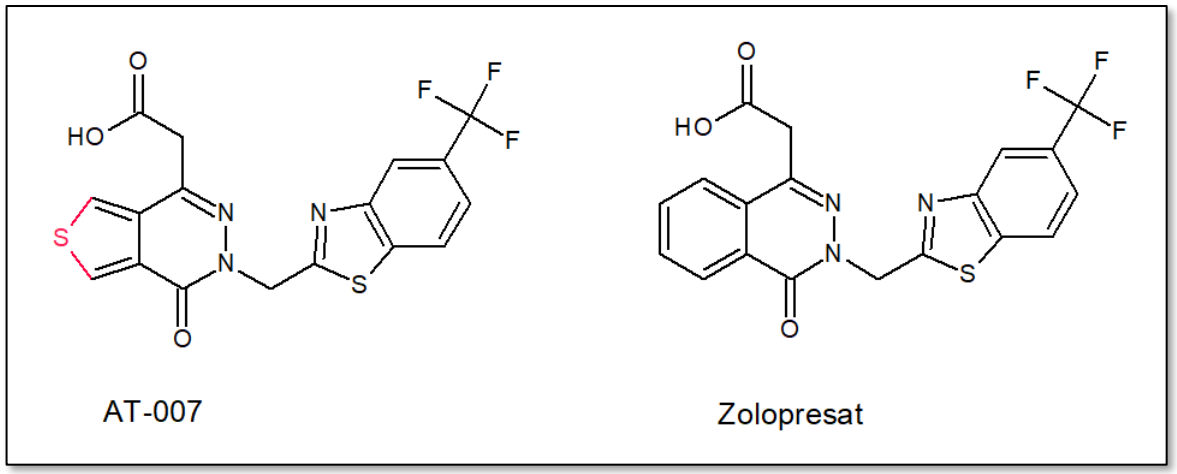
Issue 5: The Company claims it has had 'extensive… interaction' with the FDA (From the January 2020 call on the top line data):

"We've had extensive regulatory interaction regarding our design for the program and not on how we were able to get to this point and how we designed our study was based on ongoing dialog with them."

The Company doesn't detail what 'extensive regulatory interaction', nor can they provide specific or tangible evidence that the FDA agrees with their overall regulatory strategy. In fact, initially the Company said it would file an NDA based upon the adult data alone (in April). Now they are saying they will complete the pediatric trial and THEN file. Is this something the FDA required because the adult data was so underwhelming? We don't know but we certainly don't believe that is a positive development for shareholders.

Spin 5: Regulatory Issues and Path Forward

Issue 6: A predecessor AR inhibitor compound (zopolrestat) was discontinued due to liver toxicity. The liver injury occurred in a small number of patients (<10%). We find it unlikely the FDA will allow a drug to be dosed daily to children without a SUBSTANTIAL toxicology assessment. One we don't believe the Company has or can generate in any realistic timetable. Recall, the structures of AT-007 and Zopolrestat are **nearly identical**.



Summary and next steps

- We have only shown a fraction of the red flags we have found on this Company. We may release more of them in subsequent reports.
- We are shocked that investors willingly accept the fact that the urine data from the trial has not been made available. **THERE ARE ONLY 11 PATIENTS' WORTH OF DATA TO ANALYZE.**
- The purported pharmacological properties of their lead program simply do not add up to us. And we certainly don't see anything confirmed by the cherry-picked clinical data.
- In our view the most important conclusion to draw is that Applied Therapeutics presents data in an inconsistent manner that is sloppy at best and misleading at best.
- We believe this company owes its $1Bn market capitalization to the stock market bubble of 2020.

No matter where the arrow lands when spinning the Applied Therapeutics wheel, investors lose.