

## Twitter Thread by Sentiv



**Sentiv**

@sentivcapital



**\$ARPO Thread: Raz P2b glaucoma readout Dec 15 to Jan 15, assigning 90% POS, potential 3 to 5x, with (likely) partnership 1H21. Glaucoma dead for Big Pharma unless there's a brand new MOA or pathway being targeted. Here we have both...a new MOA (Tie2) and a new location (SC)**

<https://t.co/zsc2eBVI4e> Tons of great preclinical work on TIE2 MOA showing clear correlation to SC integrity, adult-onset glaucoma, and disease-modifying effects. See mosaic if interested

can you share the preclinical work you describe along with the papers?

— James Brandt (@jmsbrandt) November 20, 2020

What do KOL's think of the new MOA: Special session held at ARVO 2019 to discuss Tie2 for Glaucoma. \$ARPO then completed a closely watched P1b with a topical formulation. Now, a P2b trial in 195 pts enrolled within 3 mos, a month ahead of schedule, in the middle of a pandemic.

SOC is PG (-7 mm Hg IOP) +/- adjunct (-1 to -1.5 mm delta). Best efficacy adjunct is Rocklatan (-1.5), but AE profile: hyperemia (60 vs 15%), pruritus (8 vs 2%) site pain (20 vs 7%) vs PG, + other AE's not seen with PG: 10% conjunctival hemorrhage, 15% verticillata. Almost DOA

But, sells \$80 to \$100M/yr US (same as \$ARPO MC ha!). Every 0.3 mm reduction critical towards delaying vision loss. Rocklatan MOA was projected to make it a \$1B drug, until AE profile (& payor delays) killed launch. \$ARPO thesis: Raz efficacy >= Rocklatan, without AE baggage.

P1 trial: Difficult to draw conclusions from a 7 day trial, but clear dose response curve and nice -1.5 to -2.2 delta with QD/BID dosing in POAG/normotensive pts. 40 mg/ml QD dosing showed 35% pts with -3 delta in POAG pts. AE was stellar, limited to mild conjunctival hyperemia

What can we expect for P2b efficacy? P1 trial was 7 days, P2b is 28 days 40 mg/ml QD & BID dose + PG vs PG alone. If Tie2 is disease modifying (see preclinical studies), we can hope to see better efficacy with longer trials. BID dose & higher baseline IOP also -> higher delta

We actually have a clue from the subQ trial that \$ARPO ran for Raz in normotensive NPDR pts. Increasing separation seen for IOP change. Notice separating curves from first 7 days to first 4 weeks, and also between QD and BID doses. P2b should win on efficacy, high POS.

However, the biggest risk for this trial was always safety since it's a 4% w/w solution being tested with BID dosing now over 28 days instead of 7. <https://t.co/kxvD8AMTEI>. While we can be convinced of efficacy, how do we accommodate for safety?

No, stinging isn't the issue, it is a 4% solution given continuously that broadly inhibits phosphatases. This will have cumulative effects.

The hyperemia is at 18% with 7 days of follow up

Rhopressa has only 50-60% of their hyperemia events show up prior to 24 days (~20%)

— Drugs (@drug\_smolecules) November 30, 2020

This is where the 3Q earnings call gave us a huge clue. This trial recruited ~195 pts, of which 194 patients have completed the study! Even if they recruited a couple more than 195, that gives us a drop-out rate of 0.5 to 1%. If pts didn't drop out, AE profile likely to be clean.

Here's some Rocklatan drop-out data from their pivotal trial that [@biosleuth](#) pointed out. A 5% drop out at week 2, and a 10% dropout by week 6 for Rocklatan. Based on these data, very high POS that safety will be clean for Raz in the \$ARPO P2 trial

Trial completed Nov 15 (LPI Sep 15 + 4 wk wash-out + 4 wk trial). Data out Dec 15 – Jan 15. Based on prior company comms: If -ve, expect a short PR early. If +ve, perhaps a top-line PR in Dec with data in Jan leading into JPM. 90% it's the latter:)

Interesting question 1: <https://t.co/cOba1Wdcdd> A very pertinent issue: Raz is not yet a FDC like Rocklatan. But Aerie initially developed the ROCK inhibitor by itself (Rhopressa) and then co-formulated. \$ARPO is currently working on a FDC, and yes, an FDC is a must for P3/market

So I think all \$arpo investors should understand that \$aeri data being comped is in a fixed dose combination. Showing a 1.4mmHg reduction as a second drop is not even close to commercially viable.

— Patrick Sikorski (@pharmacreep) December 1, 2020

Interesting question 2: <https://t.co/qNiJ6bTDyq> Glaucoma market likely moving towards a 6 mo PG depot. It would be easy for a big pharma player to make a Raz+PG depot if needed. But these are all nice problems to have once you have a winning profile, which Raz will likely have.

Thanks Sentiv!

I'm curious about your long-term big picture view of glaucoma. Especially curious about impact of effective \$OCUL style 1-2/year injections on the need for adjunctive therapies. How much unmet need is there once compliance is

perfected?

— brendan (@brendan\_49) November 30, 2020

A clean safety profile and -1.8 mean delta (with follow thru on -3 mm %). That's my bar for this trial to be a big win (3 to 5x). If it hits -1.6 with clean safety, that's still a win from a valuation standpoint (2-3x), and will still be attractive for partnership. The End.