Biopharma

AAVL Data: Broader Implications For The GT Field

CONCLUSION

After the close, AAVL released topline results of the Phase 2a study of AVA-101 in wet-AMD, a highly anticipated event in the gene therapy space. While it is encouraging to see evidence of biological activity, we believe there are several important takeaways for the field which relate to ophthalmology gene therapy players like AGTC and ONCE but also extending beyond to QURE, BLUE, BMRN, MDGN, etc and even to CAR-T and gene editor companies like BLCM and CLLS. Here we discuss our thoughts on the implications for the field.

- **Gene therapy works, but not always for everyone:** Overall, we are encouraged by the results of the AAVL trial with a meaningful injection frequency reduction in a group of patients as well as improvements in BCVA in what is a difficult to treat patient population. This underscores the importance of understanding the disease and the treatment goal, and not simply assuming gene therapy is a cure for all patients. Just like any new treatment, there will be responders and non-responders, particularly in heterogeneous diseases. All the approaches are unique; there will be successes, failures, and everything in between (like this one). As the field advances and learns more, programs can be increasingly optimized to provide maximal efficacy in a targeted fashion and also be revised to address patients not deriving benefit from the first approach.

- **The importance of managing expectations**: Particularly in cases where the trial designs are nuanced like AAVL's P2a, it is important to focus investors on the appropriate endpoints and manage expectations, recognizing that gene therapy is not going to cure everyone. Although one of the exciting features about gene therapy is the promise of early signs of efficacy in small patient datasets, the flipside to this is the proclivity to over interpret these early signals. Unfortunately, it looks like AAVL was caught in this trap. Sometimes an N-of-one result represents a clear and dramatic breakthrough (like BLUE's LentiGlobin for sickle cell disease), whereas in other settings, larger datasets need to be generated to more clearly glean efficacy signals like with AAVL's AVA-101.

- **Can't stress iteration enough:** The need to continually evolve and improve vectors, promotors, etc. has been a consistent mantra of ours as the field continues to move programs forward. This is a key reason why we believe the CLDN Mydicar trial failed, and a key reason we remain enthusiastic for AAVL's earlier pipeline programs, as these utilize new vectors and new promoters designed to achieve specific expression patterns and fit a specific product profile. The ability to continually improve and evolve will also begin to differentiate companies as well as temper the impact of binary events. Furthermore, having multiple players in the gene therapy field even with overlapping initial indications will accelerate the learning and iteration process and hopefully benefit all players in the field over time, even the ones whose initial efforts prove less impactful than others.

Joshua E. Schimmer, MD
Sr Research Analyst, Piper Jaffray & Co.
212 284-9322, joshua.e.schimmer@pjc.com

Steven P. Breazzano, Ph.D.
Research Analyst, Piper Jaffray & Co.
212 284-6114, steven.p.breazzano@pjc.com

Jerry Yang, Ph.D.
Research Analyst, Piper Jaffray & Co.
212 284-9331, jerry.n.yang@pjc.com

Related Companies:	Share Price:
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BIIB	388.28
BLCM	24.99
BLUE	179.30
BMRN	121.93
CLLS	38.50
MDGN	7.39
QURE	32.33

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Analyst Certification — Joshua E. Schimmer, MD, Sr Research Analyst
— Steven P. Breazzano, Ph.D., Research Analyst
— Jerry Yang, Ph.D., Research Analyst

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