OUTCOME CAPITAL

Ophthalmology Market: Opportunity for Growth Remains

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Introduction

Total economic burden of vision loss and eye disorders surpasses $130 billion in the U.S., a figure expected to rise due to the aging population[1]. We examined recent ophthalmology market dynamics between 2015 and 2018, including industry-sponsored clinical trials, financing events, mergers and acquisition transactions (M&As) and initial public offerings (IPOs). These dynamics are utilized to assess the overall activity of the sector and interest by venture capitalists, strategic players and the public market.

Substantial Clinical Development Focused on Leading Causes of Blindness

Assessment of active clinical trials is key in evaluating clinical progress and segment maturation. There are currently 442 active or recruiting clinical trials ran by 225 different industry sponsors (Figure 1). It should be noted that diabetic macular edema is a consequence of diabetic retinopathy[2], and therefore has been combined into a single indication. While cataracts and refractive error are highly prevalent, clinical trial activity is relatively limited (Table 1 and Figure 1), likely due to the fact that current therapeutic modalities are satisfactory. Industry is supporting abundant rare disease trials, mimicking the interest in the rare disease sector, which has an expected CAGR of 11.3% from 2018 to 2024 resulting in a $262 billion market size, double the CAGR forecasted for the non-orphan drug market[3]. Rare diseases represent a unique opportunity as several rare, genetic diseases result in blindness and the eye's accessibility makes it an ideal location for gene therapy. Spark's Luxturna, the first gene therapy for an inherited disease, was FDA-approved for inherited retinal disease[4]. Glaucoma, macular degeneration and diabetic retinopathy are among the most heavily invested in and are also among the most prevalent disorders (Table 1). This is due to a lack of adequate treatments coupled with risk of severe vision loss with

Table 1

Most Prevalent Eye Disorders in the U.S.

Sources: BrightFocus Foundation, AAO, National Eye Institute, 2014.

Indication	Number of Americans Afflicted (in Millions)
Refraction Error (Near/Far-Sighted)	34.1 / 14.1
Cataract	24
Age-Related Macular Degeneration (AMD)	11
Diabetic Retinopathy	7.7
Dry Eye	4.9
Conjunctivitis	3
Glaucoma	3

disease progression.

Of note, the majority of clinical trials are dominated by a single intervention type (i.e. biological, drug/device combination, device or drug). For example, cataracts are almost exclusively treated by devices, as the clouded lens is replaced with an intraocular lens. As a consequence, the majority of clinical trials seek to improve this process. Recent elucidation of several molecular pathways has enabled several drugs to enter clinical trials, but trials remain limited[5]. A notable counterexample is glaucoma, where therapeutics account for 59% of therapies compared to 39% for devices (Figure 1). Most patients are generally treated with eye drops until the disease progresses, necessitating surgical

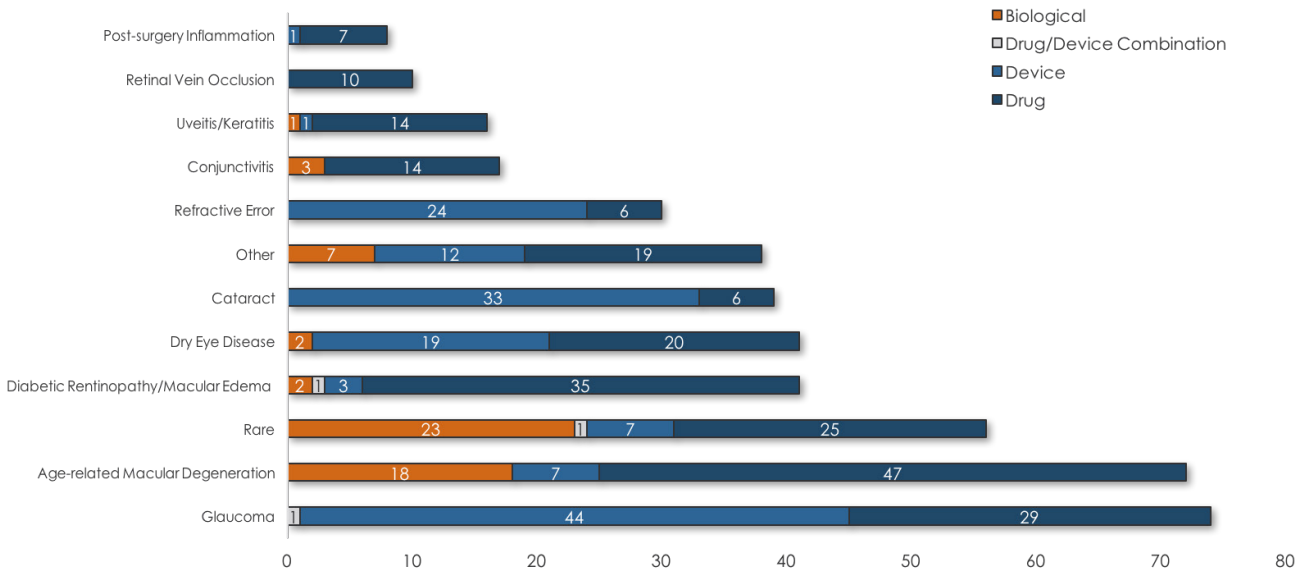

Figure 1

Clinical Trial Activity by Indication

Sources: ClinicalTrials.Gov (data pulled 2/29/2019), all active, recruiting and enrolling interventional industry-sponsored trials, removed oncology indications.

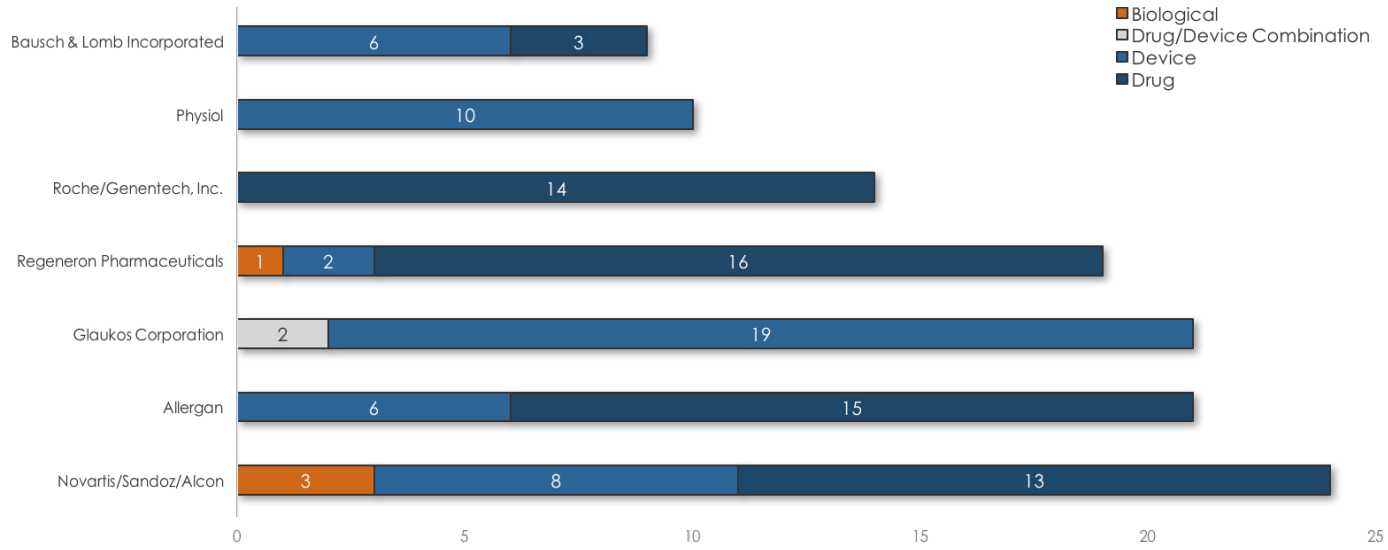

Figure 2

Novartis & Subsidaries Lead Segment In Sponsored Trials

Sources: ClinicalTrials.Gov (data puled 2/28/2019), all active, recruiting and enrolling interventional industry-sponsored trials, removed oncology indications, some trials are co-sponsored.

options to lower intraocular pressure[6]. Glaucoma is a chronic disease where treatment options are stratified based on disease stage, resulting in a market size of $3 billion by 2023[7].

Glaucoma, macular degeneration and rare diseases present as areas of opportunity for cutting edge technologies, such as regenerative medicine and gene therapy.

The space is seeing sponsorship from industry giants and specialized companies alike, with Novartis and subsidiaries sponsoring 24 trials (Figure 2). A trend in clinical trial sponsorship shows that companies are doubling down on a single intervention type due to the specific expertise necessary to clinically develop a drug versus a device. Opposing this trend are Novartis and Allergan, sponsoring trials across biologics, drugs and devices.

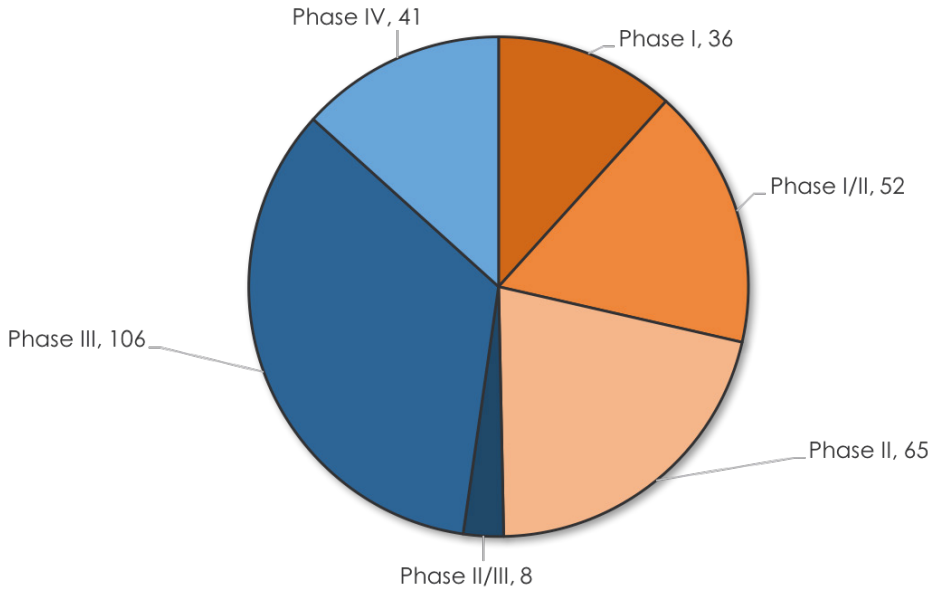

Figure 3

Late-Stage Trials Demonstrate Segment Maturity

Source: ClinicalTrials.Gov (data pulled 2/28/2019), all active, recruiting and enrolling interventional industry-sponsored trials, removed oncology indications.

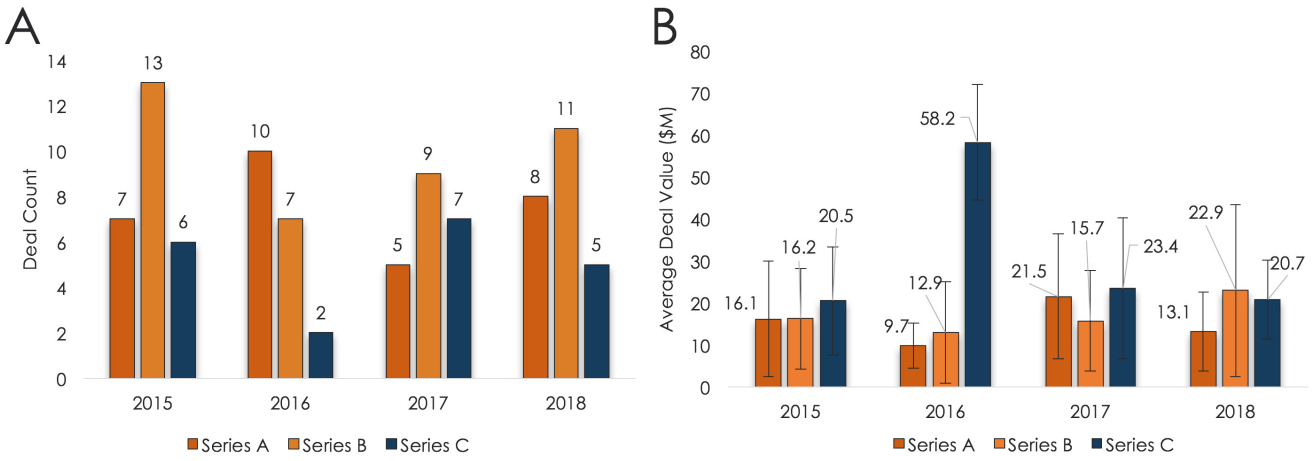

Figure 4

Limited Venture Investment

Source: Pitchbook, removed financings <$5M.

Within the segment, there are 308 active trials that have a phase associated with the trial. Phase of clinical trial breakdown indicate segment maturity with 106 therapies currently in Phase III (Figure 3). A unique dynamic of the ophthalmology segment is the high percentage, 13%, of Phase IV trials. By comparison, there are currently 100 active and enrolling industry-sponsored Phase IV oncology trials representing only 1.6% of the 6,091 trials being currently conducted. Phase IV studies are often required by the FDA to expand on the safety and efficacy (i.e. include patient subsets that were not adequately represented in the other trials or allow for a longer follow-up)[8]. A relevant example is Alcon's CyPass

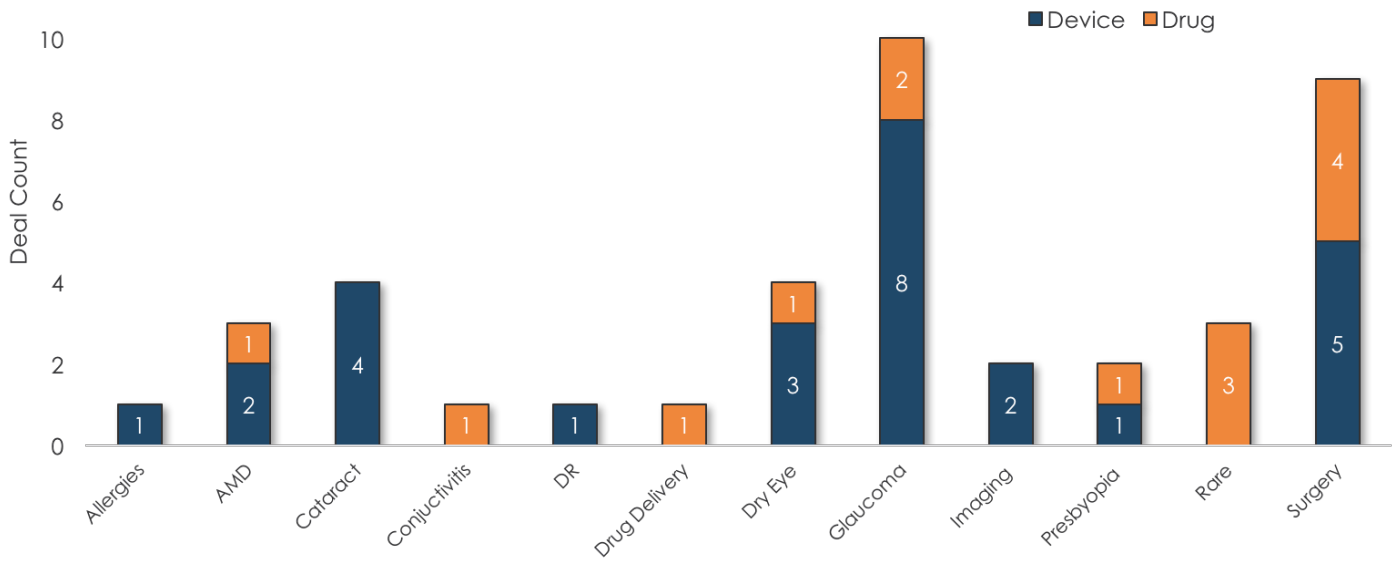

Figure 5

M&A Transactions Dominated by Glaucoma

M&As in 2015-2018; Sources: Pitchbook and press releases; Removed manufacturers & distributors; "Surgery" includes post-op inflammation, surgery adjuvants and tools; AMD: Age-related macular degeneration; DR: Diabetic Retinopathy.

Micro-Stent, which was recently withdrawn from the market due to endothelial cell loss in a Phase IV five year follow-up study[9]. This was following a favorable Phase III study with a two year follow-up, demonstrating the importance of follow-up in this sector and that Phase IV studies are often required.

Limited Venture Capital (VC) Financings

To assess the likelihood of a company gaining venture financing, we analyzed VC funding in this sector. Interestingly, despite intense clinical activity supported by strategic players, there was relatively limited investment by institutional investors (Figure 4A) with a modest 8 new Series A investments and 16 follow-on financing events in 2018. Furthermore, the average deal value was also modest (Figure 4B) in the ophthalmology segment with an average Series B of $17.7 million compared with the average of the life sciences sector as a whole of $35 million (source: Pitchbook). Therefore, coupled with the risk inherent in a competitive space, VCs have not sought ophthalmology investments when compared to the life science sector and development of new therapeutic approaches is largely driven by strategic players.

Early stage companies should seek non-dilutive funding through grants and target ophthalmology-focused venture firms.

M&A Landscape: Drugs and Devices Sought-After

Of 41 mergers and acquisitions transactions, glaucoma was the most sought-after indication (Figure 5). This follows the same trend as clinical trial data showing glaucoma to be an active sub-sector. The second most acquired indication was surgery and post-op drugs and

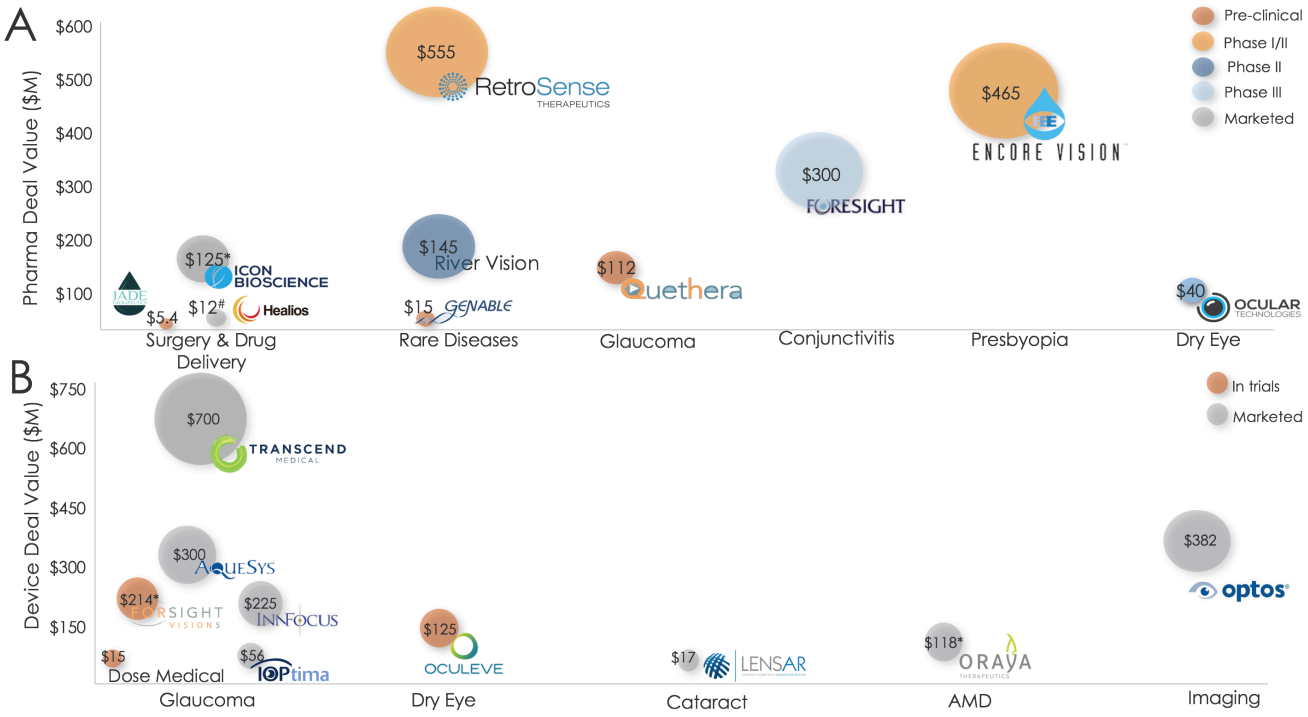

Figure 6

M&A: Large Deal Values for Disease-Modifying Treatments

*M&As in 2015-2018; Sources: Pitchbook, CapIQ, and press releases; Large outlier Abbot Optics removed; *Value only found on CapIQ; #Only acquired ophthalmic surgical adjuvant business.*

devices. Surgery proves to be an lively sub-sector driven by more than 20 million cataract surgeries performed annually[10].

Figure 6 depicts pharma and device M&A activity in various ophthalmology sub-segments and across phases of development. The average transaction value (of deals with disclosed values) in pharmaceutical M&As was $177 million (Figure 6A). In contrast with other life science sectors, no clear relationship between phase of development and acquisition value is demonstrated, suggesting an uncoupling between risk and acquisition price. First-in-class therapeutics see interest from big players. One of the largest pharmaceutical acquisitions in the space was that of Encore Vision by Novartis. Encore Vision is developing a disease-modifying treatment for presbyopia, which would be a first-in-class treatment, demonstrating value derived from novel treatments[11].

Pharma players are heavily invested in the segment (Figure 1). Disease-modifying assets garner large premiums.

Device acquisitions (Figure 6B) demonstrated an average deal value of $215 million, surpassing biotech/pharmaceutical average valuation. In line with glaucoma clinical trial activity, there has been heavy interest in glaucoma devices from large players. Allergan doubled down on glaucoma with their acquisition of a stent of AqueSys and sustained-release drug delivery implant of ForSight Vision5. The largest deal was Alcon's acquisition of Transcend Medical, with a marketed product in Europe and pre-market approval (PMA) filed for U.S. FDA

Table 2

Favorable M&A Exit Multiples

*M&As in 2015-2018; Sources: Pitchbook, CapIQ, and press releases; *Deal value found only on CapIQ; Only shown for those where both deal value and capital invested were disclosed.*

Date	Company	Acquirer	Deal Value ($M)	Capital Invested ($M)	Exit Multiple	Intervention Type	Lead Indication	Most Advanced Stage
30-Jul-2015	Foresight Biotherapeutics	Shire Pharmaceuticals	300	17	17.6	Drug	Conjunctivitis	Phase III
10-Aug-2015	Oculeve	Allergan	125	24.94	5.0	Device	Dry Eye	In Trials
16-Oct-2015	AqueSys	Allergan	300	111.2	2.7	Device	Glaucoma	CE Mark, Approved in Turkey, Canada & Switzerland, In U.S.
17-Dec-2015	LENSAR	Alphaeon	17.00	191.07	0.1	Device	Cataract	Marketed
18-FEB-2016	Transcend Medical	Alcon	700	89.76	7.8	Device	Glaucoma	CE-Mark, Filing PMA
07-Mar-2016	Genable Technologies	Spark Therapeutics	15.3	11.37	1.3	Drug	Rare	Pre-Clinical
17-Jun-2016	Oraya Therapeutics	Carl Zeiss Meditec*	117.51	114.45	1.0	Device	AMD	Commercially Available in Germany, UK, Switzerland
19-Aug-2016	InnFocus	Santen Pharmaceuticals	225	50.9	4.4	Device	Glaucoma	CE Mark, Seeking FDA Approval After 3 Year Trial
06-Sep-2016	RetroSense Therapeutics	Allergan	555.00	13.92	39.9	Drug	Rare	Phase I/II
23-Sep-2016	ForSight VISION5	Allergan*	214	50.1	4.3	Device	Glaucoma	Phase II Completed
28-Mar-2018	Icon Bioscience	EyePoint Parma.*	125	37.32	3.3	Drug	Surgery	FDA Approved
10-Aug-2018	Quethera	Astellas Pharma	112.01	0.63	177.8	Drug	Glaucoma	Pre-Clinical

approval. Transcend developed a less invasive micro-stent for mild-to-moderate glaucoma treatment backed with a 500-patient clinical trial. These examples highlight that the segment has supported late stage device acquisitions, as 70% of acquisitions had marketed assets prior to acquisition.

Device companies should anticipate longer runway with acquisition of assets near or in market.

Estimated exit multiples (deal value divided by capital invested) were highly variable (Table 2) but most acquisitions provided a return on capital to investors. While devices had a higher average deal value compared to biotech/pharmaceutical assets ($215 vs. $177 million, Table 4), exit multiple was significantly lower for device investors, with a 3.6× multiple compared with 15.5× for biotech/pharma. These results from the higher amount of capital required for device assets to achieve commercialization in order to trigger a liquidity event. It should be noted that these calculations included transactions where both acquisition price and capital invested were disclosed.

The Public Market Supports Ophthalmology Companies

To assess the public market support of ophthalmology companies, we analyzed market capitalization 6 months post-IPO to account for the typical lockout periods (Table 3). Of note, 70% of companies completed their IPO with a Phase III or marketed

Table 3

Healthy Public Market for Ophthalmology

*IPOs in 2015-2018; Sources: Pitchbook and press releases; *at time of IPO; Note: Capital invested was not available for all companies.*

Date	Company	Market Cap 6 Mo Post IPO ($M)	Capital Invested Prior to IPO ($M)	Exit Multiple	Intervention Type	Lead Indication	Most Advanced Stage
29-Jan-2015	Presbia (NAS: LENS)	83	–	–	Device	Presbyopia	Marketed in Europe in Pivotal U.S. Clinical Trial
30-Jan-2015	Spark Therapeutics (NAS: ONCE)	1322	132.75	9.96	Drug	Rare Disease	Phase III
12-Feb-2015	Eyegate Pharmaceuticals (NAS: EYEG)	35	61.90	0.57	Drug Delivery Device	Uveitis	In Trials
24-Jun-2015	Glaukos (NYC: GKOS)	834	172.70	4.82	Device	Glaucoma	Marketed in U.S.
02-Jun-2016	Clearside Biomedical (NAS: CLSD)	321	51.32	6.25	Drug Delivery Device	Macular Edema (ME)	Phase III in ME Associated With Uveitis
15-Jun-2016	Redwood Pharma (SAT: REDW)	4	–	–	Drug	Dry Eye	Pre-Clinical
13-Jul-2016	GenSight Biologics (PAR: Sight)	321	77.64	4.13	Drug	Rare Disease	Phase III
27-Mar-2017	Visioneering Technologies (ASX: VTI)	59	–	–	Device	Refractive	Marketed in U.S.
20-Jul-2017	Kala Pharmaceuticals (NAS: KALA)	366	–	–	Drug	Dry Eye & Post-op Inflammation	Phase III For Both Indications
28-Sep-2017	NightstaRx (NAS: NITE)	406	111.85	3.63	Drug	Rare Disease	Phase III-Ready
25-Jan-2018	Eyenovia (NAS: EYEN)	60	–	–	Drug Delivery Device	Glaucoma	Phase II
08-Jun-2018	MeiraGTx (NAS: MGTX)	344	–	–	Drug	Rare Disease	Phase I/II
04-Oct-2018	Kodiak Sciences (NAS: KOD)	372*	93	4	Drug	AMD	Phase II

Table 4

Liquidity Valuations

Note: Large outlier Abbott & return multiple Quethera removed.

Item	Device	Drug
Average M&A Deal Value	$215 Million	$177 Million
Average IPO Market Cap @ 6 Months	$232 Million	$448 Million
Average M&A Exit Multiple	3.6	15.5
Average IPO Exit Multiple	3.9	5.4

asset. Interestingly, four companies were developing gene therapies. This includes Spark Therapeutics, which had a market capitalization of $1.3 billion 6 months post-IPO, demonstrating investor appetite for gene therapies. Other companies developing gene therapies include GenSight Biologics, NightstaRx, and MeiraGTx.

Device companies demonstrated an average market capitalization 6 months post-IPO of $232 million compared to $448 million for biotech/pharmaceutical companies. Limited data was available to estimate exit multiples (Table 3). The majority of companies demonstrated healthy public exit multiples, with a multiple of 5.4 for biotech/pharmaceutical companies and 3.9 for device companies (Table 4).

The public market supports both device and pharma companies with innovative, first-in-class therapies. However, for pharma companies, M&A provides superior exit multiples.

Summary

The ophthalmology sector values innovative approaches for the leading causes of blindness. Both big pharma and specialized pharma are heavily investing in the space through clinical trials (Figure 1 and 2). However, additional oversight is necessary through the requirement of Phase IV trials will prove to be a barrier to small companies hoping to commercialize (Figure 3), especially given the limited VC financings going into the space (Figure 4). Modest M&A activity was focused on glaucoma treatments and general surgical tools and drugs for post-op inflammation (Figure 5). However, large deal values across both drugs and devices were represented in companies that had developed disease-modifying therapies (i.e. Encore and Transcend, Figure 6). The public market supported ophthalmology companies, especially those developing gene therapies (Table 3). Healthy exit multiples are supported through potential for large exits (Table 4).

The public market supports both device and pharma companies with innovative, first-in-class therapies. However, for pharma companies, M&A provides superior exit multiples.

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About the Author

Dr. Ben-Joseph is a Managing Director at Outcome Capital and co-lead of its life sciences practice. He brings a unique combination of executive, entrepreneurial, scientific and transactional experience to client companies. He is passionate about guiding cutting-edge life science companies through disciplined market-driven decisions toward strategic value enhancement and a path to liquidity.

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About Outcome Capital

Outcome Capital is a specialized life science and technology investment bank with a global reach, providing middle market companies with a value-added approach to mergers and acquisitions, corporate finance and advisory services. The firm uses its proven 'strategy-led execution' approach to value enhancement by assisting boards and management teams in navigating both the financial and strategic markets and in implementing the best path for success. Outcome Capital's strength stems from its unique ability to draw on its wide range of operational, strategic and investment experience, its expertise across the life science value chain, and its broad industry relationships.

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