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ACADIA Pharmaceuticals Inc. (NASDAQ:ACAD): Daybue in the Rearview

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"Here we go! Started Daybue on the 13th of July...we haven't seen any change in her at all. I know it's not been even a month yet so I am not giving up." – Daybue Caregiver, July 31, 2023

"It is with great sadness that we will be stopping Daybue... No one has seen any improvements, but have pointed out that some things are worse." – January 10, 2024

We are short ACADIA Pharmaceuticals Inc. ("ACAD", "the Company"). We believe ACADIA's April 2023 launch of Daybue – the Company's highly-anticipated "first and only" drug to treat Rett Syndrome – has been a total flop. Despite an initial outburst of interest in the drug, our research reveals that patients, caregivers, physicians, and insurers have all soured on the drug. The sell-side still calls for over $800 million in peak Daybue revenues, but our research suggests that Daybue new patient starts already topped this past summer, peak revenues will be a mere fraction of sell-side estimates, and Daybue's flop will have knock-on effects as ACADIA remains a cash-burning machine. Insiders see the writing on the wall: ACADIA's Head of R&D, its Chief Science Officer, and its General Counsel have all left in the past 3 months. We think shares are headed much lower.

We think ACADIA has misrepresented Daybue's safety profile, and in turn, patient retention rates. The Company has constantly characterized Daybue's side effects as mild and manageable, but our analysis of FAERS data suggests that roughly 1 of every 10 to 11 Daybue patients end up hospitalized. These horror stories have now made their way through the Rett community. Multiple high-prescribing physicians collectively told us that collectively, close to half of their patients are now no longer even interested in trying Daybue.

We think Daybue new patient starts have already peaked. In ACADIA's own Phase III trial, the vast majority (92%+) of patients saw adverse events ("AEs"), but just 13% of patients saw "much improved" symptoms on the drug. As such, AEs ought to mirror patient growth, and AEs peaked in August. Physicians corroborated our view. For example, one physician treating 100+ Rett patients told us less than 2 weeks ago that their rate of new patients starting Daybue have been cut almost in half since launch.

ACADIA claims that Daybue patient retention rates are 81% at 4 months and 76% at 6 months "*based on confirmed discontinuations only*." However, these figures cleverly misrepresent what is happening in practice. Physicians told us that they often don't learn that their patients have discontinued until their 6-month follow-up appointments, and it is often at these 6-month appointments that patients decide to discontinue on a go-forward basis. ACAD's reporting of retention rates *up to* 4 and 6 months cleverly sidesteps this dynamic. ACADIA's "81% retention" figure also ignores any discussion of dosages. Physicians suggested roughly 40% of patients cannot safely reach their full prescribed dose without risking their own safety. Finally, ACADIA claims that very few patients discontinue as time goes on, yet numerous comments from caregivers on Rett Syndrome support groups suggest the exact opposite, as demonstrated in the quote above.

ACADIA now faces a wall of discontinuations due to insurance reauthorization requirements. Numerous insurance plans we reviewed require tangible proof of improvement on the drug, for example, via CGI-I testing. Yet most patients fail to demonstrate any improvement on the drug – recall that even in ACADIA's own Phase III trial, 62% of patients saw zero change or even worsened symptoms on the drug. These patients are already reporting denials, and physicians confirmed to us that reauthorizations "*are going to become more and more of an issue.*"

Finally, competing treatment options are set to put a dent into Daybue's existing patient base. Notably, these treatments *don't even need to be approved or commercially successful* in order to decimate Daybue's already faltering patient base – patients must discontinue Daybue in order to participate in trials. Interest is massive. Per one physician, "*Many, many people would come off [Daybue] in order to be in a gene therapy trial*."

ACADIA hinges on Daybue. The Company claims that Nuplazid produces $300 million in cash flows (the Company does not provide any support for this claim), but the reality is the Company has burned $94 million in the LTM and has an accumulated deficit of nearly $2.5 billion. Any supposed cash flows are swallowed up by massive R&D and SG&A spending to support Daybue. In turn, the sell-side still views Daybue as a growth story capable of supporting the rest of the Company's pipeline. As Daybue's story unravels, so does ACADIA's.

Overview: Rett Syndrome, Daybue, and ACADIA

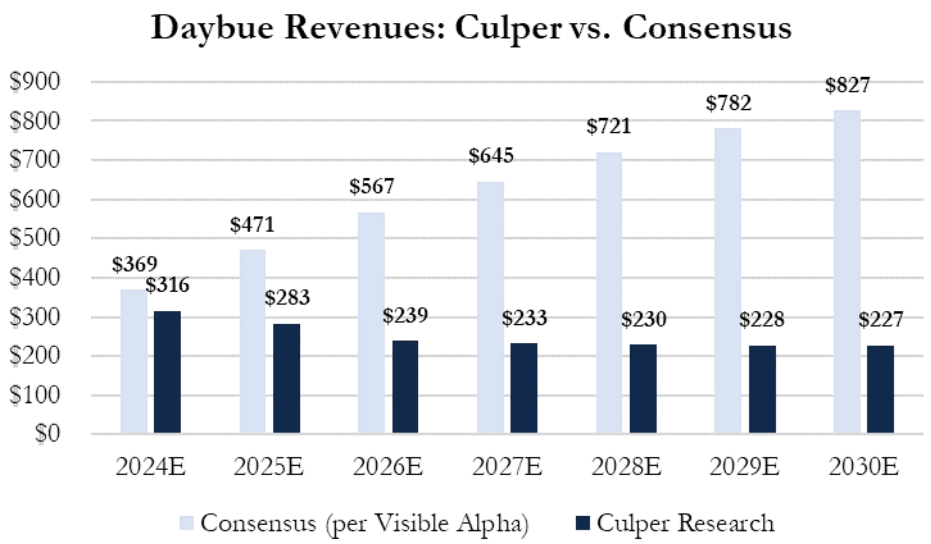
Rett Syndrome is a rare genetic neurological disorder that plagues roughly 7,000 patients in the U.S., of which only 4,500 have been diagnosed. The vast majority of Rett patients are girls, as it is caused by mutations on MECP2 on the X chromosome. Both children and adult patients often require adult caregivers – usually a parent or close family member who aids in tasks such as feeding, handholding, and using the restroom. As such, Rett not only greatly affects the lives of patients, but their loving caregivers. There is no known cure for Rett, so patients and caregivers have looked hopefully towards any treatment options.

The FDA approved Daybue (trofinetide) in March 2023, and ACADIA launched the drug a month later, marketing it as "*the first and only FDA approved medicine for Rett Syndrome*." Caregivers, eager for any hope at all, heralded Daybue as "*a pretty monumental milestone*" and "*one of the happiest moments for us as a family and hopefully for the larger community.*" ACADIA's Q3 2023 results reflected this pent-up demand, and CEO Stephen Davis claimed that "W*e're seeing strong indicators across all launch metrics underlying these results, including demand, persistency, and access*." Sell-side brokers were quick to jump on the runaway bandwagon.

> Sell-side broker 1, December 13, 2023: *"The drug will be heavily utilized as the first approved treatment option with disease-modifying potential."*
>
> Sell-side broker 2, December 13, 2023: *"Daybue likely to continue to perform following a strong 3Q print; the franchise takes center stage as a key value driver for shares..."*

Sell-side estimates we reviewed now call for Daybue market share upwards of 40% in Rett and revenues anywhere from $650 million to $880 million at peak. However, our research reveals that each of these tenets – demand, persistency, and access – have deteriorated significantly: caregivers increasingly shun Daybue as they've been bombarded with horror stories of diarrhea and hospitalizations, patients are discontinuing treatment as they are unable to tolerate the side effects or reach target doses, and insurers are denying reauthorizations as the majority of Daybue patients show zero change or even worsened outcomes on the drug.

We estimate Daybue peak annual revenues of $316 million in 2024, which will continue to decline over time as patients discontinue and ACADIA runs out of new patients to fill the gap. See our views as compared to sell-side consensus below:



Our assumptions below imply that by year-end 2030, over 5,000 patients – more than the entire diagnosed U.S. population – will have tried Daybue.[12]

Daybue Revenue Build Assumptions	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Start of period patients	956	1,006	755	730	717	710	706
Added in period	1,150	750	400	400	400	400	400
Discontinued in period	1,100	1,001	425	413	407	404	402
End of period patients	1,006	755	730	717	710	706	704
Average patients in period	981	880	743	724	713	708	705
List price	$575,000	$575,000	$575,000	$575,000	$575,000	$575,000	$575,000
Gross to net (average)	80%	80%	80%	80%	80%	80%	80%
Titration level (average)	80%	80%	80%	80%	80%	80%	80%
Neuren royalty rate	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%
Net Revenues (Culper Research)	$316	$283	$239	$233	$230	$228	$227
Consensus (per Visible Alpha)	$369	$471	$567	$645	$721	$782	$827
Difference	**-14%**	**-40%**	**-58%**	**-64%**	**-68%**	**-71%**	**-73%**

Culper Assumptions	2024-2025	2026+
Monthly Discontinuations	10%	5%
Quarterly Discontinuations	27%	14%
Annual Discontinuations	72%	46%

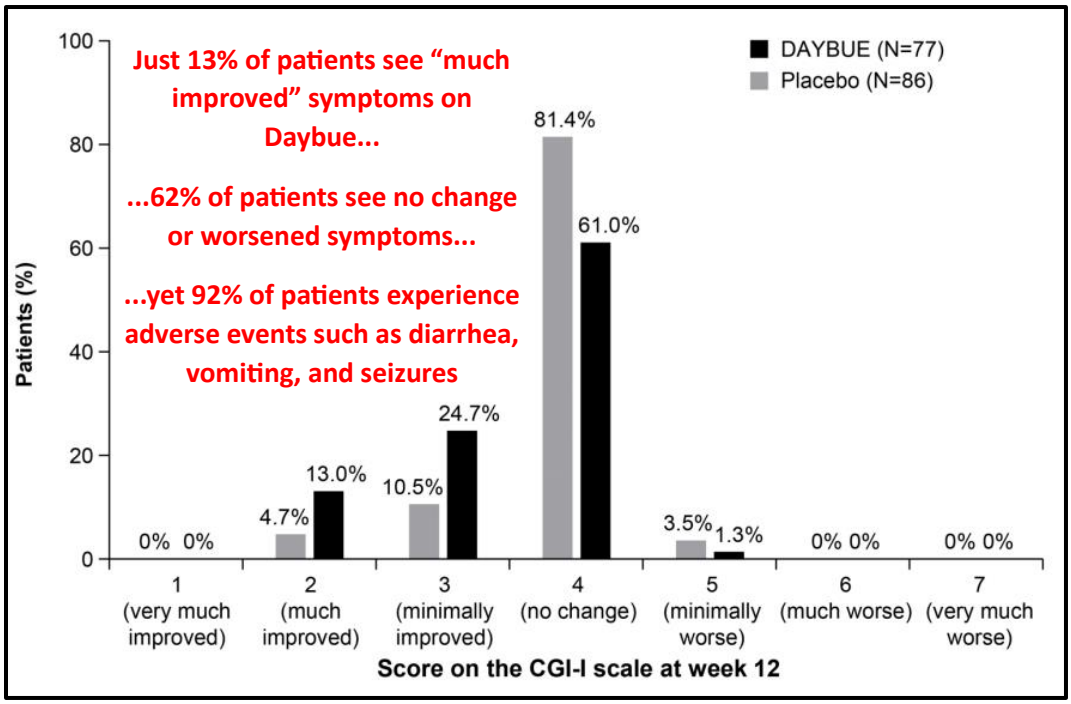
Total discontinuations	4,377
2030 ending patients	704
Total patients trying Daybue	5,081
Market share (ending)	13.8%

[1] On a March 2023 conference call, ACADIA claimed that the "average net realized cost of therapy to payers" is "approximately $375,000" based on "weight-based dosing assumptions, the average weight of our expected patient population, compliance rates to therapy and mandatory government discounts." Our estimates are for 80% gross to net pricing and 80% of full dose. Together, these estimates imply net prices of $368,000, in line with ACADIA's comments. Other sell-side reports we reviewed were even more punitive. Canaccord, for example, models $250,000 net pricing.

[2] ACADIA acquired trofinetide from Neuren Pharmaceuticals (ASX:NEU) in 2018, and ACADIA is still liable to pay tiered royalties to Neuren consisting of 10% to 15% of Daybue's North American revenues.

ACADIA Promised Daybue Side Effects Would Be Mild and Manageable. They're Not.

We believe ACADIA has grossly mischaracterized Daybue as an overwhelmingly effective drug that contains mild and manageable side effects, when the reality is that side effects are often serious, lasting, life-altering, and significantly outweigh the benefits of the drug. The FDA approved Daybue based on a consolidated view of CGI-I scores, yet Daybue's own Phase 3 results show that the drug causes adverse events in nearly everyone. 92.5% of patients saw AEs including **diarrhea (80.6%), vomiting (26.9%) and seizures (8.6%), while most patients also have zero response to the drug. Indeed, just 13% of patients showed "much improved" CGI-I scores, as shown below:**



ACADIA has reassured investors as well as the broader Rett community that Daybue's side effects are mild and manageable. See for example comments from former SVP Kathie Bishop on the Company's Q4 2022 call:

> *"In the subsequent study, LILAC-2, **we have a very low discontinuation rate and none due to the diarrhea to date** ... As we're talking about diarrhea, remember that the diarrhea is **almost all mild or moderate in nature**, and it's not a safety concern. **It does not lead to dehydration, does not lead to weight loss, does not lead to hospitalization. So this is really a management issue** and through the trials and working with some of the study nurses and clinicians, I think we put in place steps to help parents better manage it, and that's what we intend to do as we move towards hopeful commercialization."*

ACADIA's EVP Doug Williamson further claimed at the Guggenheim Neurology and Immunology Conference in November 2023 that, *"we saw higher rates of diarrhea in the trials and discontinuations due to diarrhea than what we've seen in the real world ... and I think the tolerability has generally been better in the real world."*

We think these are gross mischaracterizations of Daybue's safety profile. Coincidentally, both Kathie Bishop and Doug Williamson have left the Company within the last 3 months.

FAERS data through year-end 2023 discloses 1,115 Daybue-affiliated adverse events – astounding in its own right, yet even more so considering that 310, or **39% of these cases, were serious in nature – a far cry from ACADIA's claims of "almost all mild or moderate" AEs. These 310 serious AEs resulted in 108 reported hospitalizations and 5 reported deaths, while 92 of these 108 hospitalizations listed diarrhea among the reactions:**

Daybue Reported AEs (to 12/31/23)	
Non-Serious	805
Serious	310
Died	5
Hospitalized	108
Listed Diarrhea? Yes	92
Listed Diarrhea? No	16
Other	197
Serious as % of Total	**39%**
Hospitalized as % of Total	**10%**
Diarrhea as % of Hospitalized	**85%**

Recall that per ACADIA's own Phase 3 data, 92.5% of patients on Daybue saw AEs. FAERS data thus implies that roughly one of every 10 to 11 patients who take Daybue will end up hospitalized.[3]

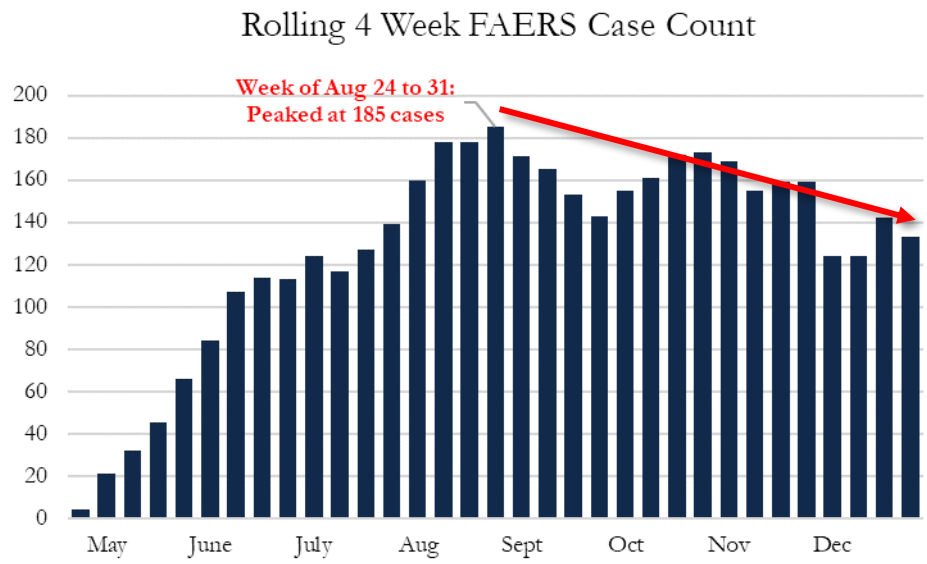
ACADIA also claims that diarrhea does not "*lead to*" further issues, yet once again the FAERS data reveals that the majority of diarrhea cases (850 of 1,115 total) were accompanied by additional reactions including vomiting (224 cases), seizures (121 cases), weight loss (101 cases), decreased appetite (86 cases), and dehydration (27 cases).

We Believe New Daybue Scripts Peaked in August 2023

Our analysis of FAERS data also suggests that new patient starts peaked this summer. Daybue is sold through specialty pharmacies and does not report IQVIA prescription data. However, Daybue's adverse event profile is so horrific – recall that over 90% of patients see AEs – that adverse event reports ought to mirror new patient growth.[4] As shown below, adverse events peaked in August:

[3] 92.5% of all patients see AEs * 10% of FAERS cases resulting in hospitalization = 9.2% of all patients hospitalized.

[4] If anything, in our view, FAERS data likely under-reports total events. Studies, for example here, report significant under-reporting of adverse events across various groups of drugs. More specifically, one high prescribing Daybue physician told us that "*we're not reporting just regular diarrhea ... because the FDA is already aware of it*."



Source: FAERS database; event count based on actual event date / earliest disclosed date available.

This was corroborated by our conversations with physicians. For example, one physician currently treating over 100 Rett patients told us that after the initial first two months, interest in Daybue has deteriorated substantially:

> *"You always have an excitement around it and people who want to start it no matter what. We had a very high interest for the first two months... We prescribed maybe 8 to 10 a month for the first like, two months... and then over the next several months it's kind of slowed down... so instead of 8 to 10 it's now like 4 to 6 new patients per month. So I'd say all in all we're 40 to 50 [Daybue prescriptions vs. ~125 total patients]."*

ACADIA reported strong Q3 2023 results, reflecting this pent-up demand for Daybue. **Yet after seeing the drug in the real-world, we believe patients, caregivers, physicians, and insurers have all soured on Daybue.**

We Believe ACADIA Misrepresents Daybue Discontinuation Rates

We believe Daybue's discontinuation rates are horrible, and worsening, and ACADIA has cleverly misrepresented both the drug's adverse event profile and true patient retention. ACADIA reassured investors on the Q3 2023 conference call that just 19% of patients discontinue at the 4-month mark, as "*measured by confirmed discontinuations only*", and that retention is 76% at 6 months, per the most recent conference call.

81% implies just 5% monthly churn, while management claims fewer patients churn as time goes on. We think churn is likely closer to double that, which is magnified over the course of a full year.

Confirmed Discontinuations Language Leaves Plenty of Wiggle Room

To begin, ACADIA's caveat of "*confirmed discontinuations only*" leaves enough wiggle room wide enough for a rolling Nikola. Physicians told us that most caregivers never inform them that patients have stopped:

> *"Most often **they don't call us to say we're stopping the medicine. We find out later once we see them** that they've just stopped taking it ... that 1-year visit is what's going to determine it for a lot of families."*

Second, ACADIA's discussion of retention rates ***up to*** 4 and 6 months cleverly ignores that many patients decide to discontinue ***immediately after*** their 6-month follow-up appointments. **One physician who is currently treating over 100 Rett patients estimated that just 30% of patients will stick around to the 12-month mark:**

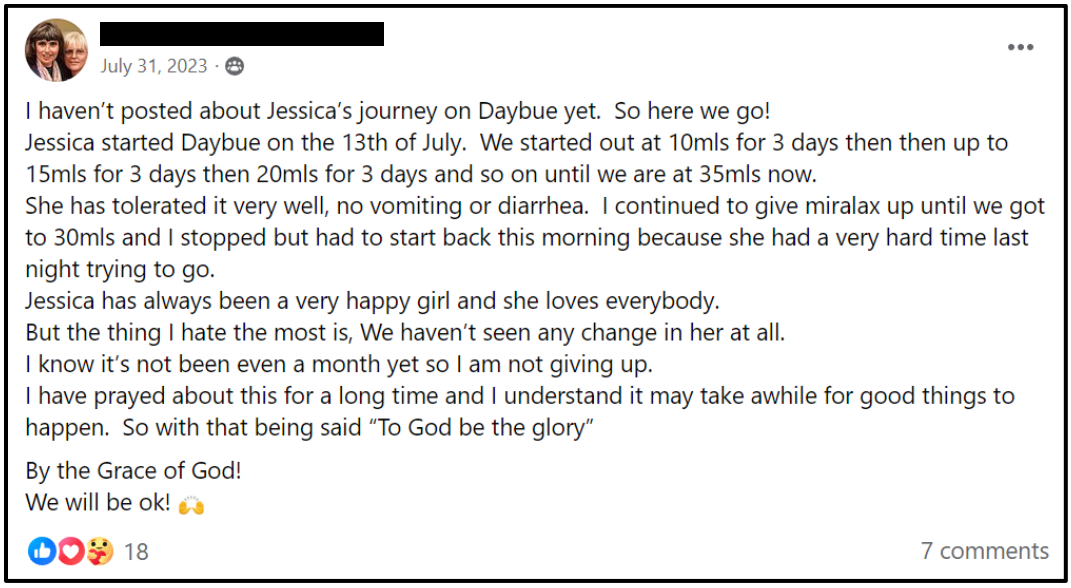
> *"When we get to 6 months is where we've had the real conversation, and there, we've lost a bunch ... We're telling everyone they should give it 6 months ... At a year, we will be about 30% [patient retention]."*

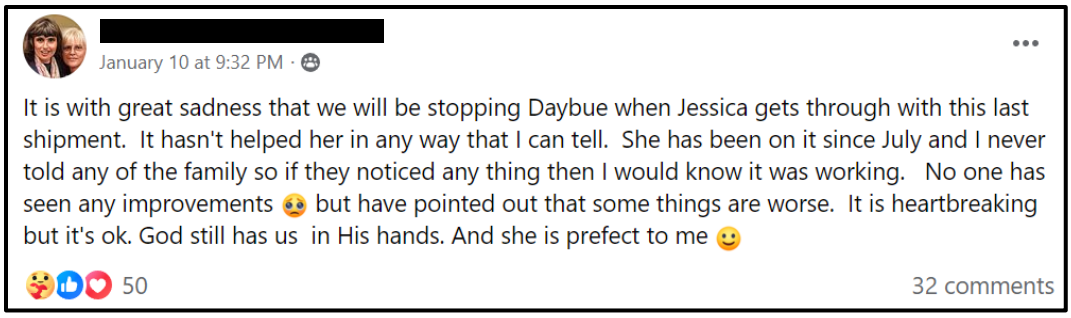
A second physician also treating over 100 Rett patients told us the same – patients are encouraged to stay on for 6 months, as the physician only sees that patient once every 6 months at best anyway. Yet, it is after the 6-month mark that discontinuations happen:

> *"A lot of the symptoms begin in the younger patients their needs are pretty intense, so we will see them every 6 months. The older patients maybe once a year or once every one-and-a-half years ... We do ask that families continue the drug, so long as it's tolerable, for at least 6 months. And then at 6 months, we get a conversation in person, and we get to do our measures again, we find out what doses they're on. At that 6 months, if there's not much going on that's clinically meaningful and they're struggling with diarrhea, then that's when we have the conversation and say it's time to stop."*

Patients Give Up Well After 6 Months, Rendering ACAD's 4- and 6-Month Claims Moot

Comments from patient caregivers also support our view. Many have lost hope in Daybue and are titrating down or discontinuing completely well after ACADIA's 4-month mark. See, for example, the stark evolution from one outspoken caregiver who started her daughter on Daybue in July, but announced that they would be stopping in January – **7 months later** – as the drug only made things worse:





Comments from many other caregivers reflect the same dynamic.[5] Caregivers have given Daybue a chance, but patients are churning off the drug well past 4 and even 6 months:

> November 14, 2023 – 5+ months: *"[Patient] has been on Daybue for 5 1/2 months with very subtle changes. Initially, I was excited because one of the improvements seemed to be his seizures (fewer and less intense). That is not the case anymore. This past month his seizures are more frequent and very intense (long, ugly, hard ones). I scheduled an appointment with Benke at the Rett clinic but the soonest is March. I just don't know anymore… keep going, stop, lower…"*
>
> December 2, 2023 – 8+ months: *"We have been on Daybue since April, its December now and we have seen no change other than dealing with Diarrhea until today. Are we the only ones...?"*
>
> December 16, 2023 – 8+ months: *"Our daughter has been on Daybue since April. Appetite decreased and then she stopped eating. In hospital now with colitis." [patient discontinued after hospital visit].*
>
> December 20, 2023 – 4+ months: *"After 4 months on Daybue...between not being able to find a happy medium with BM's, weight loss, and now the return of seizures, we are giving it a break..."*
>
> December 30, 2023 – 9 months: *"I think I am stopping the Daybue for our daughter... been on since April..."*
>
> January 10, 2024 – 7+ months: *"We started in May, saw now improvements, but it made our very happy girl unhappy ... We stopped last month."*
>
> January 10, 2024 – 7+ months: *"We stopped and started so many times over the last 7 months it's ridiculous. But after this last admission we're officially off it."*
>
> January 10, 2024 – 7+ months: *"We stopped this past week. My daughter, [redacted], has been on since June with no huge changes... she's been more awake, happy and back to her normal self since we stopped."*
>
> January 15, 2024 – 6 months: *"We are debating on taking our daughter off Daybue for the time being."*
>
> January 31, 2024 – 6+ months: *"The positives did not outweigh the negatives. [Daughter] never had diarrhea or vomiting, but she had increased seizure activity... started the first week of August... I stopped her on January 15. She's already awake all day like she used to be. Her eating is better because she's awake. We will wait for the next 'great' thing!"*

[5] Some comments have been shortened as able ("...") for brevity.

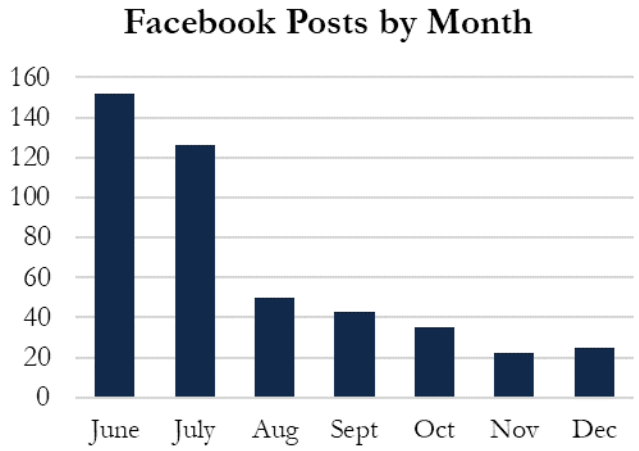
Discontinuation Rates Say Nothing About Titration: Many Patients Titrate Down Before Discontinuing

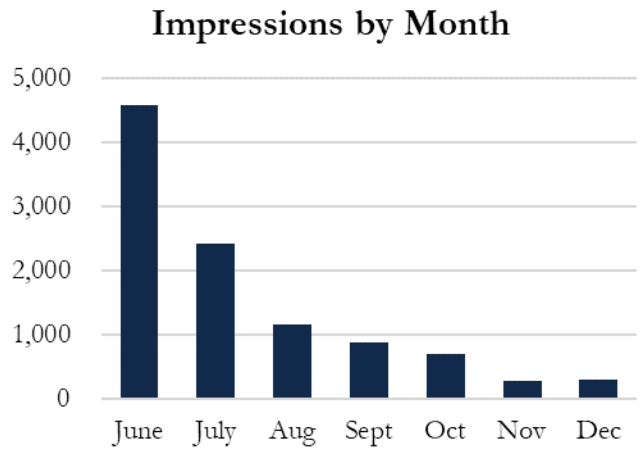
Caregiver comments also show that many caregivers opt to titrate Daybue to a lower dosage as an intermediate step prior to discontinuation. While ACADIA touts 81% retention to 4 months, this statistic says nothing as to the portion of patients that are actually taking their target dosages. For reference, see from patient caregivers in a large (900+ members) private Daybue-dedicated Facebook group:

> November 17, 2023: "*We're at day 100 and we're seriously considering taking a pause in giving Daybue. The first 70 days we titrated up to 35 mls x 2 per day but severe diarrhea resulted in lowering the dose to 20 mls.*"
>
> November 17, 2023: *"We stopped two days ago, temporarily, to give my daughter's bowels a break. We made it to her goal dose of 40ml 2x a day for 6 days, then she started diarrhea so we started immodium, banatrol, extra fluids, went down to 30 and then 20ml 2x a day ... My daughter has been super happy, vocal, and focused on Daybue, but this poop stuff is wearing her out and erasing all that..."*

Patients and Caregivers are Losing Interest in Daybue, Given the Side Effects and Lack of Efficacy

The constant need to manage side effects has taken a toll on caregivers, who have lost hope and interest. See from our data scrape of the private Daybue Facebook group that posts and impressions have declined substantially since the group's creation in June 2023:





Physicians we spoke with confirmed that many patients don't even bother to try Daybue in light of the risks and horror stories that have been shared within the Rett community.

Physician 1 (100+ patients):

This physician sees over 100 patients, and estimated that only "*about 25% of my patients want to give it a try*." Patients primarily mention diarrhea as their primary deterrent, noting that for many older patients with well-managed symptoms, "*it's a hard stop*" as soon as the physician mentions the prospect of adult diapers.

Physician 2 (10+ patients):

This second physician cared for roughly 25 Rett patients in their career, 10 currently. Of these 10 patients, 4 of them have been prescribed Daybue. **The doctor indicated that the other 6 didn't want to try the drug, as they had already heard about the adverse event profile and were not inclined to deal with constant diarrhea, nor the risk of vomiting and seizures**. Of these 4 patients, the physician told us that 2 had already discontinued due to vomiting and weight loss, while 2 remain on the drug. Of those two patients, *"One has had a dramatic response, and one not so much. We'll see after another 3 months whether or not they will continue."* The physician estimated that just 40% to 50% of patients who end up trying Daybue will remain on the drug after 12 months.

Physician 3 (100+ patients):

A third physician we spoke with stated that many caregivers never intend to try, as diarrhea isn't worth the minimal improvements that the drug might provide. This physician only starts just ~30% of their patients on Daybue.

> *"They really don't intend to ever start their child on it. And I believe it's fair to say these are usually the higher-functioning individuals. They're not going to go for the diarrhea for such small clinical improvements ... people say it's just not worth it for us to explore this. We start about 1 or 2 of every 5 patients we see."*

Physician 4 (100+ patients):

A fourth physician we spoke with cares for over 100 Rett patients, and estimated that only half of them were willing to try Daybue:

> *"Most of the patients who said they're not interested breaks down into 3 groups. One is those who just don't want to deal with the diarrhea... Second group is those who've looked at it and say I might do something but not enough to deal with it, and then there's a small group who very closely follow RSRT which has been somewhat negative about the drug, and they say we shouldn't be prescribing based on such a small effect size."*

The physician also implied that as long as caregivers wanted to continue, and as long as insurers kept covering the drug, then patients should continue:

> *"My view as a clinician is that it's worth a try... If it makes no impact, after 6 months you just stop it... If we were worried about healthcare costs it would be a different issue."*

Yet even so, the physician estimated that a mere 20% to 30% of their patients would still be on Daybue at the 1-year mark, implying run-rate market share / penetration of just 10% to 15% in total. Tellingly, this physician's concerns over the price of the drug are now coming to the forefront. At a gross price tag of roughly $575,000, we think ACADIA has put somewhat of a target on its own back, despite the relative rarity of Rett Syndrome, and insurers are already pushing back.

ACADIA Now Faces Onslaught of Insurance Reauthorizations

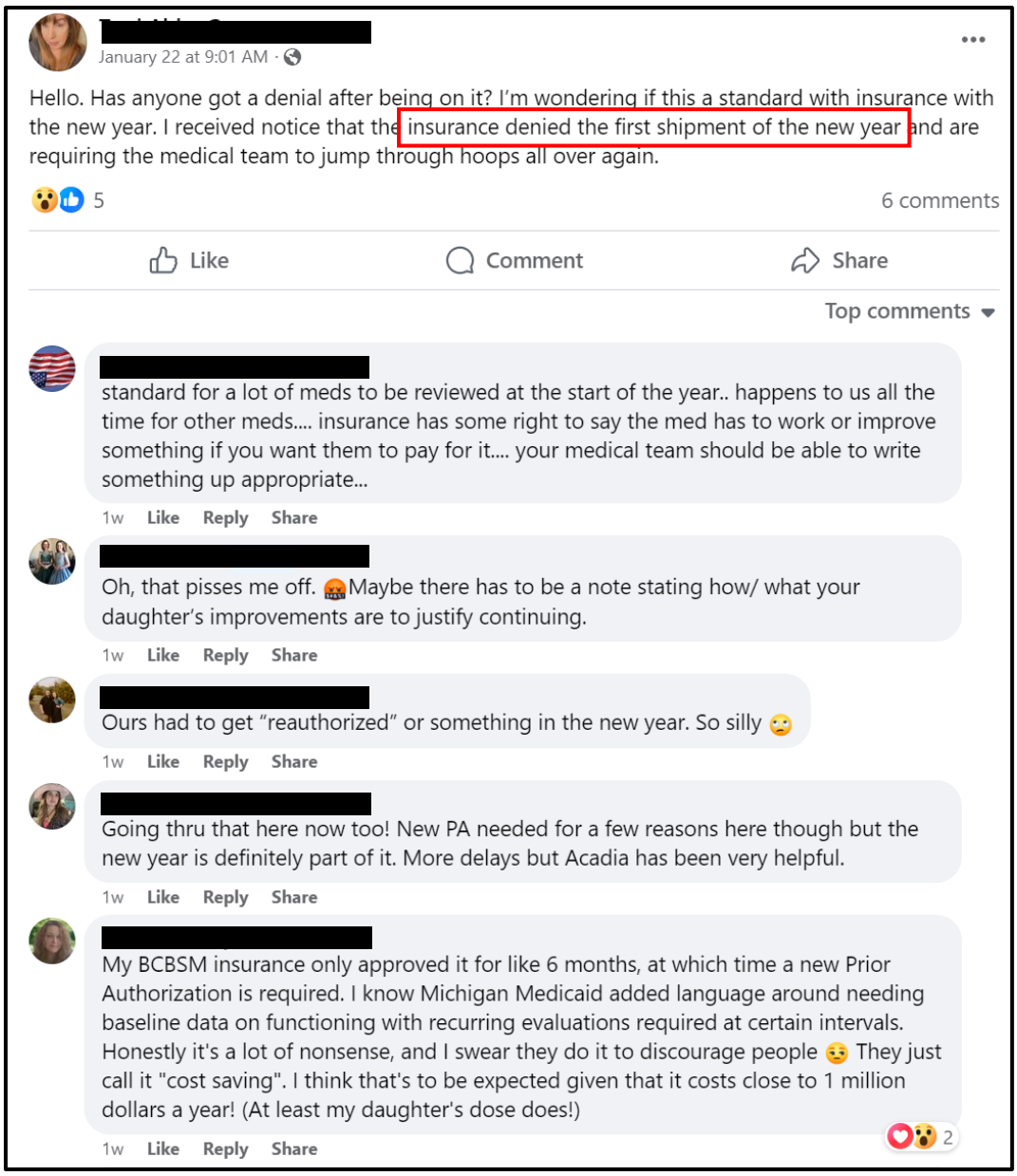
We believe ACADIA now faces a wall of discontinuations as the majority of Daybue patients are not seeing tangible improvements and will thus be unable to meet reauthorization requirements.

In ACADIA's own clinical studies, a mere 24.7% of Daybue patients saw "minimal improvement" (i.e., a CGI-I score of 3), while just 13.0% of patients saw scores of 2 – those who were "much improved." **62.5% of patients saw no**

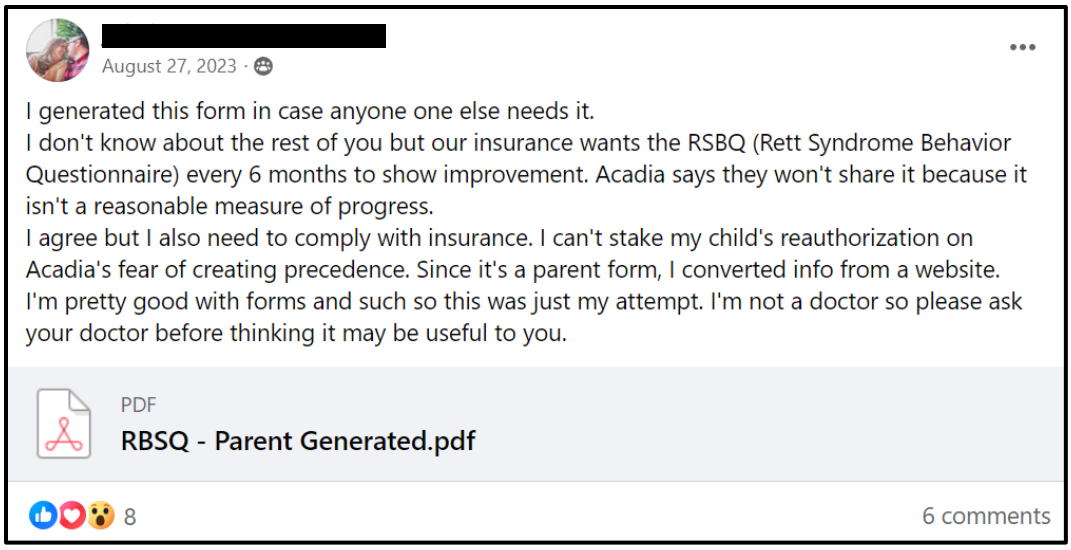
change or were even minimally worse off after Daybue. We think the vast majority of this 62.5% cohort will be forced to discontinue as insurers require proof of efficacy – which does not exist – in order to continue. And indeed, many caregivers are holding out hope despite zero improvements. Per one physician:

> *"If I had to score them, what they're telling me, it's a 4 [on the CGI-I scale]. No improvement. But if the parents find it helpful, we'll continue on it."*

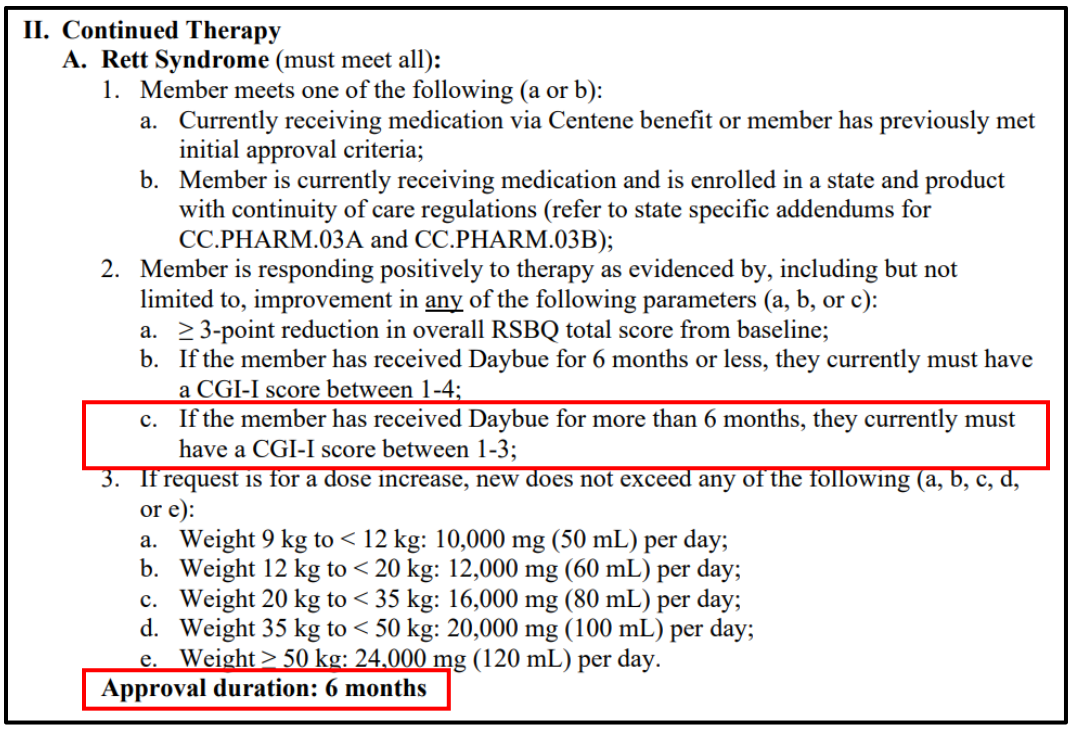
Yet these patients are now facing insurance denials. See concerns from numerous caregivers who are now dealing with problems as they've come up against the 6-month or year-end marks:



One caregiver even provided a form for other caregivers to help with reauthorizations, as they claimed that ACADIA would not help them for fear of setting some sort of precedent around reauthorization requirements.



Per our review of insurance plans, authorizations generally last from 3 to 12 months and requires re-testing and demonstrated improvement on the drug. See for example that numerous insurance plans require patients show improvement via CGI-I scores of 1 to 3 – **implying that the 62.5% of patients who showed no improvement or worsening symptoms after 6 months on Daybue would not be reauthorized[6]:**



II. Continued Therapy

A. Rett Syndrome (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters (a, b, or c):
   a. ≥ 3-point reduction in overall RSBQ total score from baseline;
   b. If the member has received Daybue for 6 months or less, they currently must have a CGI-I score between 1-4;
   c. If the member has received Daybue for more than 6 months, they currently must have a CGI-I score between 1-3;
3. If request is for a dose increase, new does not exceed any of the following (a, b, c, d, or e):
   a. Weight 9 kg to < 12 kg: 10,000 mg (50 mL) per day;
   b. Weight 12 kg to < 20 kg: 12,000 mg (60 mL) per day;
   c. Weight 20 kg to < 35 kg: 16,000 mg (80 mL) per day;
   d. Weight 35 kg to < 50 kg: 20,000 mg (100 mL) per day;
   e. Weight ≥ 50 kg: 24,000 mg (120 mL) per day.

Approval duration: 6 months

Moreover, we think patient denials are likely to be even greater than this 62% pool given many patients are on lower dosages, which provide less efficacy, per ACAD's own trials. Recall that in ACADIA's Phase II study, the Company tested 50 mg/kg (n=15), 100 mg/kg (n=16), and 200 mg/kg (n=27) dosages. While the 200 mg/kg cohort

[6] ACADIA did not provide percentage of patients breakdown that we can cross-reference to the other requirements, that we can tell. As such, we're unable to cross-reference these data with insurance requirements, yet we believe they would likely show the same problem.

formed the basis of the Company's Phase III trial and current label, **both the lower 50 mg/kg and 100 mg/kg cohorts failed miserably on every endpoint, with p values of 0.768 and 0.749, respectively.** As many current Daybue patients are stuck at lower dosages, they ought to find it more difficult to demonstrate the efficacy that insurers are requiring for reauthorization. Per one physician:

> *"It's a very expensive drug ... When I saw the price tag I was like, wow ... For a renewal, they'll [insurers] want to see is there clinical benefit. They want to ask us for some of the same outcome measures that were used in the trials – RSBQ and CGI-I, that the clinician completes... **If they're [patients] not showing any improvement, they're [insurers] not going to approve it. Parents say that it's doing something but then the RSBQ is exactly the same, so it's probably not doing anything ... That's going to become more and more of an issue** ..."*

These comments were echoed by another high-prescribing physician who also indicated that their peers are not even in the habit of conducting CGI-I tests or may not even know how to do so, in which case patients would be forced elsewhere for reauthorizations:

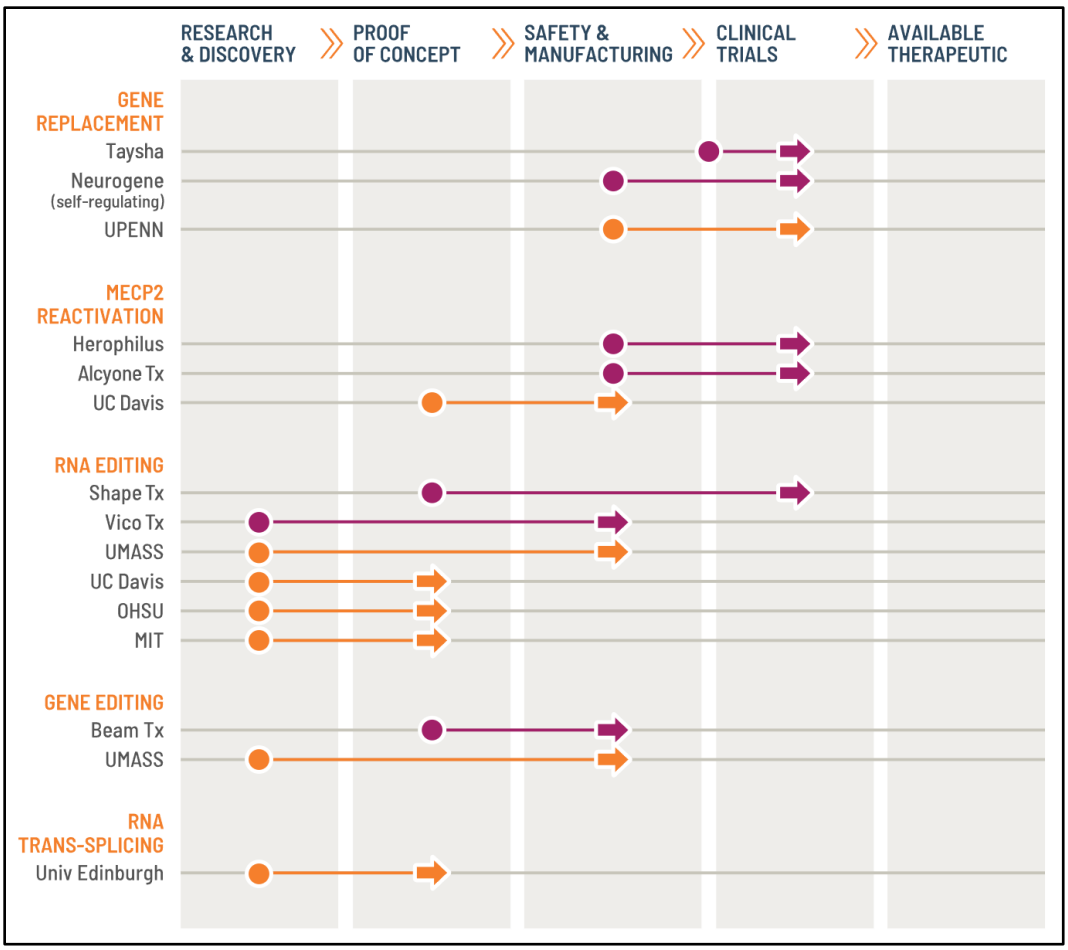
> *"For refills we may be asked to provide some tangible proof that it's actually helping the person, and that could be challenging ... There's just not enough time to do CGI-I's on every patient that I see ... It's going to be very difficult, but if it becomes necessary to do that, **then the providers will just say I'm sorry I can't prescribe this for you**, you need to go to a Rett clinic instead."*

Gene Therapy Provides Hope for Patients, a Harbinger for ACADIA

Fortunately for Rett Syndrome patients, emerging treatment options including gene therapy, MECP2 reactivation, RNA editing, and more are providing a new source of hope in the face of Daybue's many shortcomings. Unfortunately for ACADIA, these trials will present another obstacle to patient growth and retention, as patients must discontinue Daybue in order to participate in new trials. Physicians we spoke with indicated that many of their patients are well aware of the emerging trials and would be inclined to participate.

> Doctor 1: *"Many, many people would come off [discontinue Daybue] in order to be in a gene therapy trial."*
>
> Doctor 2: *"The gene therapy approaches are very compelling ... hopefully we're gonna see more [better safety and efficacy] than what we've seen in any drug trial."*
>
> Doctor 3: *"As some of the gene therapy studies begin enrollment, that [Daybue enrollment] will change ... In order to join the Neurogene trials they'll have to be off Daybue."*

In addition to Neurogene, in December 2023, Taysha Gene Therapies opened enrollment for its REVEAL pediatric gene therapy trial, and dosed its first patient on January 10, 2024. See a visual depiction of the various emerging options from the Rett Syndrome Research Trust:



The Writing Is On the Wall, Insiders are Leaving

ACADIA insiders seem to see the writing on the wall:

- In November 2023, ACAD announced that Head of R&D, Doug Williamson, M.D., would be leaving the Company. Doug had joined ACADIA less than a year earlier, in January 2023.

- In December 2023, ACAD Chief Science Officer, Kathie Bishop, Ph.D., left the Company. Bishop's LinkedIn claims she was "*responsible for all activities for rare disease business unit which included leading successful Phase 3 program and FDA approval for DAYBUE TM (trofinetide) in Rett syndrome*." Bishop even spoke on the Company's 2023 conference calls regarding Daybue's launch. Despite her stature, Bishop's departure was never disclosed by ACADIA, as far as we can tell – ACADIA simply removed her biography from its website (see October 2023 website via Wayback Machine for reference).

- On January 30, 2024, ACAD announced in a cleverly-worded press release that its EVP and General Counsel, Austin Kim, would be departing the Company. Kim had been with ACADIA since 2018.

ACADIA Hinges on Daybue; Its Unraveling Will Have Knock-On Effects

We think Daybue's failure will have significant knock-on effects, as Daybue's growth was meant to provide ACADIA with a new source of cash flows, which we don't believe will ever come to fruition. ACADIA continually claims that its longstanding drug Nuplazid, approved in April 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP), generates over $300 million in annual cash flows. ACADIA never discloses how it calculates these figures, but in either event, ACAD continues to incinerate cash, burning $93 million in cash from operations over the LTM and racking up an accumulated deficit of nearly $2.5 billion. We think investors will become far less lenient of ACAD's cash burn as the Daybue story unravels and Nuplazid's patent expiry approaches in 2030, and thus see significant downside to the shares.