Financial ecosystem of pharmaceutical R&D

Annex A

September 2021

SiRM. Strategies in Regulated Markets

L.E.K.

Annex A exists out of 6 sections, divided into multiple building blocks

1. Introduction	2. R&D Execution	3. R&D Funding	4. Investment rationale	5. Drug developer corporate finance	6. Case studies
R&D Mapping	Analysis of ongoing development programs	Quantification of R&D	Methods of valuation	Accounting principles	
Initial stakeholder characterisation	Development routes	Venture capital investment	eNPV modelling	Dividend payments	
		Financial instruments analysis	ROI and quantification of loss	Share buy-backs	
		Transaction timelines	Summary of R&D decision making		
		Revenue potential analysis	Financial investor portfolio strategy		
		Preliminary analysis ROI			

Please click on the text in each block for quick access to this part of the annex.

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Methodology and glossary

L.E.K. has conducted 25 interviews with industry experts in U.S. and Europe

Stakeholder group	Subgroup	Interviewed experts	Interviews conducted		
			U.S.	Europe	Total
Financial investors	Standalone venture capital	• Partner, U.S. standalone venture capital firm • Partner, European standalone venture capital firm • Managing director, U.S. venture capital fund • Former senior management, UK venture capital fund	2	2	**11**
	Corporate venture capital	• Former Venture Advisor, multinational corporate venture capital fund • Former Director, U.S. corporate venture capital • Former managing director, multinational biopharma venture capital fund	3		
	Big pharma business development	• Former Director of Business Development, multinational biopharma • Director of Business Development (Oncology), multinational biopharma	2		
	Public research funders / not-for-profits	• Board member, National Cancer Advisory Board • Director of clinical operations, U.S. governmental research entity	2		
Executors	Academic institutions	• C-suite executive, top UK university technology transfer office • Executive director, top U.S. university technology transfer office	1	1	**9**
	Small to medium biopharma	• VP Innovation and Strategy, emerging biopharma • Adviser, EU small / medium biopharma • CEO and founder, U.S. small / medium biopharma	2	1	
	Big pharma	• Senior Director, Global R&D, multinational biopharma • Associate Director R&D Planning and Consolidation, multinational biopharma • Former director of business development, multinational biopharma • Former head of external innovation, multinational biopharma	2	2	
Accounting experts	Deloitte report author	• Former Senior Consultant, Deloitte	1		**3**
	Big pharma corporate finance	• Former R&D Finance Leader, multinational biopharma	1		
	Other accounting expert	• Former Partner (Audit and Assurance, Life Sciences), big four accounting firm	1		
Case studies	Kalydeco	• Former VP, Vertex Pharma	2		**2**
	Zolgensma	• Former VP, AveXis			

L.E.K. also conducted extensive secondary research to provide a fact base for this project (1/2)

Summary of secondary sources – Section 1, 2 & 3

R&D mapping
- Abrantes-Metz et al. (2004)
- Adams and Brantner (2006)
- Adams and Brantner (2010)
- Biomedtracker (2016)
- Department of Human and Health Services (2014)
- DiMasi and Grabowski (2007)
- DiMasi et al. (2003)
- DiMasi et al. (2016)
- Hays et al. (2014)
- Jayasundara et al. (2019)
- Martin et al. (2017)
- Paul et al. (2010)
- Wong et al. (2019)
- Wouters et al. (2018)

Initial stakeholder characterisation
- Bay Bridge Bio
- Company website
- Cytiva
- Drug, Chemical and Associated Technologies Association (DCAT)
- Ernst & Young
- Fierce Biotech
- Holgersson and Aaboen (2019)
- Journal of Clinical Investigation
- Schumacher et al. (2013)
- Trade press
- U.C. Davis

Analysis of ongoing development programs
- Citeline
- Cortellis
- Eikon
- Orbis

Development routes
- Company press release
- Deloitte
- Evaluate Pharma
- Godfrey et al 2020
- Life Science Nation
- Nature
- Pharmaprojects
- Science Translational Medicine
- X-Mol

Quantification of R&D
- Eikon
- Evaluate Pharma
- HealthResearchFunders.org
- Organisation for Economic Cooperation and Development (OECD)

Venture capital investment
- Cortellis
- Eikon

Financial instruments analysis
- Cortellis

Transaction timelines
- Bay Bridge Bio
- Bio Industry Analysis
- Cortellis
- Deloitte
- Evaluate
- Life Science Nation

Revenue potential analysis
- Datamonitor
- Eikon
- OECD

Preliminary analysis on ROI
- Deloitte
- Ledley et al 2020
- Pitchbook

L.E.K. also conducted extensive secondary research to provide a fact base for this project (2/2)

Summary of secondary sources – Section 4, 5 & 6

Methods of valuation
- Bay Bridge Bio
- EvaluatePharma
- Harvard Business Review
- Investopedia

eNPV modelling
- Abrantes-Metz, Adams and Metz (2004)
- BioMedTracker (2016)
- FDA
- Jayasundara et al., (2019)
- Miller et al., (2020)
- Office of Orphan Products and Development
- Paul et al., (2010)

ROI and quantification of loss + Summary of R&D decision making
- Abrantes-Metz, Adams and Metz (2004)
- BioMedTracker (2016)
- Jayasundara et al., (2019)
- Paul et al., (2010)

Financial investor portfolio strategy
- Clincialtrials.gov
- Company annual reports
- Press releases
- Pitchbook

Drug developer corporate finance
- Clinicaltrials.gov
- Company annual reports
- Eikon
- EvaluatePharma
- Grant Thornton
- KPMG
- Ledley et al, (2020)
- Orbis
- PwC

Case studies
- Alexander (2016)
- Biomedtracker
- Company press release
- Cortellis
- Cystic Fibrosis Foundation
- EMA
- FDA
- Pharmaprojects

Glossary of terms (1/3)

Terminology	Definition
PoS	Probability of success for a therapeutic to launch
Target identification	Identifying a biological target that is potentially 'druggable' to influence a disease state
Target validation	Process of demonstrating the functional role of the identified target in the disease phenotype
Target-to-hit identification	The identification of a selection of potential compounds that potentially modulate that pathway
Hit-to-lead	The evaluation and validation of desirable compounds to identify promising lead compounds
Lead optimisation	The optimisation of lead compounds involving artificial synthesis of new analogues with optimal pharmacokinetics
Preclinical development	Trials with in vitro and in vivo models for which dosing (pharmacokinetics) and drug safety (toxicology) data are collected
IND	Investigational New Drug, where a company obtains permission for human clinical trials and transportation of experimental therapies
NDA	New Drug Application, the process in the U.S. through which drug sponsors formally propose the FDA to approve a new pharmaceutical
BLA	Biologics License Application, a request for permission to introduce, a biologic product
POC	Proof of concept – generally refers to human proof of concept demonstrating potential benefit in humans
Seed round	Initial round of financing done by companies looking to set up a business
Series A	First significant round of venture capital financing done by companies with preliminary data and business model
Series B and C	Second and third round of venture capital financing for initial business development and up-scaling

Glossary of terms (2/3)

Terminology	Definition
IPO	Initial Public Offering, offering of company shares sold to institutional and retail investors on the stock exchange
FOPO	Follow On Public Offering, Issuance of shares by a public companies whose shares are already listed to an exchange
ROI	Return on investment, ratio between net income and investment
NPV	Net present value, investment returns expressed as amount of capital at present time
IRR	Internal rate of return, rate of return of a potential investment calculated excluding external factors
BD	Business development, the business function in biopharma that manage the development of assets and portfolios
NME	New molecular entity, drugs that are compounds with no active ingredients previously approved by the FDA
Biologics	Drugs that are biological products produced from living organisms
Orphan designation	A status assigned to a medicine intended for use against a rare condition (e.g., EMA defines as EU prevalence < 5 in 10,000)
Breakthrough therapy designation	Status assigned for a drug that treats a serious / life-threatening condition and clinical evidence indicates the drug is superior in clinical improvement over available therapies
Milestone payment	Payments from asset owners to license partners / research collaborators when assets reaches certain development / sales milestones
Royalty payment	Payments from asset owners to license partners / research collaborators for sales
CAGR	Compound annual growth rate

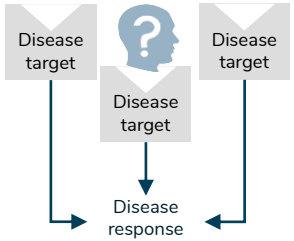
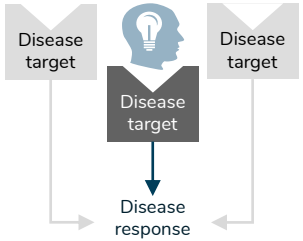
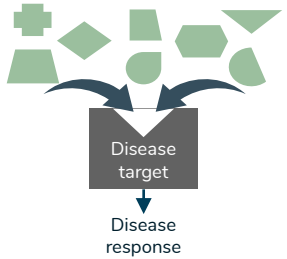
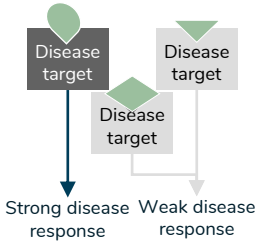
Glossary of terms (3/3)

Terminology	Definition
Time to peak	The amount of time it takes for a drug to reach its peak sales
NOL	Net operating loss - the result when a company's allowable deductions exceed its taxable income within a tax period
Allowable additions to NOL	Proportion of negative EBITDA that can be added to cumulative net operating loss
COGS	Cost of goods sold
SG&A	Selling, general and administrative expenses
Working capital	Working capital is the difference between a company's current assets and its current liabilities
EBITDA	Earnings before interest, taxes, depreciation, and amortization,
Free cash flow	Free cash flow represents the cash a company generates after accounting for cash outflows to support operations and maintain its capital assets
Discount rate	The weighted average cost of capital (WACC) is the discount rate that should be used for discounting future cash flows with a risk that is similar to that of the overall firm
Terminal value	Terminal value is the value of an asset, business, or project beyond the forecasted period when future cash flows can be estimated

1. Introduction

R&D Mapping

Early drug development involves identifying disease targets, then finding and optimising a drug candidate that interacts with that target

Stage	Target selection		Drug discovery		
Process	Target identification	Target validation	Hit identification	Hit-to-lead	Lead optimisation
					
Questions	• What disease or condition is being targeted? • Which parts of the disease system can be targeted to impact the disease state or symptoms?	• Which parts of the disease system are the most directly associated with the disease state or symptoms?	• Which molecules interact with the disease target? • Are certain molecules or molecule classes promiscuous or do they have high fidelity to the desired disease target?	• Of the molecules that interact with the disease target, which have the desired effect on the disease or symptom?	• How can the lead molecule be altered in order to: - strengthen interaction with disease target? - increase selectivity of interaction? - modify duration of interaction?
Output	• Discovery of pathways associated with disease processes	• Confirmation of relevance to disease	• Identification of groups of therapeutic candidates that interact with target	• Narrowing down of identified therapeutic candidates into a short list	• Selected modification of lead candidate in order to improve performance

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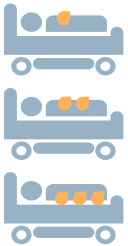
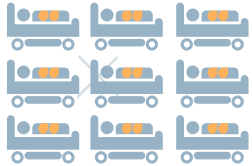
Source: L.E.K. research and analysis

Once a drug candidate has been identified, its safety and efficacy profiles are tested first in animal models and then in human trials

Stage	Preclinical development			Clinical development		
Process	ADME* testing	Toxicity testing	Efficacy testing	Phase I trials	Phase II trials	Phase III trials
						
Questions	• How does this molecule behave in animal models?	• What is the toxicity profile of the molecule?	• How effective is the molecule in combating the disease in animal models?	• What is the safety profile of this molecule in humans?	• What dose is required for efficacy of this molecule in humans?	• Can this efficacy be achieved in a large and diverse population pool?
Output	• Characterisation of how candidate is absorbed, distributed, metabolised and excreted	• Testing that candidate is not toxic in animals	• Testing candidate for efficacy in animal models of disease	• Safety testing (n=10-30)	• Dose selection and efficacy testing (n=25-100)	• Large scale efficacy testing (n=250+)

Some drugs also undergo Phase IV trials (also known as post-marketing surveillance trials) that characterise their long-term safety profiles

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Note: *Absorption, distribution, metabolism, and excretion
Source: L.E.K. research and analysis

A consensus of secondary research characterising R&D costs, duration and PoS to outline a comprehensive R&D map was leveraged

Secondary research summary

Study	Year published	Description	Data used by L.E.K.		
			Cost	Duration	PoS
DiMasi et al.	2003	Analysis of 68 new drugs from 10 global pharmaceutical firms which accounted for 42% of industry R&D expenditure, contains pre-human R&D costs and phase I – III data	■	■	
Abrantes-Metz et al.	2004	Analysis of 3,136 trials (Phase I – III) from PharmaProjects		■	
Adams and Brantner	2006	Replication of DiMasi (2003) by analysis of R&D expenditure of 183 pharma companies, no preclinical development data		■	
DiMasi and Grabowski	2007	Analysis of 522 therapeutic recombinant proteins and monoclonal antibodies, pre-human R&D costs and phase I – III data available	■	■	
Paul et al.	2010	R&D productivity model using industry benchmarking data and academic publications, discusses drug discovery and preclinical R&D costs in detail	■	■	■
Adams and Brantner	2010	Replication of DiMasi (2003) and follow up study of Adams and Brantner (2006)	■	■	
Hay et al.	2014	Analysis of BioMedTracker data set of c.4,450 drugs with c.5,820 phase transitions			■
DHHS*	2014	R&D productivity model using industry benchmarking data and academic publications, no preclinical data	■		
BioMedTracker	2016	Analysis of c.7,500 clinical development programs across c.1,100 companies, contains granular PoS data			■
DiMasi et al.	2016	Analysis of 106 new drugs from 10 global pharmaceutical firms which accounted for 35% of top-50 pharmaceutical sales & R&D expenditure, contains pre-human R&D costs and phase I – III data	■	■	
Martin et al.	2017	Analysis of 726 new drugs from 7 top-20 biopharma companies, does not include preclinical costs	■		
Wong et al.	2019	Analysis of clinical trial data of c.21k compounds from Citeline		■	
Jayasundara et al.	2019	Analysis of 100 non-orphan and 100 orphan drugs, with a modality focus and view on new molecular entities	■	■	

Key data source for L.E.K. consensus view

Data availability: Available and used; Unavailable / unused

Note: *Department of Human and Health Services

We have considered the strengths and limitations of the different secondary research papers when deciding which data to use

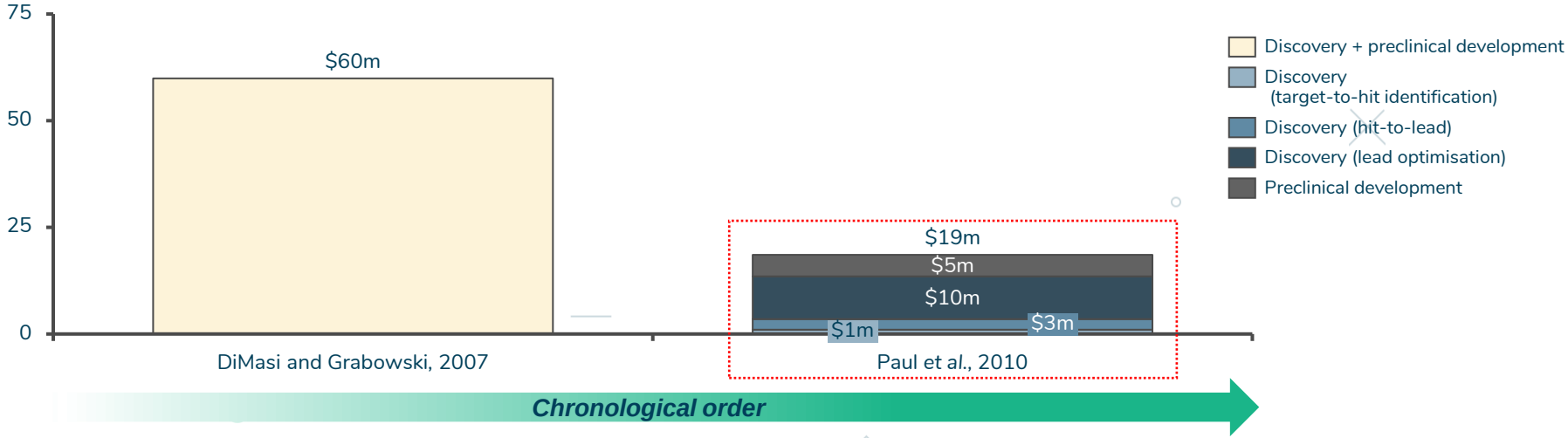
Secondary research summary

Study	Year published	Strengths	Limitations
DiMasi et al.	2003	Uses 10 largest firms and has good data for cost and duration across the majority of R&D spend as a result	Oldest paper used that doesn't take into account drug development from smaller companies, newer estimates by the same author exists
Abrantes-Metz et al.	2004	Significant coverage of 3,136 trials with the most comprehensive data source for R&D trial duration by modality	Data now reasonably old, and predominantly covers duration rather than other key data points
Adams and Brantner	2006	Replication of DiMasi et al. study but with coverage of 183 pharma companies	Newer estimates by the same author exists and the paper does not provide any insight into preclinical development phases
DiMasi and Grabowski	2007	Good sample size with 522 products evaluated to provide comprehensive data on clinical trial cost & duration including preclinical development	Data for recombinant proteins and monoclonal antibodies only which skews data in the direction of the biotech sector
Paul et al.	2010	Most comprehensive for R&D parameters in drug discovery and preclinical development stages with utility for cost, duration and PoS across all stages	Unclear sample size, only captures R&D parameters of NMEs
Adams and Brantner	2010	Replication of DiMasi et al. study and follow up to 2006 study with cost and duration data across 183 pharma companies	Author suggests model might have misallocated expenditure in different stages of development
Hay et al.	2014	Commonly used source for PoS between orphan / non-orphan based on BioMedTracker data set of c.4,450 drugs with c.5,820 phase transitions	Focused only on PoS
DHHS*	2014	Granular per study trial cost estimates by component	Only captures cost for single trials, not successful drugs (lower estimates)
BioMedTracker	2016	Comprehensive data set of c.7,500 clinical development programs with good PoS data by phase and modality	Only captures PoS data
DiMasi et al.	2016	Uses 10 largest firms and has good data for cost and duration across the majority of R&D spend as a result, best source for cost by modality	Smaller sample compared to some other literature and may be biased towards drugs with higher clinical costs given larger company sizes
Martin et al.	2017	Analyses R&D expenditure for reasonable sample of 726 new drugs	Only captures cost for single trials, not successful drugs (lower estimates)
Wong et al.	2019	Paper with highest number of compounds analysed, duration info and good clinical PoS data which L.E.K. cross-checked against sources used	PoS data does not capture information on type of drug, therefore BioMedTracker used for consistency
Jayasundara et al.	2019	Most comprehensive and recent paper for orphan / non-orphan R&D cost and duration comparisons	Lower end estimates for cost of one successful asset, therefore primarily used for comparison rather than average baseline

Note: *Department of Human and Health Services

The cost of drug discovery and preclinical R&D is estimated to be $15-20m for a single successful compound

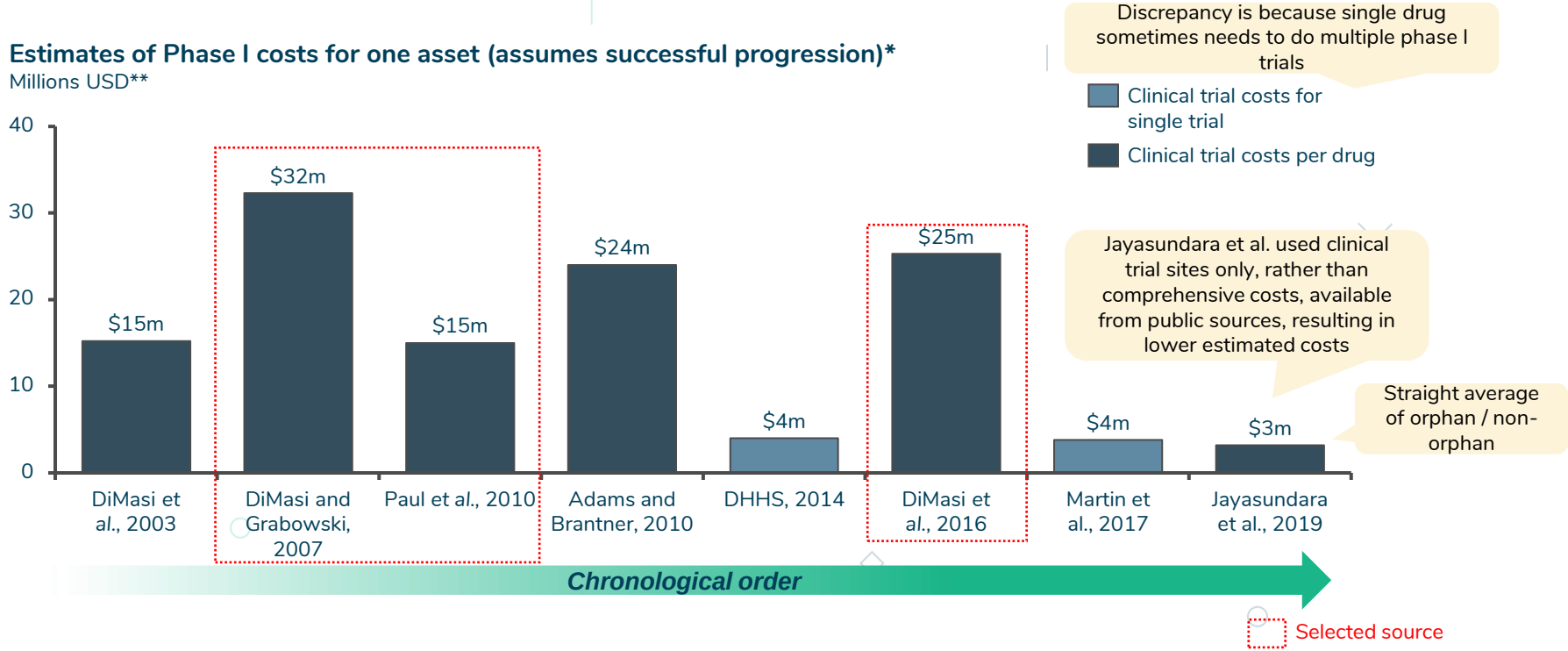
Estimates of drug discovery + preclinical development costs for one asset (assumes successful progression)*
Millions USD**



L.E.K. recommends Paul et al. as the reference for pre-phase I costs, as it includes cost estimates in each of the drug discovery and preclinical stages of development and is in line with L.E.K. market understanding. The DiMasi and Grabowski paper estimates preclinical development cost based on a ratio of preclinical : clinical development cost

Note: * Data in this chart has not been adjusted to account for inflation; DHHS: Department of Human and Health Services; **Based on USD year of primary paper
Source: DiMasi et al., 2003; DiMasi and Grabowski, 2007, Paul et al., 2010; DiMasi et al., 2016; L.E.K. research and analysis

The cost of Phase I R&D is estimated to be $15-30m for a single compound (assuming successful progression)



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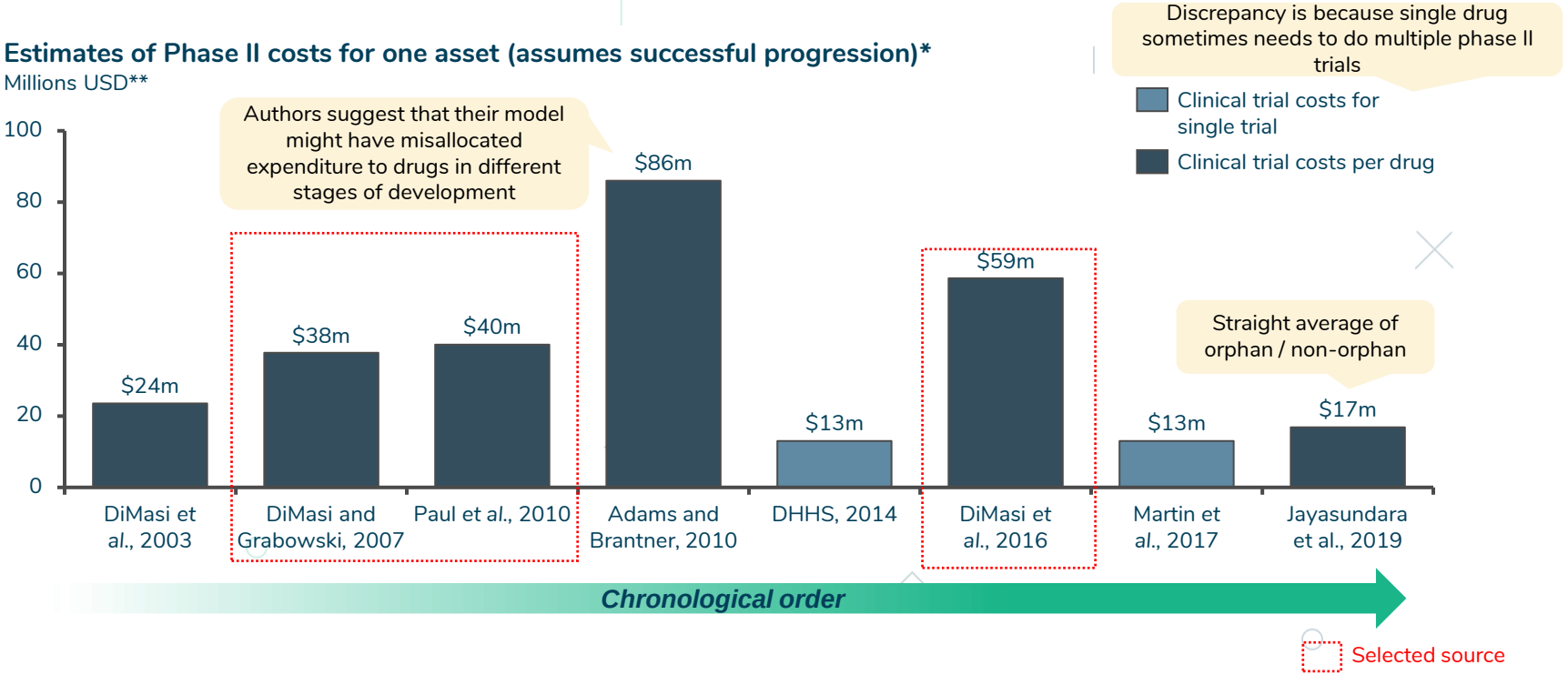
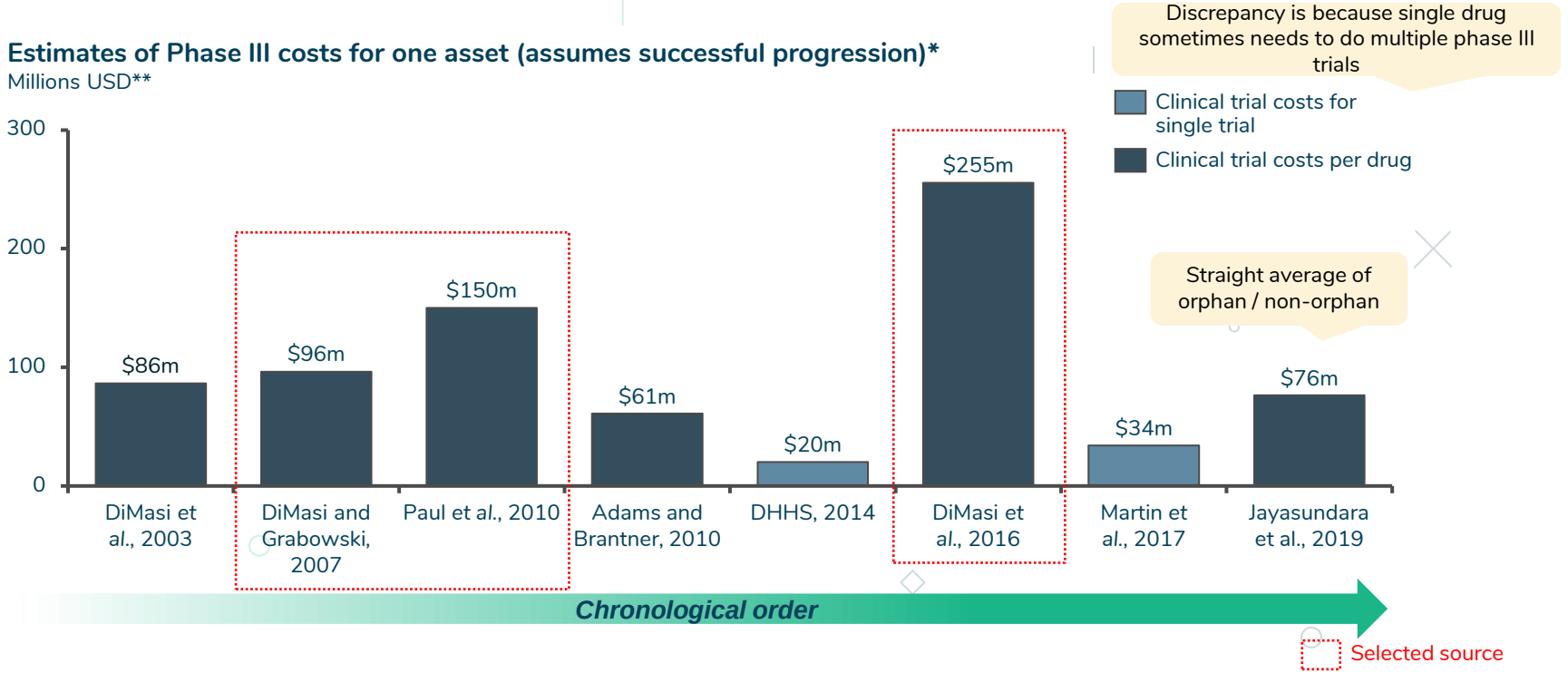
Note: * Data in this chart has not been adjusted to account for inflation; DHHS: Department of Human and Health Services; **Based on USD year of primary paper
Source: Mestre-Ferrandiz et al., 2012; DiMasi et al., 2003; DiMasi and Grabowski, 2007, Paul et al., 2010; DiMasi et al., 2016; Adams and Brantner, 2010; Battelle; Martin et al., 2017; DHHS; L.E.K. research and analysis

The cost of Phase II R&D is estimated to be $40-60m for a single compound (assuming successful progression)



Note: * Data in this chart has not been adjusted to account for inflation; DHHS: Department of Human and Health Services; **Based on USD year of primary paper
Source: Mestre-Ferrandiz et al., 2012; DiMasi et al., 2003; DiMasi and Grabowski, 2007, Paul et al., 2010; DiMasi et al., 2016; Adams and Brantner, 2010; Battelle; Martin et al., 2017; DHHS; L.E.K. research and analysis

The cost of Phase III R&D is estimated to be $100-250m for a single compound (assuming successful progression)



Note: * Data in this chart has not been adjusted to account for inflation; DHHS: Department of Human and Health Services; **Based on USD year of primary paper
Source: Mestre-Ferrandiz et al., 2012; DiMasi et al., 2003; DiMasi and Grabowski, 2007, Paul et al., 2010; DiMasi et al., 2016; Adams and Brantner, 2010; Battelle; Martin et al., 2017; DHHS; L.E.K. research and analysis

The cost to successfully develop an orphan drug is circa two thirds that of a non-orphan; data suggests large molecules* are 20-25% higher

Cost of clinical development split by type of drug / modality

Source	Type of drug	Cost of successful candidate (millions of USD**)			
		Ph.I	Ph.II	Ph.III	**Total**
DiMasi et al., 2016	**Small molecule**	26	50	246	**322**
	Large molecule*	24	92	281	**397**
Jayasundara et al., 2019	**Non-orphan**	3	10	103	**116**
	Orphan	4	24	50	**78**

- The trial costs for orphan drugs are lower than non-orphan drugs due to trial characteristics (e.g., number of subjects enrolled) although trials are generally longer
- Phase I/II trials can be used as pivotal trials for orphan drugs, and some orphan drugs may not be tested in a phase III setting, depending on their approval status which confounds this picture
- There is limited existing literature that directly compares cost of clinical development between different drug modalities
  - data from DiMasi et al. 2016 suggests higher mean cost for large molecules vs. small molecules

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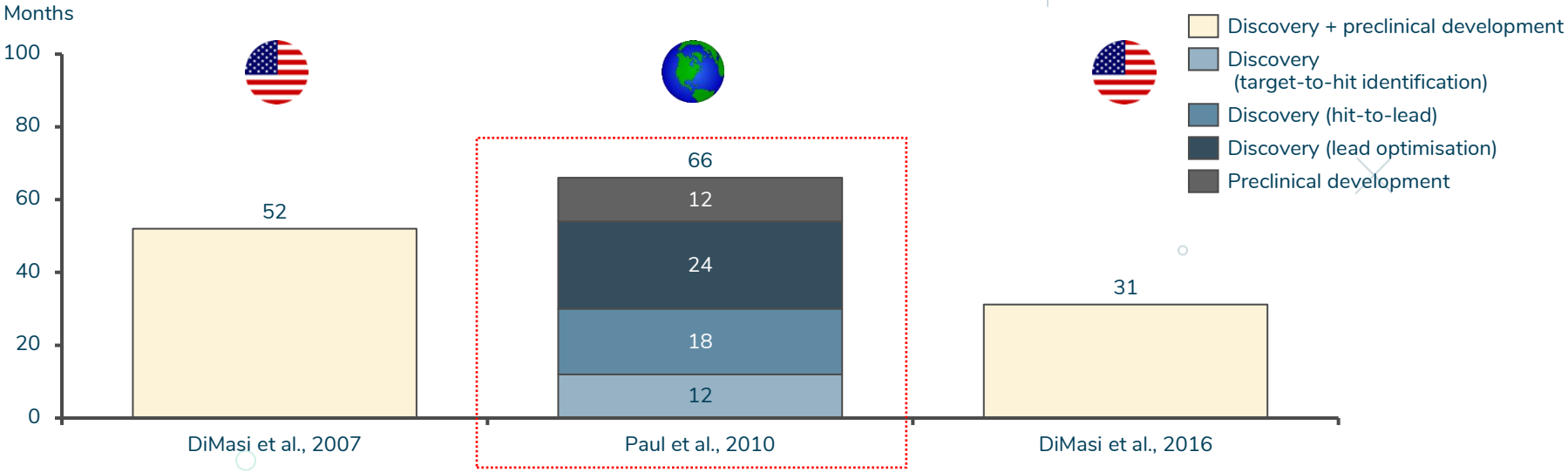
Notes: *Biologic drugs; **Based on USD year of primary paper
Source: Jayasundara et al., 2019; DiMasi et al., 2016; L.E.K. research and analysis

The expected duration for pre-Phase I R&D is between 5-6 years

Estimates of drug discovery + preclinical development duration



L.E.K. recommends Paul et al. as the reference for pre-phase I timelines, as it includes estimates in each of the drug discovery and preclinical stages of development and is in line with L.E.K. market understanding

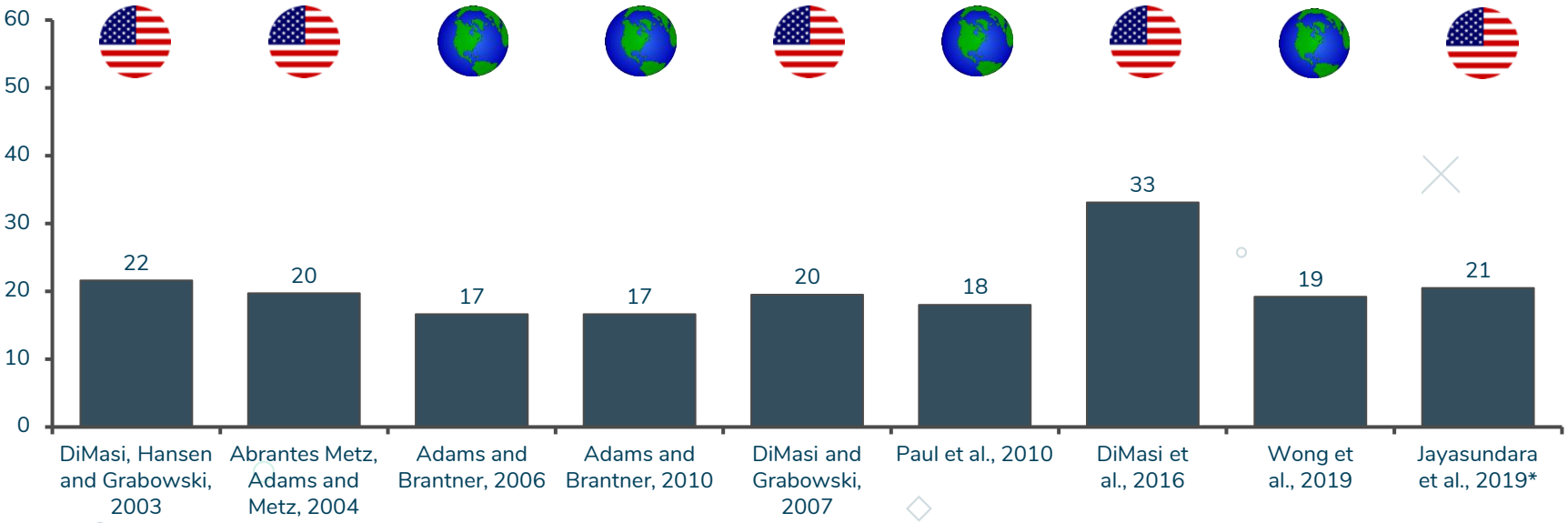
Selected source

Source: DiMasi et al., 2007; Paul et al., 2010; DiMasi et al., 2016; L.E.K. research and analysis

The duration of a Phase I study is expected to be c.1.5 years

Estimates of Phase I study duration

Months



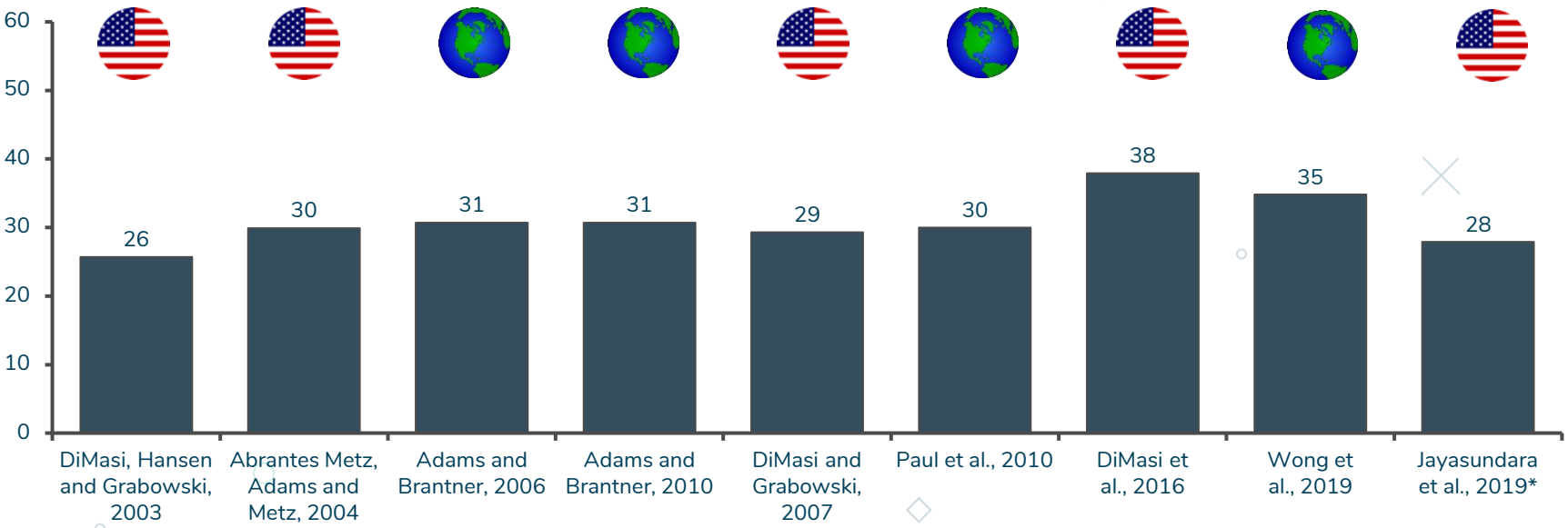
Note: * Represents trial duration estimates of non-orphan drugs only

Source: DiMasi et al., 2003; Abrante-Metz et al., 2005; Adams and Brantner, 2006; DiMasi et al., 2007; Pau et al., 2010; DiMasi et al., 2016; Wong et al., 2019; Jayasundara et al., 2019; L.E.K. research and analysis

The duration of a Phase II study is expected to be 2-3 years

Estimates of Phase II study duration

Months



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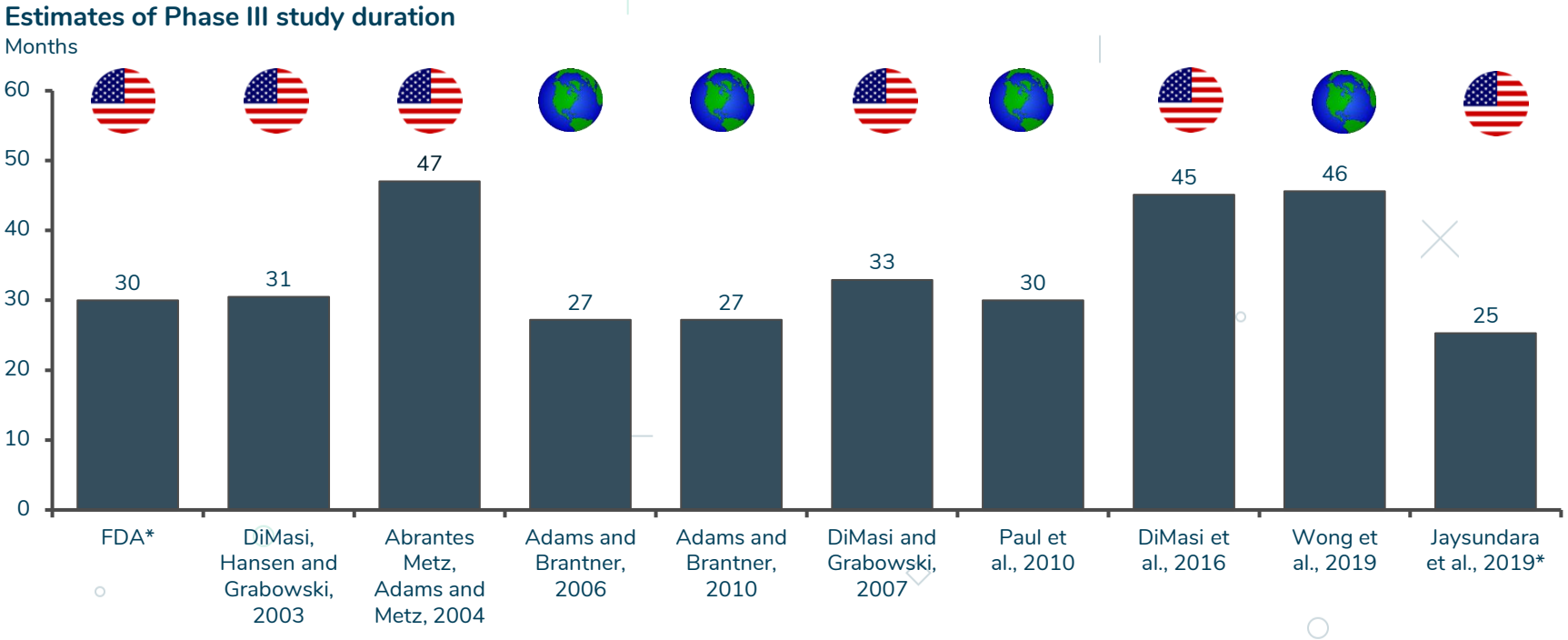
Note: * Represents trial duration estimates of non-orphan drugs only

Source: DiMasi et al., 2003; Abrante-Metz et al., 2005; Adams and Brantner, 2006; DiMasi et al., 2007; Pau et al., 2010; DiMasi et al., 2016; Wong et al., 2019; Jayasundara et al., 2019; L.E.K. research and analysis

The duration of a Phase III study is expected to be c.3 years



Note: * Represents trial duration estimates of non-orphan drugs only
Source: FDA; DiMasi et al., 2003; Abrante-Metz et al., 2005; Adams and Brantner, 2006; DiMasi et al., 2007; Pau et al., 2010; DiMasi et al., 2016; Wong et al., 2019; Jaysundara et al., 2019; L.E.K. research and analysis

Orphan drugs take nearly twice as long to develop vs. non-orphan drugs; biologics and small molecules have similar durations

Duration of clinical development split by type of drug / modality

Source	Type of drug	Duration (months)			
		Ph.I	Ph.II	Ph.III	**Total**
Abrantes-Metz, Adams and Metz, 2004	**Biologics**	18	32	46	**96**
	Small molecules	20	29	48	**97**
	Natural products	22	19	46	**87**
Jayasundara et al., 2019	**Non-orphan**	21	28	25	**74**
	Orphan	39	48	50	**137**

- The trial timelines for orphan drugs are higher than non-orphan drugs due to lower disease prevalence / incidence
  - lack of data on natural disease progression
  - recruitment challenges due to geographic disperson of eligible participants
  - lack of community medical expertise to conduct trials
- However, as mentioned, favourable clinical trial dynamics may mean that orphan drugs do not need to undergo a separate Phase 2 and 3 trial and may be on accelerated access pathways, given patient unmet need
- There is limited existing literature that directly compares duration of clinical development between drug modalities
  - data from Abrantez-Metz, Adams, and Metz, 2004 suggests similar development times for biologic and small molecule products

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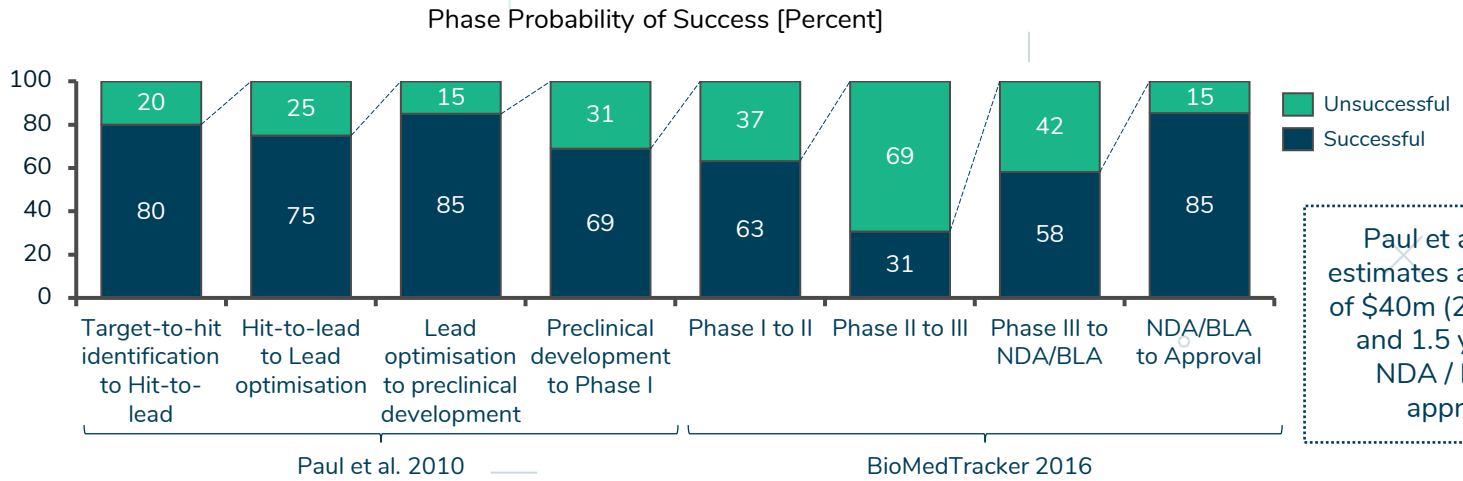
L.E.K.

Source: Jayasundara et al., 2019; Abrantes- Metz, Adams and Metz, 2004; L.E.K. research and analysis

From target selection to successful approval the cumulative probability of success (PoS) is 3%, with the lowest PoS between phase II and III



Paul et al. 2010 estimates an average of $40m (2008 USD) and 1.5 years for NDA / BLA to approval

Phase to launch PoS	Target to hit identification	Hit-to-lead	Lead optimisation	Preclinical development	Phase I	Phase II	Phase III	Approval
Cumulative PoS	3%	4%	6%	7%	10%	15%	49%	85%

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Source: Paul et al., 2010; BioMedTracker Clinical Development Success Rates report (2016); L.E.K. research and analysis

Orphan drugs are c.3 times more likely to be approved than the average; across modalities, NMEs have the lowest Po

Data by drug modality and type only available from Ph I onwards. Drug discovery and preclinical development estimate showed previously

PoS of clinical development split by type of drug and modality

Source	Type of drug	PoS				
		Phase I - II	Phase II - III	Phase III – NDA/BLA	NDA/BLA to Approval	**Overall (Phase I - approval)**
BioMedTracker (2016)	**NME (mostly small molecules)**	61%	27%	49%	78%	**6%**
	Biologic	66%	34%	57%	88%	**12%**
	Non-NME	70%	48%	74%	90%	**23%**
	Vaccine	66%	33%	74%	100%	**16%**
Hay et al., 2014 (source of Jayasundara et al*)	**All indications**	65%	32%	60%	83%	**10%**
	Orphan	87%	70%	67%	81%	**33%**

- BioMedTracker analysis reveals NMEs to have the lowest PoS (likely as less specifically targeted), followed by biologics; non-NMEs have higher PoS rates as a consequence of proof of concept from previous trial successes of the initial NME products
- Hay et al. (2014) shows that orphan drugs are more likely to be approved due to higher rates of Phase I and II success, likely due to the high unmet need in these conditions and the favourable clinical trial / approval dynamics that result from orphan designation
- Drugs can receive orphan status at all stages of development: preclinical development (9%), phase I (22%), phase II (45%), phase 3 (16%) and approval (2%). This introduces a positive bias as some drugs that fail in early stages may not yet be classified as orphan at the point of failure

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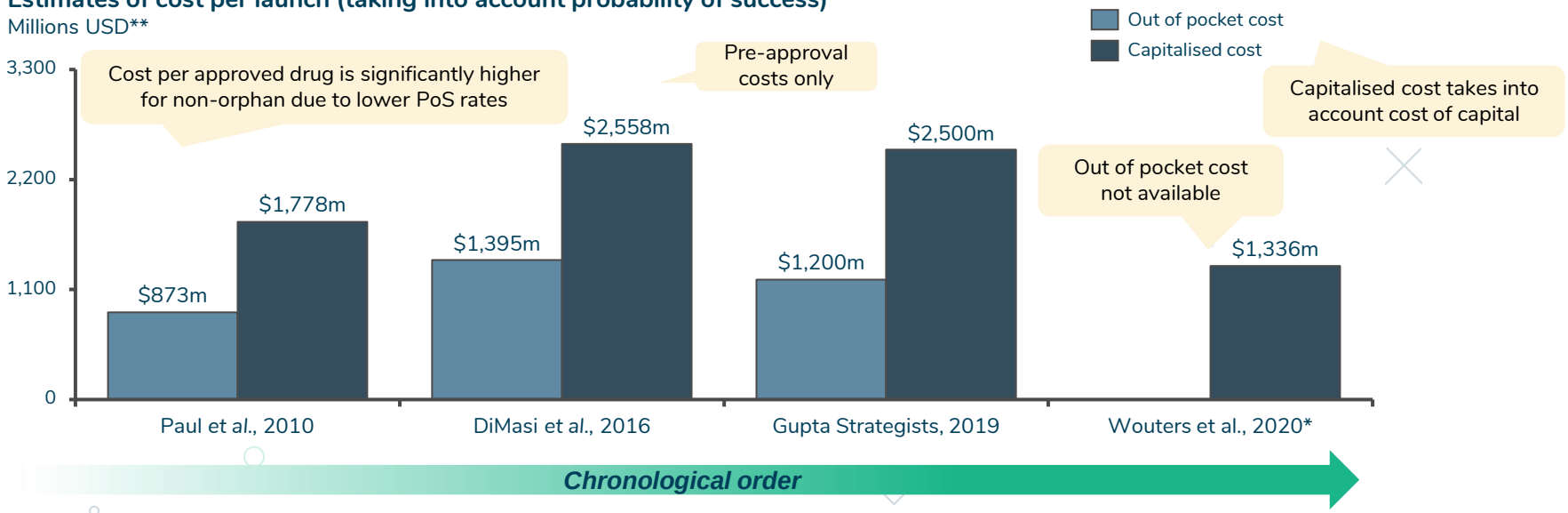
Note: *Jayasundara et al did not directly measure PoS, their PoS values (captured here) were from Hay et al., 2014
Source: Hay et al., 2014; BioMedTracker (2016); Jayasundara et al., 2019; L.E.K. research and analysis

Estimates for total OOP costs per approval range from c.875m to c.1.4bn with capitalised cost ranging from c.1.3bn to c.$2.6bn

Estimates of cost per launch (taking into account probability of success)

Millions USD**



- For out-of-pocket (OOP) cost the significant range is driven by a combination of the assumptions used for phase PoS and cost per attempted phase / trial while capitalised cost is function of the same factors plus clinical development timelines and cost of capital assumption

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Note: *Included in research only for risk adjusted cost estimate; **Based on USD year of primary paper

Source: Paul et al., 2010; DiMasi et al., 2016; Wouters et al. 2018; L.E.K. research and analysis

Following inflation to 2020 USD, the cost per stage of development for a single compound was triangulated across three sources

Cost of clinical development – inflated to 2020 USD

Source	Cost of successful candidate (millions of USD, inflated to 2020 dollars)							
	Target to hit identification	Hit to lead	Lead opt.	Pre-clinical development	Ph.I	Ph.II	Ph.III	Approval
DiMasi et al., 2007	-	-	-	-	43	51	130	-
Paul et al., 2010	1	3	12	6	18	48	179	48
DiMasi et al., 2016	-	-	-	-	28	66	286	-
Selected mid-point	1	3	12	6	30	50	180	48
Illustrative range	1	3	12	6	20-40	40-60	150-210	48

Inflation rates

2005 USD:2020 USD	1.35
2008 USD:2020 USD	1.22
2013 USD:2020 USD	1.12
2017 USD:2020 USD	1.06
2018 USD:2020 USD	1.04

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Source: DiMasi et al., 2007; DiMasi et al., 2016; Paul et al., 2010; L.E.K. research and analysis

Out of pocket costs during the R&D process are estimated to be $1.25-1.70bn and capitalised costs are estimated to be $2.35-3.15bn

	Target to hit identification	Hit-to-lead	Lead optimisation	Preclinical development	Phase I	Phase II	Phase III	Approval
Phase success PoS	80%	75%	85%	69%	63%	31%	58%	85%
Cum. PoS to launch	3%	4%	6%	7%	10%	15%	49%	85%
Attempts per launch	29.5	23.6	17.7	15.1	10.4	6.5	2.0	1.2
× Cost per attempt (2020 USD m)	1	3	12	6	20-40	40-60	150-210	49
= Total phase cost per approved drug (2020 USD m)	30	71	213	90	415 (208)	393 (262)	426 (304)	58
Timing (Years)	1	1.5	2	1	1.5	2.5	3	1.5
Cost of capital (%)	10%							

= Total out of pocket cost per approved drug (2020 USD): $1,235-1,695m

= Total capitalised cost per approved drug (2020 USD): $2,370-3,160m

SiRM. Strategies in Regulated Markets

L.E.K.

Source: Paul et al., 2010; BioMedTracker Clinical Development Success Rates report (2016); L.E.K. research and analysis

Depending on the cost of capital, total capitalised cost may range from $2.07Bn to $3.59Bn, whilst out-of-pocket total does not vary

	Target to hit identification	Hit-to-lead	Lead optimisation	Preclinical development	Phase I	Phase II	Phase III	Approval
Phase success PoS	80%	75%	85%	69%	63%	31%	58%	85%
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Total out of pocket cost per approved drug (2020 USD)

= $1,235-1,695m

Total capitalised cost per approved drug (2020 USD)

Cost of capital (%)		
8%	Cost of capital is $835-1,085m	= $2,070-2,780m
10%	Cost of capital is $1,135-1,465m	= $2,370-3,160m
12%	Cost of capital is $1,475-1,895m	= $2,710-3,590m

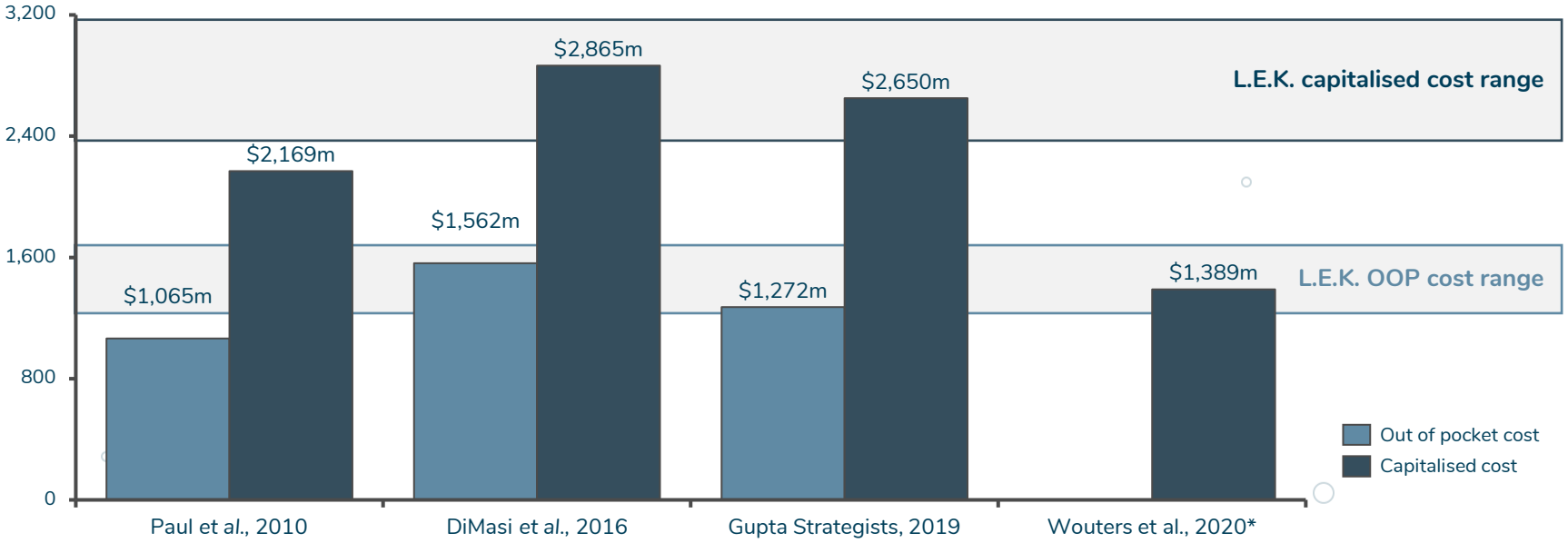
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Paul et al., 2010; BioMedTracker Clinical Development Success Rates report (2016); L.E.K. research and analysis

When inflated to 2020 USD, L.E.K. OOP and capitalised cost estimates broadly triangulate with other studies conducted

Estimates of cost per launch, inflated to 2020 USD (taking into account probability of success)
Millions 2020 USD



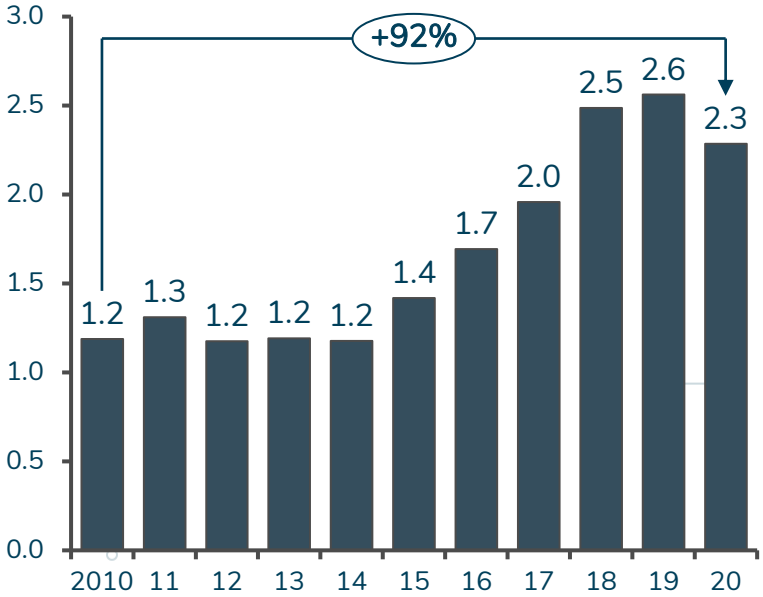
SiRM. Strategies in Regulated Markets

L.E.K.

Note: *Included in research only for risk adjusted cost estimate
Source: Paul et al., 2010; DiMasi et al., 2016; Wouters et al. 2018; L.E.K. research and analysis

R&D costs have risen 92% over the last decade mainly due to increased competition and more complex drug development

Total cost of R&D from drug discovery to launch – Deloitte (2010-20)
Bn of USD inflation adjusted



- Based on Deloitte data, R&D total costs from drug discovery to launch of an asset has increased of 92%, from c.$1.2Bn in 2010 to c.$2.3Bn in 2020
  - according to DiMasi et *al.* (2016), there has been an increase of c.172% in total R&D costs from late 1980s to late 2000s
  - studies report a 6.3 fold increase in capitalised costs (from preclinical development to launch) from 1980-mid 1990s to 2000s-mid 2010s
- This increase in the Deloitte data is mainly due to an overall reduction in the number of late-stage assets in the pipeline
  - the overall clinical success rate has reportedly decreased from c.21% in the 1990s to c.11% in the 2010s, requiring greater investment in early stage assets to ensure success
- Recent studies also show that the total length of clinical development (from Phase I to completion of Phase III) has increased over the years to reach c.7.14 years in 2020
  - this is the result of a growing complexity in trial design, with a higher bar to reach endpoints, leading to a challenging drug development pathway
  - there is also a higher competition in enrolling given the numerous trials happening simultaneously and issues in data capture and analysis using increasingly costly techniques

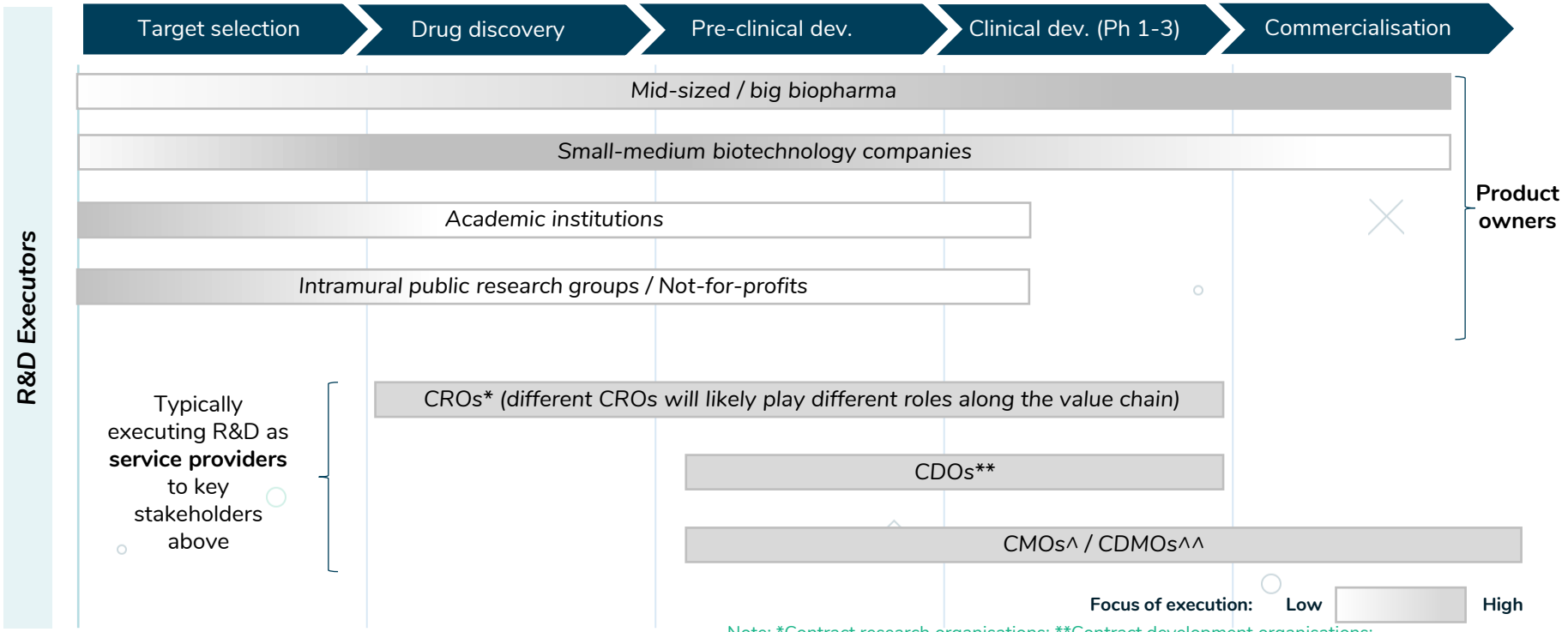
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Deloitte 2021; DiMasi et al. 2016; L.E.K. research and analysis

Initial stakeholder characterisation

A number of key stakeholders perform early-stage R&D; for late-stage development, responsibility is typically transferred to pharma



Note: *Contract research organisations; **Contract development organisations; ^Contract manufacturing organisations; ^^Contract development and manufacturing organisations

Source: Trade press, U.C. Davis, Cytiva, Journal of Clinical Investigation, L.E.K. research and analysis

Summary of key R&D executors (1 of 2)

Product owners

Stakeholder	Examples	Role
Mid-sized / big biopharma	gsk, ucb, Roche, Pfizer, SANOFI, EMD SERONO, novo nordisk, Daiichi-Sankyo	• Mid-sized and big biopharma have internal research departments that can typically perform all stages of R&D • Pharma companies have varying degrees of focus on internal R&D, some have strong internal R&D capabilities and some tend to contract out R&D, in-licence assets or undertake collaborations
Small – medium biotechnology companies	TESSERA, Handl Therapeutics, Pulse Biosciences, vera therapeutics, IMMUNOCORE	• Small-medium sized biotech companies often have only a few assets in development and mainly finance their clinical development via external funds and / or partnerships with mid / large sized pharma • After early clinical development, the assets or the companies themselves may be acquired by big pharma
Academic institutions	HARVARD UNIVERSITY, UNIVERSITY OF CAMBRIDGE, OXFORD UNIVERSITY INNOVATION, delftenterprises	• Academic institutions generally conduct the earliest stage of research, enabling the understanding of potential targets and role in pathology • Some academic labs may progress through drug discovery and preclinical / clinical development though assets are generally spun out as companies or transferred via tech transfer offices to pharma / biotech companies with more comprehensive capabilities and capital for clinical research

SiRM. Strategies in Regulated Markets

L.E.K.

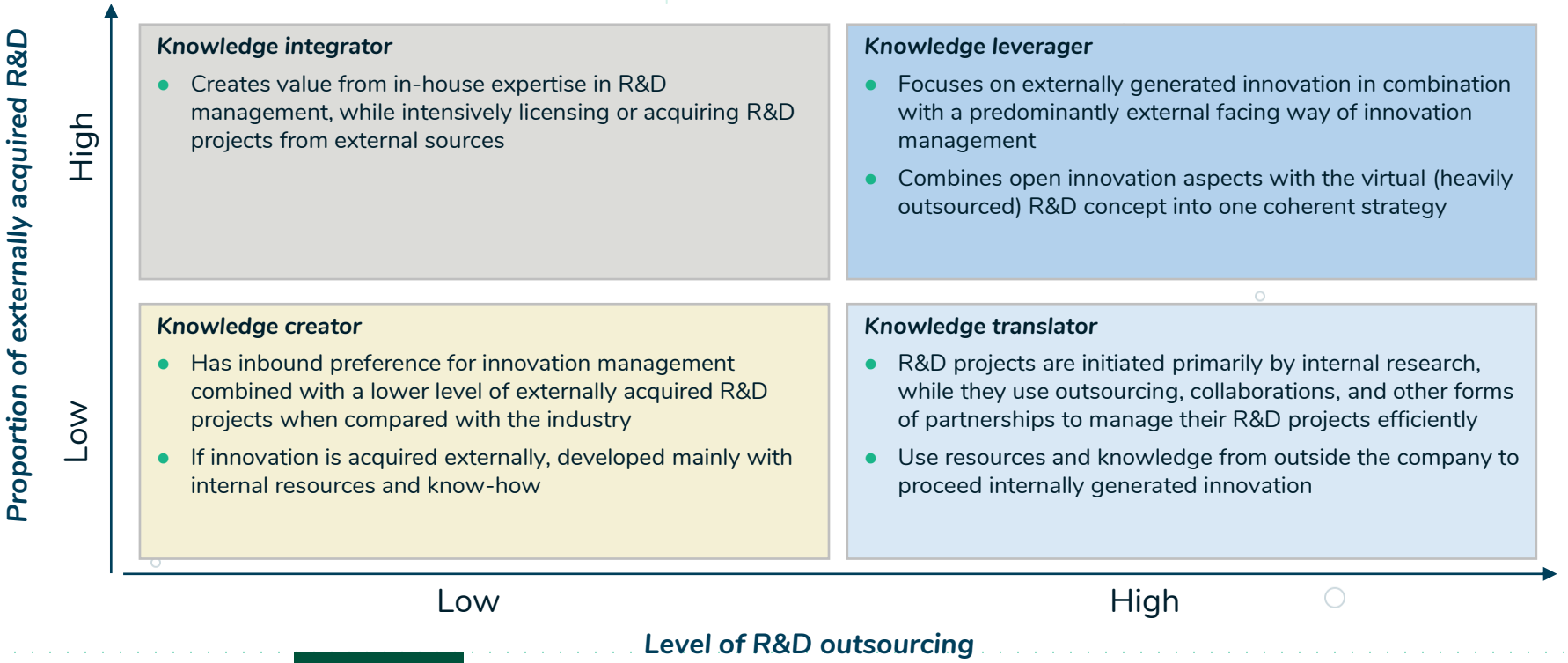
Source: Trade press, U.C. Davis, Cytiva, Journal of Clinical Investigation, L.E.K. research and analysis

Summary of key R&D executors (2 of 2)

	Stakeholder	Examples	Role
Product owner	Intramural public research groups / Not-for-profits		• Public research groups and not-for-profits with intramural labs / capabilities are generally similar to academic institutions (and may be housed in universities), they conduct early-stage research and may oversee asset development until early clinical development • Assets are often transferred to pharma / biotech companies with more comprehensive capabilities and capital for clinical research
Service providers	CROs		• CROs provide support to biopharma companies through outsourced service provision across a range of offerings (e.g., drug discovery, development, preclinical development research, clinical trials etc.) • CROs may specialise in different parts of the value chain and range from large, international full service-organisations to niche, specialty firms
	CDOs, CMOs and CDMOs		• CDOs, CMOs and CDMOs are involved in development and / or manufacturing of assets • Big biopharma typically prefer large CDMOs as they have the ability to support large clinical trials, while small to mid-sized pharma may prefer smaller, more agile CDMOs as assets are typically licensed out for late-stage development

Source: Trade press, U.C. Davis, Cytiva, Journal of Clinical Investigation, L.E.K. research and analysis

Big pharma players can generally be divided into four key archetypes based on approach to external innovation



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Source: Schumacher et al 2013; L.E.K. research and analysis

Big biopharma are partnering earlier with small / medium biopharma and adopting more complex deals driven by declining R&D ROI

External innovation is increasingly important

- Companies are mindful of reduced return on investment (ROI) for in-house R&D and are generally increasingly looking towards external sources of innovation

"… Big pharma increasingly in-license external innovation as they know small biotechs are more flexible and hence able to innovate; their resources has shifted to utilising their late stage clinical development and commercialisation strengths …"
Former Director of Business Development, multinational biopharma

Companies are looking for new technologies earlier in the value chain

- As competition for breakthrough technologies is high, pharma are looking towards earlier stages of the R&D value chain to identify the most promising new technologies

"… Breakthrough technology is highly sought after, if you do not partner up early, you miss the opportunity to capture the technology and potentially bringing it in house …"
Former Head of External Innovation, multinational biopharma

Different deal structures are used depending on stage / risk profile

- Companies are looking to collaborate / license as soon as there is a patentable product (e.g., lead optimisation) or conduct M&A when clinical proof of concept is shown (i.e., phase Ib / II)
  - for riskier / earlier stage assets, big pharma may invest by taking equity in the company initially with an option to license at a later stage
- Biopharma players are increasingly comfortable with more complex collaboration and co-development to maximise R&D outcomes

"… Biopharma players are becoming more established with making and executing complex deals; they understand in codevelopment deals, respective stakeholders add value in the different stages in R&D and may result in better outcomes than in-licensing …"
Former Director of Business Development, multinational biopharma

Source: L.E.K. interviews, research and analysis

Interviewees from early stage biotechs are driven by practical application of their ideas; access to funding can drive decision making

Biotechs are mainly motivated by building a product from basic research

- Interviewees report that biotech founders are mainly driven by seeing their ideas becoming an impactful real world product
  - financial rewards are clearly a consideration but generally not the principle motivator to those interviewed*

"... Most biotech founders want to see their research become realised as a therapy; money is not the most important driver..."
Adviser, EU small / medium biopharma

Access to funding before preclinical development data is a challenge that is improving

- Stakeholders note that obtaining funding to produce preclinical development data has historically been a challenge although more VCs are supporting at seed stage and taking an active role in spinning out companies
  - not-for-profit funding can provide limited support beyond seed stage but can generate traction and VC interest
- Only the best funded biotech companies will be able to perform Phase III alone; this is generally limited to those in the rare disease space and is considered a risk

"... Only biotechs with hundreds of millions of dollars from IPO can consider performing phase III alone, which is risky and comes with practical challenges ..."
Founder, U.S. small / medium biopharma

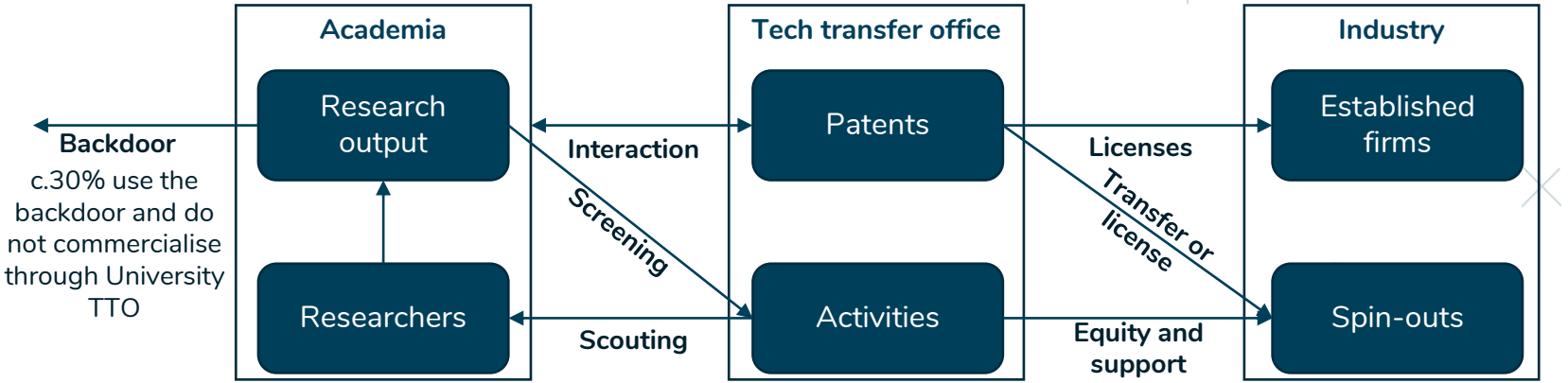
It is difficult managing motivations of different groups of investors / partners

- Small biotech fundraising rounds can be backed by both pharma and VC funders; however they have different objectives and this can be challenging to balance particularly as the biotech is looking to innovate
  - pharma may invest to keep close focus on asset and acquire if it looks promising and therefore would prefer to have terms and conditions that secure this
  - VCs are looking to maximise growth and want to be open to exit the company to a full range of competitors

"... Both pharma and VCs want as much control and access over the asset as possible, but they have differing strategic goals; pharma invests with a strategic consideration of in-licensing, whereas VCs need their financial returns..."
Founder, U.S. small / medium biopharma

Note: *Small sample size (n=2) means views expressed may not be more broadly representative of early-stage biotechs as a whole although similar motivations expressed by both interviewees
Source: L.E.K. interviews, research and analysis

TTOs generally facilitate interactions between Academia and Industry



Backdoor
c.30% use the backdoor and do not commercialise through University TTO

Researcher seniority, attitudes towards open science and funding source drive patenting behaviour

Role of an incubator is to support research of scientists while patenting lies with TTO who will screen research outputs and scout for innovation

Established firms will liaise with TTOs regarding licensing and TTOs will also play a role in the formation of spin-off companies

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Source: Holgersson and Aaboen 2019; L.E.K. interviews, research and analysis

Academics are mainly motivated by improving scientific knowledge, though there is increasing drive towards translation

Academic research is mainly driven by improving scientific understanding

- The core aim of academic research is publication and generally focuses on target identification and understanding of biological pathways
  - in the UK, the research excellence framework measures the number of publications and impact beyond academic for university research and determines how much centralised government funding universities receive

"... The research excellence framework directly impacts the amount university funding and is largely measured by societal impact..."
C-suite executive, top UK university technology transfer office

Translation of basic research into drug discovery is facilitated by TTOs

- With the exception of institutions with significant clinical departments / attached hospitals, universities are not well set up to progress molecules into the clinic themselves
- Translational impact is increasingly valued in academic R&D and TTOs assist with IP generation once a development candidate is identified
  - generally, across most geographies^, academic institutions own IP generated by research and they develop their own distribution model to split future licensing revenues (e.g., University, departments, academics)

"... Licensing revenue is allocated to inventors, department, central university and some third-party funders depending on individual institutions; as the revenue increases, the percentage share attributed to inventors decrease ..."
C-suite executive, top UK university technology transfer office

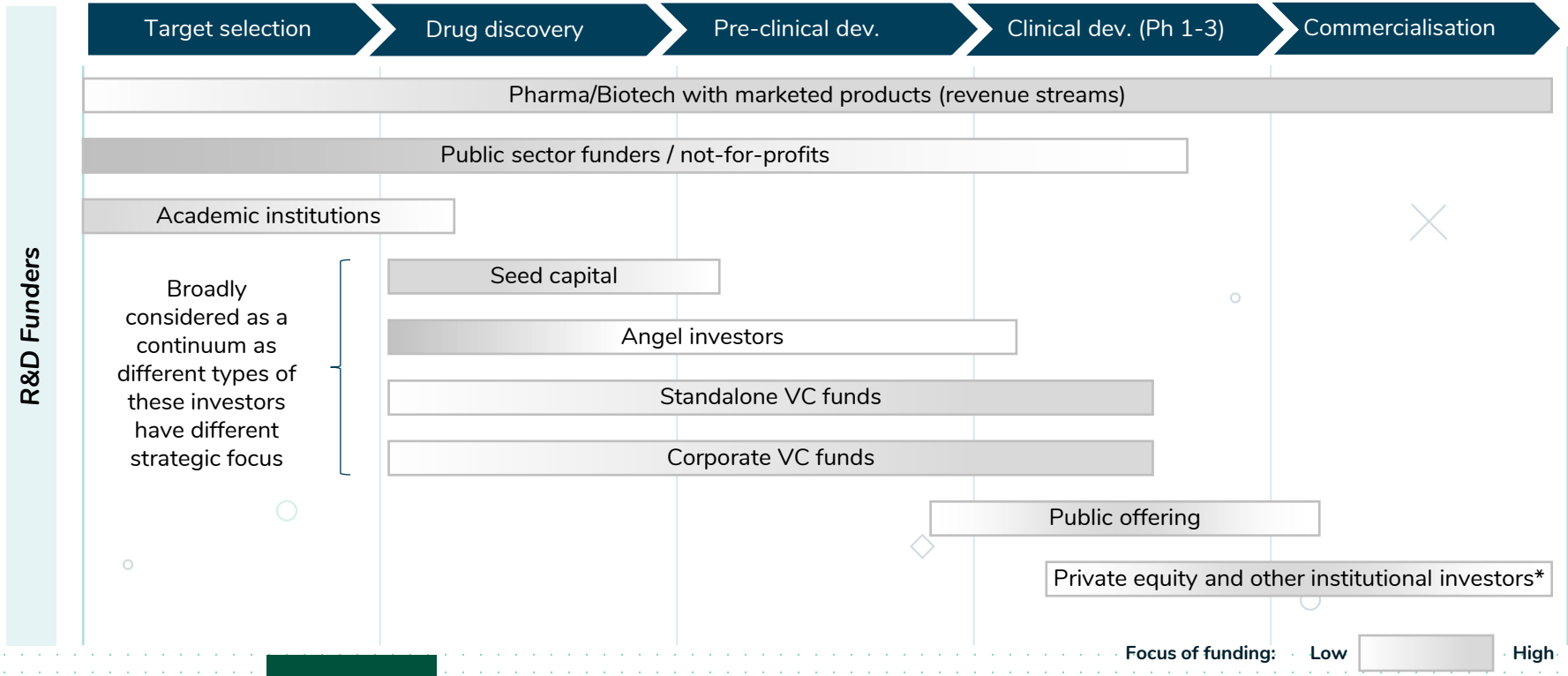
Pharma increasingly collaborate with academics

- Although the majority of academic funding for early stage research comes from PRGs / not-for-profits, academia generally needs corporate partners to generate toxicology and PK* data pre IND** application
- The difference between main motivation (e.g., publication vs. launching new drugs) can limit success, but as understanding between parties grow it is thought that collaborations will become more impactful

"... In a biopharma / academic collaboration agreement, universities very often maintain the right to publish research done on an asset; to balance biopharma's interests to protect an asset, we may delay publications until a patent application has been filed..."
Executive Director, top U.S. university technology transfer office

Note: *Pharmacokinetics; **Initial new drug; ^Sweden was highlighted in interviews as a potential exception to this, where the researchers own the IP
Source: L.E.K. interviews, research and analysis

Academic and public sector funders are more involved in early-stage R&D; other investors will generally play a role at later stages



Note: *Hedge funds, groups buying royalty streams, pension funds
Source: Trade press, U.C. Davis, Cytiva, Journal of Clinical Investigation, L.E.K. research and analysis

Summary of key R&D funders (1 of 2)

Stakeholder	Examples	Role
Pharma / biotech with revenue stream	gsk, Roche, Pfizer, SANOFI, novo nordisk, EMD SERONO, Seagen	• Reinvestment of drug revenue into internal R&D pipeline – in 2019, c.20% of top-10 pharma's revenue was reinvested into R&D • Small to medium pharma rely on a mixture of both external funding and internal R&D investment, depending on their operating cash flow
Public sector funders / not-for-profits	erc, wellcome, NIH, UKRI Innovate UK	• Common source of early R&D funding with social impact as the primary investment objective (hence investments in early-stage development with high risk of failure) • Their funding nature is typically non-dilutive, meaning companies can continue to build on their equity as R&D progresses
Academic institutions	HARVARD UNIVERSITY, UNIVERSITY OF CAMBRIDGE, OXFORD UNIVERSITY INNOVATION, delftenterprises	• Some academic institutions have internal funding sources (e.g., revenue earned from technology transfer spin-outs), some of which is reinvested in research programs
Seed capital	UK INNOVATION & SCIENCE SEED FUND, Y Combinator, European Commission, SOSV, techstars_	• A seed capital funding round occurs before series A, which is the first significant VC funding round for a pharma company. Seed capital can originate from a number of sources including early stage VC funds and is designed to translate basic research / drug discovery into a company

Source: Trade press, U.C. Davis, Cytiva, Journal of Clinical Investigation, L.E.K. research and analysis

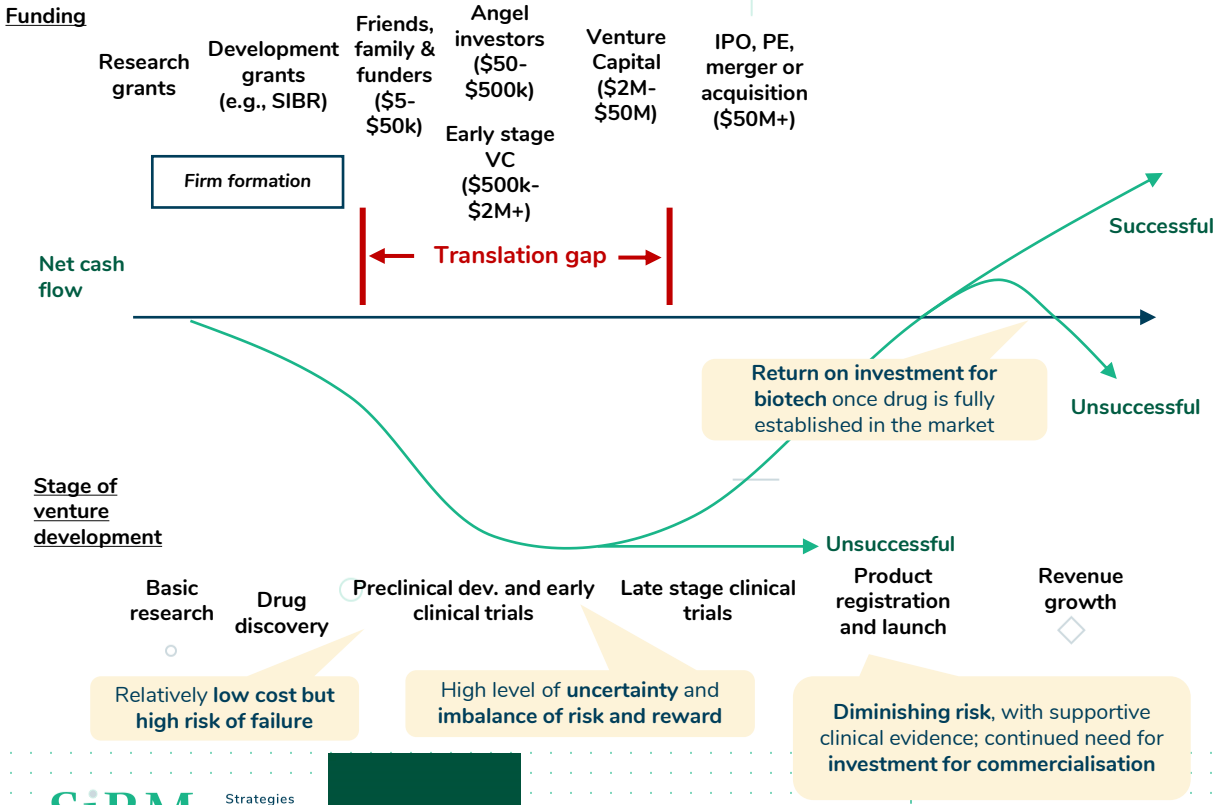
Summary of key R&D funders (2 of 2)

Stakeholder	Examples	Role
Angel investors	LIFE SCIENCE ANGELS, Investing For Life; Sand Hill Angels; KEIRETSU FORUM; Individual investors; TECH COAST ANGELS	• Angel investors are industry experts with an interest in funding R&D; they are more likely to invest in earlier stages given the high costs of clinical development • More sophisticated angel investors may support early clinical trials
Standalone VCs	ARCH VENTURE PARTNERS; Forbion; Life Science Investing ABINGWORTH; Syncona	• Standalone VC funds are individual companies that manage venture funds • VCs increasingly make high risk investments on early stage technologies but also may invest in clinical development stages (Ph I/II) once preliminary data is available
Corporate VCs	Pfizer Ventures; M. VENTURES	• Corporate VCs are the investment arms of biopharma companies who may invest according to the financial or strategic goals of the associated parent company
Public offering	Spark THERAPEUTICS; Pulse Biosciences; Voyager THERAPEUTICS; LEGEND BIOTECH	• IPOs can happen across all phases of clinical development although they are more common for companies in clinical dev (Phase I and II represent a large share of IPOs) • IPOs enable companies to access a global pool of capital to support business scale-up, debt repayment and investments in future R&D projects
Private equity*	BainCapital; Advent International GLOBAL PRIVATE EQUITY; Blackstone	• Private equity has typically focused on branded consumer and specialty pharma / generic products rather than R&D • Firms are beginning to increasingly invest in emerging companies that are developing new drugs and / or partnering with global biopharma companies to develop portfolios of new drug candidates that are low priority at the company

Note: *Other institutional investors (e.g., hedge funds, pension funds etc.) may also play a similar role
Source: Trade press; U.C. Davis; Cytiva; Bay Bridge Bio; Journal of Clinical Investigation; DCAT; L.E.K. research and analysis

A Biotech goes through various stages of development, with a translation gap that typically needs to be filled by venture funding

Illustrative



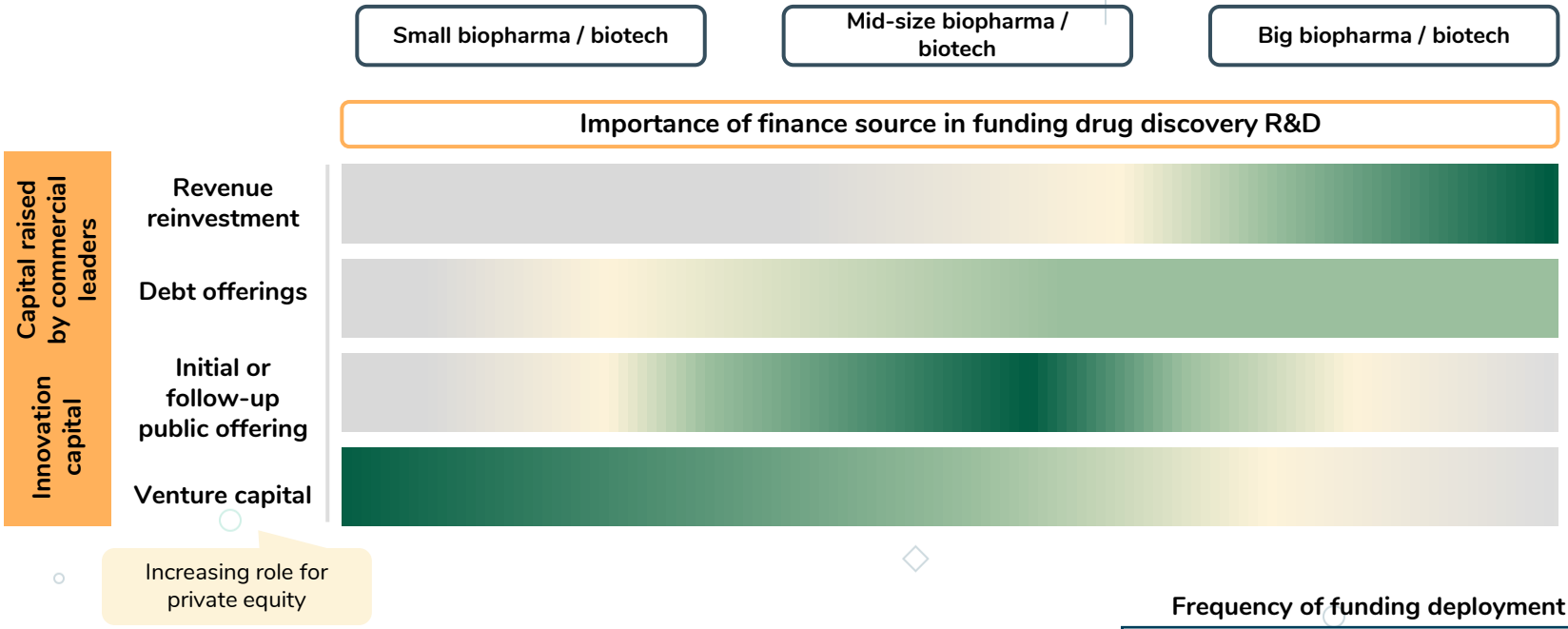
- The translation gap captures the challenges of raising capital during R&D as a result of the high-risk which can deter some investors
- Public investors which fund research for social impact, angel funders, and early stage VCs with high industry expertise are willing to invest in early stage high-risk settings
- After preclinical development, later stage VC increasingly invest and pharma companies may look towards M&A, as assets are backed by preliminary trial data and risk becomes lower

SiRM. Strategies in Regulated Markets

L.E.K.

Source: UC Davis, L.E.K. interviews and analysis

Venture funding and public offerings drive most small biotech R&D, larger companies rely on revenue reinvestment and debt financing



Source: Company Websites; Fierce Biotech; EY; L.E.K. research and analysis

Standalone VCs invest in companies that fulfil an unmet need; the portfolio is driven mainly by finding innovation to drive ROI

VCs will assess scientific rationale and unmet need before investing

- In order to assess a new technology, VCs will conduct diligence focusing on the technical capabilities of the technology and the ability to potentially fill an unmet need
  - VCs are looking increasingly towards earlier stages of supporting starting up the business (e.g., through seed funding) to help define the strategy, typically during the "drug discovery" stage (e.g., after initial hits)

"... As size of funds increase, more venture investors are involved in seed funding; they want to be involved in starting up the business and defining its strategy ..."

Former senior management, UK venture capital fund

VC funds need to provide sufficient ROI to their investors

- Investors typically expect a 2.5-3x net return on investment (ROI) and / or a 20-25% internal rate of return (IRR); ROI indicates total growth from start to finish for an investment, whilst IRR is an annual growth rate
- For VC funds to achieve the above expectations, they generally need a c.4-5x ROI multiple averaged across investments in their portfolio with a 3-8 year holding period depending on stage
  - to arrive at this, they will typically invest in a mixture of low risk (c. 2-3x ROI) and high risk investments (c. 10x ROI), understanding that a proportion of these may generate no returns

"... To support high-risk, high-return investments, we also make low-risk, low-return investments, so that overall it averages to 5x ROI..."

Managing Director, U.S. venture capital fund

Investment sizes are thought to be growing

- Funds are growing in size generally without equivalent corresponding increase in the number of partners in the VC fund to drive new investments meaning that the overall size of investments is trending upwards currently
- On top of this, in the U.S. there is thought to be a high level of competition leading to deal inflation, as evidenced by a rise in competing term sheets; VC in Europe is thought able to be more collaborative which allows companies to share risk

"... In the U.S., there is too much capital and not enough good deals, hence you see competing term sheets and deal inflation; funds in Europe are more collaborative and do not chase after the same deals..."

Managing Director, U.S. venture capital fund

Source: L.E.K. interviews, research and analysis

Corporate VCs may lean towards financial or strategic incentives, but are looking to invest across similar criteria to standalone VCs

Strategic focused CVCs aim to develop the portfolio of the parent company

- CVCs may lean towards financial or strategic incentives based on their relationship with their parent company
  - CVCs that report to BD typically have more strategic alignment with company portfolio looking to fill pipeline
  - CVCs that report to CFO typically have more financial motivation and may invest in potential competitors
- There is sometimes tension resulting from financial / strategic alignment within companies but corporate VCs often form investment syndicates with other CVCs or standalone VCs to share risk and expertise / skills

"… For big investments, syndicates comprised of corporate and standalone VCs are often formed, which ensures a balance of financial and strategic interests …"

Former managing director, multinational biopharma venture capital fund

CVCs tend to invest locally, based on team, science and PoS

- Interviewees report that the key factors for investments are team, science, unmet need, and ease of execution
- Geographical proximity is important as early-stage companies require extensive management and structuring
  - hiring management and sourcing facilities are easier in established R&D ecosystems (e.g., Boston, Oxford)

"… Many funds invest locally because early-stage companies require a lot of nurturing. There are also advantages in leveraging established R&D ecosystems - it is easier to source the right management hires, expertise and technology…"

Former managing director, multinational biopharma venture capital fund

CVCs look at IRR / ROI and portfolio building in a similar way to standalone VC

- VCs don't typically conduct NPV analysis but look at comparators for benchmarking also aiming for 3x net ROI / sufficient IRR depending on the company
  - valuation of companies increases as R&D progresses, driven by increased efficacy / scientific data and PoS
- CVCs build a portfolio based on stage of development / risk; firms reporting to BD organisation may have more late stage investments aligned more towards M&A, with a lower potential multiple

"… If funds are geared more towards a strategic / acquisitional goal, they may invest in more late stage assets with a smaller multiple …"

Former managing director, multinational biopharma venture capital fund

Source: L.E.K. interviews, research and analysis

PRGs / not-for-profits fund mostly early research with the aim of social impact; PRGs may also fund innovative companies

PRGs / not-for-profits focus funding projects to support public good

- PRGs and not-for-profits fund R&D to achieve social impact by tackling existing and future public health needs
  - for example, in the U.S., the opioid crisis has triggered emergency funding from the NIH for therapies to alleviate abuse
- PRGs are big proponents of innovative drugs as they can fulfil unmet needs and improve treatment outcomes, benefiting overall public health

"... We specifically seek out innovation and give grants to investigator-led innovative research, particularly in our oncology arm ..."
Director of clinical operations, U.S. governmental research entity

Most funding is on early stages and there is inconsistency on returns potential

- PRGs fund drug discovery and preclinical development research, with smaller amounts of early stage clinical research; in clinical stages, PRGs are involved more through pharma partnerships than pure funding
- There is limited consistency on the extent of financial return sought by PRGs In the U.S.
  - In the U.S. PRGs largely do not seek financial return (currently a topic of debate) and in the U.K. the Medical Research Council in the UK expect a return but other PRGs view involvement in R&D as a public mission

"... Our ultimate goal is to advance public health by driving research to facilitate therapeutic discovery ..."
Director of clinical operations, U.S. governmental research entity

PRGs also aim to support small biotech company R&D

- Apart from traditional funding, seed funds or accelerator programs from PRGs / not-for-profits have been formed to support small biopharma and their generation of early data (e.g., preclinical development data)
  - NIH's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are established with express purpose of supporting innovation from small biopharma

"... A portion of our funds is devoted to support small bioenterprise research efforts; with the SBIR / STTR programs, we provide seed capital for small biopharma to perform in-house R&D and generate their first batch of data ..."
Director of clinical operations, U.S. governmental research entity

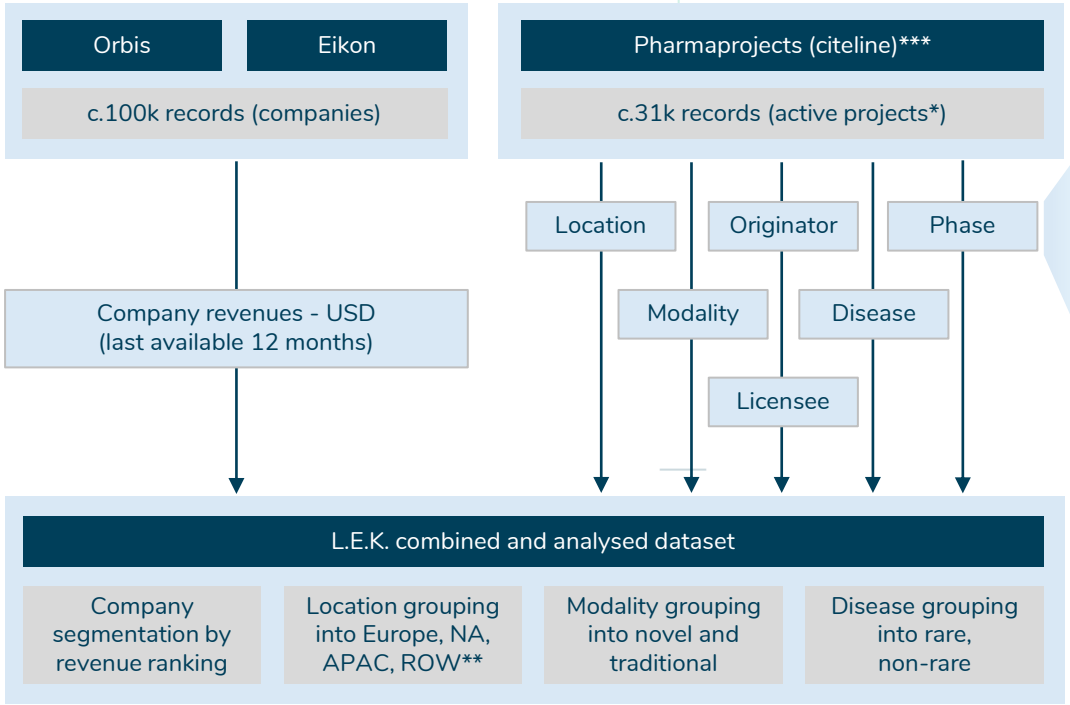
Source: L.E.K. interviews, research and analysis

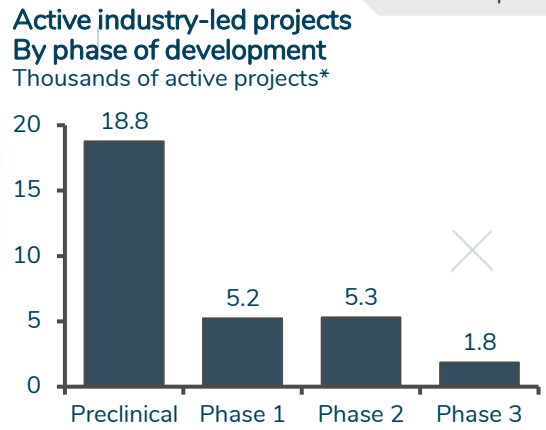
2. R&D Execution

Analysis of ongoing development programs

Development program analysis was conducted using proprietary project data from Citeline and company data from Orbis and Eikon

Data capture: **01/2021**





Citeline coverage of ongoing preclinical development studies is likely relatively low, given that it relies on public disclosure by the trial sponsor, which is not mandated to the same extent as for in-human trials

Notes: * Each drug-disease combination counted as a single project; **Rest of World; ***Assets segmented by originator and licensee; for purposes of this analysis if an asset has both an originator and licensee, the licensee is assumed to be the current executor – limitation in situations where there is specific geographical licensing although not considered to have a significant impact on this analysis
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

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L.E.K. has segmented all industry R&D players in the PharmaProjects database by size based on estimated revenue from Orbis / Eikon

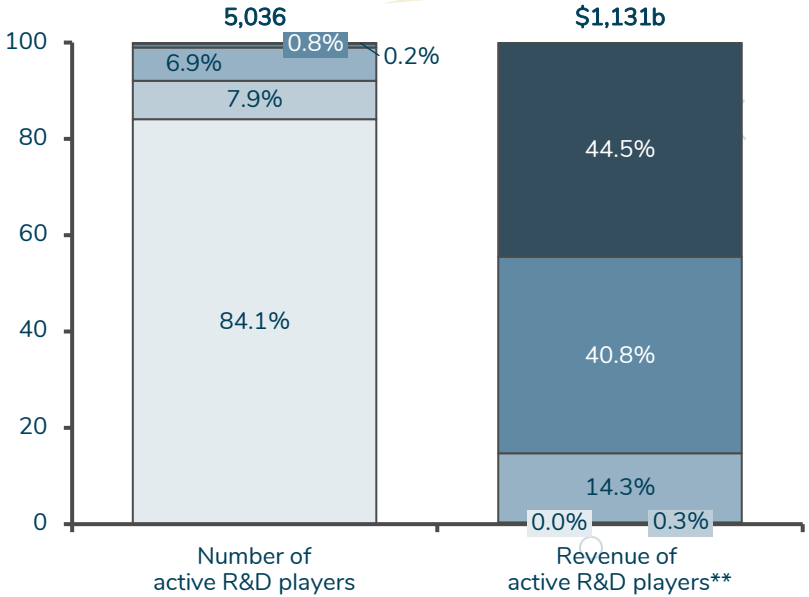
Segment by revenue ranking	Sub-segment by revenue ranking	Revenue range (indicative)
Top 10	Top 10	c.$30b – $80b
Top 10-50	Top 10-25	c.$3b – $30b
	Top 25-50	
Top 50-400	Top 50-100	c. $30m – $3b
	Top 100-200	
	Top 200-400	
Top 400-800	Top 400-800	c.$1m – $30m
Below 800	Below 800	<$1m

L.E.K. have segmented players based on revenue; sub-segment cut-offs have been doubled from the top 25 onwards; sub-segments have been aggregated into segments in the rest of this section for illustrative purposes, but all data is available at the sub-segment level

Data capture: **01/2021**

Pharma companies with currently active development programs by company size (revenue)**
% of players; % of billons of USD

Includes all project executors and originators



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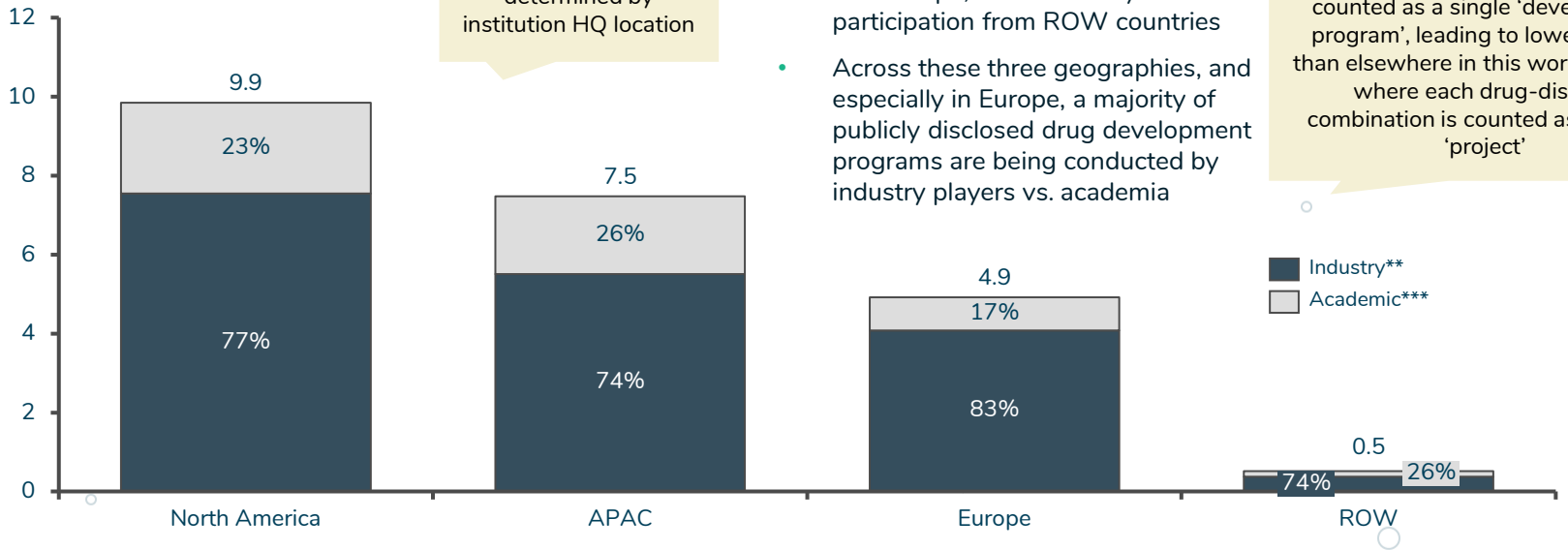
Notes: *Companies not listed on Orbis/Eikon are assumed to be pre-revenue; ** Revenue from last available year
Source: Citeline; Eikon; Cortellis; L.E.K. research and analysis

A majority of active drug development programs are conducted by industry across the three key relevant regions for pharma R&D

Data capture: **01/2021**

Active drug development programs by region by executor type (Excludes public research groups)
% of thousands of drugs*



Executor region determined by institution HQ location

- A majority of programs are being conducted in North America, APAC, and Europe, with relatively low participation from ROW countries
- Across these three geographies, and especially in Europe, a majority of publicly disclosed drug development programs are being conducted by industry players vs. academia

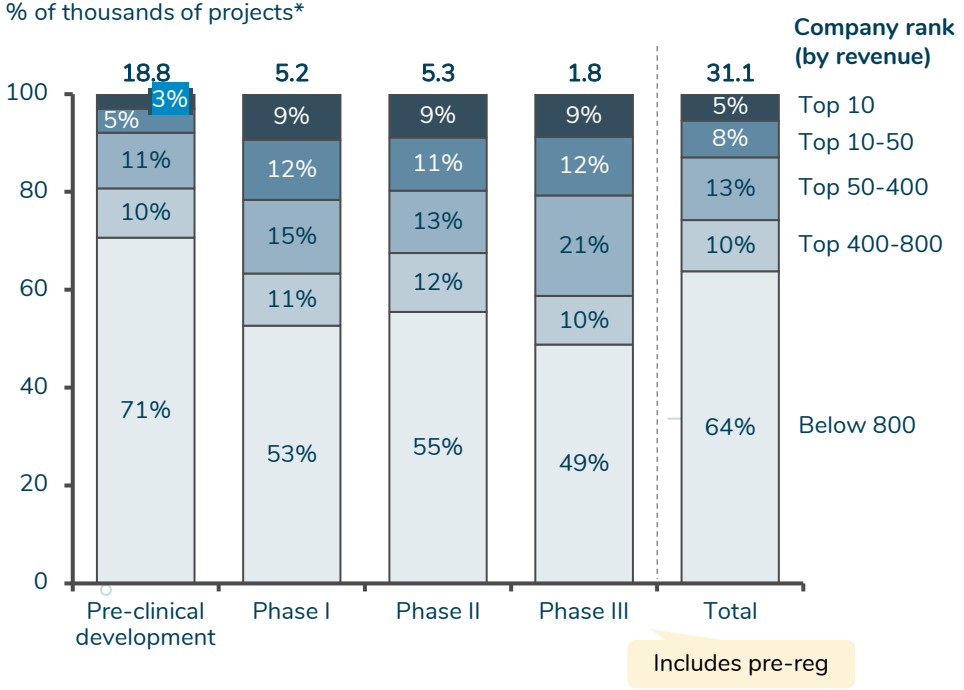
Each drug-region combination is counted as a single 'development program', leading to lower counts than elsewhere in this work-package where each drug-disease combination is counted as a single 'project'

Note: *Drugs defined in this case as unique drug name / region combination; **PharmaProjects; ***Cortellis
Source: Citeline; Eikon; Orbis; Cortellis; L.E.K. research and analysis

A majority of early-stage projects are executed by small companies, while later-stage projects involve larger players more heavily

Data capture: **01/2021**

Active Industry-led projects by executor company size (revenue)
% of thousands of projects*



- Small and very small companies appear to play a significant role in the execution of industry-led projects across phases
  - this is in-part driven by heavy fragmentation in the biopharma R&D industry
  - this is potentially reflective of larger players' preference to take a stake in external opportunities through financing rather than internalising assets for further development
- Active pre-clinical projects are largely conducted by pre-revenue companies, who tend to be more focused on early stage R&D
- Conversely, later stage projects more frequently involve direct execution by larger players, who tend to be more focused and capable of running phase II/III trials

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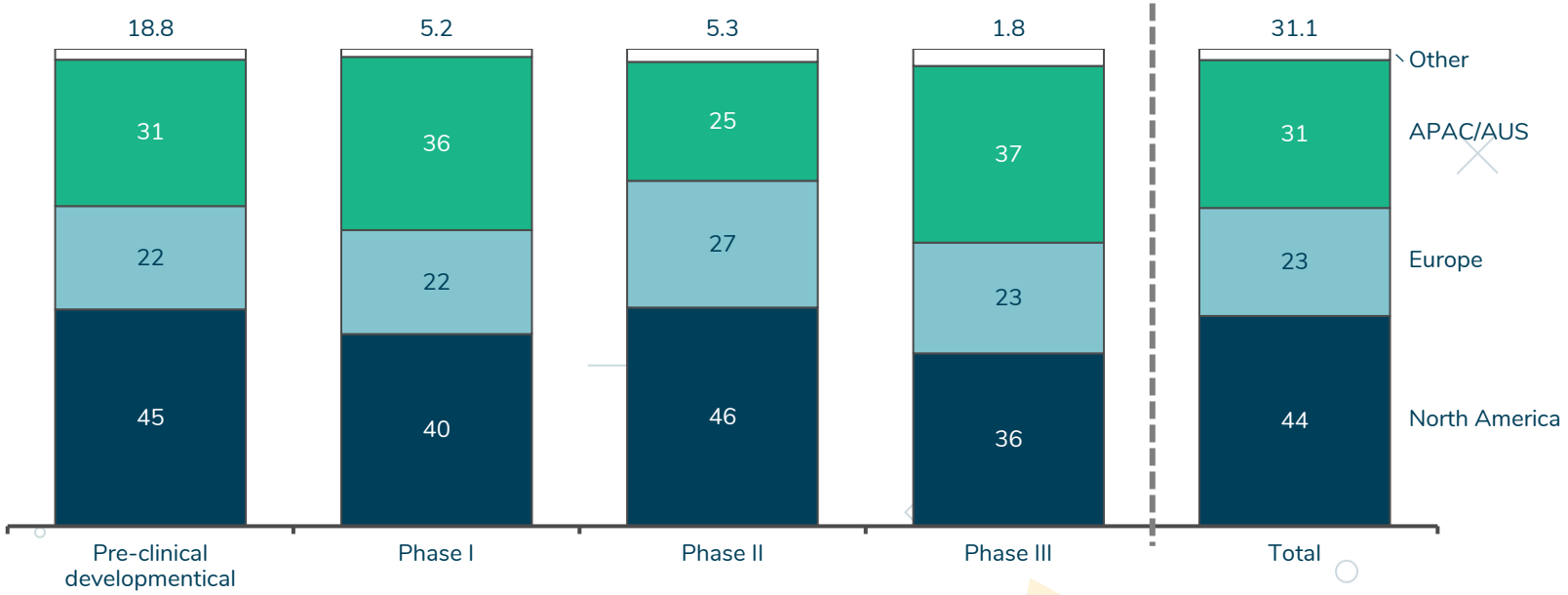
Notes: *Each drug-disease combination counted as a single project
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

The regional distribution of early vs. late stage projects does not appear to vary significantly

Data capture: **01/2021**

Active Industry-led projects by executor location [% of thousands of projects*]

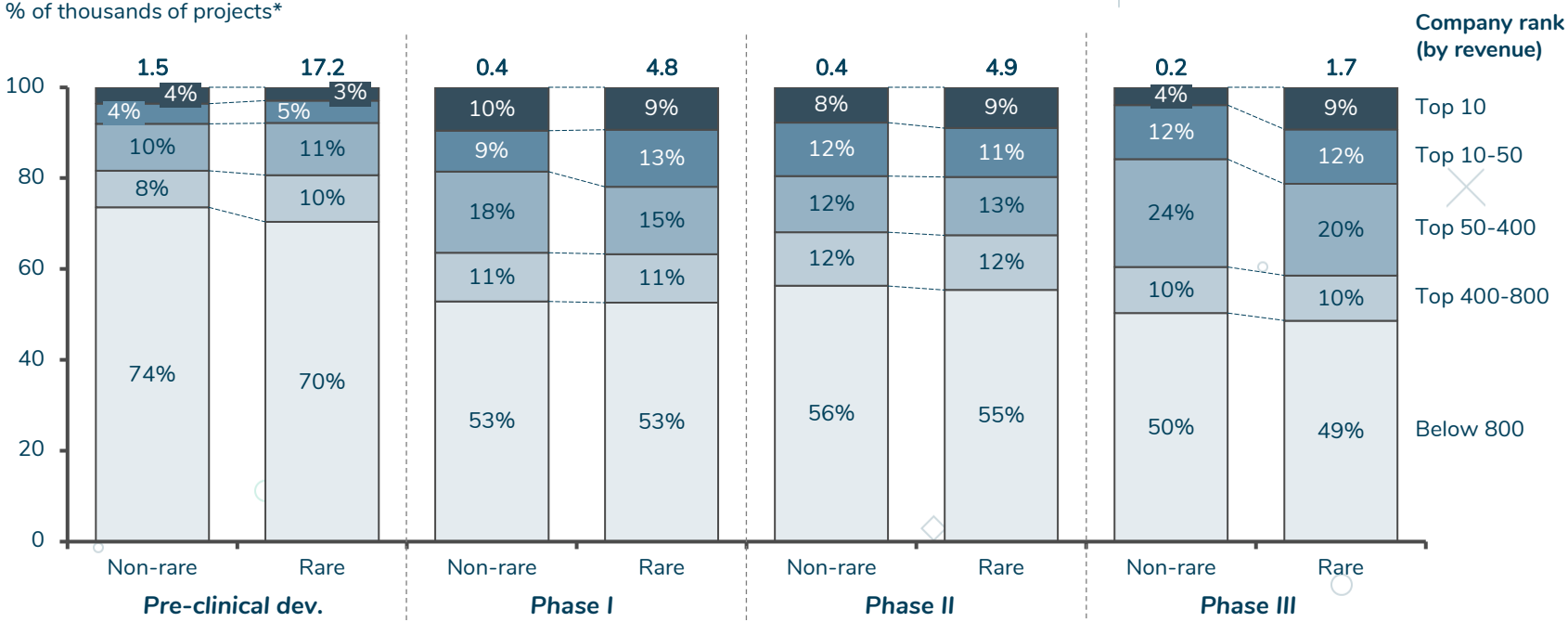


Notes: *Each drug-disease combination counted as a single project
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

Participation of small vs. large players along the value chain appears largely independent of whether a drug is for a rare disease or not

Data capture: **01/2021**

Active Industry-led projects for rare and non-rare diseases by executor company size (revenue)
% of thousands of projects*



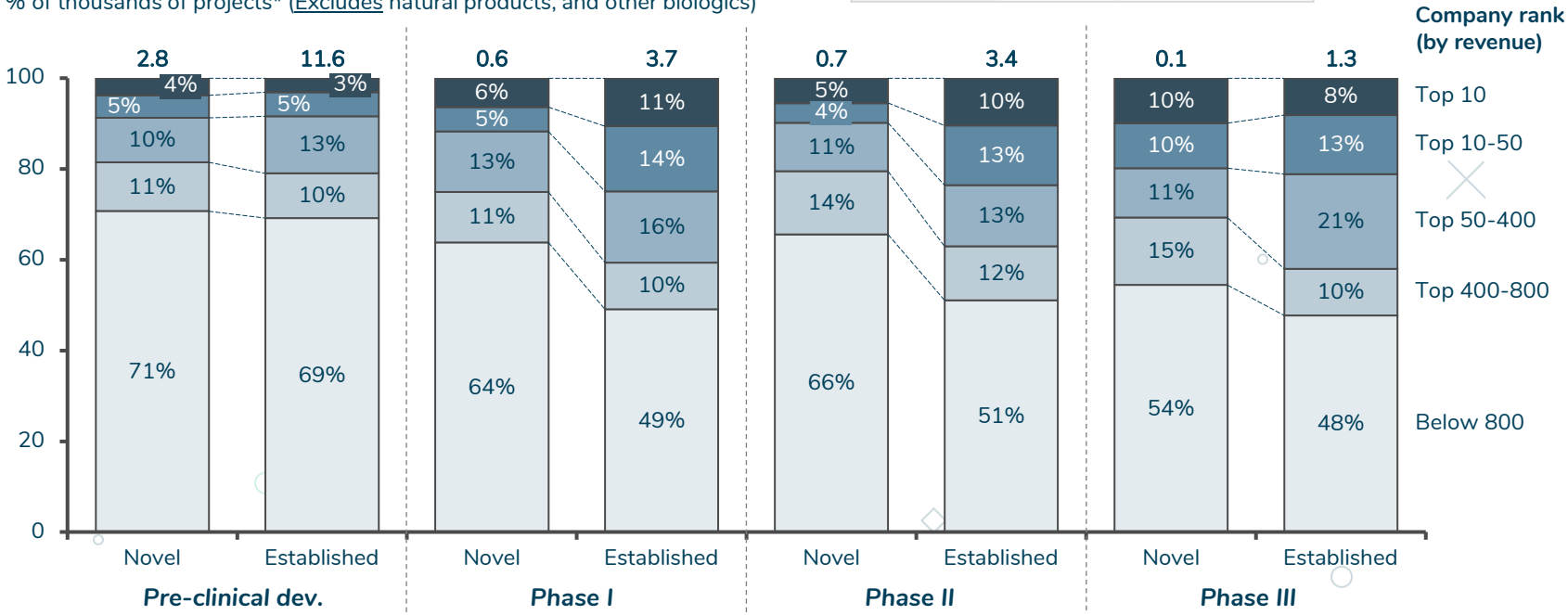
Notes: *Each drug-disease combination counted as a single project
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

Larger players are involved in early-stage clin-dev for established modalities, whereas smaller players do a majority of novel modalities

Active Industry-led projects for established and novel modalities by executor company size (revenue)
% of thousands of projects* (Excludes natural products, and other biologics)

Established:	Small molecules, mAbs
Novel:	Cell therapies, Gene therapies

Data capture: **01/2021**

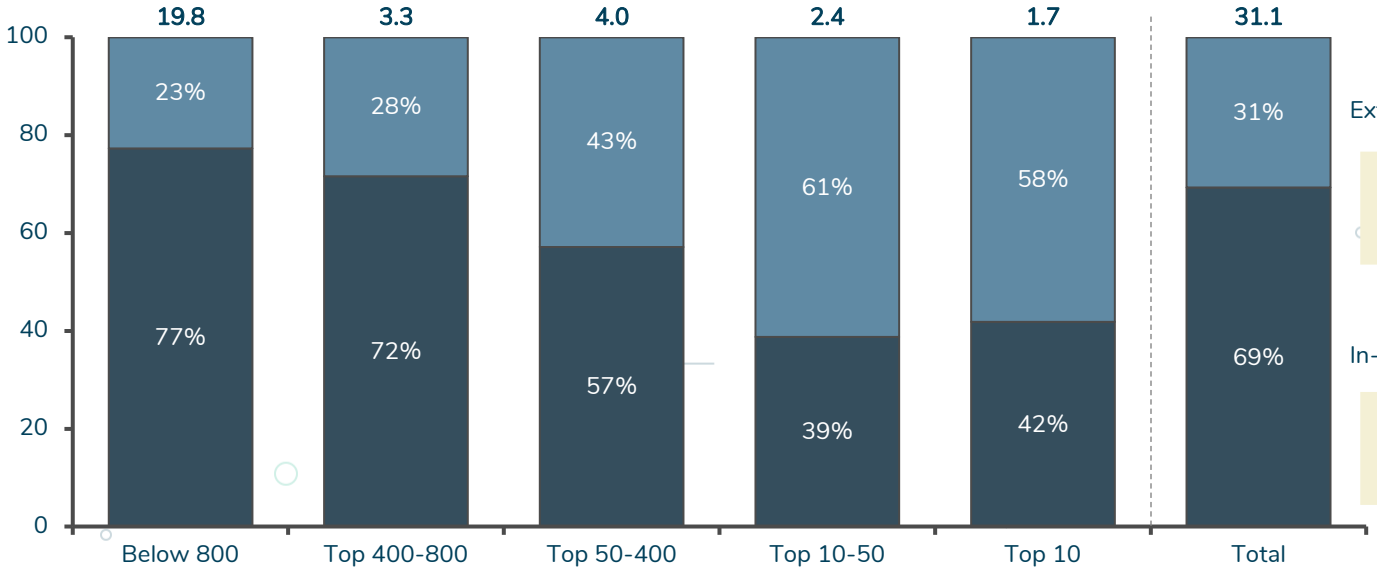


Notes: *Each drug-disease combination counted as a single project
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

Larger players, who have more cash and a sharper focus on late-stage development source more assets externally

Data capture: **01/2021**

Active Industry-led projects by executor company size (revenue) and asset type (in-house, externally sourced)
% of thousands of projects*



Externally sourced

Includes assets in-licensed/acquired and those inherited through M&A

In-house (originated)

May include assets sourced from academic institutions (i.e., not from industry)

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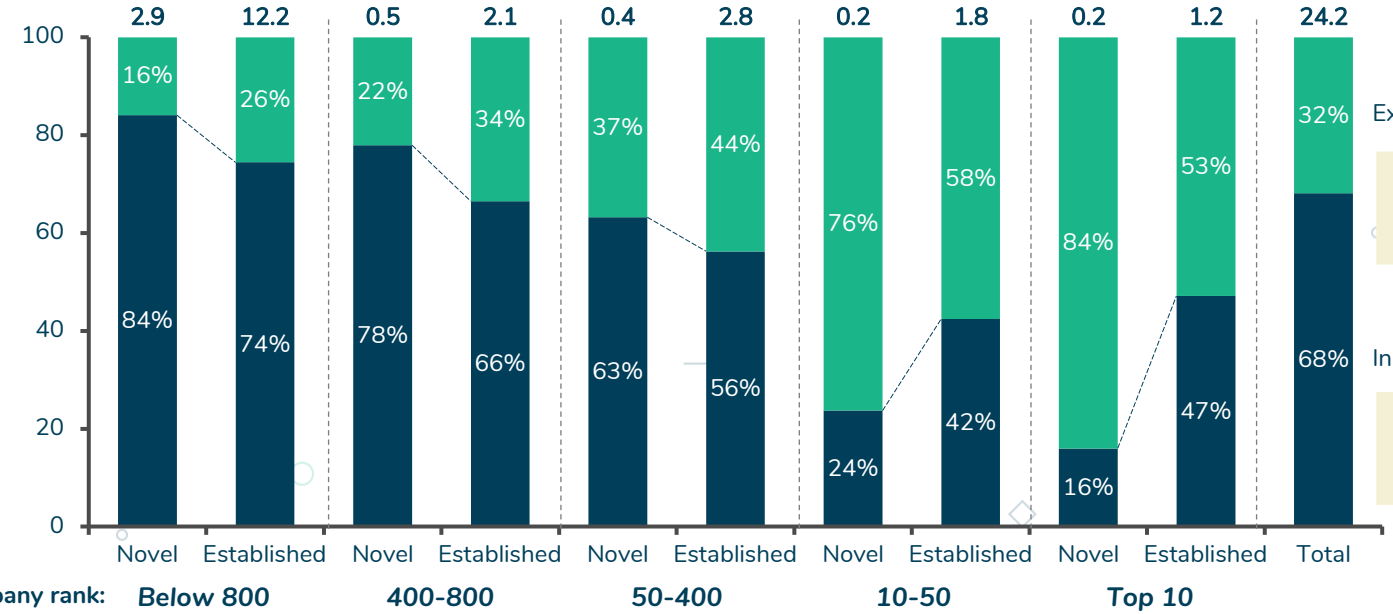
Notes: *Each drug-disease combination counted as a single project; **As PharmaProjects merges these to become originator products for acquiring company
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

Large players rely more on in-licensing/acquisitions to fill their pipelines for novel modalities than for conventional modalities

Active Industry-led projects by executor company size (revenue) and asset type (in-house, external), novel vs. conventional modalities
[% of thousands of projects* (Excludes natural products, and other biologics)]

Established:	Small molecules, mAbs
Novel:	Cell therapies, Gene therapies

Data capture: **01/2021**



Externally sourced

Includes assets in-licensed/acquired and those inherited through M&A

In-house

May include assets sourced from academic institutions (i.e., not from industry)

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Notes: *Each drug-disease combination counted as a single project
Source: Citeline; Eikon; Orbis; L.E.K. research and analysis

Development routes

Novel lead assets typically originate from 5 key points depending on the stakeholders involved

Big biopharma

Big biopharma internal drug discovery – in-house R&D used to discover lead compounds (includes in-house repositioning)

Big biopharma carve-out – assets owned by big pharma which are not in active development may be carved out as a small / medium biopharma company

Small / medium biopharma

Collaboration between stakeholders may be important for lead generation

External company drug repositioning* – assets that have been previously trialled / launched in other indications repurposed as a lead for use in a novel indication

Small / medium biopharma drug discovery – in-house R&D used to discover lead compounds (includes academic spin outs founded off basic research / early hits)

Academic institutions / intramural PRGs

Academic / intramural PRG drug drug discovery – in-house R&D used to discover lead compounds (where researchers take early hits through to IP formation, typically with commercial collaboration or subsequent academic spin out)

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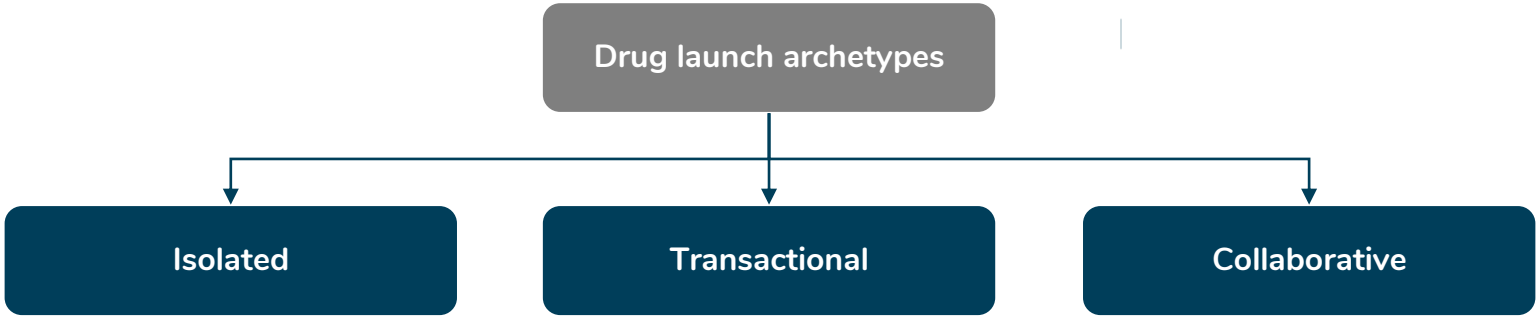
Note: *Assumes origination point as a lead for novel indication
Source: Evaluate Pharma; L.E.K. interviews, research and analysis

L.E.K. has defined a number of different archetypes based on the ultimate actions of the drug marketer



- Big biopharma in-house
- Small / medium biopharma "go-it-alone" (through to launch)

- Company M&A
- Asset in-licensing / acquisition

- Industry – industry collaboration
- Industry – academic collaboration
- Industry – public research group / not-for-profit collaboration

Source: PharmaProjects; Company press release; L.E.K. research and analysis

Isolated asset development occurs in big pharma from internal R&D and in small / medium biopharma who choose to "go-it-alone"

Isolated archetypes	Origin of asset	Typical timing	Recent examples

Big biopharma in-house 	• Big biopharma internal drug discovery (includes in-house repositioning)	• Drug discovery / preclinical development through to launch	• **Piqray** (Novartis) – small molecule (alpelisib) targeting various oncology indications
			  – drug discovery and development by Novartis through to launch
			• **Rinvoq** (AbbVie) – 2nd generation JAK inhibitor (upadacitinib) for rheumatoid arthritis
			  – originator is Abbott who spun out as AbbVie and developed the product in-house

Small / medium biopharma "go-it-alone" 	• Big biopharma carve-out
	• External company drug repositioning
	• Small / medium biopharma drug discovery (inc. academic spinout off early hits)
	• Academic / intramural PRG drug discovery (inc. academic spinout once lead identified)
		• Drug discovery / preclinical development through to launch	• **Zynteglo** (Bluebird bio) – gene therapy (betibeglogene autotemcel) for transfusion-dependent β-thalassaemia
			  – drug discovery and development by Bluebird bio through to launch
			• **Oxbryta** (Global Blood Therapeutics) – allosteric modifier (voxelotor) for sickle cell disease
			  – drug discovery and development conducted in-house by GBT through to launch

Source: PharmaProjects; Company press release; L.E.K. research and analysis

A transactional route-to-market archetype is common, with transfer of asset ownership during R&D via company M&A or in-licensing

Transactional archetypes	Origin of asset	Typical timing	Recent examples
Company M&A 	• Big pharma carve out • External company drug repositioning • Small / medium biopharma drug discovery • Academic / intramural PRG drug discovery	• **M&A by most advanced asset in 2018**: 36% preclinical development, 11% Ph I, 32% Ph II and 21% Ph III	• **Leqvio**, an RNA interference (RNAi) therapeutic (inclisiran) directed to proprotein convertase subtilisin/Kexin type 9 (PCSK9) – ownership to Novartis via acquisition of The Medicines Company
Asset in-licensing / acquisition 	• Big pharma internal drug discovery • Big pharma carve out • External company drug repositioning • Small / medium biopharma drug discovery • Academic / intramural PRG drug discovery	• **In-licensing deals by stage in 2018:** 39% research, 21% preclinical development 12% Ph I or Ph I / II, 10% Ph II, 10% Ph III, 8% filed	• **Vitrakvi**, a small molecule kinase inhibitor (larotrectinib) for anti-cancer treatment, discovered by Loxo Oncology – Bayer in-licensed asset during Phase II development • **Copiktra**, a small molecule kinase inhibitor (duvelisib) for hematologic cancers, discovered and developed by Infinity Pharma – Verastem Oncology in-licensed asset from Infinity Pharma during Phase III, Secura Bio in-licensed and commercialised after Phase III

Source: PharmaProjects; Life Science Nation; Company press release; L.E.K. research and analysis

Collaborative development between pharma, academia and not-for-profits combines expertise/resources needed to take an asset to market

Collaborative archetypes	Origin of asset	Typical timing	Recent examples
Industry – industry collab 	• Big pharma internal drug discovery • Big pharma carve out • External company drug repositioning • Small / medium biopharma drug discovery • Academic / intramural PRG drug discovery	• DD** / preclinical dev. through to launch	• Shionogi and Roche co-development of **Xofluza** (baloxavir marboxil), an oral endonuclease inhibitor for influenza virus • ViiV Healthcare (GSK / Shionogi / Pfizer JV) and Janssen collaboration for phase III and commercialisation of **Vocabria** (cabotegravir), for treatment and prevention of HIV/AIDS
Industry – academic collab 	• Academic / intramural PRG drug discovery • Small / medium biopharma drug discovery	• DD / preclinical dev. through to launch	• University of Washington and Sage Therapeutics for **Zulresso** (brexanolone), a neuromodulator for postpartum depression • George Washington University and La Jolla Pharmaceuticals for **Giapreza**, a small molecule catecholamine-resistant hypotension
Industry – PRG* / not-for-profit collab 	• Academic / intramural PRG drug discovery • Small / medium biopharma drug discovery	• DD / preclinical dev. through to launch	• Roche, PTC therapeutics and Spinal Muscular Atrophy Foundation for **Evrysdi** (risdiplam), an oral splice modifier in SMA • Karyopharm, Barrow Neurological Institute and National Cancer Institute research for **Xpovio** (selinexor), a first-in-class oral therapy in diffuse large B-cell lymphoma and multiple myeloma

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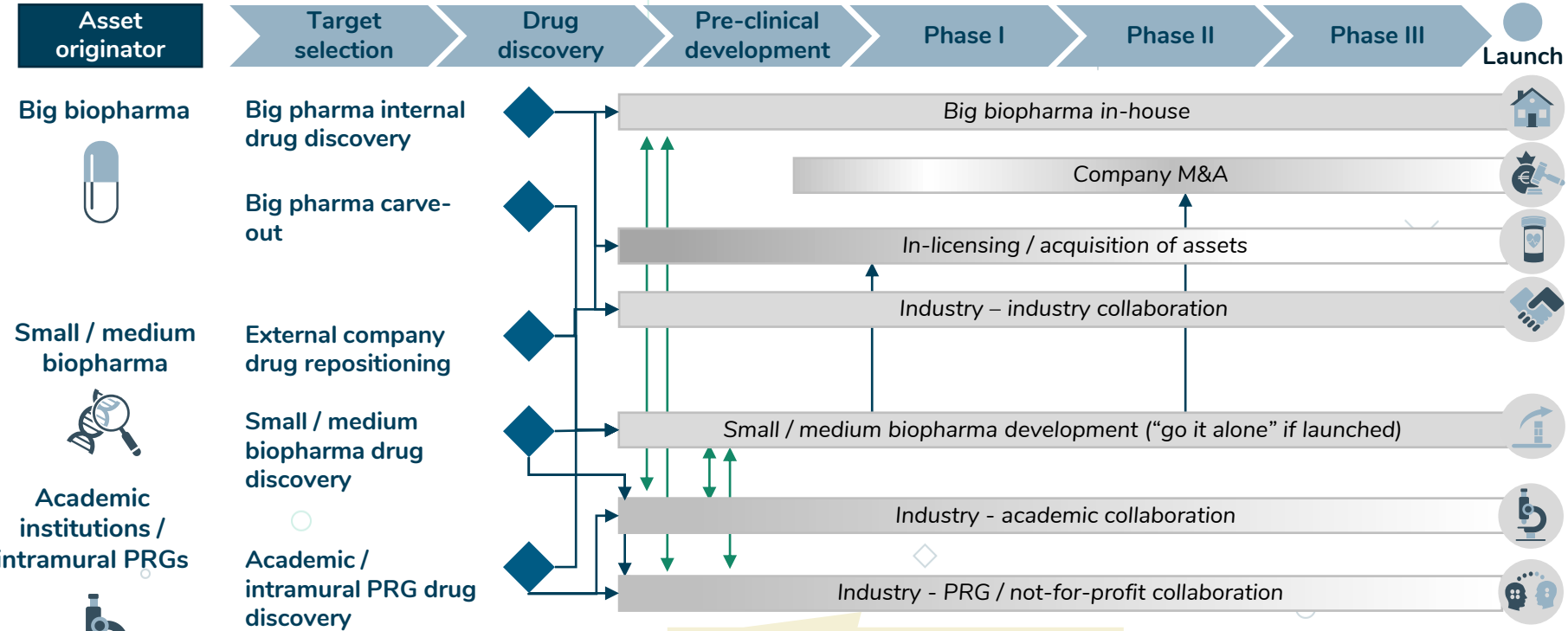
Note: *PRG – public research group; **Drug discovery
Source: PharmaProjects; Company press release; L.E.K. research and analysis

The number of potential routes to launch are complex and may involve multiple steps



Both industry and academic collaboration requires industry partner who may be big pharma or small-medium biopharma

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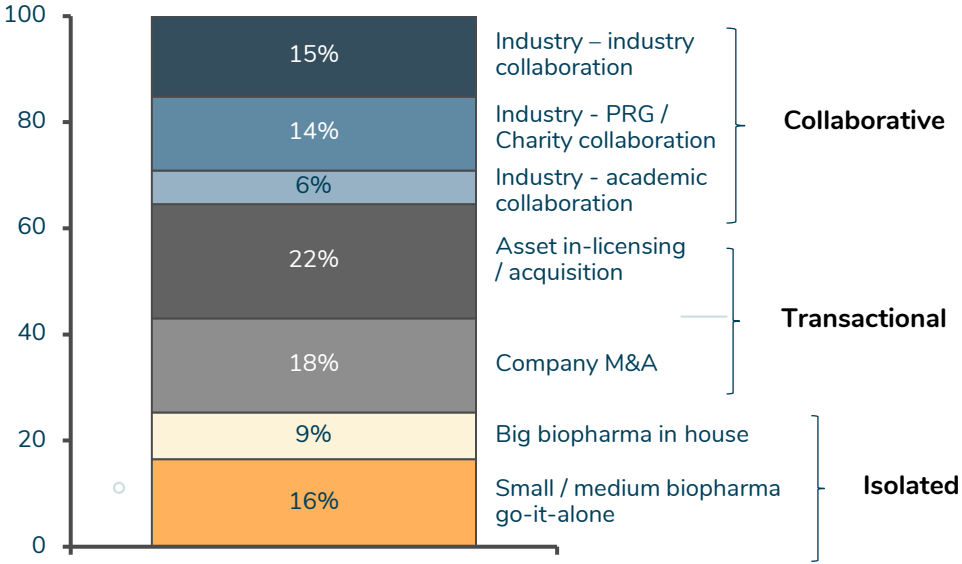
Source: Evaluate Pharma; L.E.K. interviews, research and analysis

L.E.K.'s research shows that all archetypes are used in the launch of NMEs; the pathway to the ultimate marketer is generally complex

Development route archetype of 79 NMEs* launched by U.S. / European companies (2018-21)
Percentage



INDICATIVE ONLY**

- We have conducted analysis on the route to market based on the drug marketer archetypes**
  - multiple transactional and collaborative agreements can occur throughout an asset's pathway to market
- Asset in licensing / acquisition and company M&A are the most common archetypes seen with small / medium biopharma go-it-alone and industry – industry collaboration also common
- Data from Deloitte shows that the 12 leading biopharma companies are increasingly reliant on M&A and asset in-licensing / acquisition as a source of innovation for their late stage pipeline
  - the four other more specialised companies studied are increasingly relying on in-licensing and co-development suggesting a move towards partnering to access innovation

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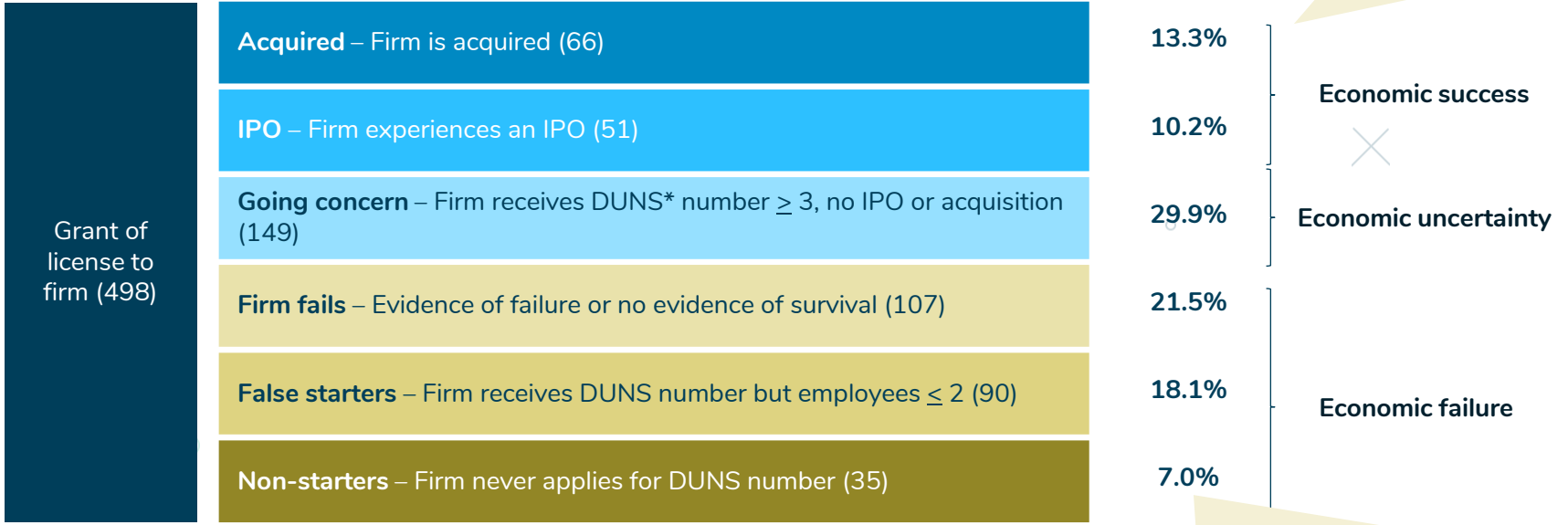
Note: *New molecular entity; **Based on L.E.K. assessment of archetype classification
Source: PharmaProjects; Company press release; Deloitte; L.E.K. research and analysis

U.S. data suggests that <25% of university licensed LS start-ups succeed, with c.50% failing and c.30% having an uncertain outcome

Outcomes for 498 university-licensed life science start ups – United States (Published 2020, covers 1980-2013 period)

The study notes that firms that are founded in, or re-locate to, areas with the right scientific resources required by the start-up are most likely to succeed and not fail



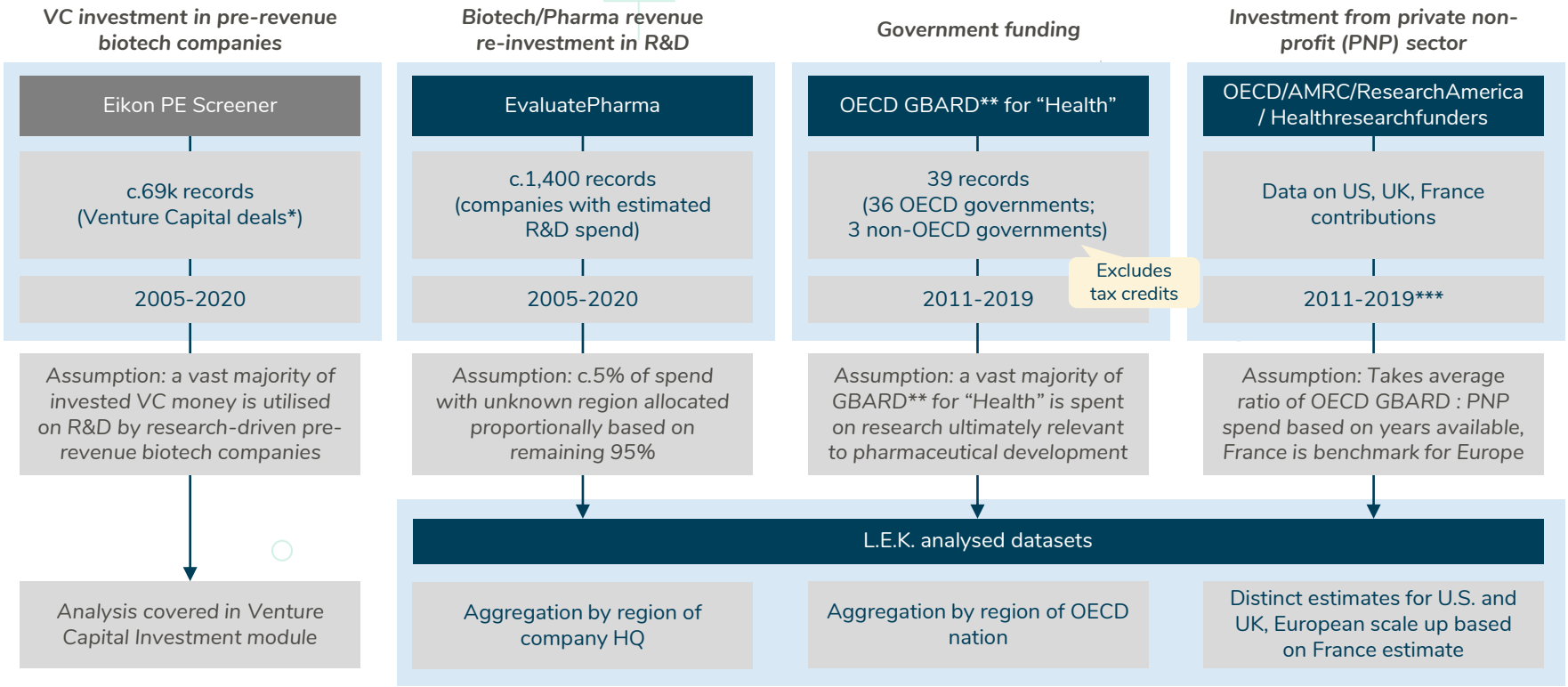
The study highlights non-starters and false starters are set up as symbolic activity by the university to boost their reputation in the short-term, rather than representing legitimate investment in the long-term

Note: *Dun & Bradstreet Data Universal Numbering System, which is considered a comprehensive registry of firms that appear to be (or have been) going concerns
Source: Nature; Science Translational Medicine; X-Mol; Godfrey et al 2020; L.E.K. interviews, research and analysis

3. R&D Funding

Quantification of R&D

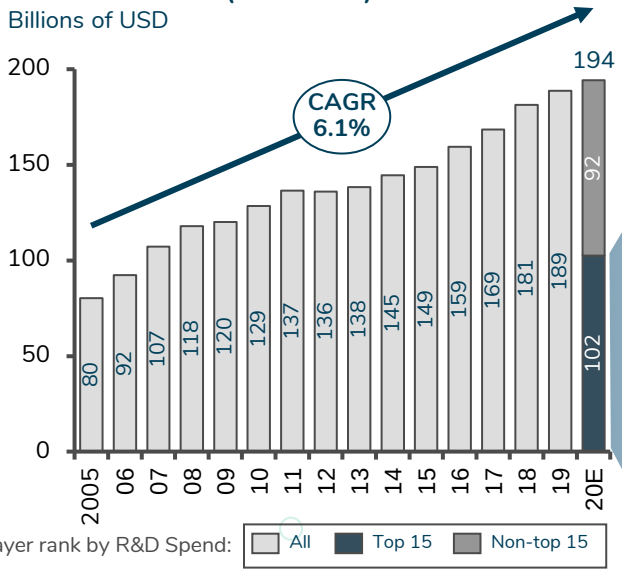
Overall quantification of R&D investment is derived from separate data sources for each major source of research investment



Notes: * Each investor-investee-investment round combination is counted as a single "deal"; ** Government Budget Allocation for Research and Development; ***For AMRC UK data, other countries had less accessible data
Source: Eikon; L.E.K. Research and Analysis

Private-sector R&D spend has grown at c.6% p.a. over the last 15 years; in 2020 the Top 15 spenders contributed more than 50% total

Global Private-sector R&D spend
EvaluatePharma (2005-20E)
Billions of USD



EvaluatePharma extracts R&D expenditure from company reports and excludes any exceptional expenses; R&D spend of c. 1,300 pharma companies are summed up to generate worldwide spend

Rank	Company	R&D Spend (Billions of USD, 2020)	Share of private sector R&D spend	HQ country
1	Roche	11.2	5.7%	
2	MERCK	9.4	4.9%	
3	Bristol Myers Squibb	9.4	4.8%	
4	Johnson & Johnson	9.0	4.6%	
5	Pfizer	8.8	4.5%	
6	NOVARTIS	8.6	4.4%	
7	SANOFI	5.9	3.0%	
8	Lilly	5.8	3.0%	
9	AstraZeneca	5.8	3.0%	
10	abbvie	5.8	3.0%	
11	gsk	5.8	3.0%	
12	GILEAD	4.7	2.4%	
13	Takeda	4.4	2.3%	
14	AMGEN	4.3	2.2%	
15	BAYER	3.6	1.9%	

Source: Evaluate Pharma (2005-20)

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Ten of the Top thirty spenders are European players; they contribute 40% of spend by the top 30 players

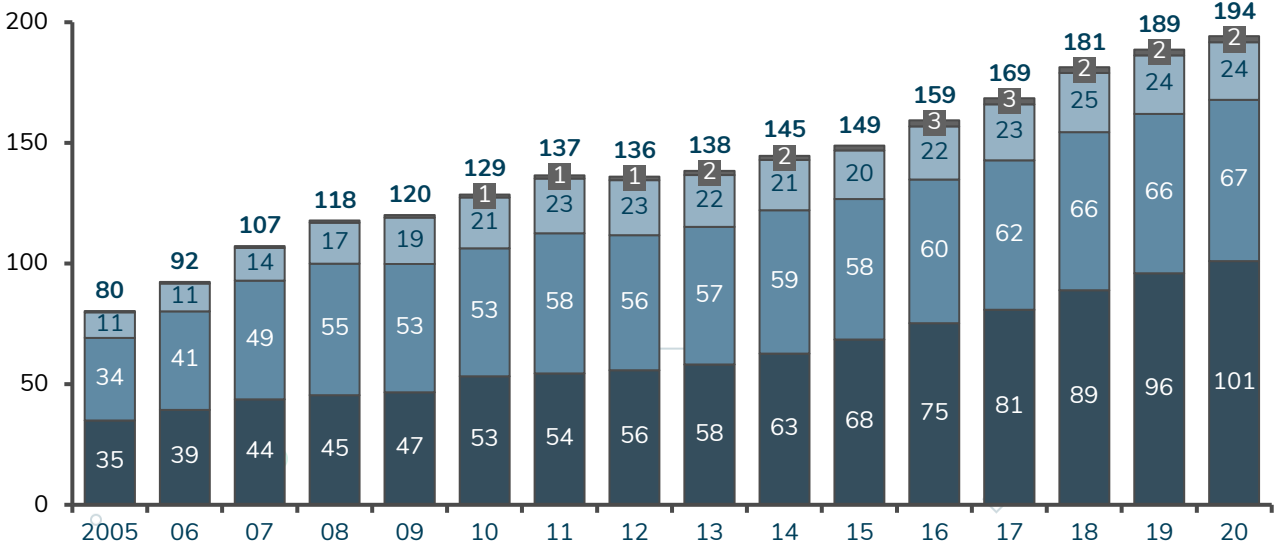
Rank	Company	R&D Spend (Billions of USD, 2020)	Share of private sector spend	HQ country
1	Roche	11.2	5.7%	Switzerland
2	Merck & Co	9.4	4.9%	US
3	Bristol-Myers Squibb	9.4	4.8%	US
4	Johnson & Johnson	9.0	4.6%	US
5	Pfizer	8.8	4.5%	US
6	Novartis	8.6	4.4%	Switzerland
7	Sanofi	5.9	3.0%	France
8	Eli Lilly	5.8	3.0%	US
9	AstraZeneca	5.8	3.0%	UK
10	AbbVie	5.8	3.0%	US
11	GlaxoSmithKline	5.8	3.0%	UK
12	Gilead Sciences	4.7	2.4%	US
13	Takeda	4.4	2.3%	Japan
14	Amgen	4.3	2.2%	US
15	Bayer	3.6	1.9%	Germany

Rank	Company	R&D Spend (Billions of USD, 2020)	Share of private sector spend	HQ country
16	Boehringer Ingelheim	3.2	1.7%	Germany
17	Regeneron	2.7	1.4%	US
18	Novo Nordisk	2.4	1.3%	Denmark
19	Biogen	2.3	1.2%	US
20	Astellas Pharma	2.2	1.1%	Japan
21	Daiichi Sankyo	2.1	1.1%	Japan
22	Incyte	2.1	1.1%	US
23	Otsuka Holdings	2.0	1.0%	Japan
24	Merck KGaA	1.8	0.9%	Germany
25	Vertex	1.7	0.9%	US
26	UCB	1.7	0.9%	Belgium
27	Eisai	1.5	0.8%	Japan
28	BeiGene	1.2	0.6%	China
29	Alexion	1.1	0.6%	US
30	Chugai	1.1	0.6%	Japan

Source: Evaluate Pharma (2005-20)

A majority of private-sector spend is from Europe/North America; growth is significantly higher in North America than total

Global Private sector R&D spend by Region (Company HQ)*
EvaluatePharma (2005-2020)
Billions of USD



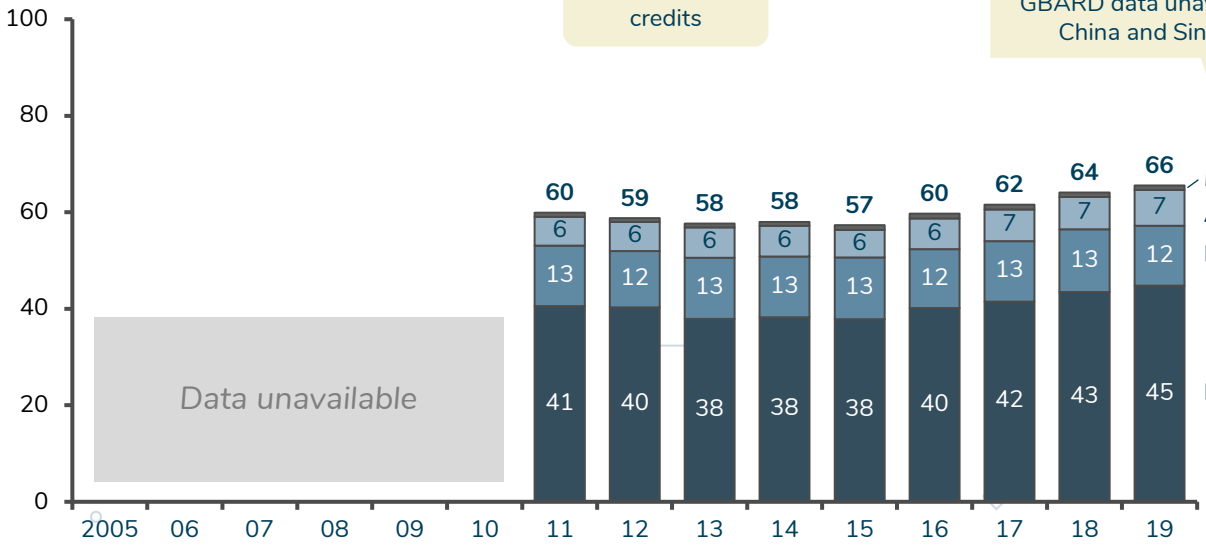
	% CAGR (2005-20)
Total	6.1
ROW	10.9
APAC	5.5
Europe	4.6
North America	7.3

According to clinicaltrials.gov as of March 1st 2021, c.33% of clinical studies are registered in the U.S. only, 50% in non-U.S. only, 5% in both U.S. and non-U.S., and 12% not provided

Notes: * c.5% of companies per year could not be allocated to a region – the remaining R&D spend has been allocated proportionally to the rest of global spend
Source: EvaluatePharma; Eikon; Orbis; clinicaltrials.gov; L.E.K. research and analysis

Government contributions appear largest in North America and Europe; growth has been low or stagnant across regions

Government Budget Allocations for R&D (GBARD)*
OECD Countries only (2011-2019)
Billions of USD**

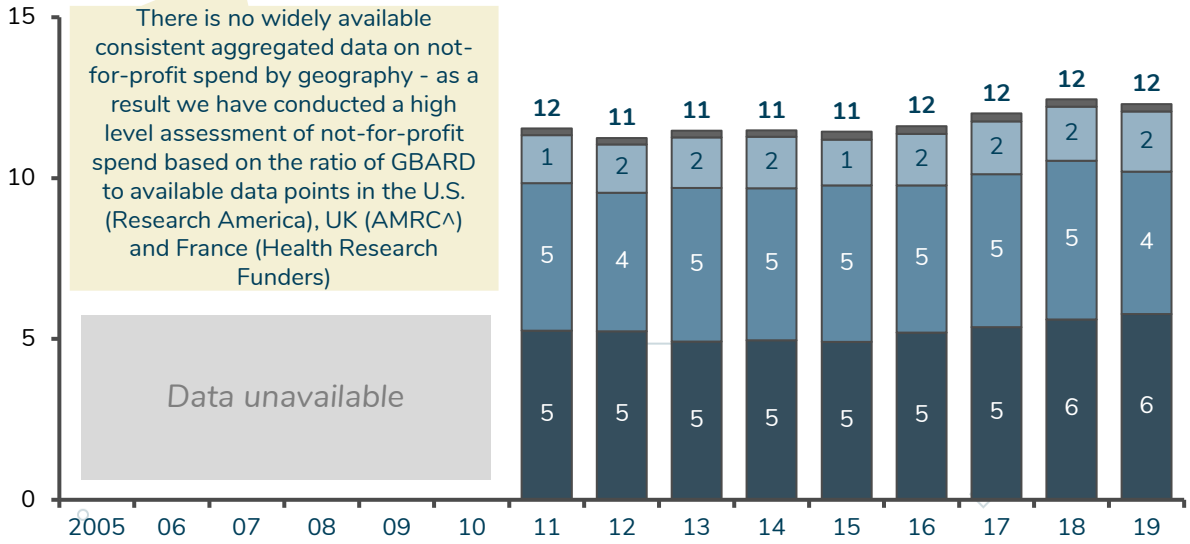


	% CAGR (2011-19)
Total	**1.1**
ROW	1.5
APAC	2.8
Europe	(0.1)
North America	1.3

Notes: * encompass all allocations met from sources of government revenue foreseen within the budget; for years without data, the preceding year's value was taken
**Converted from 2015 USD to 2020 USD
Source: OECD; L.E.K. Research and Analysis

North American and European not-for-profits are estimated to contribute the most to overall R&D spend

Estimate for not-for-profit R&D spend* by geography
OECD Countries only (2011-2019)
Billions of USD**



GBARD data unavailable for China and Singapore

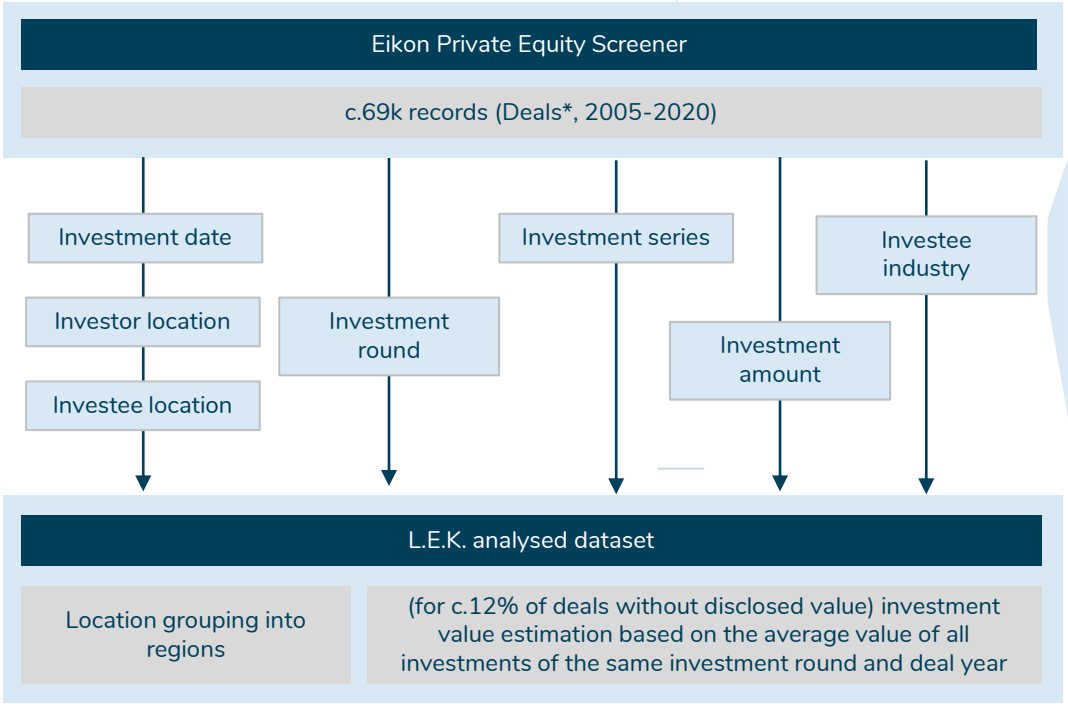
INDICATIVE ONLY*

	% CAGR (2011-19)
Total	**0.8**
ROW	1.5
APAC	2.8
Europe	(0.4)
North America	1.2

Notes: *Assuming constant ratio of GBARD to not-for-profit spend – U.S. 12.5% of GBARD, UK 70%, other geographies 25% based on estimates for France benchmark; **Converted from 2015 USD to 2020 USD; ^Association of Medical Research Charities
Source: OECD; AMRC; ResearchAmerica; HealthResearchFunders.org; L.E.K. Research and Analysis

Venture capital investment

Venture Capital investment analysis was conducted leveraging proprietary deals data from Eikon's Private Equity Screener



Included Primary industry sub-groups

- Biotechnology and Pharmacology
- Other Biotechnology Related
- Biotech Related Research & Other Services
- Other Biotechnology Services
- Pure & Contract Biotechnology Research
- Genetic Engineering
- Human Biotechnology
- Immune Response Effectors (interferons, vaccines)
- Other Therapeutic Biotechnology
- Other Therapeutic Proteins (incl. hormones & TPA)
- Therapeutic Biotechnology Products
- Therapeutic Monoclonal Antibodies
- Medical Therapeutics
- Other Pharmaceutical NEC
- Pharmaceutical Equipment
- Pharmaceutical Production
- Pharmaceutical Research
- Pharmaceutical Services
- Pharmaceuticals
- Pharmaceuticals/Fine Chemicals (non-biotech)

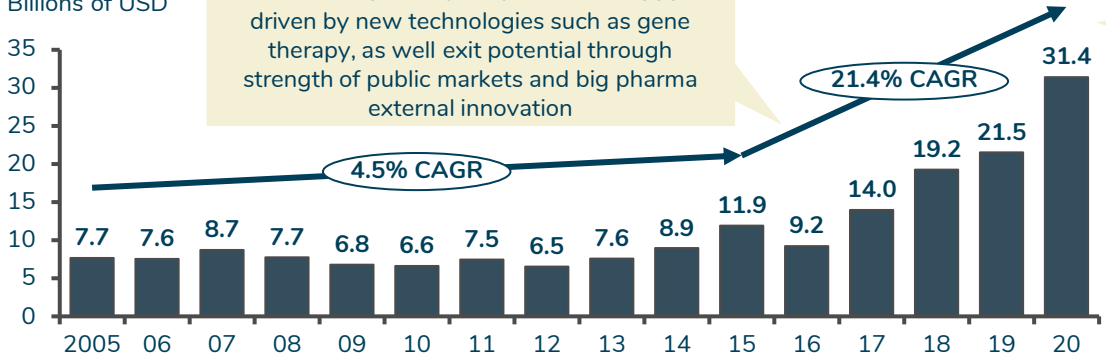
Notes: * Each investor-investee-investment round combination is counted as a single "deal"
Source: Eikon; L.E.K. Research and Analysis

After a decade of relatively modest growth, Global VC investment has seen strong and accelerating growth over the past 5 years

VC investment

Estimated global VC investment in Biopharma (2005-2020)

Billions of USD



Increase in VC investment since mid-2000s is driven by new technologies such as gene therapy, as well exit potential through strength of public markets and big pharma external innovation

Increase in VC investment in 2020 thought to be partly driven by COVID

For the c.12% of deals without deal values disclosed on Eikon, L.E.K. has assigned an estimated deal value based on the average of deals from the same year and of the same investment round*

	2005	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20
% deals with USD value	88%	93%	92%	91%	88%	78%	83%	85%	86%	89%	90%	94%	92%	90%	88%	88%

Triangulation (Billions of USD)

JP Morgan				3.9	4.0	4.7	4.8	6.3	10.5	9.6	11.8	17.9	17.3
BIO Industry analysis			4.4	4.1	4.2	4.5	5.2	6.8	10.4	9.4	11.4	17.5	

BIO industry analysis used Cortellis and JP Morgan used the Dealforma database

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Notes: *Three-series moving average applied to remove the impact of bridging rounds

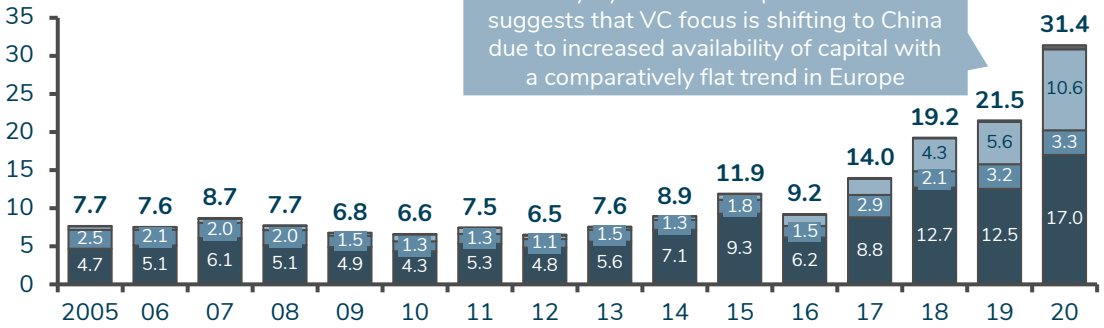
Source: Eikon; JP Morgan; BIO Industry analysis; L.E.K. Research and Analysis

Most VC investment originates from North America and APAC; growth appears to be driven mostly by growing deal value

VC investment

Estimated global VC investment in Biopharma by investor region* (2005-2020)

Billions of USD



Recent growth in APAC is driven almost entirely by China and Japan - feedback suggests that VC focus is shifting to China due to increased availability of capital with a comparatively flat trend in Europe

	% CAGR (2005-15)	% CAGR (2015-20)
Global	4.5	21.4
ROW		
APAC	4.8	70.5
Europe	(3.1)	12.5
North America	7.1	12.8

Average deal value*

Millions of USD

Deal values driven by increased valuations, increased competition and increased fund sizes

APAC	4.9	15.3
Europe	3.6	7.6
North America	7.4	10.2

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Notes: *For deals without a known investor location, L.E.K. has allocated to regions proportionally to regional distribution of the year; Each investor-investee-investment round combination is counted as a single "deal"

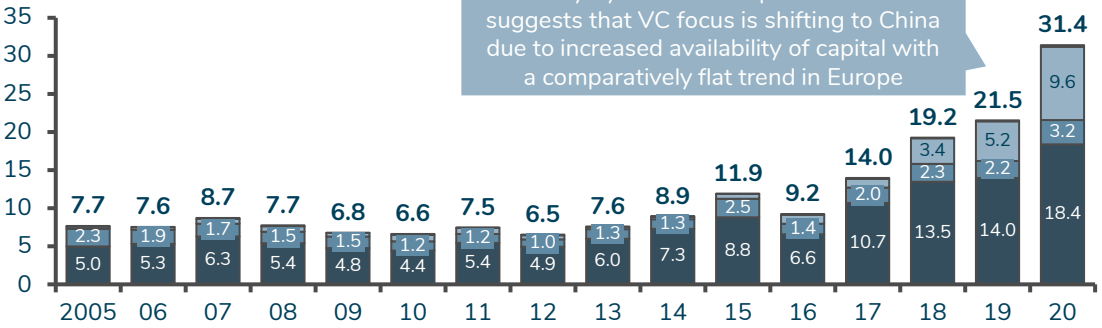
Source: Eikon; L.E.K. Research and Analysis

Most VC investment is directed at North America and APAC; growth appears to be driven mostly by average deal value

VC investment

Estimated global VC investment in Biopharma by investee region* (2005-2020)

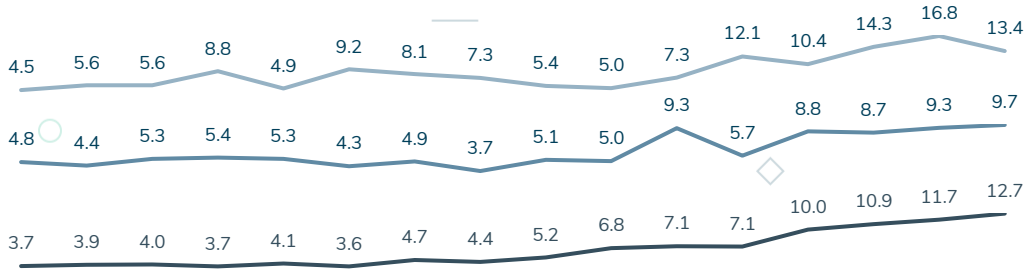
Billions of USD



	% CAGR (2005-15)	% CAGR (2015-20)
Global	4.5	21.4
ROW		
APAC	7.0	73.0
Europe	0.5	5.2
North America	5.9	15.9

Average deal value*

Millions of USD



APAC	4.9	12.8
Europe	6.8	0.8
North America	6.7	12.2

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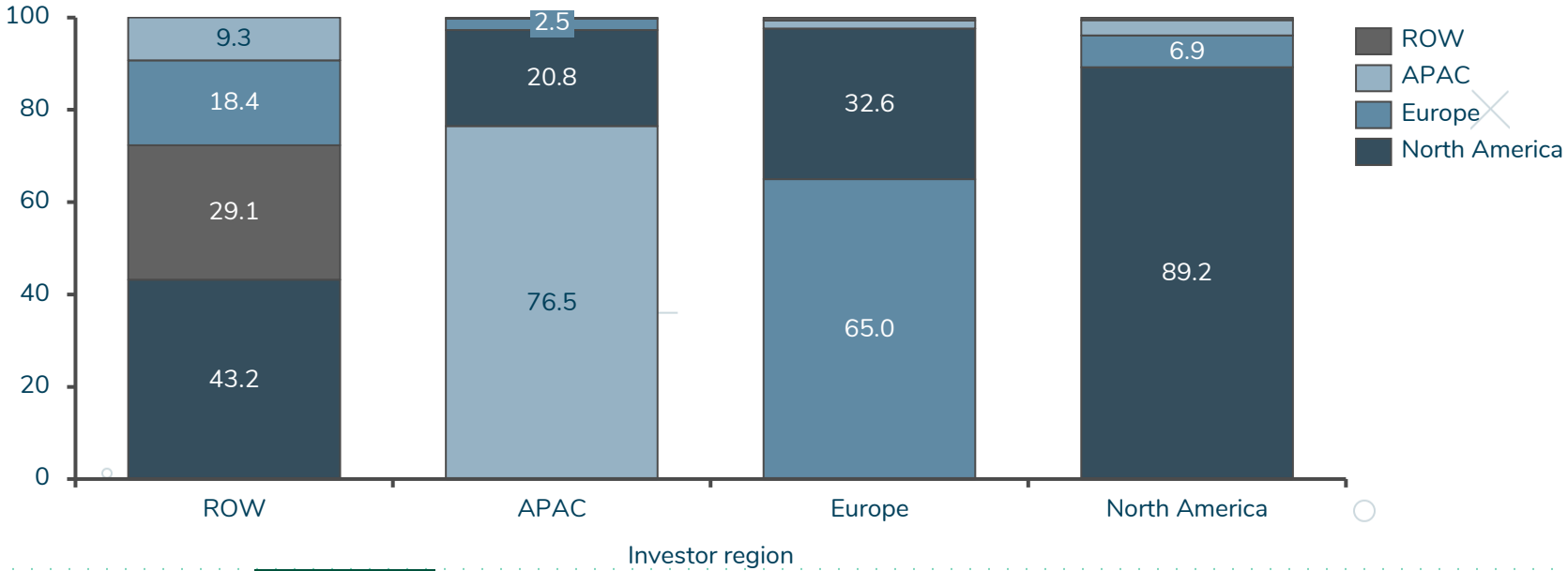
L.E.K.

Notes: *For deals without a known investor location, L.E.K. has allocated to regions proportionally to regional distribution of the year; Each investor-investee-investment round combination is counted as a single "deal"
Source: Eikon; L.E.K. Research and Analysis

VC investment is more commonly directed at companies in the same region

Distribution of investee regions split by each investor region
% of VC investment value



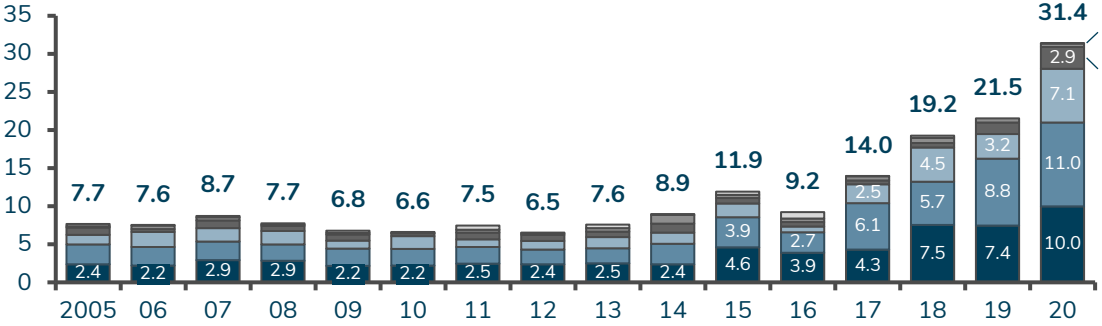
Source: Eikon; L.E.K. Research and Analysis

Most aggregate investment is going towards earlier series; for earlier series, a majority of growth is being driven by increasing deal values

VC investment

Estimated global VC investment in Biopharma by investment Series* (2005-2020)

Billions of USD



	% CAGR (2005-15)	% CAGR (2015-20)
Total	4.5	21.4
Further series		
Series D	(2.7)	31.9
Series C	3.7	31.4
Series B	4.1	22.7
Series A	6.9	16.8

Average deal value*

Millions of USD

Series C	7.7	13.3
Series B	6.8	9.5
Series A	6.1	9.5

Notes: *For deals without an assigned series, L.E.K. has allocated to series proportionally to series distribution of the year; Each investor-investee-investment round combination is counted as a single "deal"

Source: Eikon; L.E.K. Research and Analysis

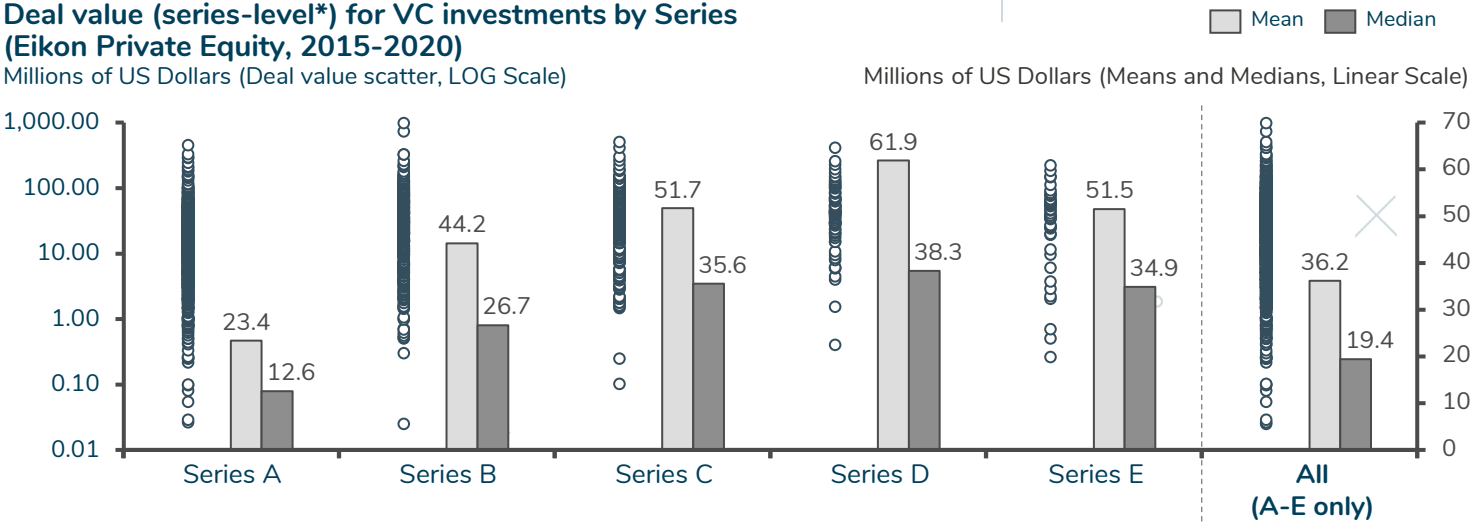
Average VC investment series values increase significantly from Series A to Series D

VC investment

Data capture: **02/2021**

L.E.K. have used the last 5 years of deals for representative benchmarking, given the strong growth in deal value over the last 15 years

Deal value (series-level*) for VC investments by Series (Eikon Private Equity, 2015-2020)



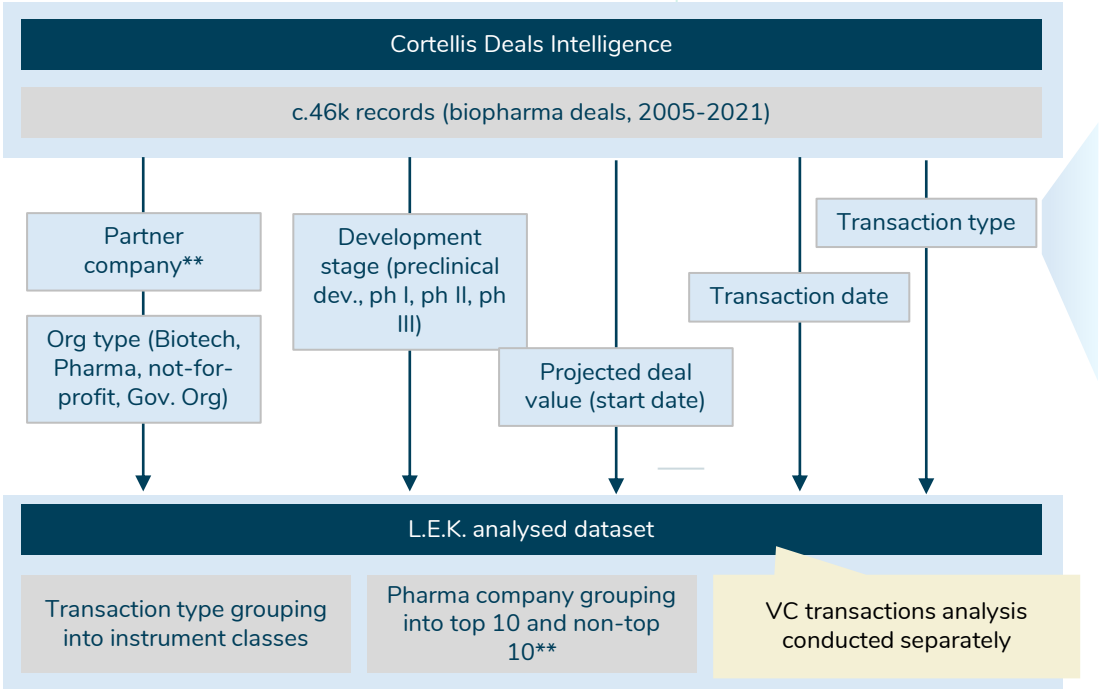
	Series A	Series B	Series C	Series D	Series E	All (A-E only)
Total series* (2015-20)	c.1,000	c.600	c.280	c.90	c.40	**c.2,000**
% with disclosed value	c.90%	c.93%	c.95%	c.95%	c.100%	**c.92%**

Notes: *Analysis conducted at the series-level (each investee-investment round counted as a single deal)
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Financial instruments analysis

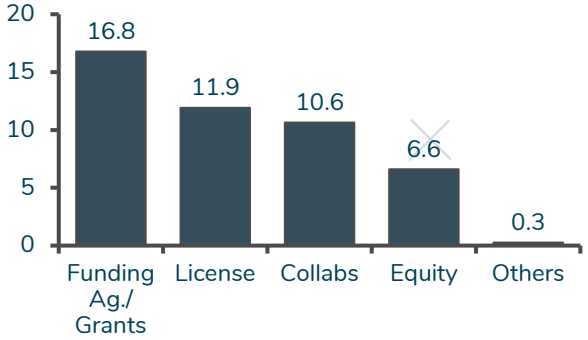
Financial instruments analysis was conducted leveraging proprietary deals data from Cortellis and company data from Orbis and Eikon

Data capture: **02/2021**



Biopharma deals by instrument class

Thousands of deals (2005-2021)*



Cortellis provides the highest coverage of biopharma transactions of all proprietary datasets available to L.E.K. – however coverage is likely to be relatively limited for some transaction types (e.g. grants) and has some exclusions*

Notes: *Records are not created for (1) Donations to research centers/institutes; (2) Requests for financial support/R&D funding; (3) Funding for interest/bank loans; (4) Funding challenges (5) VC financing rounds (e.g. Series A financing); **"Partner company" is the entity that provides funds to a "Principal company"; ***L.E.K. has used the same list of top 10 players (based on revenue) from the development programs analysis

Source: Cortellis Deals Intelligence; L.E.K. research and analysis

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L.E.K. has used the Cortellis Deals database to analyse deals from the last 15 years across four main categories of profit and non-profit

Non-Profit (Examples)

Governmental organisations

NIH NATIONAL CANCER INSTITUTE

EUROPEAN UNION

Government of the Netherlands

Not-for-profits

CYSTIC FIBROSIS FOUNDATION

INSTITUT PASTEUR

NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK

BILL & MELINDA GATES foundation

For-Profit (Examples)

Pharmaceutical companies

Pfizer

AstraZeneca

MERCK

NOVARTIS

Roche

Biotech companies

Biogen

bicycle therapeutics

STORM THERAPEUTICS

horizon precision genome editing

Biotech vs. pharmaceutical company split based on Cortellis classification; L.E.K. extracted top 10 pharma from pharmaceutical companies based on development programs analysis

Source: Cortellis Deals Intelligence; L.E.K. research and analysis

L.E.K. has leveraged the Cortellis Deals to classify all deals from the last 15 years into instrument classes based on the "transaction type"

Instrument Class	Transaction type*	Definition
Collaboration	Joint Venture	Principal and Partner establish a joint venture company/branch
	Co-Development	Companies share the costs of future R&D and/or commercialization
	Collaboration (Shared responsibilities)	Both continue to conduct development work; the Licensee may or may not reimburse the Licensor for expenses
Equity	Equity/Equity Option	One company acquires or obtains an option to acquire equity in another company (<50%)
	M&A - Acquisition – Full	One company acquires 100% of the outstanding shares of another company
	M&A - Acquisition - Majority Stake	One company acquires control (greater than 50% of voting shares) of another company
	M&A - Merger	Two companies merge into a new company with a new name and stock symbol.
	Acquisition – Option	One company obtains an option to acquire another company.
License	Asset Purchase	One company acquires legal control (i.e., the right to develop, manufacture and sell) over an asset
	License - Basic License	Buyer/Licensee assumes all subsequent control of and payment for development and commercialization
	License - Co-Marketing	both parties book revenue for product sales within the same territory under different brand names
	License - Co-Promotion	share responsibilities for promotion (detailing/advertising) of the product
	License - Equity	Buyer makes a minority investment in the Licensor company in the context of executing a License agreement
	License - Option to take a license	Licensee is granted the right to execute a license agreement at a future point in exchange for a payment today
	License - Supply	Licensor/Seller continues to supply product to the Licensee/Buyer within the context of a License agreement
Funding Agreem./ Grant	Grant	Transactions where the core event is an exchange of money or funding to support research
	Research-Only	Company engages another to perform R&D services with no provision for the commercialization and associated royalties
Others	Loan/Convertible Loan	a large amount of capital is provided upfront in exchange for future repayment plus interest
	Combinations of deals (multi-class)	Combinations of across instrument classes (represents less than 1% of total deals)

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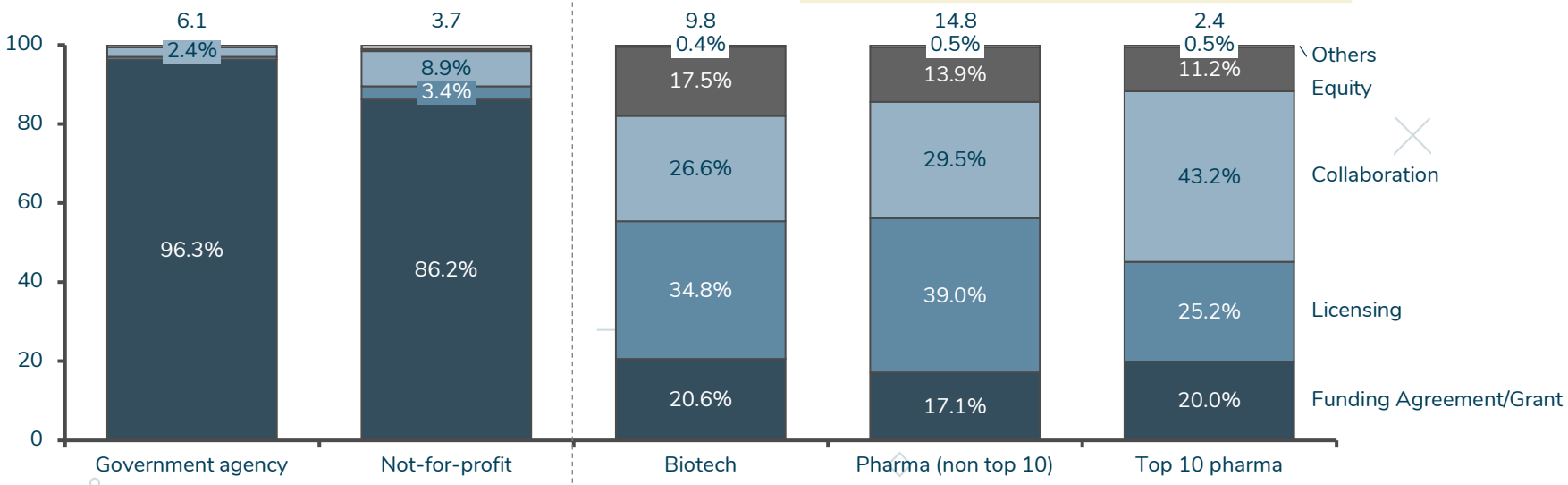
Notes: *Excluded transaction types: Distribution-only; co-promotion; Supply-only; Lawsuit settlements; Service agreements
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Public sector players primarily use grants/funding to invest in R&D, for-profit players also invest in collaborations, assets, and equity

Data capture: **02/2021**

Biopharma deals by instrument class by Partner company type*
(Cortellis Publicly disclosed deals, 2005-2021)
% of thousands of deals (2005-21)

"Partner company" is the entity that provides funds to a "Principal company" in a given deal



Industry may have funding agreements / provide grants to further basic research understanding in an area of interest

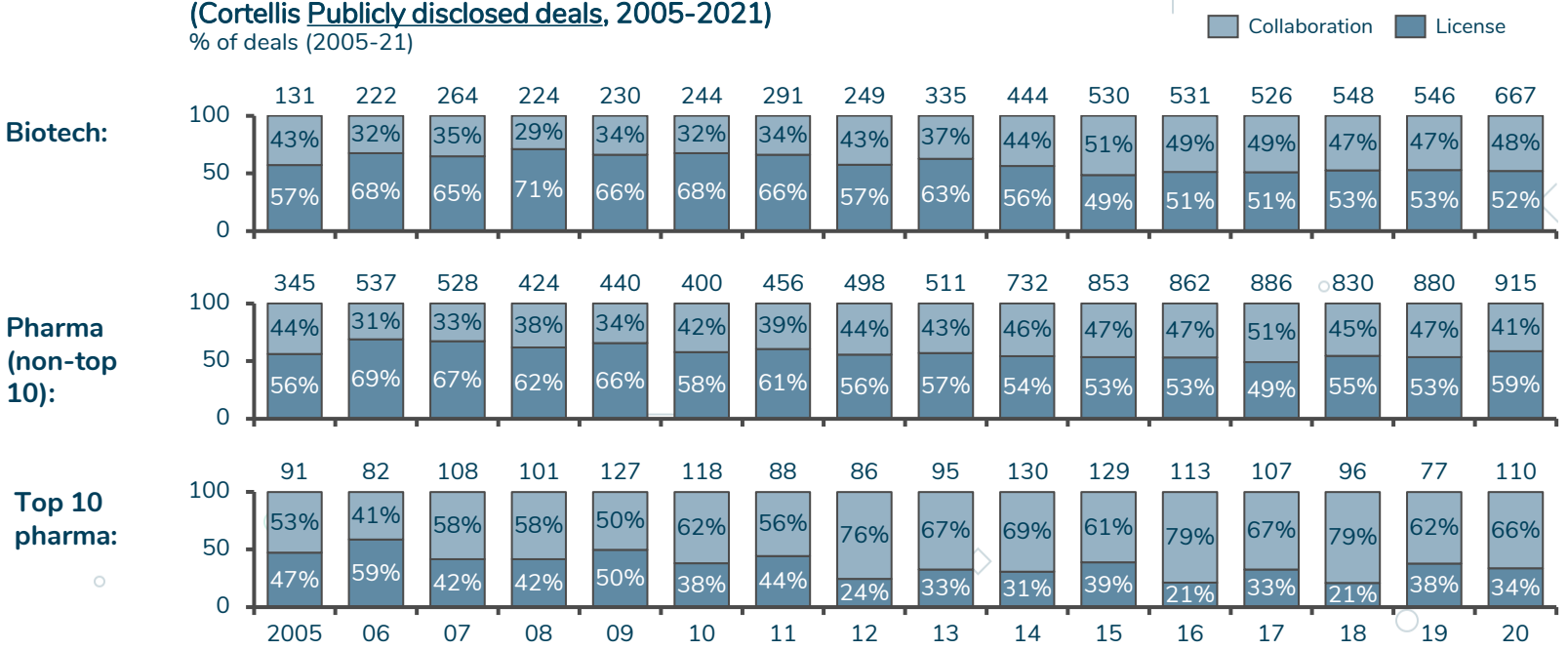
L.E.K. has used the same list of top 10 players (based on revenue) from the development programs analysis

Notes: *Excludes deals from player types outside of the major categories displayed
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

A transition from basic licensing to collaboration has occurred in big biopharma and is occurring moderately for other for-profit players

Data capture: **02/2021**

Biopharma licensing and collaboration deals by partner type (Cortellis Publicly disclosed deals, 2005-2021)
% of deals (2005-21)

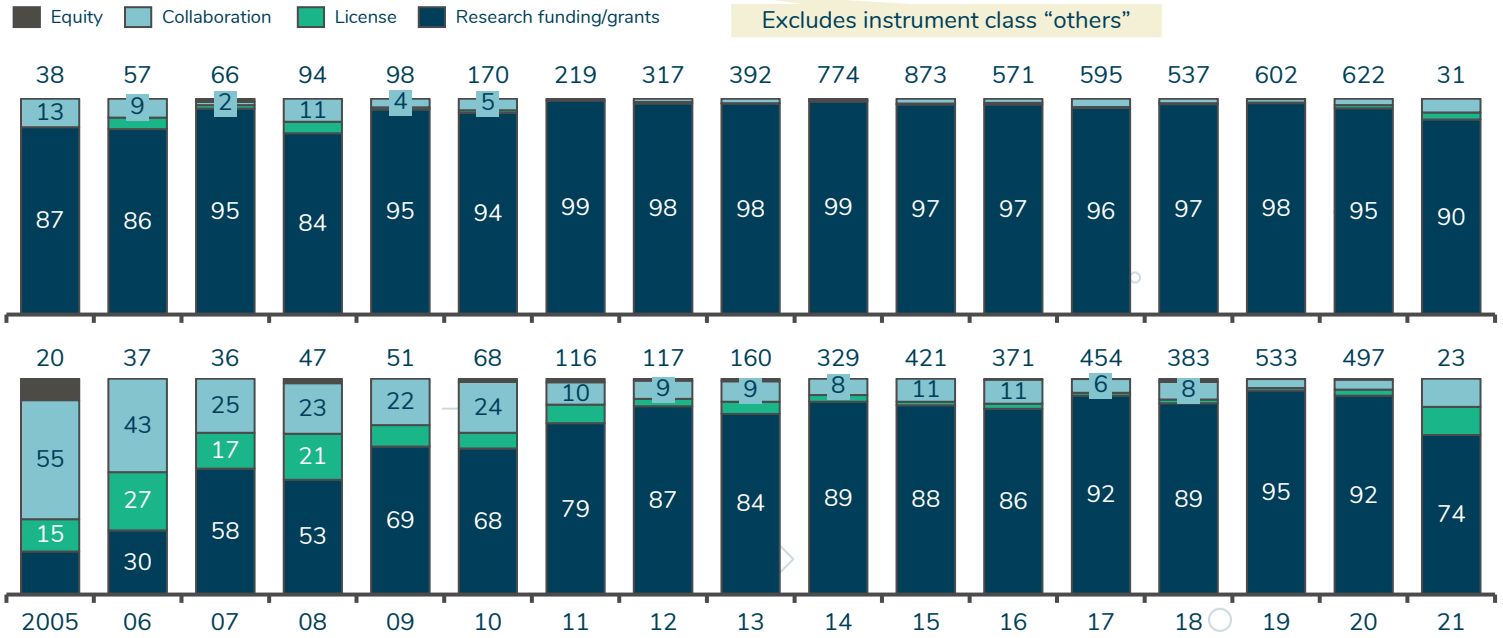


Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Governments and not-for-profits use mostly research funding/grants to invest in R&D

Biopharma deals by instrument class by partner type
(Cortellis Publicly disclosed deals, 2005-2021) [% of deals]

Data capture: **02/2021**



Observed trend likely to be confounded increasing data availability from 2005 through 2015

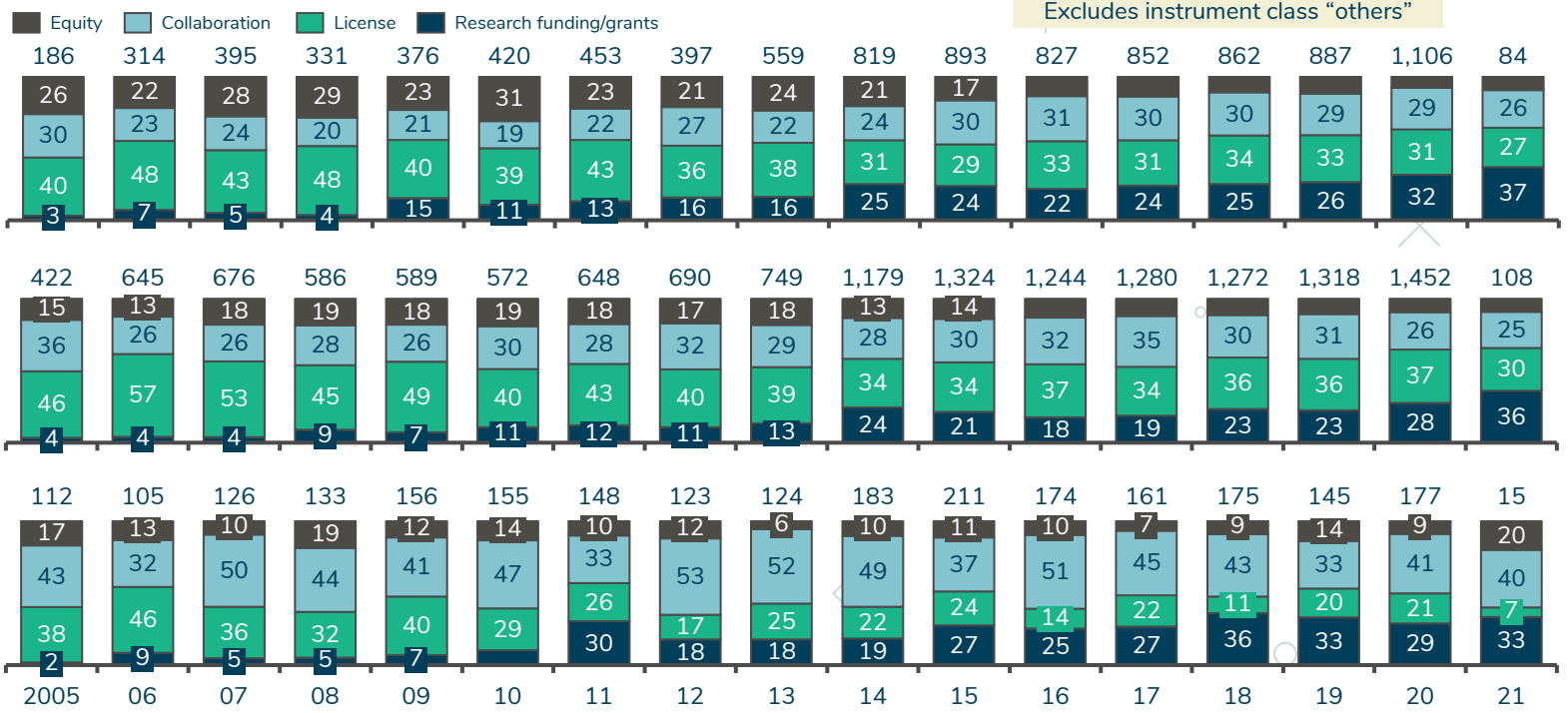
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Research funding/grants for biotech, non-top 10 pharma and top 10 pharma increases, while licencing decreases

Biopharma deals by instrument class by partner type
(Cortellis Publicly disclosed deals, 2005-2021) [% of deals]

Data capture: **02/2021**

Excludes instrument class "others"



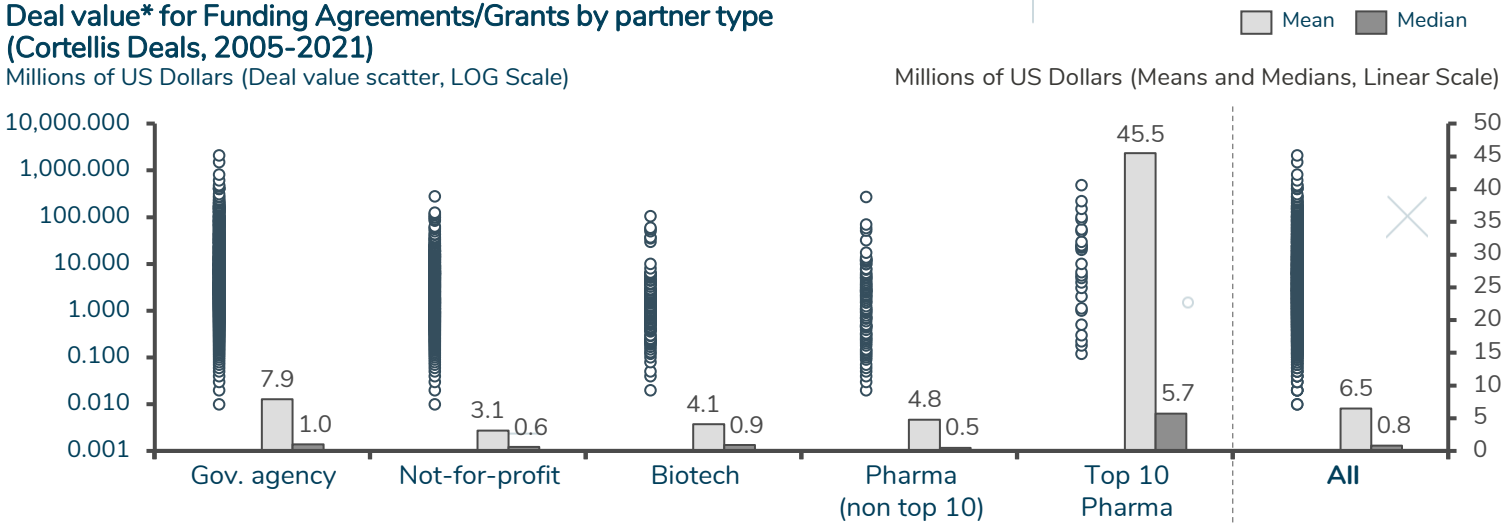
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Funding agreements/Grants vary widely in value; Top-10 pharma deals are larger than those coming from other partner types

F.A./Grants

Data capture: **02/2021**

Deal value* for Funding Agreements/Grants by partner type (Cortellis Deals, 2005-2021)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	c.5,900	c.3,200	c.2,000	c.2,500	c.500	**c.14,100**
% with disclosed value	c.70%	c.56%	c.8%	c.7%	c.7%	**c.45%**

Notes: *Projected deal value at start date;
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Licensing deals vary widely in value; pharma companies have used in-licensing more than biotechs and spend more per deal

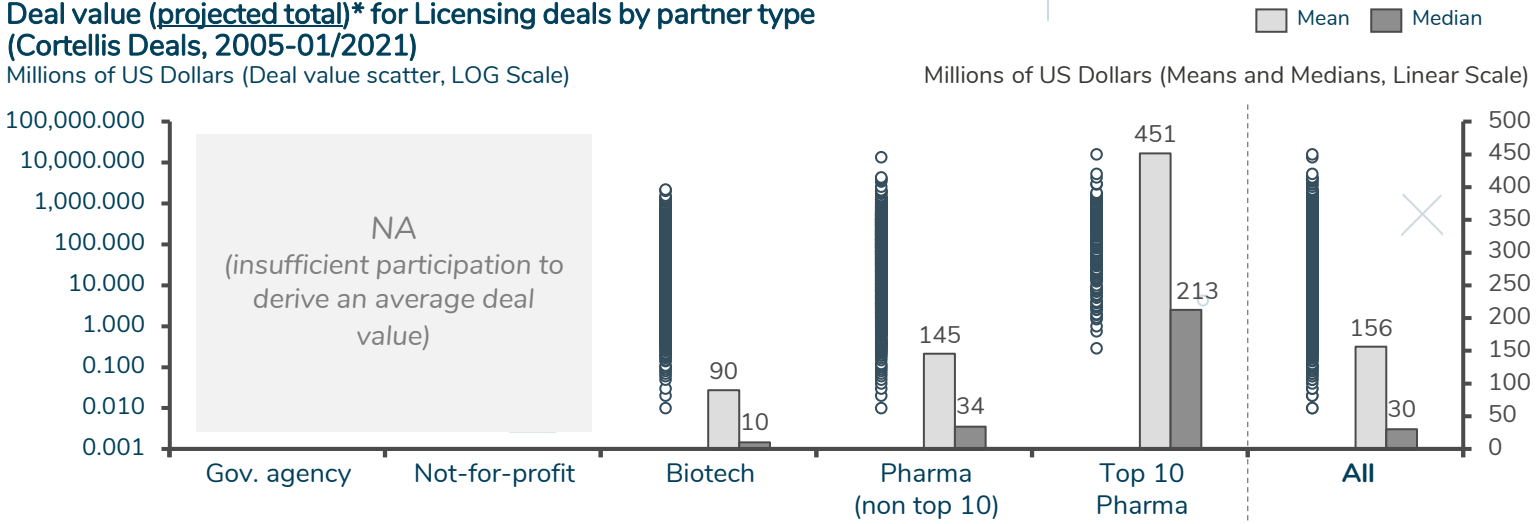
Licensing

Upfront

Total

Data capture: **02/2021**

Deal value (projected total)* for Licensing deals by partner type (Cortellis Deals, 2005-01/2021)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	NA	NA	c.3,400	c.5,800	c.600	**c.10,000**
% with disclosed value	NA	NA	c.24%	c.34%	c.41%	**c.30%**

Notes: *Projected deal value at start date;
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Licensing deals vary widely in value; pharma companies have used in-licensing more than biotechs and spend more per deal

Licensing

Upfront

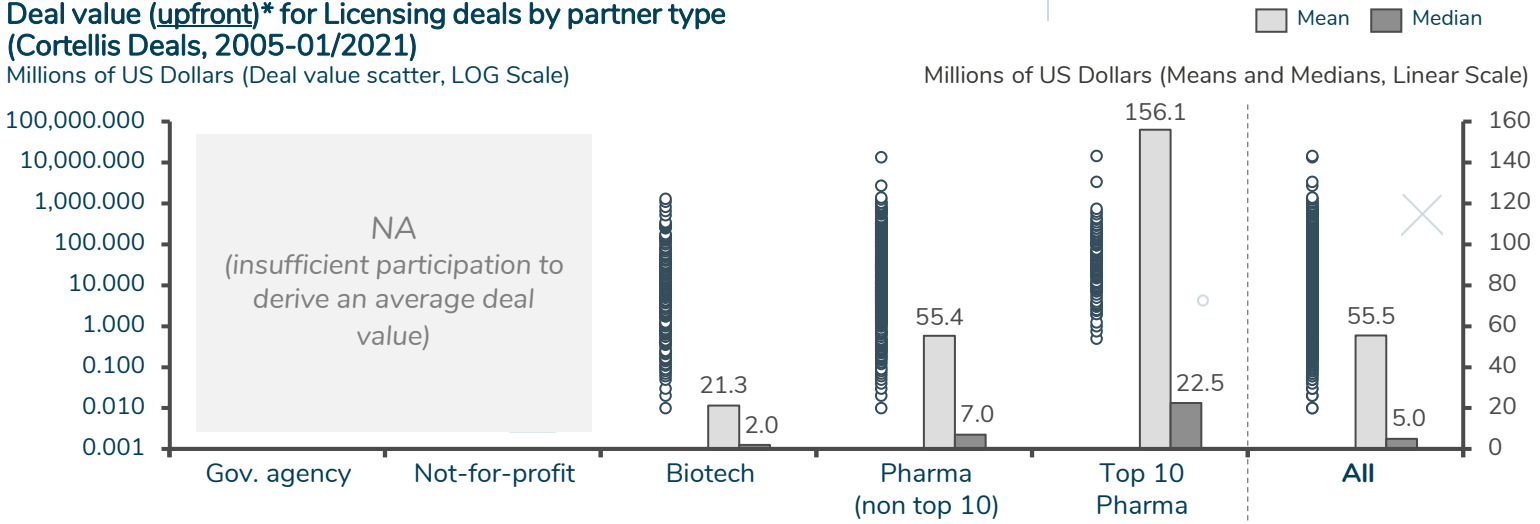
Total

Data capture: **02/2021**

Deal value (upfront)* for Licensing deals by partner type (Cortellis Deals, 2005-01/2021)

Millions of US Dollars (Deal value scatter, LOG Scale)

Millions of US Dollars (Means and Medians, Linear Scale)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	NA	NA	c.3,400	c.5,800	c.600	**c.10,000**
% with disclosed value	NA	NA	c.16%	c.25%	c.30%	**c.22%**

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Notes: *Upfront payment (before milestones and royalties);
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Collaborations vary widely in value; frequency and spend-per-deal appears higher in the for-profit sector

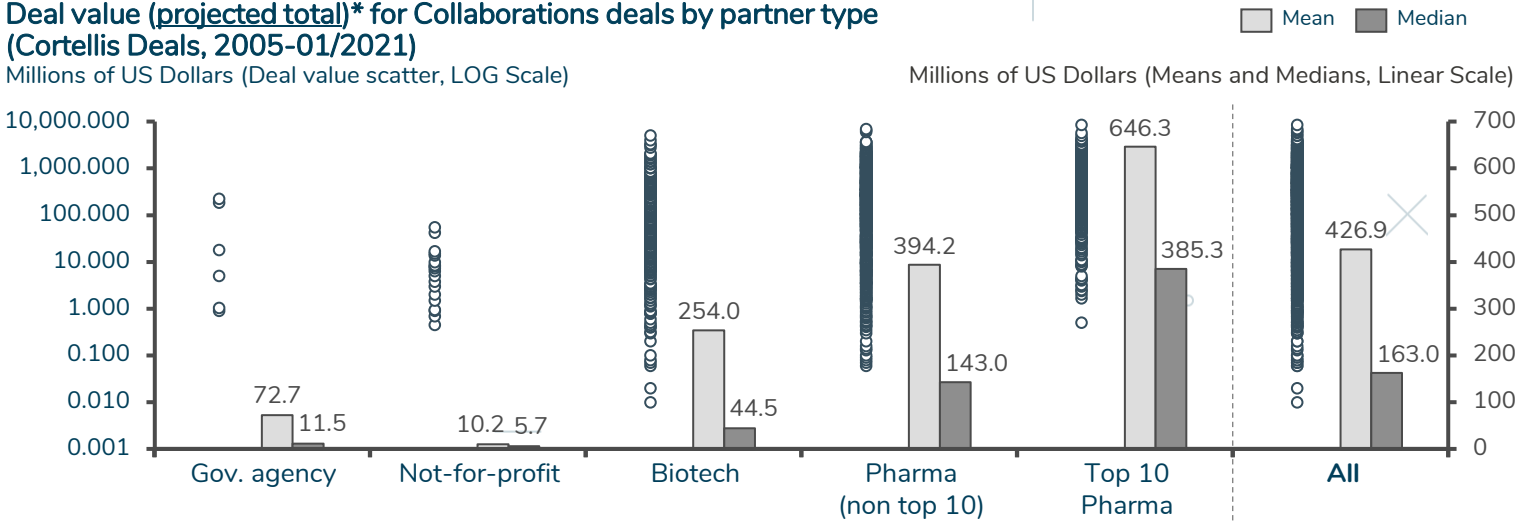
Collaborations

Upfront

Total

Data capture: **02/2021**

Deal value (projected total)* for Collaborations deals by partner type (Cortellis Deals, 2005-01/2021)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	c.150	c.330	c.2,600	c.4,400	c.1,100	**c.8,500**
% with disclosed value	4%	6%	11%	23%	41%	**21%**

Notes: *Projected deal value at start date;
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Collaborations vary widely in value; frequency and spend-per-deal appears higher in the for-profit sector

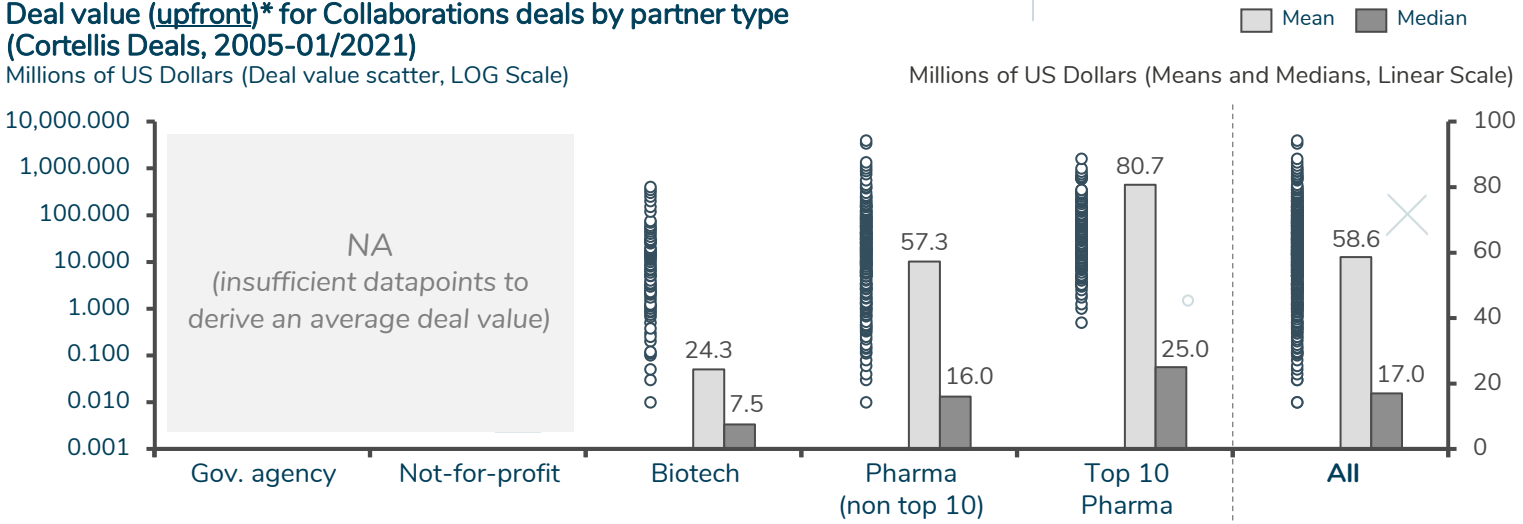
Collaborations

Upfront

Total

Data capture: **02/2021**

Deal value (upfront)* for Collaborations deals by partner type (Cortellis Deals, 2005-01/2021)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	NA	NA	c.2,600	c.4,400	c.1,100	**c.8,500**
% with disclosed value	NA	NA	6%	15%	25%	**13%**

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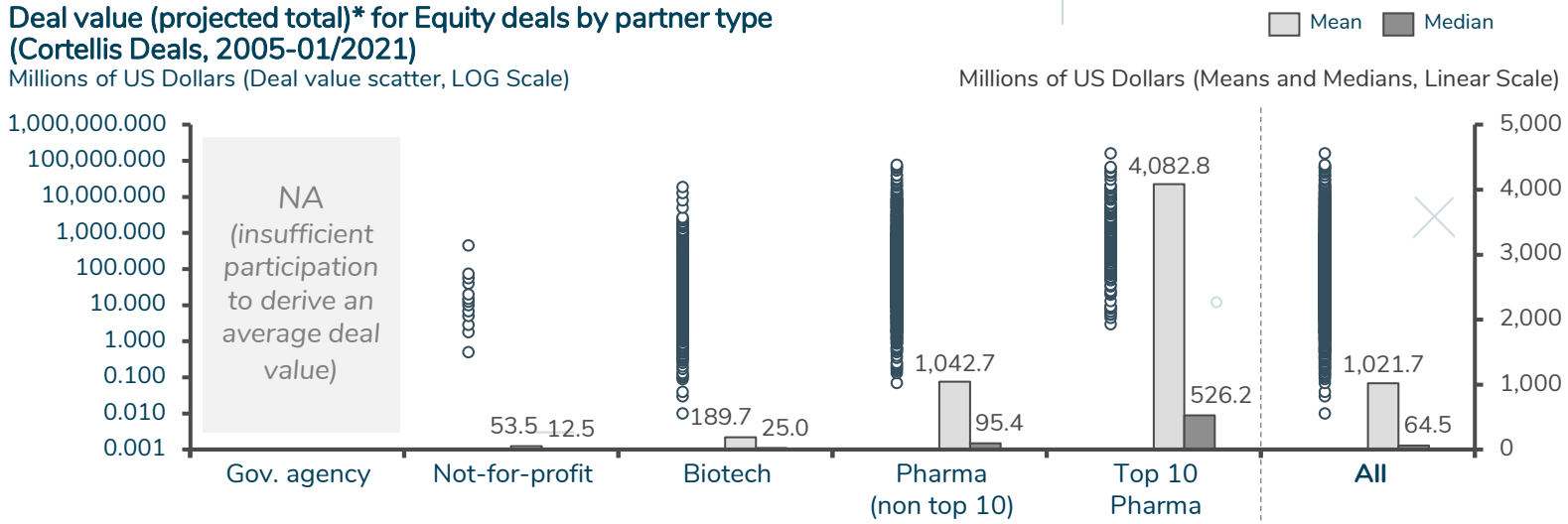
Notes: *Upfront payment (before milestones and royalties);
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Equity deals vary widely in value; the for-profit sector is generally most involved in buying equity, with pharma spending more

Equity deals

Data capture: **02/2021**

Deal value (projected total)* for Equity deals by partner type (Cortellis Deals, 2005-01/2021)



	Gov. agency	Not-for-profit	Biotech	Pharma (non top 10)	Top 10 Pharma	All
Total deals (2005-21)	NA	c.20	c.1,700	c.2,000	c.270	**c.4,100**
% with disclosed value	NA	c.62%	c.45%	c.64%	c.76%	**c.57%**

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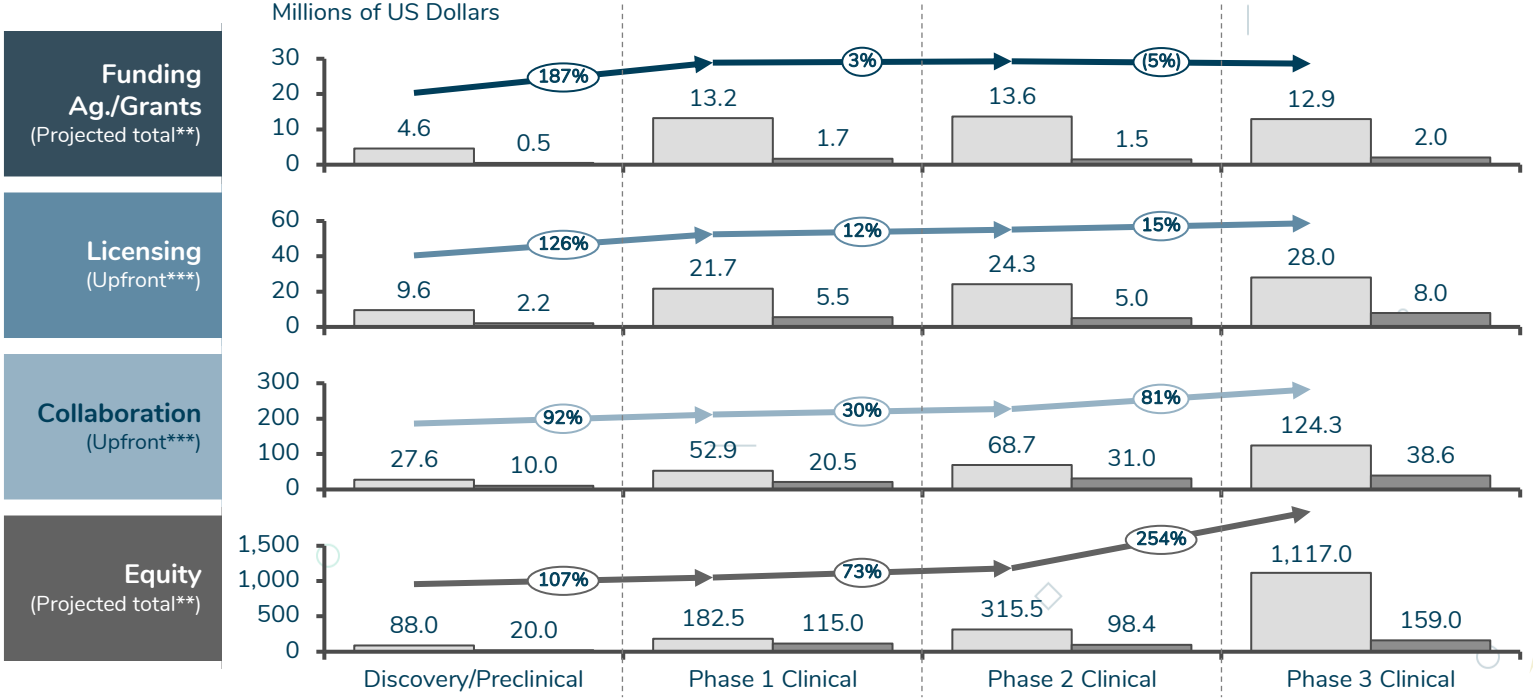
Notes: *Projected deal value at start date;
Source: Cortellis Deals Intelligence; L.E.K. research and analysis

Average deal values grow significantly as targeted assets move through the value chain and become increasingly de-risked

Data capture: **02/2021**

Biopharma deals by instrument class by development stage* (Cortellis Deals, 2005-2021)

Millions of US Dollars

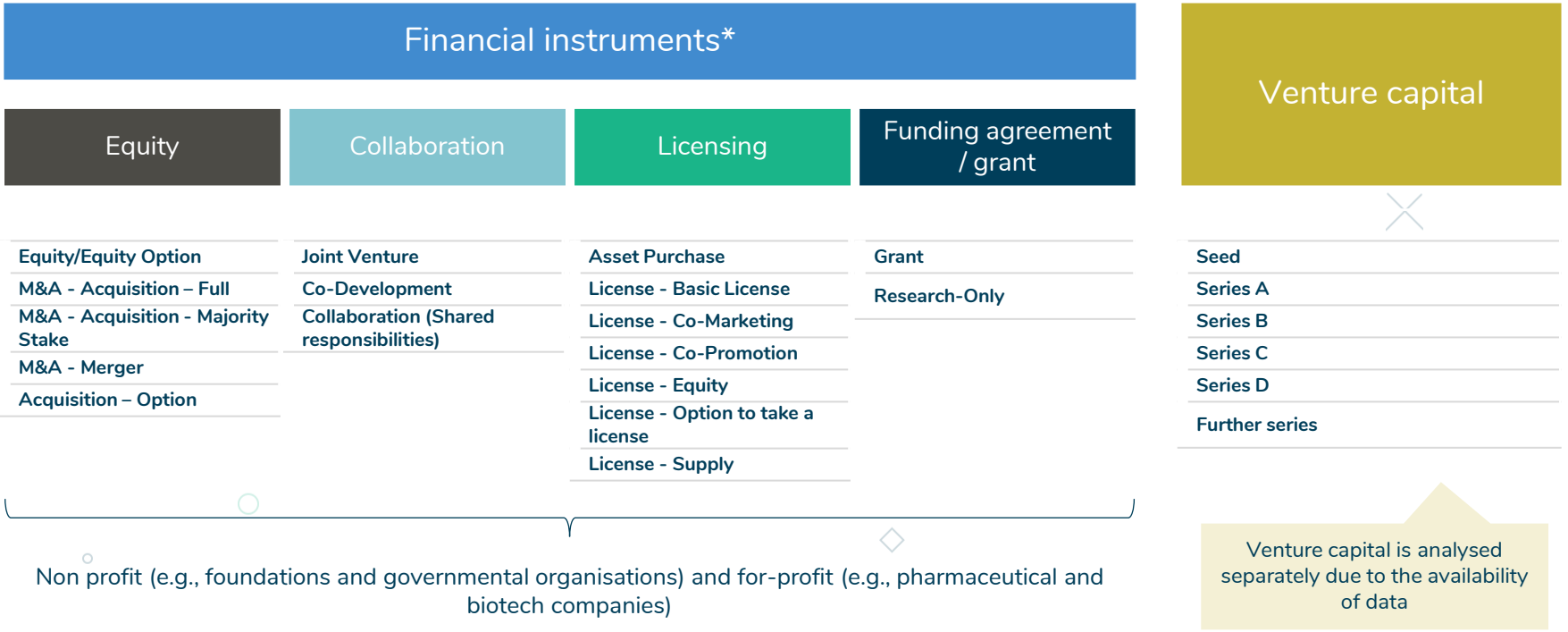


Analysis excludes deals for launched assets, reducing the overall deal value relative to those shown in the deal value benchmarking by player

Notes:*development stage of furthest progressed asset of principal company within scope of agreement; ** Projected deal value at start date; ***Upfront payment (before milestones and royalties)
Source: Cortellis; L.E.K. research and analysis;

Transaction timelines

Research and analysis into the distribution of transaction types was conducted and segmented due to the availability of data



Note: * Database characterizes each transaction as a single entity considering the principal transaction type – although mixed financial instruments may co-exist in hybrid funding models which is a potential limitation of the data
Source: Cortellis; L.E.K. research and analysis

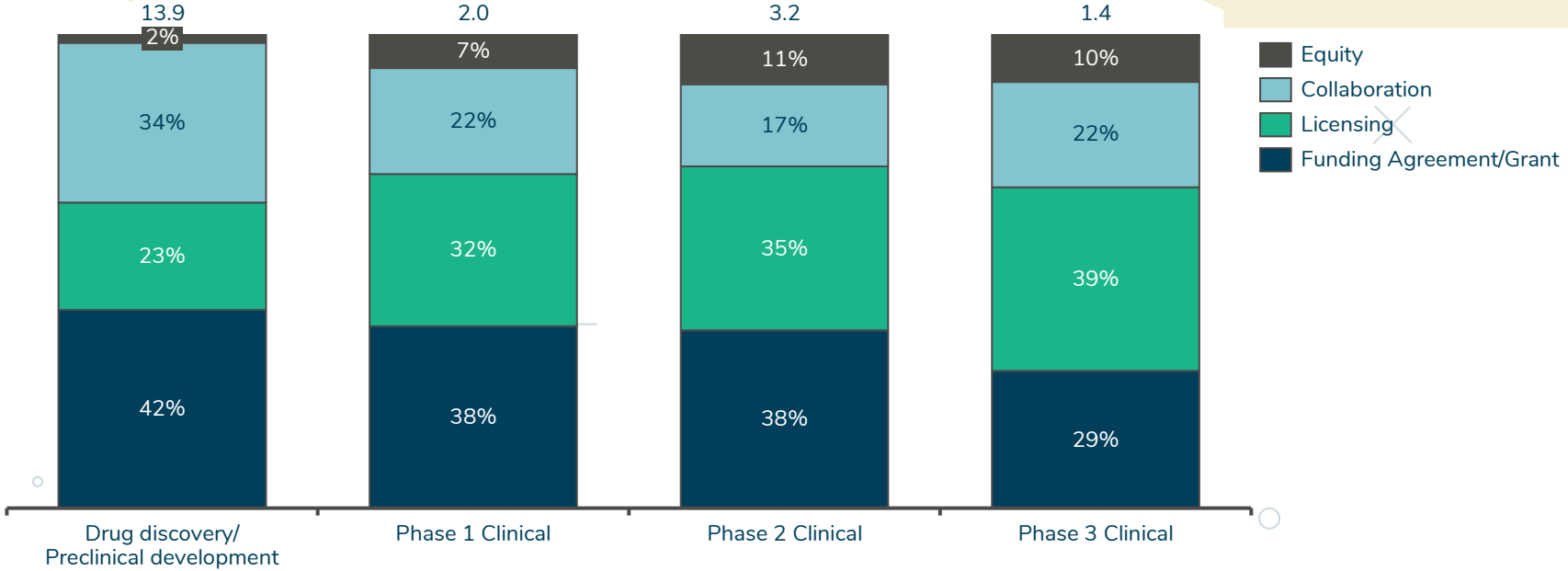
Funding/grants and collaborations are used earlier in the development process, while equity deals are more common later on (1 of 2)

Data capture: **02/2021**

Total represents thousands of deals

Estimated number of deals by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [% of total deals]

Excludes c.40% of deals without a recorded development stage



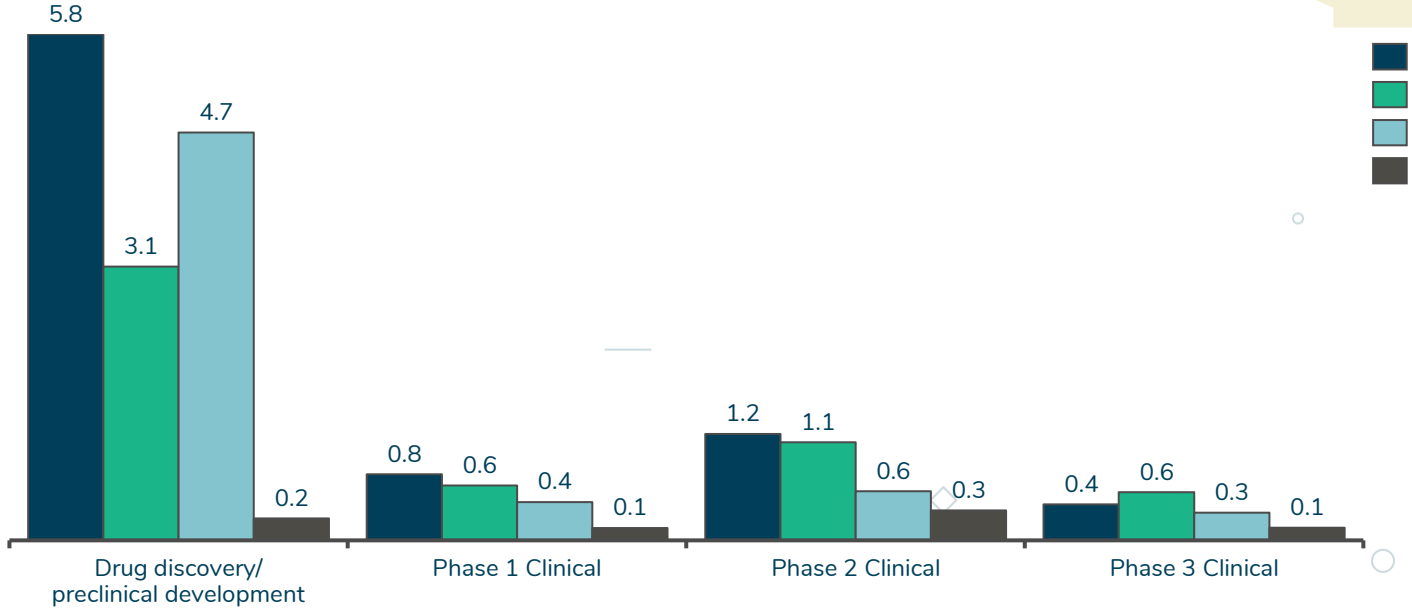
Notes:*development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets;
Source: Cortellis; L.E.K. research and analysis;

Funding/grants and collaborations are used earlier in the development process, while equity deals are more common later on (2 of 2)

Data capture: **02/2021**

Estimated number of deals by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [Thousands of deals]

Excludes c.40% of deals without a recorded development stage



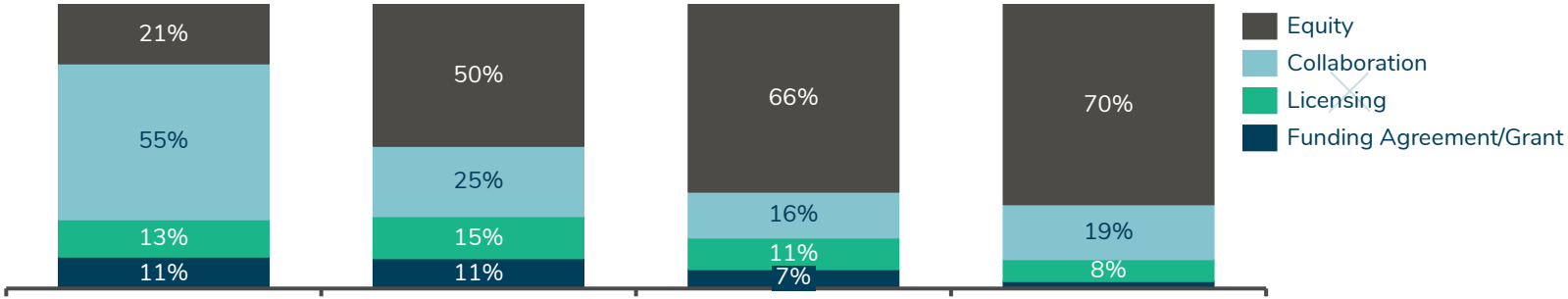
Notes:*development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets;
Source: Cortellis; L.E.K. research and analysis;

As a proportion of estimated spend, equity deals increase as programs progress through development

Data capture: **02/2021**

Estimated % of spend by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [% of spend]

L.E.K. has used average deal value** to enable approximate analysis of spend by instrument type



Excludes c.40% of deals without a recorded development stage

% of deal count*	Discovery/Preclinical	Phase 1 Clinical	Phase 2 Clinical	Phase 3 Clinical
Equity	2%	7%	11%	10%
Collaboration	34%	22%	17%	22%
Licensing	23%	32%	35%	39%
Funding Ag./Grants	42%	38%	38%	29%

Notes: *Development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets; **For Collaborations and Licensing deals, upfront payment is used rather than total projected value at start date
Source: Cortellis; L.E.K. research and analysis;

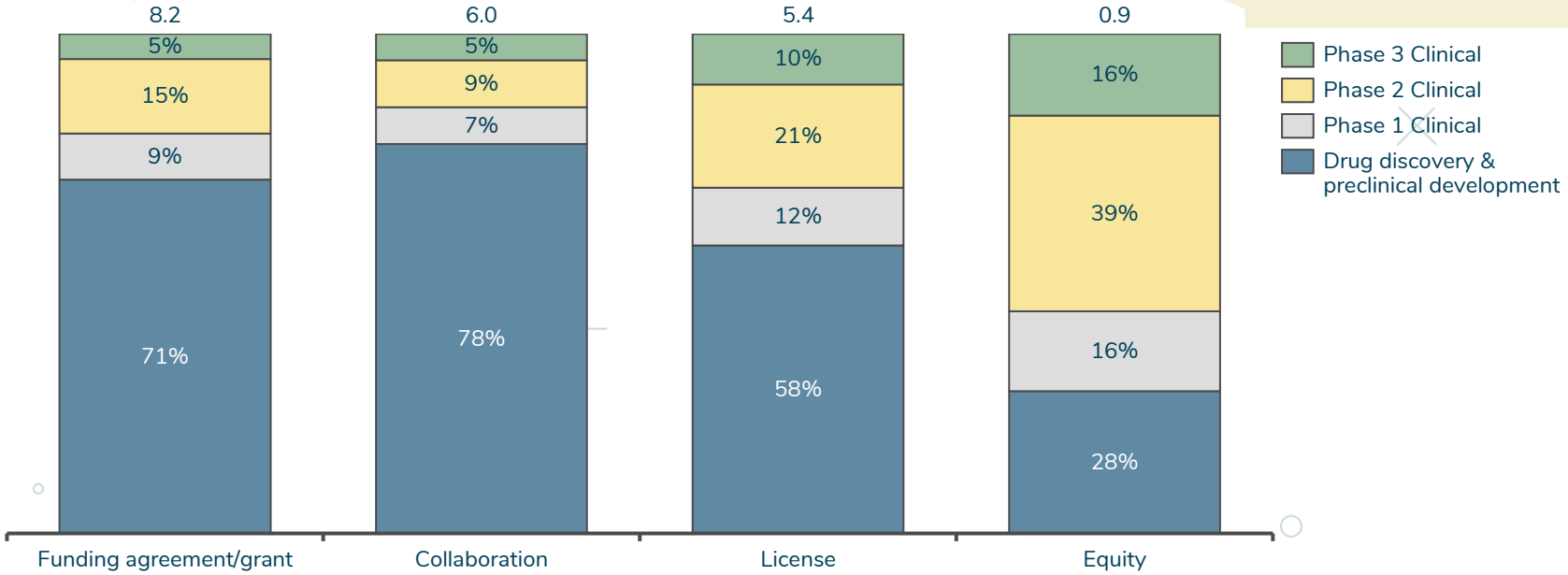
Drug discovery/preclinical dev. and phase 2 represent the largest share of deals; equity and licensing deals tend to take place later

Data capture: **02/2021**

Total represents thousands of deals

Estimated number of deals by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [% of total deals]

Excludes c.40% of deals without a recorded development stage

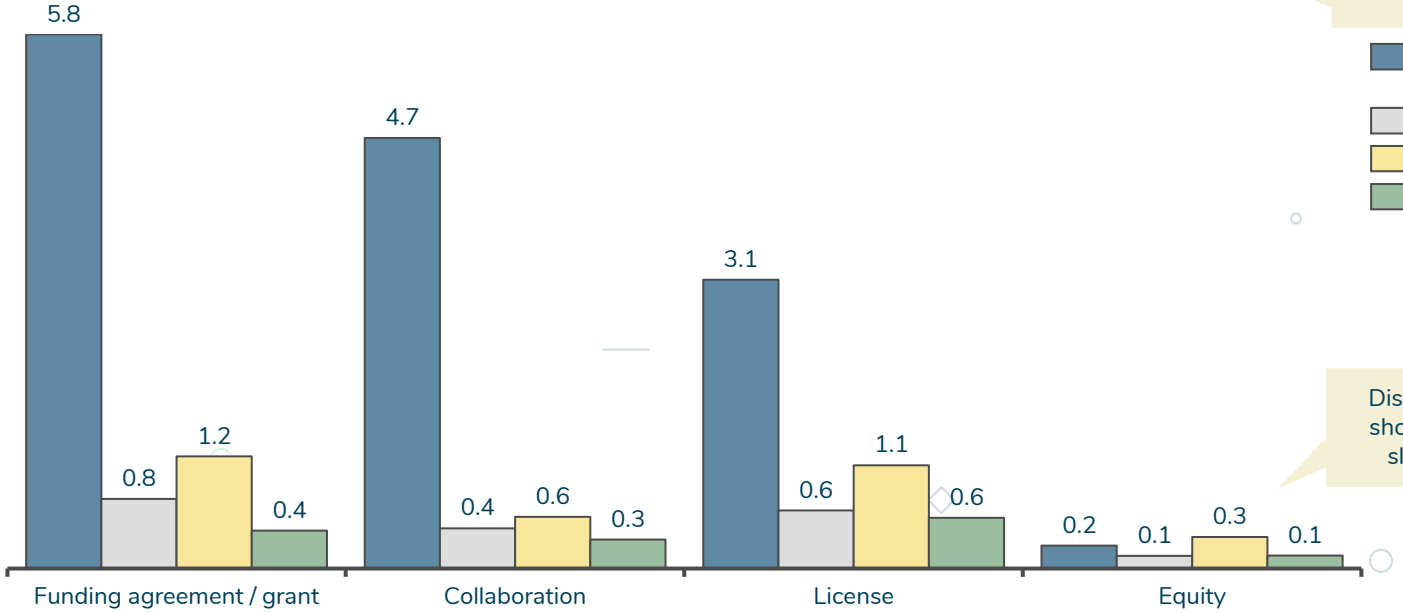


Notes: *Development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets;
Source: Cortellis; L.E.K. research and analysis;

Grants, collaboration, and licenses have the largest number of deals are in drug discovery/preclinical dev.; equity deals in Phase 2

Data capture: **02/2021**

Estimated number of deals by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [Thousands of deals]



Excludes c.40% of deals without a recorded development stage

- Drug discovery & preclinical developlemt
- Phase 1 Clinical
- Phase 2 Clinical
- Phase 3 Clinical

Discrepancies between total shown here and on the prior slide are due to rounding

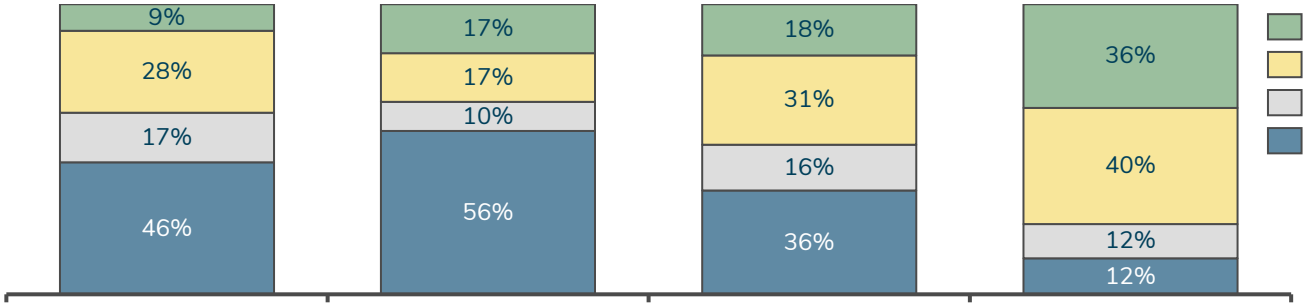
Notes: *Development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets;
Source: Cortellis; L.E.K. research and analysis;

As a proportion of estimated spend, later stages are more important across all instrument classes given increased average deal value

Data capture: **02/2021**

Estimated % of spend by instrument class by development stage*
(Cortellis Publicly disclosed deals, 2005-2021) [% of spend]

L.E.K. has used average deal value** to enable approximate analysis of spend by instrument type



Excludes c.40% of deals without a recorded development stage

% of deal count*	Funding agreement/grant	Collaboration	Licensing	Equity
Phase 3 clinical	5%	5%	10%	16%
Phase 2 clinical	15%	9%	21%	39%
Phase 1 clinical	9%	7%	12%	16%
Drug discovery/preclinical development	71%	78%	58%	28%

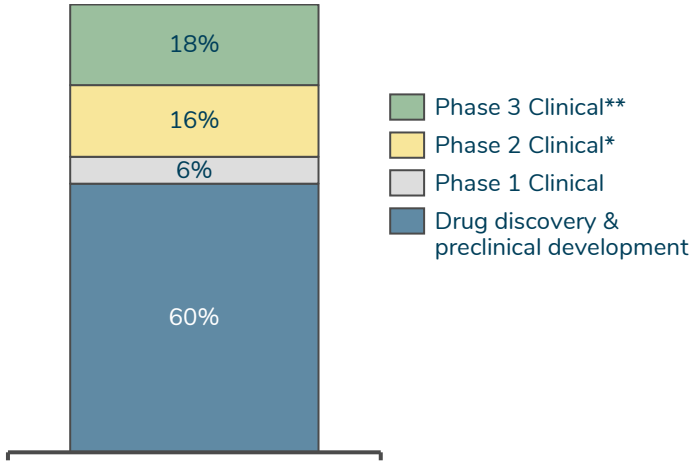
Notes: *Development stage of furthest progressed asset of principal company; Excludes "others" deal category; excludes deals for registered/launched assets; **For Collaborations and Licensing deals, upfront payment is used rather than total projected value at start date
Source: Cortellis; L.E.K. research and analysis;

Secondary research supports the phase specific trends shown in L.E.K.'s analysis

M&A secondary research is equivalent, but not identical, to the equity category used in L.E.K.'s analysis

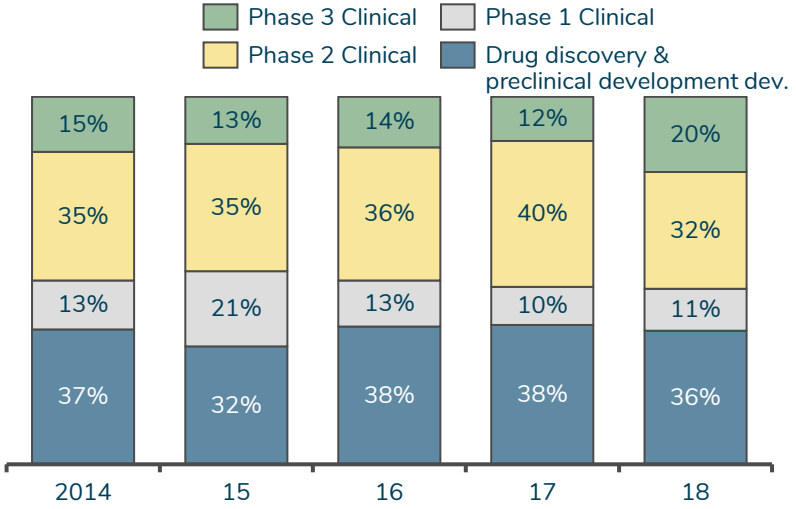
Licensing secondary research

% of licensing deals by development stage
(2018) [% of total deals]



M&A secondary research (equity)

% of M&A deals by development stage
(2014-18) [% of total deals]



Note: * Includes 6% of deals for Phase 1/2 assets (in licensing data only); **Includes 8% of deals for filed assets (in licensing data only)
Source: Life Science Nation; Evaluate; L.E.K. research and analysis

Interviewees note that the majority of equity transactions by big pharma are focused on later stages, with collaborations largely earlier

Equity investments and corporate M&A become more attractive as development progresses

- For big pharma companies, the availability of data is a key consideration in identifying equity investments

  "... Usually, it makes sense to acquire a company once they have an asset that is at the PoC stage. When you start seeing safety data and early signs of efficacy data, that is the golden sweet spot to acquire an asset..."
  Financial investor #3, big pharma BD (U.S.)

  - this data requirement results in acquisitions after human PoC, which is typically from Phase Ib or Phase II onwards

  "... For acquisitions, I would say that we usually try to go somewhere from Phase I onwards because you want to get an asset that has some data to support it. In pharma, you generally wait to acquire until there is supporting evidence..."
  Head of R&D #1, big pharma (EU)

  - big pharma is well-placed to conduct late-stage clinical trials due to in-house capabilities and experience with the logistics and data requirements, resulting in greater willingness to acquire assets in Phase II

  "... We have a lot of experience with clinical trials, so are not necessarily put off by having to do a large pivotal trial..."
  Head of R&D #2, big pharma (U.S.)

Collaboration and licensing allows big pharma companies to source innovation externally

- Biotech companies have nimble structures and processes that big pharma accesses through collaborations and licensing

  "... Generally speaking, biotechs are much more agile than biopharma, and are therefore better placed for innovation and early stage development than bigger companies. Collaborations and licensing in earlier stages reflect the fact that big biopharma wants to source more innovation externally, but doesn't have the right operating model to do this in house..."
  Financial investor #1, big pharma BD (EU)

Within licensing, asset purchases typically occur later than basic licenses

- Asset purchases, which account for a small proportion of 'licensing' deals, are more likely to occur in clinical development, whereas the majority of licensing agreements, such as basic licenses, occur in drug discovery or preclinical development

  "... Licensing is attractive for early-stage assets because you can still leverage the expertise of the smaller company. For later stage assets, a company may choose to acquire the asset, rather than engage in a licensing agreement ..."
  Head of R&D #2, big pharma (U.S.)

Source: L.E.K. research, interviews, and analysis

Majority of investments occur at drug discovery / preclinical dev., particularly in the U.S., with investments dropping at Phase III

Distribution of investments by R&D stages*

	Development stage of companies at first investment			
	Drug discovery / preclinical development	Phase I	Phase II	Phase III
European venture firms	52%	18%	24%	7%
U.S. venture firms	81%	8%	9%	3%

A detailed analysis of distribution of investments by R&D stages within a fund are presented in section 3, Financial investor portfolio strategy

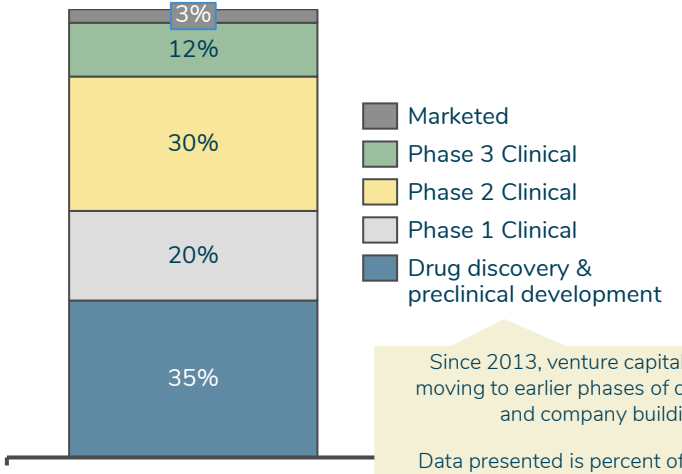
Percentage of total investments in the region: 0-20% | 21-40% | 41-60% | 61-80% | 81-100%

Note: *Based on weighted averages from financial investor portfolio strategy analysis
Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

Venture funding has historically been concentrated in early development stages to help bridge the gap through proof of concept

Venture capital funding secondary research

% of venture capital funding by development stage
(2004-13) [% of total spend]

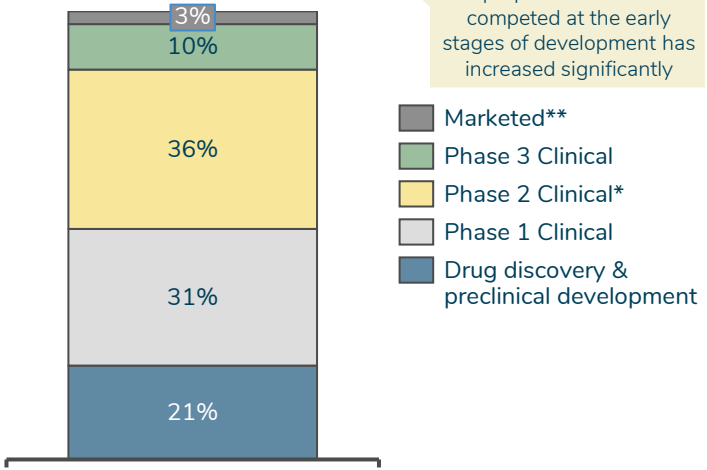


Since 2013, venture capital funding is moving to earlier phases of development and company building;

Data presented is percent of spend, and investment per deal is typically lower for early stage investments so the number of deals in early development is likely to be higher in earlier phases

IPO distribution secondary research

% of global IPOs by development stage*
(2018-20) [% of total deals]
177



In recent years, the proportion of IPOs competed at the early stages of development has increased significantly

Note: * Includes Phase 1/2;**Includes NDA and submission
Source: Bio Industry analysis; Bay Bridge Bio; Deloitte; L.E.K. research

VC investments are typically focused on early stage development, with divestments to big pharma or IPOs in early clinical development

VC investments are essential for early-stage development of innovative opportunities

- VCs focus equity investments on small, early-stage biotechs, which can then be acquired by big pharma / IPO, and are able to take on larger development risk than pharma companies due to their diversified portfolio

  "… What we do is to identify and fund, usually through equity investments, early stage research which can then eventually sold to big pharma who have the capabilities to do the later development and commercialization. Those early stage opportunities are often too risky for pharma, but because we have portfolios, we are willing to take on the risk …"
  Financial investor #2, standalone VC (U.S.)

  - in recent years, VCs are increasingly investing in earlier stages of development and working on company building, such as building management teams and supporting development of operational capabilities

  "… Lately there has been an influx of capital into VC financing, which is pushing investors into earlier stages…"
  Financial investor #2, standalone VC (U.S.)

VCs typically divest their investments in early clinical development due to high cost of late-stage development

- Standalone VCs typically divest their equity investments in early clinical development, following human proof of concept, through sale to pharmaceutical companies or through IPO (which are also happening earlier)

  "… Usually once we have data read out, typically Phase I or Phase II data readout, that is when we project being able to exit either through a sale to big pharma or through IPO…"
  Financial investor #2, standalone VC (U.S)

  - VC funds are incentivized to divest in early clinical development due to the high costs associated with late-stage pivotal clinical trials

  "…Our divestments are usually early clinical. This is partly because clinical trials are really expensive, so ideally you want to pass this off to big pharma who have more capabilities to do trials…"
  Financial investor #4, standalone VC (EU)

Big pharma is better placed to develop late-stage assets

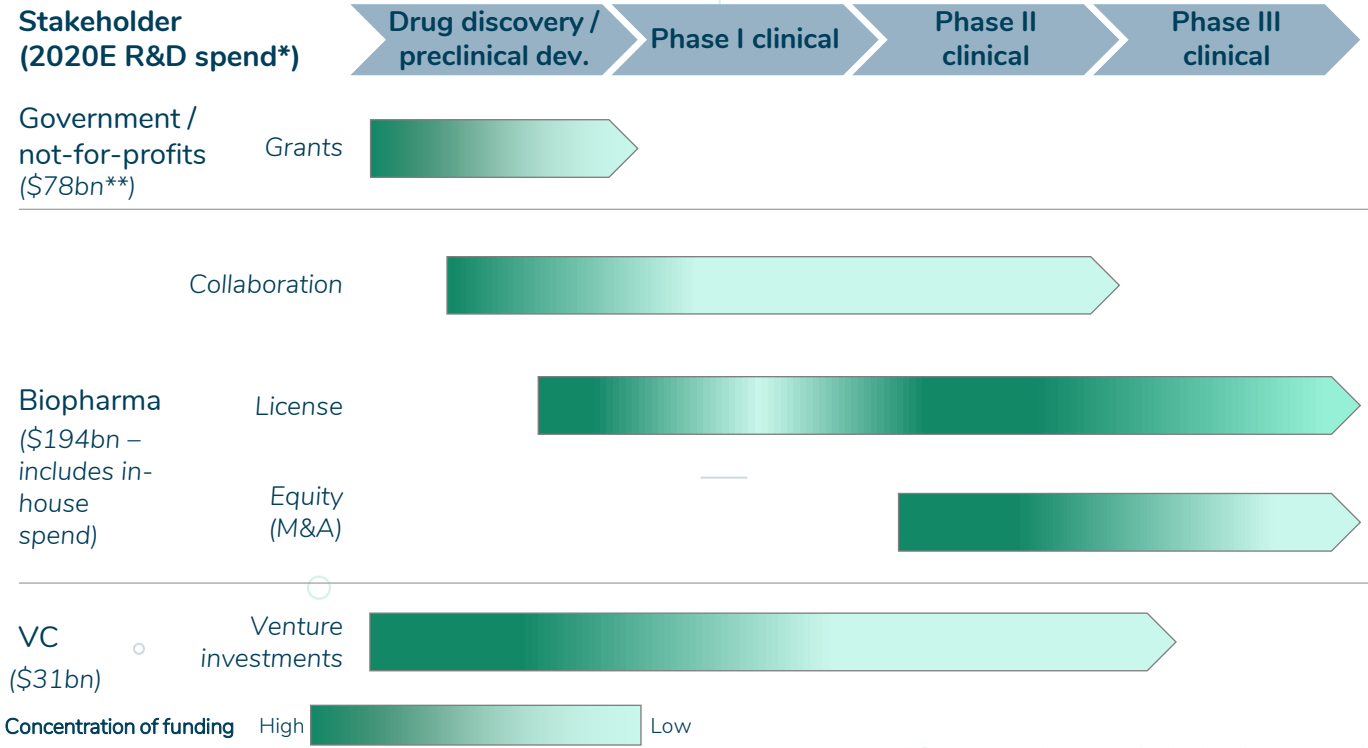
- Big pharma companies are typically better placed to conduct late-stage clinical trials due to in-house capabilities

  "… As big pharma, I have very little incentive to acquire anything pre-PoC because I would be taking on all the risk. It suits big pharma better to wait until PoC and to have data available before purchasing…"
  Financial investor #2, standalone VC (U.S)

Source: L.E.K. research, interviews, and analysis

Majority of deals occur in drug discovery / preclinical and phase II, with big pharma focused more later stages of development

R&D Funders and annual spend



Comments

- Governments and not-for-profits provide funding to small biotech through **grants**, which are typically used for early stage basic research (i.e., before drug discovery / preclinical dev.)
- Biopharma uses **collaboration agreements** in earlier stages of development, typically before clinical development
- **Licenses** are used by big pharma predominantly for preclinical development assets and for Phase II clinical development
- **Corporate M&A** is most common in late-stage assets, with big pharma acquiring small, innovative biotech companies ahead of conducting large pivotal trials
- VCs usually engage in **equity investment** in early drug discovery and pre-clinical development, with divestment in clinical development

Note: * Data is based on spend, which is likely skewed towards later stages of investment due to the higher deal values in later stages of development **Based on estimated 2019 spend assuming limited growth

Source: Bio Industry analysis; Bay Bridge Bio; Deloitte; Life Science Nation; Evaluate; L.E.K. research and analysis

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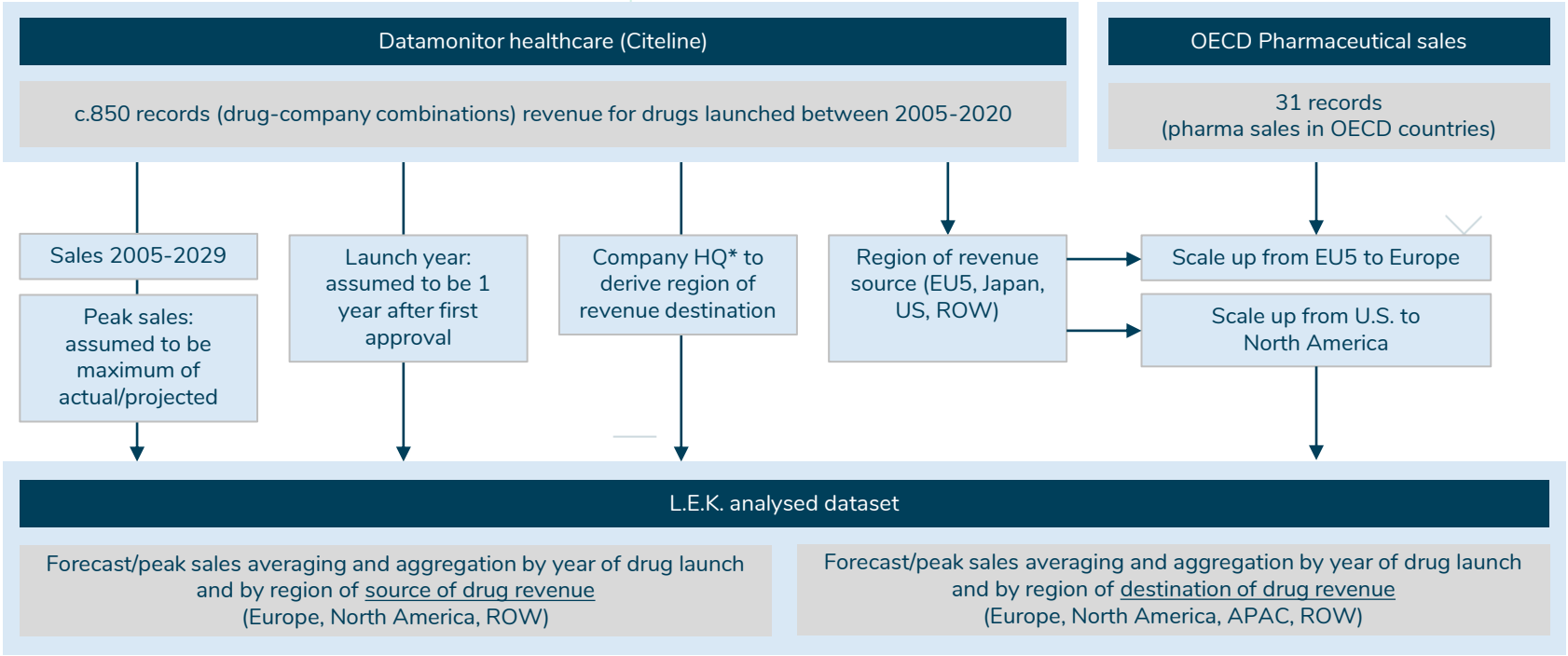
Revenue potential analysis

The revenue potential analysis is derived from Datamonitor actual / forecasted revenue for all specialty drugs launched 2005-2020



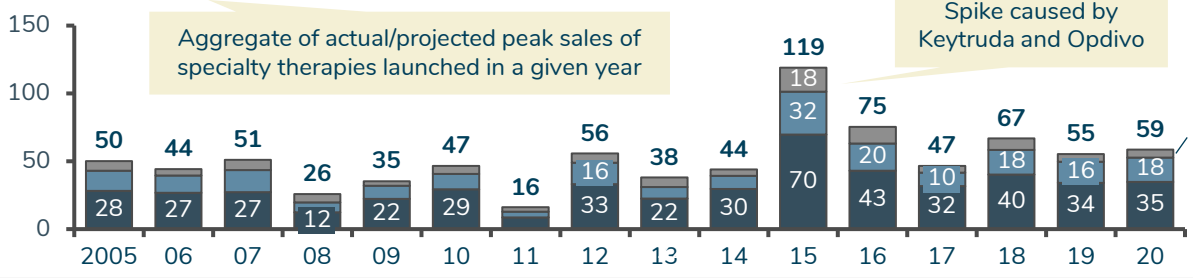
Notes: * Eikon and manual searches used to determine company HQ countries
Source: Datamonitor; OECD; Eikon; L.E.K. Research and Analysis

Average global annual peak drug sales has broadly remained between USD 0.5-2.0bn since 2005; most revenue comes from Europe and NA

Datamonitor forecasts potentially skewed by key outliers and assessment of competition

Aggregate peak annual sales of specialty pharmaceuticals by launch year* by location of revenue source - Datamonitor (2005-2020)**

Billions of USD



	% CAGR (2005-20)
Global	1.0
ROW	(1.4)
Europe	1.3
North America	1.4

Spike caused by Keytruda and Opdivo

Avg. Peak Sales per product Bn of USD	2005	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	% CAGR (2005-20)
Global	**1.4**	**1.6**	**1.3**	**0.8**	**0.9**	**0.9**	**0.6**	**1.4**	**1.0**	**1.5**	**2.3**	**1.9**	**1.9**	**1.6**	**1.3**	**1.5**	**0.5**
Europe	0.4	0.5	0.4	0.2	0.2	0.2	0.1	0.4	0.2	0.3	0.6	0.5	0.4	0.4	0.4	0.4	0.8
North America	0.8	1.0	0.7	0.4	0.6	0.6	0.3	0.8	0.6	1.0	1.4	1.1	1.3	0.9	0.8	0.9	0.9
Number of launches																	
Drug count	37	28	38	32	39	51	27	41	38	29	51	39	25	43	42	40	0.5

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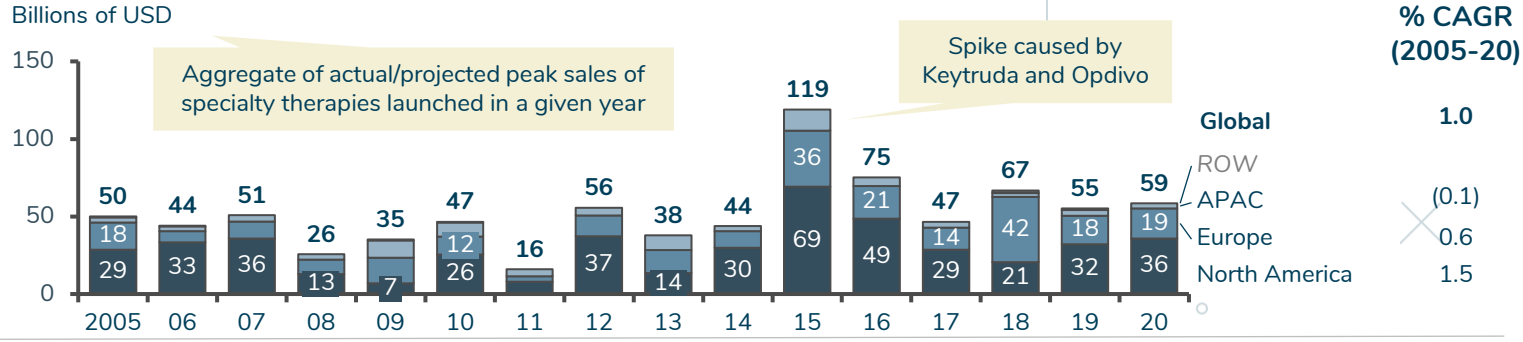
Notes: * Launch year is taken as the first year after first approval; ** EU5 scaled-up to Europe using OECD ratio of pharmaceutical spend in Europe vs EU5 nations, U.S. Scaled up to North America using OECD ratio of pharma spend in EU5 to Canada
Source: Datamonitor; OECD; L.E.K. Research and Analysis

Drugs launched by North American firms have significantly higher revenue potential than other regions in most years

Datamonitor forecasts potentially skewed by key outliers and assessment of competition

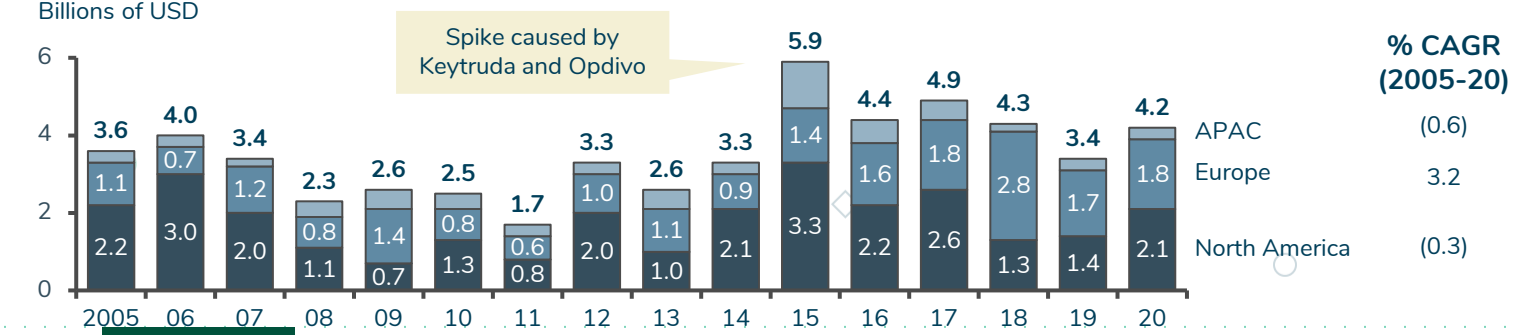
Aggregate peak annual sales of specialty pharmaceuticals by launch year* by location of drug marketer - Datamonitor (2005-2020)

Billions of USD



Average global peak sales per product by HQ region- Datamonitor (2005-2020)

Billions of USD



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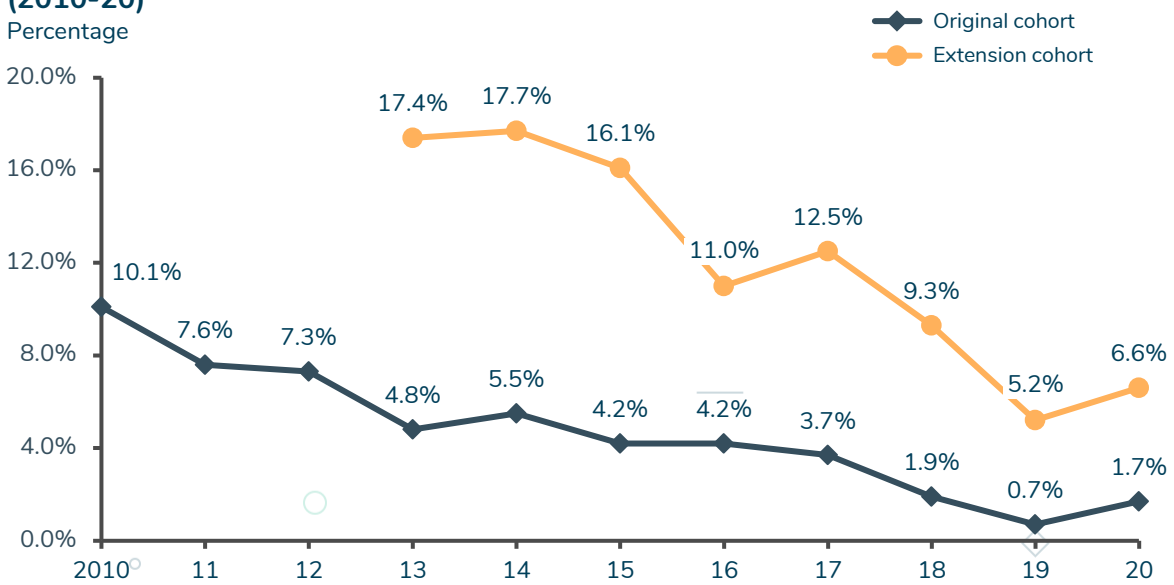
Notes: * Launch year is taken as the first year after first approval;
Source: Datamonitor; OECD; L.E.K. Research and Analysis

Preliminary analysis on ROI

R&D returns for the leading biopharma companies studied have declined steadily since 2010

Mean static IRR to demonstrate return on late stage pipeline – Deloitte (2010-20)

Percentage



- Since 2010, Deloitte has tracked expected ROI on late-stage pipelines for 12 leading biopharma companies (Original cohort)
- Since 2013, it has done the same analysis for four, more specialised biopharma companies (Extension cohort)
  - In 2020, two of the companies merged, reducing the extension cohort to 3
- Late stage pipeline is defined as assets that are filed, in Phase III or Phase II with breakthrough therapy designation

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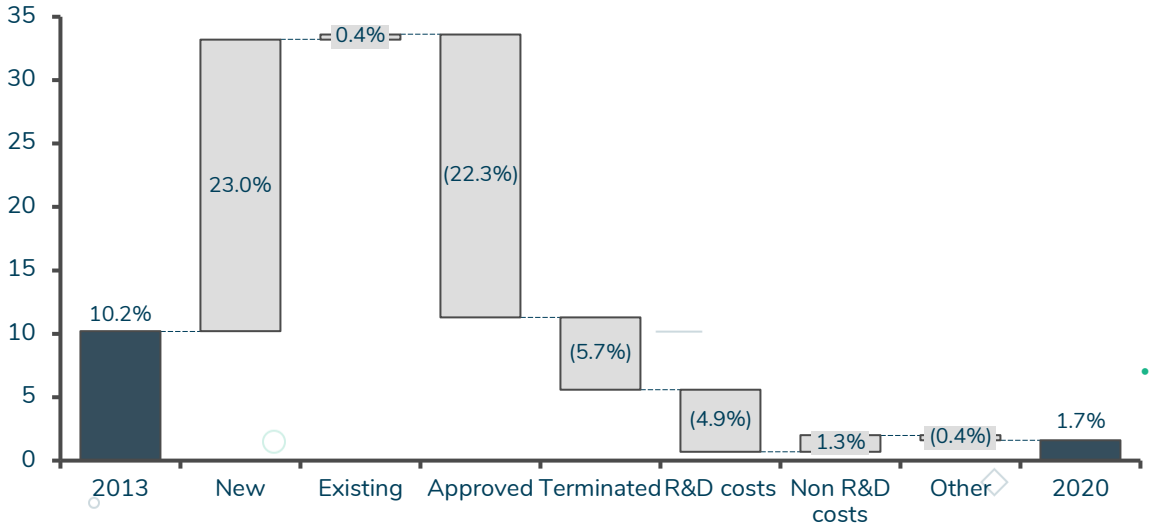
Source: Deloitte; L.E.K. Research and Analysis

Key drivers of IRR decline are late stage failures not sufficiently offset by new products entering the pipeline, and rising R&D costs

Drivers of change in IRR of the original cohort – Deloitte (2013-20)
Percentage



- Dynamic IRR analysis illustrates the impact of underlying levers on changes in IRR over time
  - transition of new assets (from earlier phases, in-licensed, acquired)
  - existing assets (sales forecast up / down)
  - forecast sales from approved and launched assets fall out
  - forecast sales from terminated assets fall out
- This does not necessarily imply that there are more late stage failures than before, just that the IRR decline associated with these terminations is not offset by new drugs in the pipeline

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Source: Deloitte; L.E.K. Research and Analysis

Deloitte's IRR methodology takes into consideration annual R&D expenses as cash outflows and risk-adjusted revenues as inflows

Cash outflows are based on R&D expenses and therefore do not include cost of capital, which would typically be reported as financing expenses

Static IRR*

Calculated by equating cash outflows with cash inflows to generate an IRR value

Cash outflow elements

Annual R&D expenses for the prior 10 years, which represents the cost associated with bringing the basket of assets to a particular stage of development

Four key outflow elements:

- R&D cost
- Cost phasing
- Licensing
- Tax rates

Cash inflow elements

Annual risk-adjusted revenues forecast for the future 21 years, which estimates the likely returns that the basket of assets will deliver

Two key inflow elements:

- Forecast revenue, consisting of terminated, approved, existing, and new revenues
- margin

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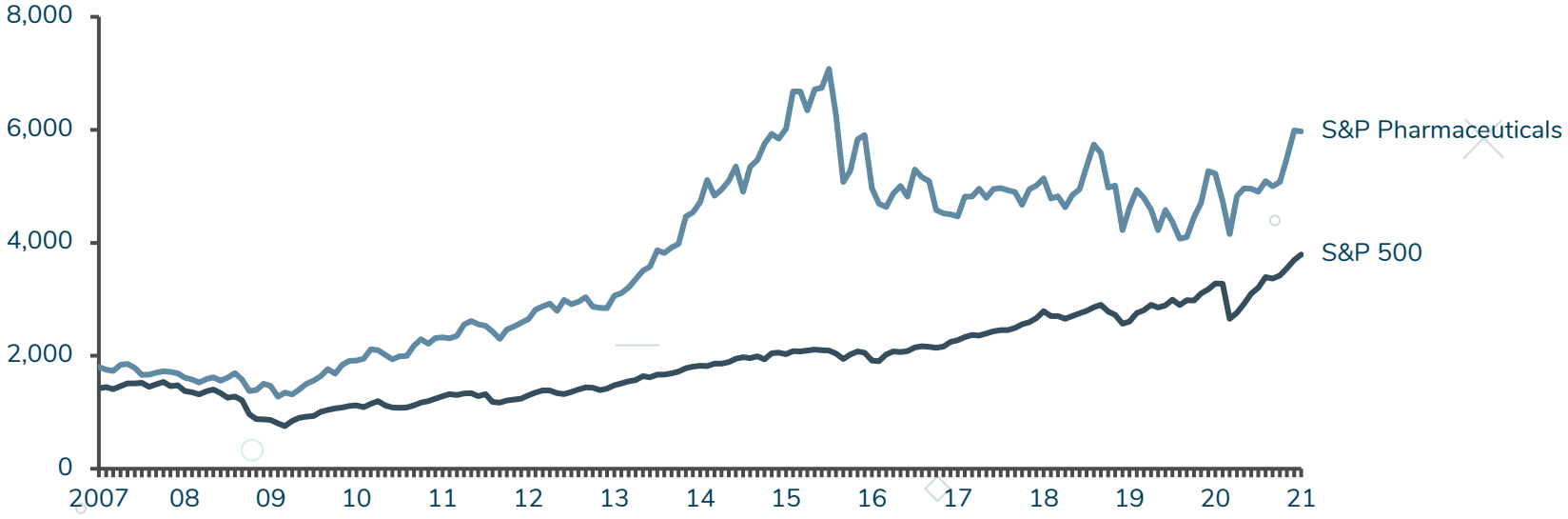
Note: *IRR - Internal rate of return, rate of return of a potential investment calculated excluding external factors
Source: Deloitte; L.E.K. Research and Analysis

Comparison of S&P 500 vs. S&P pharma shows the pharma index generally outperforms though gap has narrowed since a 2015 peak

Performance S&P 500 vs S&P Pharmaceuticals (2007-21)
Absolute performance of index



Source: Multipl.com; Investing.com; L.E.K. research and analysis

Even after accounting for failure rate and timelines, LS investments generate returns above/in-line with other VC-focused sectors

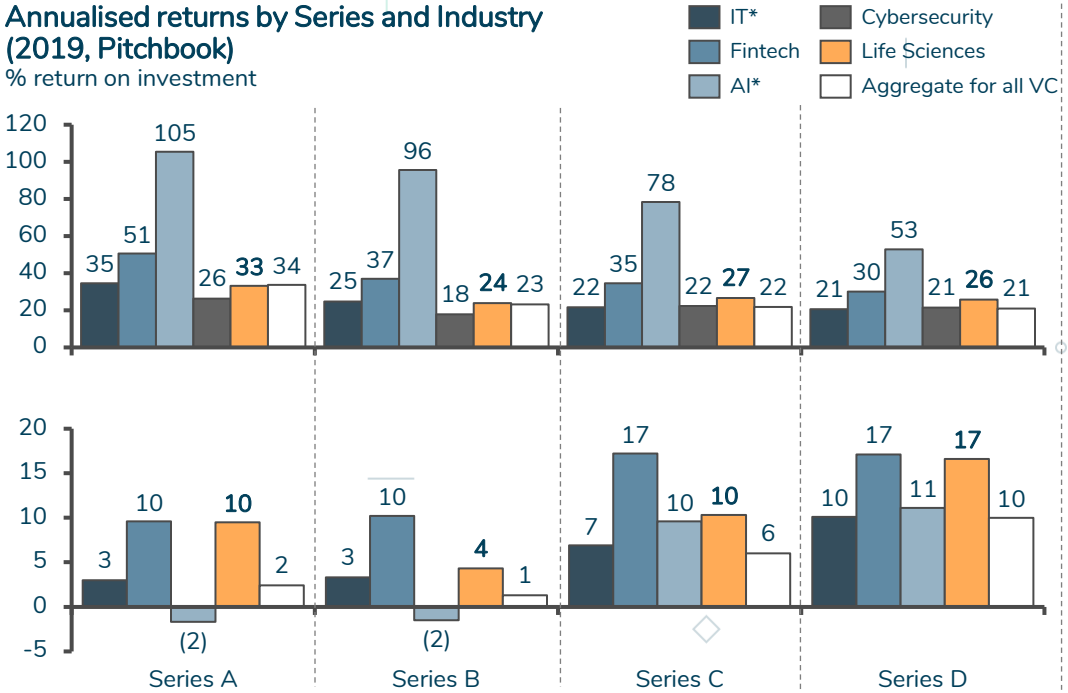
Non risk-adjusted:

Risk adjusted:

Out-of-business adjustment (compounded failure risk) used to account for capital investment that went into companies that never reached an exit

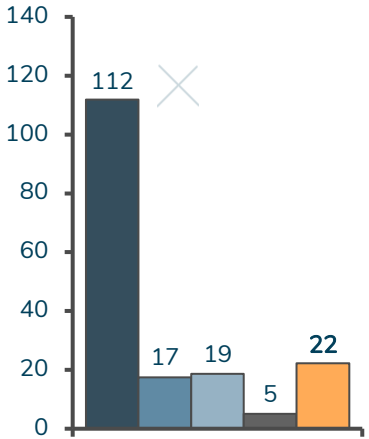
Annualised returns by Series and Industry (2019, Pitchbook)

% return on investment



Deal value by Industry (2019, Pitchbook)

Billions of USD



Notes: * Information Technology
Source: Pitchbook; L.E.K. research and analysis

4. Investment rationale

Methods of valuation

While many financial metrics exist; ROI, NPV / eNPV, IRR and comparables analysis are the most commonly used metrics to value pharmaceutical assets

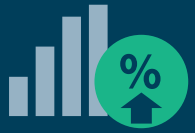
Return on investment

ROI is a simplified measurement of the profitability of an investment, expressed as a multiple of the initial investment

Net present value

NPV measures profitability based on the present value of the cash expected from the investment; eNPVs are NPV values risk-adjusted based on PoS

Internal rate of return



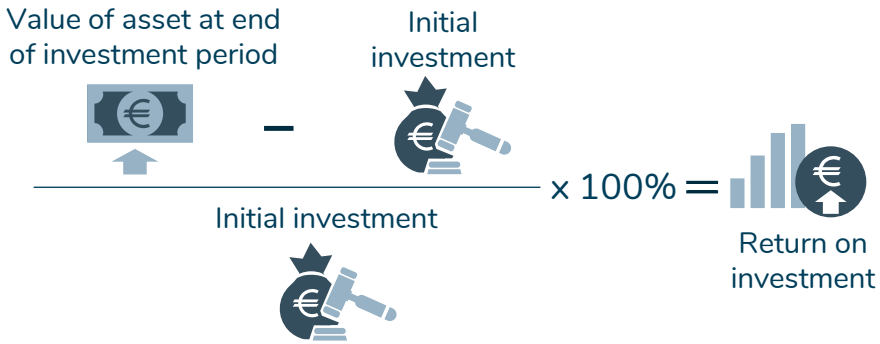
IRR indicates the annualised rate of return for a given investment and a given expected future cash flow

Comparables analysis

Comparables analysis values early-stage investments, against equivalent assets / transactions

ROI is a simplified measurement of the profitability of an investment, which is expressed as a percentage of the initial investment

Calculation methodology – Return on investment



- Return on investment (ROI, also refered to as cash on cash) measures the total growth of an investment over a given investment period expressed as a percentage of the initial investment
- ROI is commonly used to communicate the profitability of an investment in a simplified context as it is the most straightforward method to measure investment returns
- However, as the period of investment is not factored into the calculation, it should be articulated when discussing ROI to provide context – a 10% ROI may be impressive over a 3-year period but less so over 20 years
- Another limitation of ROI is that the estimation of future asset value may also be difficult to accurately estimate at at the time of initial investment, based on fluctuations in inflation rate, market growth, and production costs
- When comparing across different investment options with varying time / risk profiles, ROI is not sufficient in capturing variations in investment risk and cost of capital
  - under these circumstances a net present value (NPV) model is more commonly applied

Sources: Investopedia; Harvard Business Review; L.E.K. research and analysis

NPV measures profitability based on the present value of expected returns; eNPVs are NPV values risk-adjusted based on PoS

Calculation methodology – Net present value

$$NPV = \sum_{t=1}^{n} \frac{\text{Net cash inflow at year t}}{(1+r)^{t}} - \text{Initial investment}$$

To calculate eNPV all revenues / costs assumed in the NPV model are multiplied by the probability of realising / incurring them and these adjusted values are used to calculate net cash inflow (i.e., the revenues are multiplied by the probability of the product launching, R&D costs are multiplied by the probability of the product reaching that phase)

NPV = net present value
t = time in years
r = interest or discount rate
n = number of periods (usually in years)

- A net present value (NPV) model expresses the profitability of an investment by measuring the present value net cash inflow over a period of time
- NPV models are useful as a means of comparing different investment options, as it accounts for the time value of money
  - for example, investments with the similar ROIs, but with different time intervals of investment return payments (i.e., cash inflows), will carry different NPVs
- The calculation of NPVs relies on a discount rate (r), which is the cost of capital required to make the investment; the discount rate is typically determined in two ways:
  - the interest rates of the capital which is borrowed to finance this investment, or
  - the expected rate of return of alternative projects with similar risk levels
- For relatively risky investments (e.g., pharmaceutical assets in clinical development with risk of trial failure), a risk adjusted NPV is used where NPVs are multiplied by PoS rates across trial phases / modalities / orphan status

Sources: Investopedia; Harvard Business Review; L.E.K. research and analysis

IRR is an alternative way to express investment profitability that takes into account annual growth rate of an investment

Calculation methodology – Internal rate of return

$$0 = NPV = \sum_{t=1}^{n} \frac{\text{Net cash inflow at year t}}{(1+IRR)^t} - \text{Initial investment}$$

NPV = net present value
t = time in years
r = interest or discount rate
n = number of periods (usually in years)

- An alternative way to express investment profitability based on the NPV is the internal rate of return (IRR)
  - the IRR is the discount rate that makes the NPV of future cash flows equal to zero
  - it indicates the annualised rate of return for a given investment and a given expected future cash flow
- IRR is back-calculated as a discount rate in an NPV analysis; the higher the IRR, the more profitable an investment
- IRR is often used as a comparison metric for investments based on a benchmark minimum rate of return, which is calculated in one of two ways:
  - from the IRRs of historical investments carried out by an individual / corporation, or
  - from the interest rate of the capital which is borrowed to finance the investment
- IRR assumes that dividends and cash flows are reinvested at the discount rate, so if the reinvestment rate is not as robust IRR will make a project look more attractive than it is

Sources: Investopedia; Harvard Business Review; L.E.K. research and analysis

Comparables analysis is an alternative investment valuation typically applied to early stage assets / companies carrying negative cash flows

Comparable company analysis

Historical basket of comparable investments / analogue companies and associated valuations

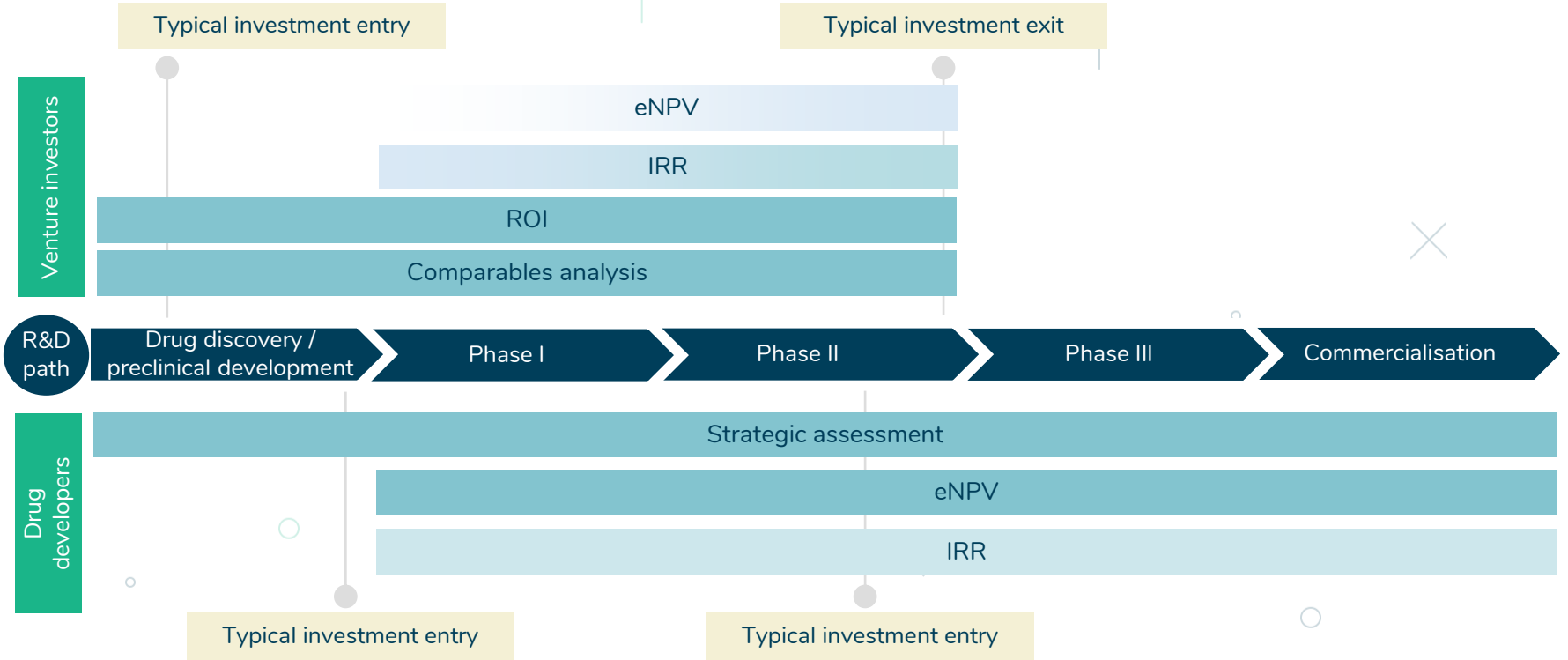
Assessment of potential pre-money value of company

Potential returns modelling based on analogue company evolution and exit multiples

- When evaluating an investment in an early-stage company / asset with limited visibility on future cash flow, NPVs may not be the most meaningful model to convey investment potential
- Under these circumstances, investors often conduct a comparables analysis to estimate the growth potential of an investment against the historical investment returns of a basket of comparables of similar backgrounds, size, and risk
- Investors aim to determine the pre-money valuation of the company and then determine the potential profitability based on the multiple at exit of comparators
  - this can be based on analysis of a series of investment rounds and multiples achieved for companies at different phases / therapeutic areas / peak revenue potential
- Scenario modelling can then be used to understand a potential weighted average return on investment
  - this is based on risk (i.e., 50% chance the company generates no returns, 25% 5x, 25% 10x) and different sizes of investment / exit potential

Sources: Investopedia; Harvard Business Review; L.E.K. research and analysis

Investors select the most suitable financial metrics at different stages of the R&D pathway based on data available and purpose of valuation



Degree of utilisation: Low High

Source: Bay Bridge Bio; EvaluatePharma; Investopedia; L.E.K. interviews, research and analysis

Venture investors and drug developers use different valuation methods in investment decision-making based on how they measure financial returns

Venture investors

- For venture investors, ROI is often the most suitable for fundraising and investment decision-making
- As venture investors exit investments pre-launch, they assess investments by the value they successfully added within the investment period in ROI multiples
  - this is as opposed to the value the asset generates throughout its life cycle, which is more accurately presented by NPV / IRR
- ROI is also more suitable as venture investors often invest at preclinical development stages, where eNPV values tend to be negative; PoS values which determine risk-adjusted NPVs are also difficult to estimate accurately

Drug developers

- For drug developers, eNPV is often the most suitable for capital allocation and investment decision-making
- The majority of investment risk in pharmaceutical development is associated with R&D failure, eNPVs are most suitable as they reflect the risks associated with each stage of clinical development
- eNPVs are informed by the risk adjustment of the product's potential revenue forecast and estimated costs
  - as assets progress along the development pathway and risk of failure lowers, risk adjusted revenues increase and the amount of remaining R&D cost decreases

Source: Bay Bridge Bio; EvaluatePharma; Investopedia; L.E.K. interviews, research and analysis

Venture investors prefer ROI to communicate investor and portfolio renumeration, and to show the value of early-stage investments

Venture investors

ROI is most commonly used among venture capital firms

- Return on investment (also refered to as cash on cash) is commonly used in venture firms as it articulates the amount of capital generated at the end of an investment period and potential returns for investors

"...We use cash on cash because that is what our renumeration is based on and shows the amount we will receive. Our investors are also more interested in cash on cash..."
Partner, U.S. standalone venture capital firm

ROI is used to convey the returns of an overall portfolio and its investments

- The expected returns of a portfolio overall and that of its investments are also communicated to investors by ROI; this is used to show that the portfolio comprises a mixture of investments of varying degrees of risk and expected returns, and that it overall averages to an optimal ROI (3-5x)

"...When fundraising, we are confident in the portfolio yielding 3-5x ROI. We then show how we plan to achieve this by having a mix of investments of 1x, 5x, and 10-20x ROIs of varying degrees of risk..."
Partner, European corporate venture capital firm

ROI best articulates early-stage venture investments with long time to exit

- Some venture investors also prefer ROI because it is not time-sensitive, which accommodates for the longer time to exit some early-stage investments require to mature and deliver returns

"...In our industry where we work with long product cycles, we need time for transformational technologies or therapeutics to mature. IRR is not as suitable here as the time element potentially undermines the value and attractiveness of an investment..."
Partner, U.S. standalone venture capital firm

Source: L.E.K. interviews, research and analysis

ROIs and comparables analyses are used when comparing early-stage investments and determining the amount to invest

Venture investors

Drug discovery / preclinical development stage investments are assessed based on ROI

- Venture investments tend to begin at preclinical development stages – ROI is used at this stage as it is the most suitable for expressing cash on cash returns and can be used to compare investments
  - eNPVs are less suitable assessments at such an early stage and typically carry negative values
  - there is often insufficient data to accurately inform NPV analysis at this stage

"…At preclinical development stages using NPVs is not very helpful – there is not enough evidence to substantiate PoS and your NPV ends up being very sensitive to a data point which is not well-supported…"
Partner, European standalone venture capital firm

Comparables analysis and ROI are used together to determine amount of capital to invest

- Venture firms have internal ROI benchmarks to inform the amount of capital they can invest in an asset based on the projected asset value at exit from comparables analysis
  - total value of capital to invest is the expected exit value divided by ROI benchmark, this investment can then be spread across different development milestones to derisk

"…We invest in a preclincial asset and conduct a comparables analysis of the deal values of similar assets at phase 2 – when we plan to exit. We divide that by our desired ROI multiple to get to the total amount we invest. We then spread this investment across series, which is driven by risks / expected R&D progression…"
Former Venture Advisor, European corporate venture capital firm

Source: L.E.K. interviews, research and analysis

NPVs and IRRs are used more commonly by venture investors in the valuation of clinical assets and are important for deal exits

Venture investors

Clinical-stage investments are increasingly assessed by eNPVs / IRRs

- As investments mature and enter clincial stages, the safety and efficacy data generated enables NPV and IRR to be estimated more accurately based on PoS and expected revenue

"...From clincial data we can support an accurate PoS value but also make estimations on peak sales ..."
Former Venture Advisor, European corporate venture capital firm

NPVs and IRRs are particularly relevant at exits as they are preferred by pharma buyers

- NPVs and IRRs become particularly useful when venture firms are determining the deal value of investments at exit stage, as these are the metrics buyers (e.g., pharma) use to evaluate assets
  - venture firms can differentiate asset attractiveness using eNPVs and IRRs as it accounts for the timeline to achieve investment returns, which becomes increasingly relevant as assets approach commercialisation

"...We evaluate our assets at exit stage, we valuate assets using both ROI and NPV. ROI for calculating investment returns to our portfolio, NPV values to get a sense of the value of our asset to our buyers..."
Partner, U.S. standalone venture capital firm

Source: L.E.K. interviews, research and analysis

Pharma investors use IRR to assess overall returns of an asset; and use eNPVs for valuing external assets and determining investment timing

Drug developers

Pharma companies measure external and internal assets against IRR targets

- Pharma companies have internal IRR benchmarks for assessing profitability of both internal and external assets based on the expected returns of an investment throughout its product life cycle
  - assets acquired externally typically have to surpass IRR thresholds, and some pharma investors have higher targets for IRR to compensate for the cost of in-licensing*
  - internal assets are assessed at the end of each developmental stage based on emerging data, whether it meets IRR benchmarks and is sufficiently profitable to be carried to the next stage

"...We have internal IRR benchmarks, which is typically used when we talk about return of the asset as a whole. This is used to assess both external investments and our internal assets..."
Director of oncology BD, multinational biopharma

eNPVs are used in the valuation of external assets

- Pharma companies also use eNPVs to determine the value of an external asset in in-licensing deals as it provides a dollar value for the investment

"... There is an internal return rate (or hurdle rate) threshold which assets will have to first pass. Then we use eNPVs to determine acquisition values using the peak sales forecast and the current PoS..."
Director of oncology BD, multinational biopharma

eNPV is also used to determine the timing of investments

- eNPVs are used to determine when in the product life cycle to invest based on cost of capital and expected revenue yield over time; accounting for the time of investment is particularly relevant for life cycle management strategies which can incur additional R&D costs

"...We invest in indication expansions and reformulations. NPVs are helpful to inform when we should make these investments based on expected profits over time and the cost of capital..."
Former Associate Director of Business Development, multinational biopharma

Notes: *Such as transactional price premium, operational costs of bringing asset in-house
Source: L.E.K. interviews, research and analysis

Pharma investors value preclinical development assets based on comparables, but use advanced metrics - risk adjusted eNPVs and IRRs - for clinical assets

Drug developers

Early stage assets are assessed based on strategic fit and comparables analysis

- Asset valuation at early drug discovery / preclinical development stages are largely based on strategic fit, but comparables analyses are also used to estimate investment returns for preclinical development in-licensing agreements

"...The most suitable metric for preclinical development transactions would be comparables. At that point no one has a good understanding of PoS or possible market share, so the best way to value an asset is against its peers..."

VP strategy and innovation, emerging biopharma

Assets that are entering clinical stages are subjected to rigorous financial valuation

- When an asset transitions from preclinical to clinical development, they are evaluated by more robust financial metrics such as eNPVs and revenue forecasting, driven by high costs of clinical trials and the need to understand cost / benefit trade offs at a granular level

"...The most critical hurdle is from preclinical development to clinical. There is stringent prioritisation of capital at this point, we select the most promising candidates to progress into clinical trials..."

Senior director of R&D, multinational biopharma

eNPVs and IRRs are used to inform investment decisions at each stage of clinical development

- An improved understanding of the asset's likelihood to succeed, revenue projections and uptake in early clinical development allow advanced financial metrics (e.g., risk adjusted NPVs, IRRs) to be calculated; at the end of each development stage assets are measured against internal benchmarks

"...Around the clinical proof of concept stage which is when we will have data to make a revenue forecast, which is then used to inform returns both in terms of eNPV and IRR..."

Former Associate Director of Business Development, multinational biopharma

Source: L.E.K. interviews, research and analysis

Pharma investments on an asset level tend to follow existing expertise, but M&A can be considered to enter new areas

Drug developers

Investments on an asset level tend to adhere to current strategy

- Financial metrics are used to assess investment attractiveness, but pharma investors express that their investments are also heavily driven by strategic objectives
  - some CVC investors view their primary role to be at the forefront of innovation in core therapeutic areas; and while ability to generate favorable financial returns is important, it can be secondary to the parent company's strategic goal (depending on type of CVC)

"…Our role is to track innovation in the relevant strategic areas and to also partner with other venture firms to increase exposure. Our financial returns only makes a small contribution to the company's balance sheet…"
Former Venture Advisor, European corporate venture capital firm

  - BD investors focus more on financial valuation as they consider the asset's profitability over a 10-15 year horizon, but note their investments also tend to align to company strategy

"…I consider also on top of financial returns whether an asset is synergistic to existing drugs in our portfolio…"
Former Associate Director of Business Development, multinational biopharma

Investments outside of core areas tend to happen via M&A

- Investments on an asset level tend to adhere to existing expertise due to the high cost of building out sales forces in novel therapeutic areas / R&D organisation for novel modalities
- Pharma investors note companies can also acquire new therapeutic area / modality expertise, but it typically occurs via M&A

"…With increased competition for external innovation, high quality assets are few and far between. We are starting to see companies play in novel therapeutic areas. But companies tend to consider M&A here, as you can acquire an entire portfolio of pipeline assets and R&D expertise…"
Former Director of Oncology BD, multinational biopharma

Source: L.E.K. interviews, research and analysis

PoS increases significantly when assets reach phase III as most R&D risks are resolved, this drives up eNPVs and valuation of assets

Product "value inflation" is generally driven by PoS and increased data availability

- Pharma investors note that the business cases of assets inflate as they progress along clinical development, which they view to be mostly driven by higher PoS and subsequent eNPV values, and favorable trial data increasing revenue expectations
  - as assets progress through development they are typically supported by stronger efficacy data than earlier stage counterparts, which increases revenue expectations and subsequently eNPV
  - at phase III, assets have proven to be both safe and efficacious in the target diseases; as the most significant risks of failures are resolved, PoS is high at phase III which increases eNPV

"...Most of the R&D risks lie in phase II when the assets have to prove they are efficacious in their target diseases. Once they are past that most of the R&D risks are gone. That is why valuation increases exponentially at phase III but not before..."
VP Innovation and Strategy, emerging biopharma

"...If phase III head-to-head trials return more favorable outcomes than competitors that would also increase revenue expectations, which is why late stage assets are so much more expensive..."
Associate director R&D, multinational biopharma

Pharma companies may be willing to pay a premium on later stage deals

- Some investors note that phase III deals are valued higher because they are competitive among big pharma companies looking to fulfill short-term pipeline shortages

"...Phase III deals are few and far between and as a result there is a lot of competition for them which drives up their values. Pharma companies are sometimes wiling to pay the premium because they have a shortage in their pipeline from late-stage R&D failure which they have to fill ..."
Director of oncology BD, multinational biopharma

Source: L.E.K. interviews, research and analysis

Companies are increasingly willing to pay premiums to diversify their portfolio and support their own R&D pipeline, on top of increasing R&D

Companies are willing to pay premiums for strategic reasons

- Pharmacos are increseasingly willing to pay premiums when acquiring a company, even with early stage pipeline assets, given the confidence they have in the deal being of added-value for them
  - over the last two decades, the goodwill intangible assets of the 10 largest pharma companies has risen from almost zero in 2000 to c.$270Bn in 2018 and McKinsey data shows a 60% median premium for H1 2018 deals on publicly traded companies
- Goodwill payment are often driven by the need to fill short-term pipeline or sales goals, whilst it also broadens the portfolio and can further boost a company's reputation and investors confidence
- Goodwill would typically be registered as an intangible asset in the acquirer's balance-sheet, without impacting the P&L, whilst actual R&D expenditure of the acquired company would appear in the P&L as incurred
  - independently of goodwill, acquirers would often significantly invest in the newly acquired R&D pipeline to help drive company success

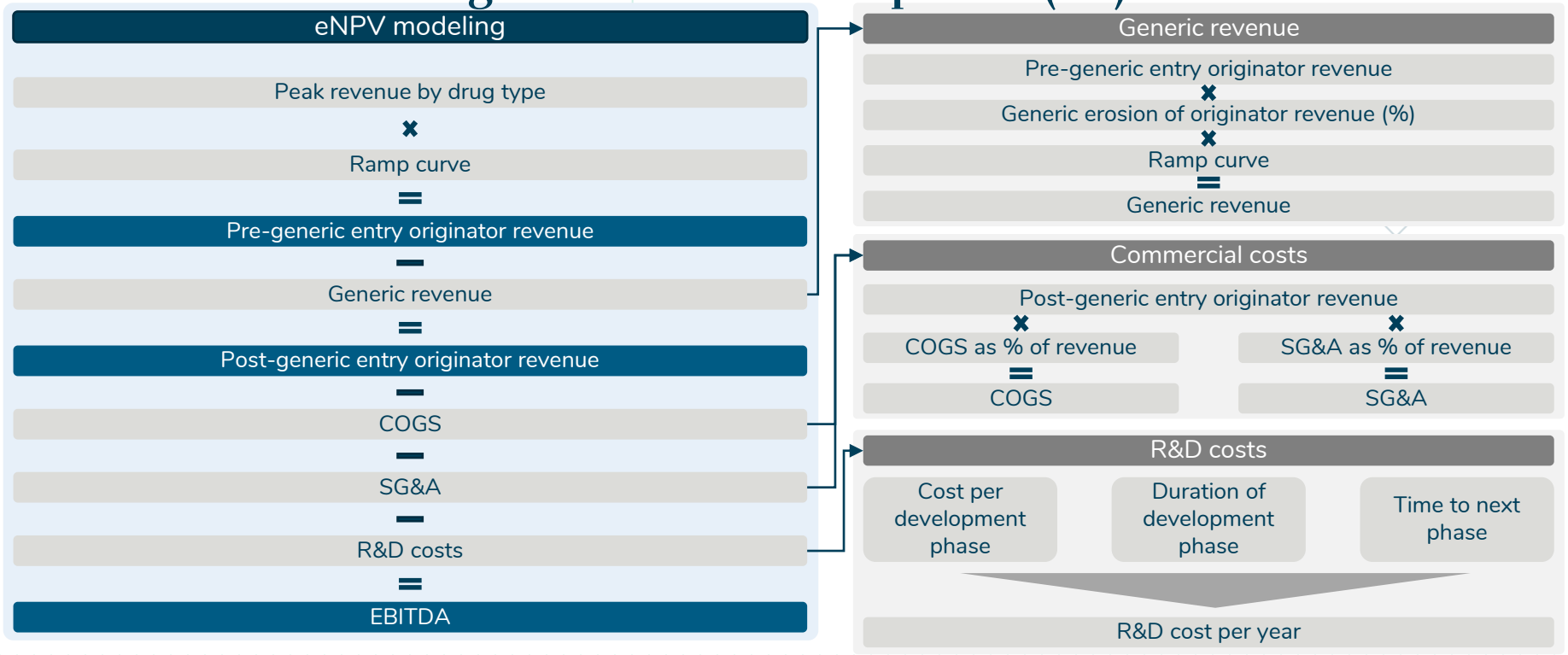
Juno case study

- Juno Therapeutics is an oncology-focused company, specialising in CAR T cells
- Celgene announced its acquisition of Juno in January 2018 for $9Bn ($87 per share), thus paying c.90% premium, financing the deal with debt and existing cash
  - Juno share price was initially c.$46 and rose to c.$67 after the deal was reported in the news with promising targeted asset JCAR017 still in early pipeline
- Celgene aimed to build out and diversify its own oncology pipeline, given the soon expiry the Revlimid patent and given the poor results for Otezla - the deal was also needed to regain investors' confidence after the failure of a promosing Crohn's disease drug

Source: McKinsey 2018; Somo 2020; L.E.K. interviews, research and analysis

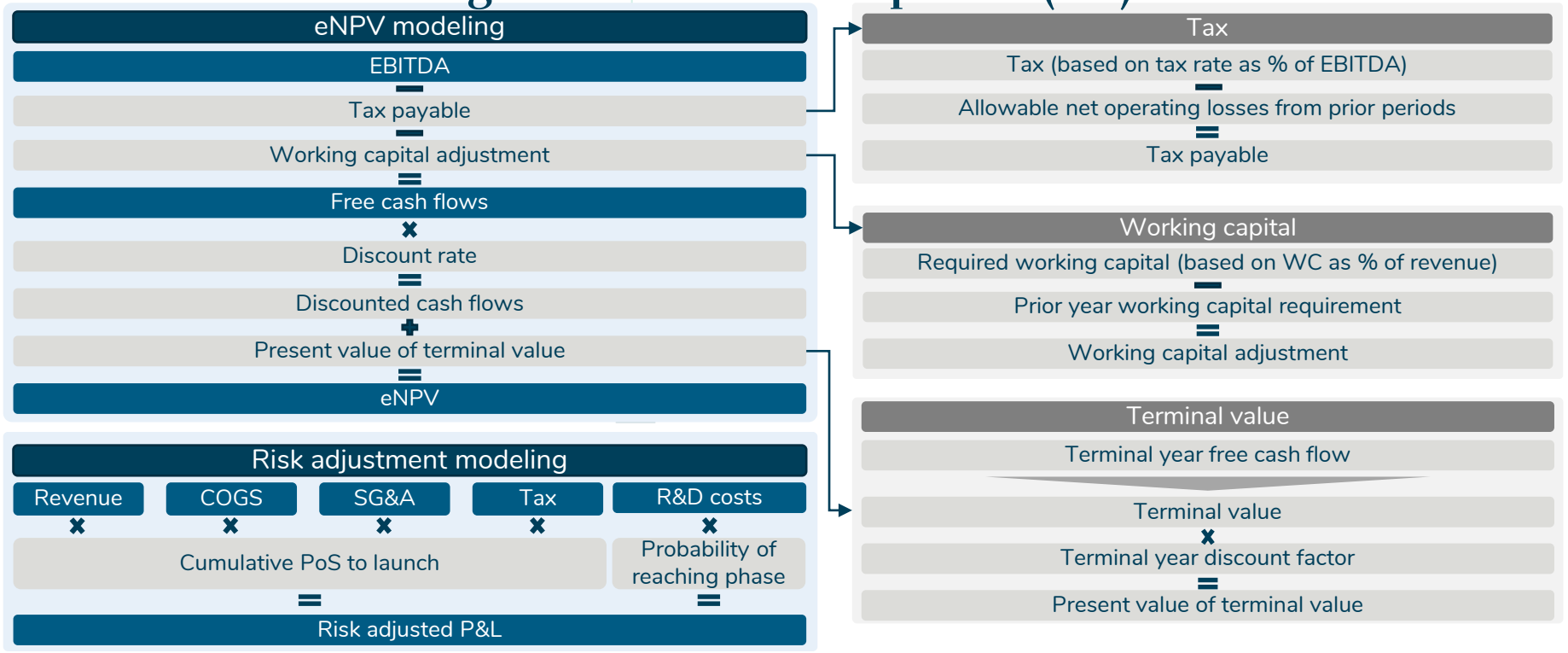
eNPV modelling

The following model methodology was used to quantify the eNPV of assets at each stage of clinical development (1/2)



Source: L.E.K. research and analysis

The following model methodology was used to quantify the eNPV of assets at each stage of clinical development (2/2)



Source: L.E.K. research and analysis

The following assumptions have been used as the base-case and represent the weighted average of the assumptions for each drug type

Key revenue model assumptions			Source
Peak revenue (mUSD)		610	• *L.E.K. analysis of Datamonitor*
COGS (as % of revenue)		15%	• *L.E.K. standard assumption*
SG&A (as % of revenue)		25%	• *L.E.K. standard assumption*
Working capital (as % of revenue)		10%	• *L.E.K. standard assumption*
Time to peak (years)		6	• *L.E.K. prior case experience*
Corporate tax rate (U.S.)		27%	• *KPMG tax report*
Allowable additions to NOL		90%	• *L.E.K. standard assumption*
Time to next phase (months)	Target to hit identification	12	
	Hit to lead	18	
	Lead opt.	24	• *L.E.K. R&D mapping*
	Preclinical development	12	• *Abrantes-Metz, Adams and Metz, 2004*
	Phase I	18	
	Phase II	30	• *Jayasundara et al., 2019*
	Phase III	36	
	Approval	18	
R&D cost per phase (millions of USD)	Target to hit identification	1	
	Hit to lead	3	
	Lead opt.	12	
	Preclinical development	6	• *L.E.K. analysis of Datamonitor*
	Phase I	30	
	Phase II	50	
	Phase III	180	
	Approval	49	

Key eNPV assumptions		
Working capital	10%	• *L.E.K. standard assumption*
WACC	10%	• *L.E.K. standard assumption*
Growth in perpetuity	(10%)	• *L.E.K. prior case experience*

Generic entry assumptions		
Peak generic erosion	80%	• *L.E.K. prior case experience*
Generic years to launch after originator	10	• *L.E.K. prior case experience*
Generic years to peak	2	• *L.E.K. prior case experience*

PoS assumptions		
Target to hit identification	80%	
Hit to lead	75%	
Lead opt.	85%	
Preclinical development	69%	• *BioMedTracker (2016)*
Phase I	63%	• *Paul et al., (2010)*
Phase II	31%	
Phase III	58%	
Approval	85%	

Assumptions to be flexed by drug type

SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Paul et al., (2010); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Peak revenues were estimated by drug type based on the median peak revenue presented by Datamonitor, with key outliers excluded

L.E.K. analysis of average peak revenue in Datamonitor data was skewed by key outliers

- L.E.K.'s analysis of Datamonitor data resulted in an average peak revenue that was skewed upwards by key outliers such as Keytruda, Ocreus, and Opdivo
  - these drugs are not considered typical for their relevant drug types as their peak revenues were significantly higher than the other drugs in that category
- L.E.K. has triaged the Datamonitor data to exclude forecast data that is not representative of the drug type as a whole

Datamonitor data is forecast through 2030

- Datamonitor includes forecasts for each drug through to 2030
  - these forecasts, especially for the large, outlier drugs, can be seen as optimistic compared to real peak revenues seen, as forecast do not necessarily account for competition accurately
- L.E.K. has used the median peak revenue, rather than the average peak revenue, to account for the high forecasts at the tail of the 2030 forecast period

Source: Datamonitor; L.E.K. research and analysis

This illustrative P&L shows non-risk adjusted revenues and costs for an asset from target-to-hit identification to 5 years post generic entry

	Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Illustrative P&L	Revenue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	102	203	305	407	508	610	610	610	610	610	366	122	122	122	122	122
	R&D costs	1	2	4	6	6	13	20	20	20	40	60	60	46	33	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15	31	46	61	76	92	92	92	92	92	55	18	18	18	18	18
	SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	25	51	76	102	127	153	153	153	153	153	92	31	31	31	31	31
	EBITDA	(1)	(2)	(4)	(6)	(6)	(13)	(20)	(20)	(20)	(40)	(60)	(60)	(46)	(33)	61	122	183	244	305	366	366	366	366	366	220	73	73	73	73	73
	Tax payable	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	18	66	82	99	99	99	99	99	59	20	20	20	20	20
	Earnings after tax	(1)	(2)	(4)	(6)	(6)	(13)	(20)	(20)	(20)	(40)	(60)	(60)	(46)	(33)	61	122	165	178	223	267	267	267	267	267	160	53	53	53	53	53
Discounted cash flows	Change in working capital	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(10)	(10)	(10)	(10)	(10)	(10)	-	-	-	-	24	24	-	-	-	-
	Free cash flow	(1)	(2)	(4)	(6)	(6)	(13)	(20)	(20)	(20)	(40)	(60)	(60)	(46)	(33)	51	112	154	168	212	257	267	267	267	267	185	78	53	53	53	53
	Discount factor	0.95	0.87	0.79	0.72	0.65	0.59	0.54	0.49	0.44	0.40	0.37	0.33	0.30	0.28	0.25	0.23	0.21	0.19	0.17	0.16	0.14	0.13	0.12	0.11	0.10	0.09	0.08	0.07	0.07	0.06
	Discounted cash flows	(1)	(2)	(3)	(4)	(4)	(8)	(11)	(10)	(9)	(16)	(22)	(20)	(14)	(9)	13	26	32	32	36	40	38	34	31	28	18	7	4	4	4	3

★ Launch

★ Generic entry

SiRM. Strategies in Regulated Markets

L.E.K.

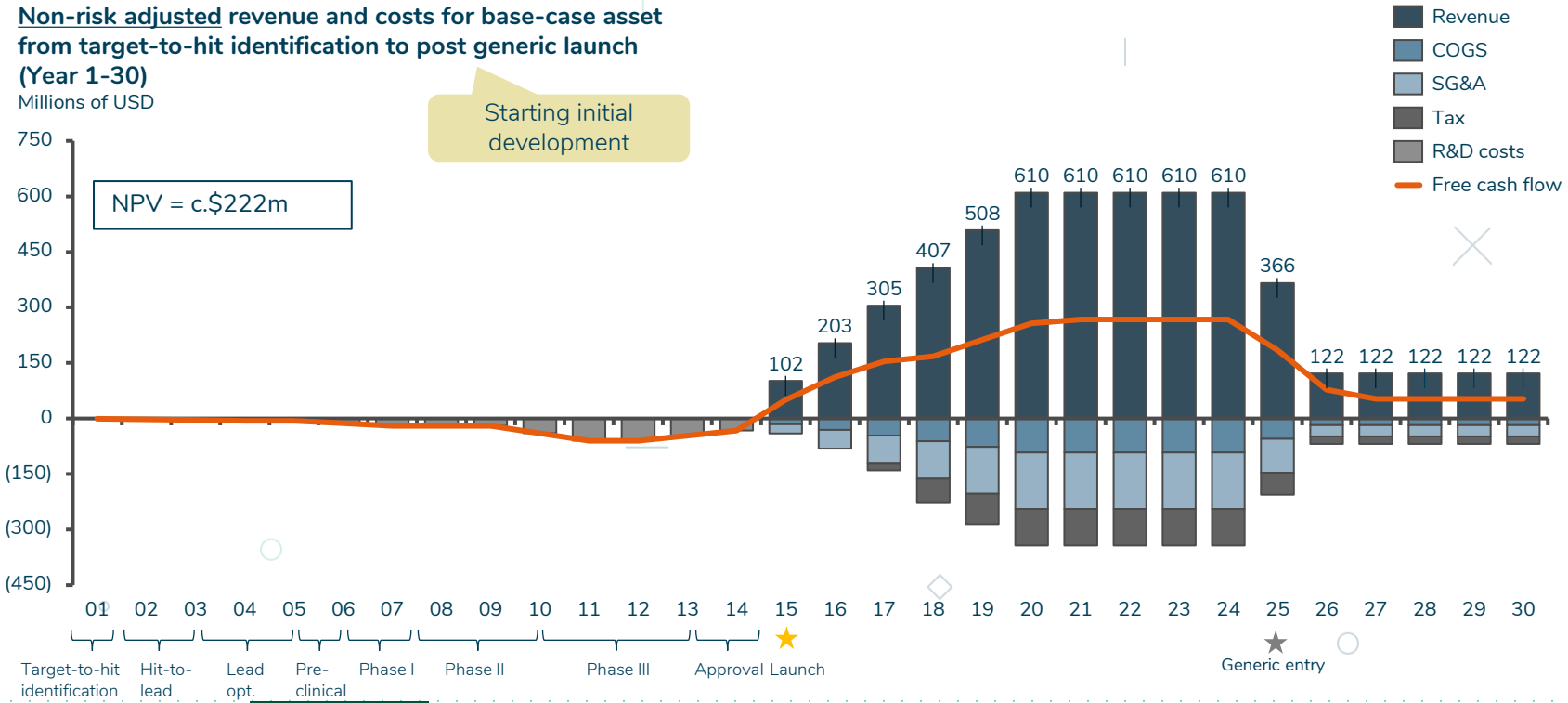
Note: *Numbers in brackets are negative numbers according to accounting systems

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

The base-case asset starting from target-to-hit identification reaches peak revenues of $610m in year 20, with non-risk adjusted NPV of $222m

Non-risk adjusted revenue and costs for base-case asset from target-to-hit identification to post generic launch (Year 1-30)

Millions of USD



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Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

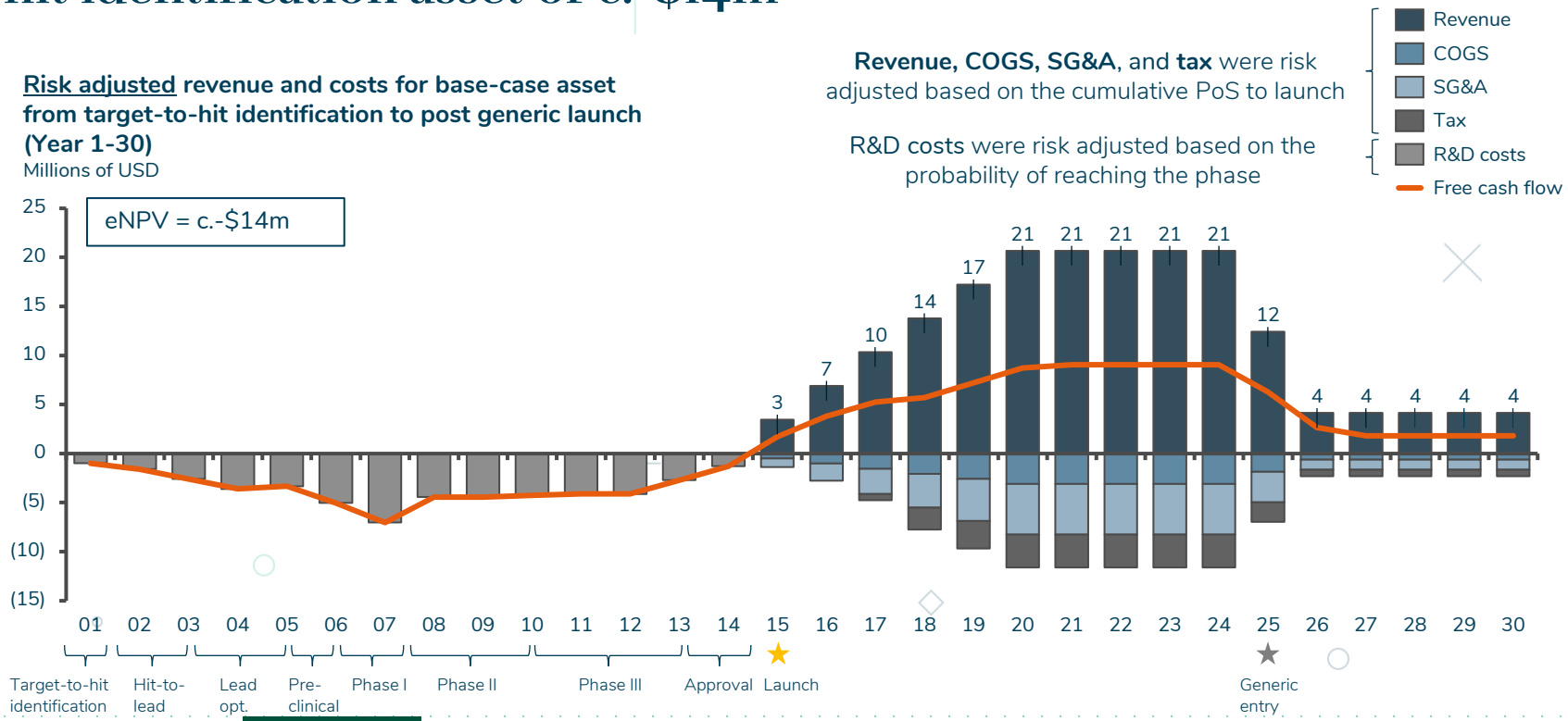
Risk adjusting revenues and costs leads to an eNPV for a target-to-hit identification asset of c.-$14m

Risk adjusted revenue and costs for base-case asset from target-to-hit identification to post generic launch (Year 1-30)

Millions of USD

Revenue, COGS, SG&A, and **tax** were risk adjusted based on the cumulative PoS to launch

R&D costs were risk adjusted based on the probability of reaching the phase



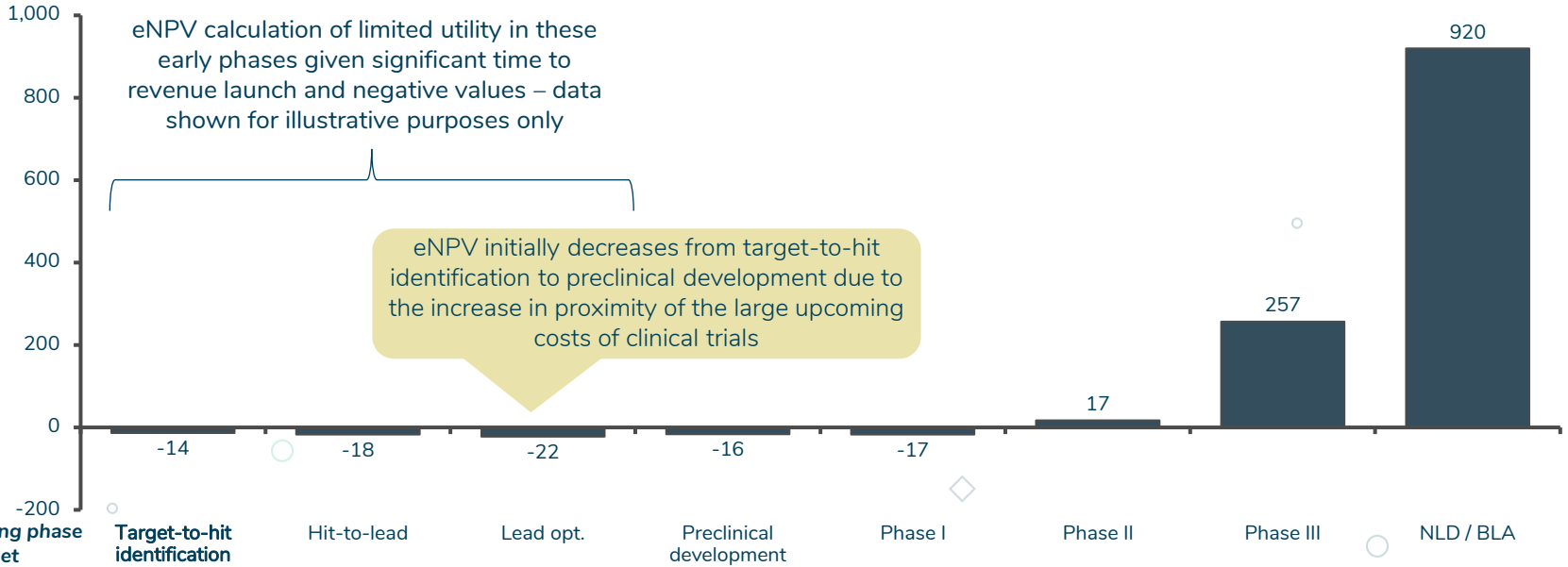
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Risk adjusted eNPV increases with each stage for the base-case asset in clinical development, with positive eNPV from phase II onwards

Base-case risk adjusted eNPV at the start of the development phase, based on initial phase of asset
Millions of USD



SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Assumptions for the base case were carefully checked and pressure tested, although there are some important caveats

L.E.K. modelling of eNPV is based on a series of base case assumptions which can vary by different factors

- eNPV has been modeled based on available data, from several reliable souces such as DataMonitor, PubMed, KPMG, Deloitte giving confidence in the model assumptions
  - numbers were cross-checked and pressure tested in interviews to ensure that the model is reliable though differences will clearly exist for different types of product (e.g., different therapeutic areas)
- L.E.K. also assumed some numbers (e.g.,SG&A or COGS % revenues) based on expertise within this segment

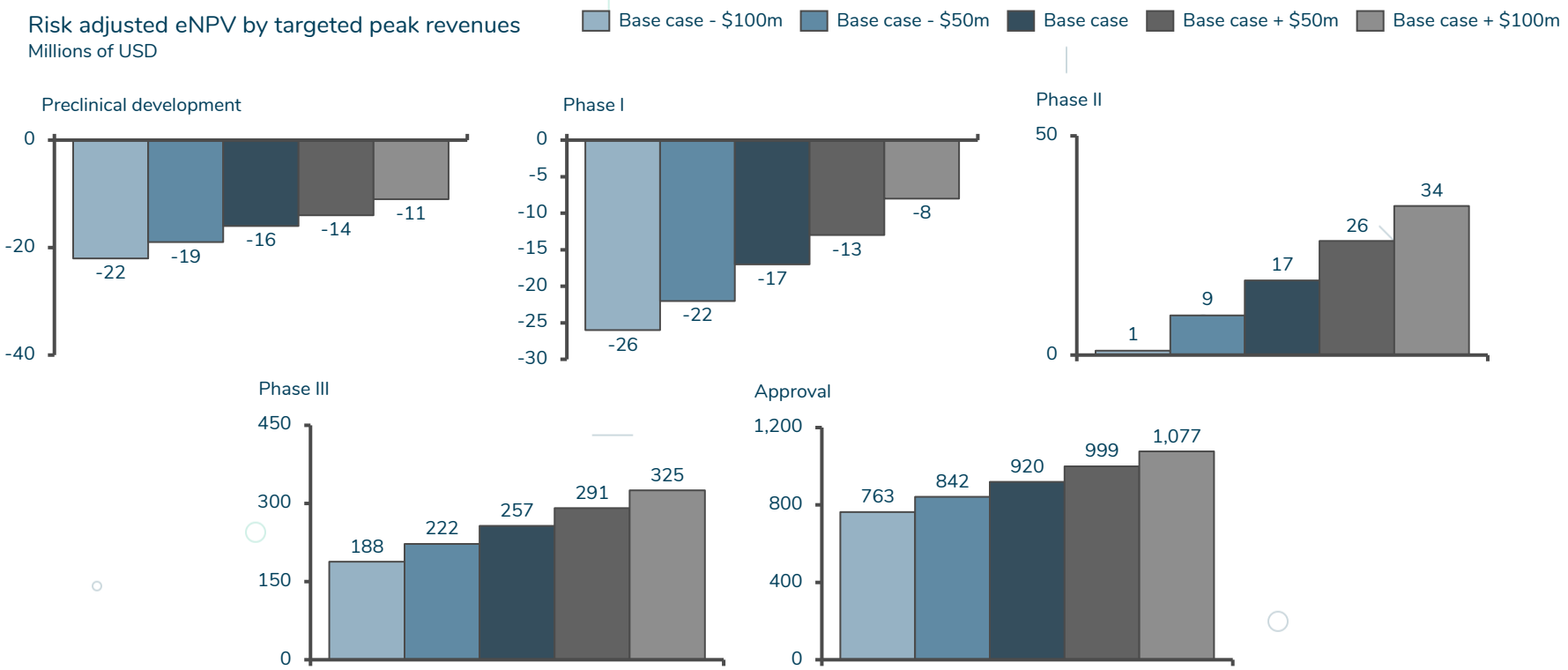
Different peak revenues and R&D costs were used to illustrate how these might impact on eNPV

- L.E.K. identified key drivers of the model, especially the peak revenues and R&D costs, and modeled eNPV according to different assumptions from the base case to illustrate the impact on eNPV
  - PoS is also a key criteria that may be adjusted given the type of asset or the capabilities of the considered company but this is best illustrated through the orphan drug sensitivity
- Although corporate tax rates vary depending on geography and company type, this is not a significant driver of eNPV sensitivity based on L.E.K. analysis

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

eNPV sensitivity based on different expected peak revenues in the base case

Risk adjusted eNPV by targeted peak revenues
Millions of USD

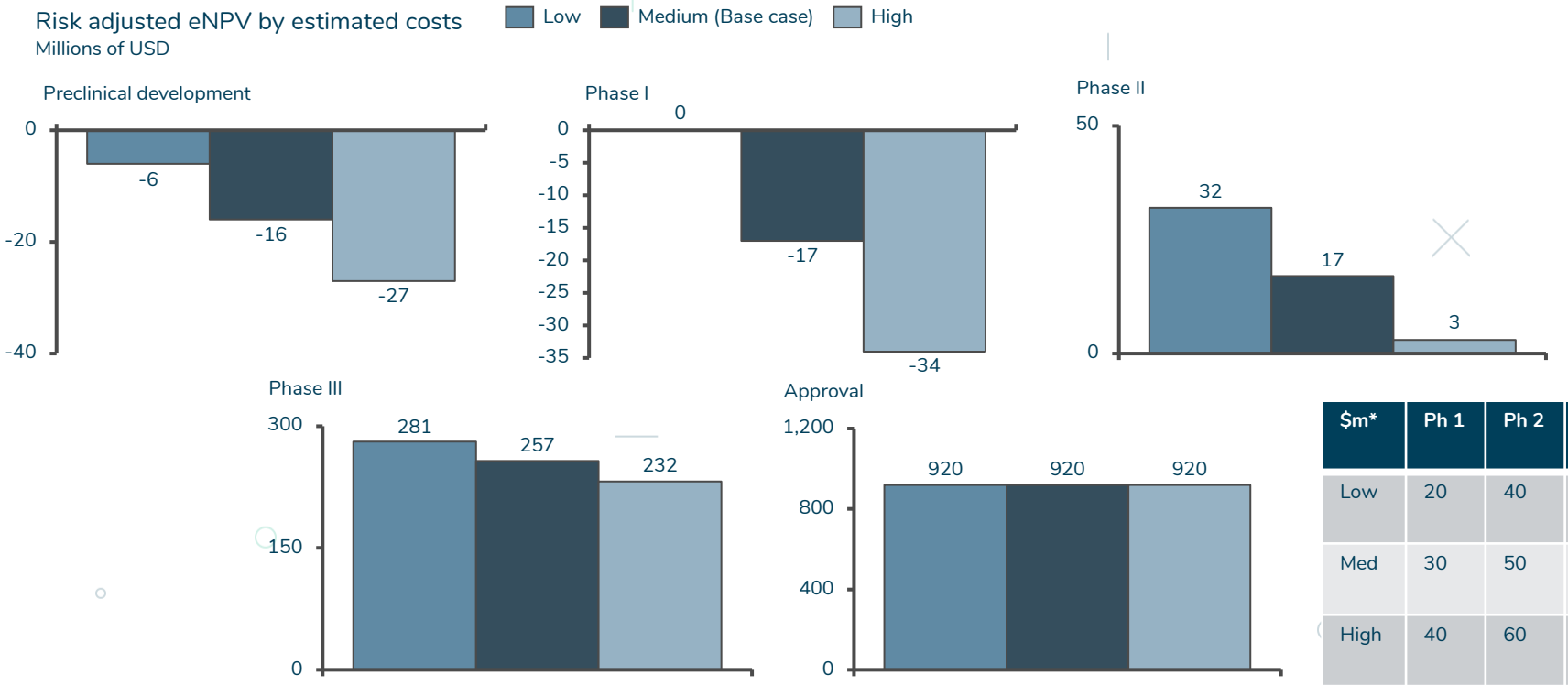


SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

eNPV sensitivity based on different cost scenarios in the base case



$m*	Ph 1	Ph 2	Ph 3
Low	20	40	150
Med	30	50	180
High	40	60	210

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Note: *2020 USD; preclinical and pre-reg costs same as base case
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

The following assumptions have been adjusted for each drug type to reflect their different characteristics (1/2)

Key revenue model assumptions							Rationale
Drug type		Base-case*	Orphan	Non-orphan	Large molecule	Small molecule	• *Analysis of Datamonitor data, adjusted for outliers in the forecast, resulted in higher peak sales for orphan and large molecule drugs compared to non-orphan and small molecule drugs*
Peak revenue (mUSD)		610	770	600	945	480	
COGS (as % of revenue)		15%	15%	15%	20%	10%	• *Large molecule drugs typically have more complex manufacturing processes, resulting in higher COGS as a % of revenue compared to small molecules*
Peak generic erosion		80%	80%	80%	70%	85%	• *Generics for small molecule drugs are seen as equivalent to originator drugs, resulting in higher generic erosion* • *Biosimilar drugs generally have lower uptake due to restrictions on substitution and physician perception*
Generic years to launch after originator		10	10	9	12	9	• *Analysis of biosimilar and generic drug entries has illustrated a longer period between originator launch and generic entry for large molecules compared to small molecules*
Generic years to peak		2	2	2	5	2	• *Substitution practices result in faster uptake of small molecule generics*
Time to next phase (months)	Target to hit identification	12	Methodology described in detail in appendix				• *Base-case duration of phases was assessed in the R&D mapping* • *The ratio between orphan and non-orphan trial durations identified in Jayasundara et al. (2019) were applied to the base-case phase durations to flex these assumptions for orphan and non-orphan drugs* • *Similarly, the ratio between large and small molecule trial durations identified in Abrantes-Metz et al. (2004) were applied to the base-case phase durations to flex these assumptions for large and small molecule drugs*
	Hit to lead	18					
	Lead opt.	24					
	Preclinical dev.	12	12	12	12	12	
	Phase I	18	24	12	18	18	
	Phase II	30	36	24	30	30	
	Phase III	36	48	24	36	36	
	Approval	18	18	18	18	18	

Notes: *Base-case assumptions represent the weighted average of other drug types
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

The following assumptions have been adjusted for each drug type to reflect their different characteristics (2/2)

Key revenue model assumptions							Rationale
Drug type		Base-case*	Orphan	Non-orphan	Large molecule	Small molecule	
R&D cost per phase (millions of USD)	Target to hit identification	1					• *Base-case cost per phase of development was determined in the R&D mapping* • *The ratio** between orphan and non-orphan cost per phase identified in Jayasundara et al. (2019) was applied to the base-case assumptions to adjust these for orphan and non-orphan trials* • *Similarly, the ratio between large and small molecule cost per phase noted in DiMasi et al. (2016) were applied to the base-case assumptions to flex these for large and small molecule drugs*
	Hit to lead	3					
	Lead opt.	12					
	Preclinical dev.	6	6	6	6	6	
	Phase I	30	35	25	28	30	
	Phase II	50	73	30	80	45	
	Phase III	180	115	240	200	175	
	Approval	49	49	49	49	49	
Probability of success	Target to hit identification	80%					• *Base-case probability of success to next phase was assessed in the R&D mapping* • *The ratio** between orphan and non-orphan PoS, from Jayasundara et al. (2019), were applied to the base-case assumptions to adjust these for orphan and non-orphan drug types* • *The PoS for large and small molecules is based on BioMedTracker (2016) analysis*
	Hit to lead	75%					
	Lead opt.	85%					
	Preclinical dev.	69%	69%	69%	69%	69%	
	Phase I	63%	85%	61%	66%	61%	
	Phase II	31%	67%	28%	34%	27%	
	Phase III	58%	65%	57%	57%	49%	
	Approval	85%	83%	85%	88%	78%	

Drugs with orphan designation may have lower sales and marketing costs, which are not modeled here, due to concentration of patients at a small number of specialist call-points

Notes: *Base-case assumptions represent the weighted average of other drug types; **Methodology described in detail in the appendix
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research; interviews, and analysis

Orphan drugs may be granted accelerated approval based on Phase II data, which can be modelled by removing Phase III assumptions

Companies can receive orphan designation for specific drugs and conditions

- Both the FDA and EMA have special pathways for rare diseases or conditions that meet specific criteria
  - The orphan drug designation program provides orphan status to drugs that treat, diagnose, or prevent rare diseases that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 people but are not expected to recover the costs of developing and marketing a treatment
- The FDA Office of Orphan Products and Development (OOPD) is responsible for assessing products and identifying and designating products as orphan products
  - OOPD also operates an Orphan Products Grants Program to encourage the development of new medical products for rare diseases

Assets with orphan designation can have accelerated approval based on Phase II data

- Drug manufacturers can use orphan designation to file for accelerated approval based on a pivotal Phase II trial
- A study of OOPD clinical trial grants offered between 2007 and 2011 illustrated that 5 of the 9 (56%) assets approved were approved based on Phase II clinical trials
  - The remainder of assets, 4 out of 9 (44%), were approved based on Phase III clinical trial results

L.E.K. has modelled orphan drugs assuming progression to a Phase III trial; Accelerated approval based on Phase II trials, which represents c.50% of orphan drugs, could be modelled by removing Phase III assumptions

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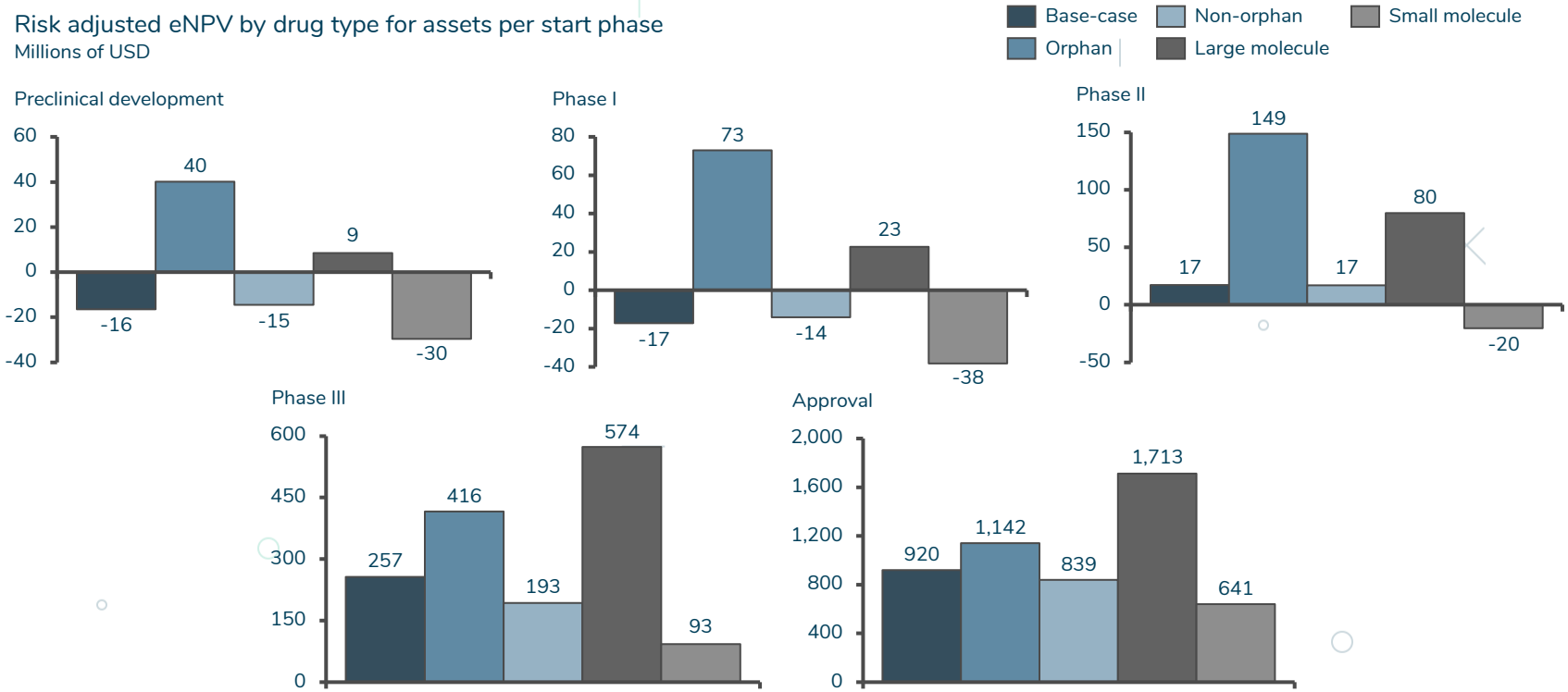
L.E.K.

Source: Miller et al., (2020); FDA; Office of Orphan Products and Development; L.E.K. research, interviews, and analysis

In clinical phases, small molecule drugs become eNPV positive when they transition to Phase III

Risk adjusted eNPV by drug type for assets per start phase
Millions of USD



SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Orphan assets have the highest eNPV up to Phase II due to higher PoS; from Phase III, large molecules have higher average eNPV

Orphan drugs have a high eNPV through development due to higher Phase I to Phase III PoS

- Orphan drugs have higher eNPV throughout development due to higher PoS per stage from Phase I to Phase III, leading to a higher overall PoS to launch
  - the largest discrepancy is in Phase II PoS, with c.67% for orphan drugs and c.28% for non-orphan drugs
- As assets progress past Phase II, the difference in eNPV between orphan and non-orphan assets decreases as PoS of orphan and non-orphan drugs become similar
- Orphan assets have a higher eNPV than non-orphan drugs at approval due to higher peak revenues for orphan drugs

Following Phase II, large molecules have the largest eNPV due to their high peak revenue potential

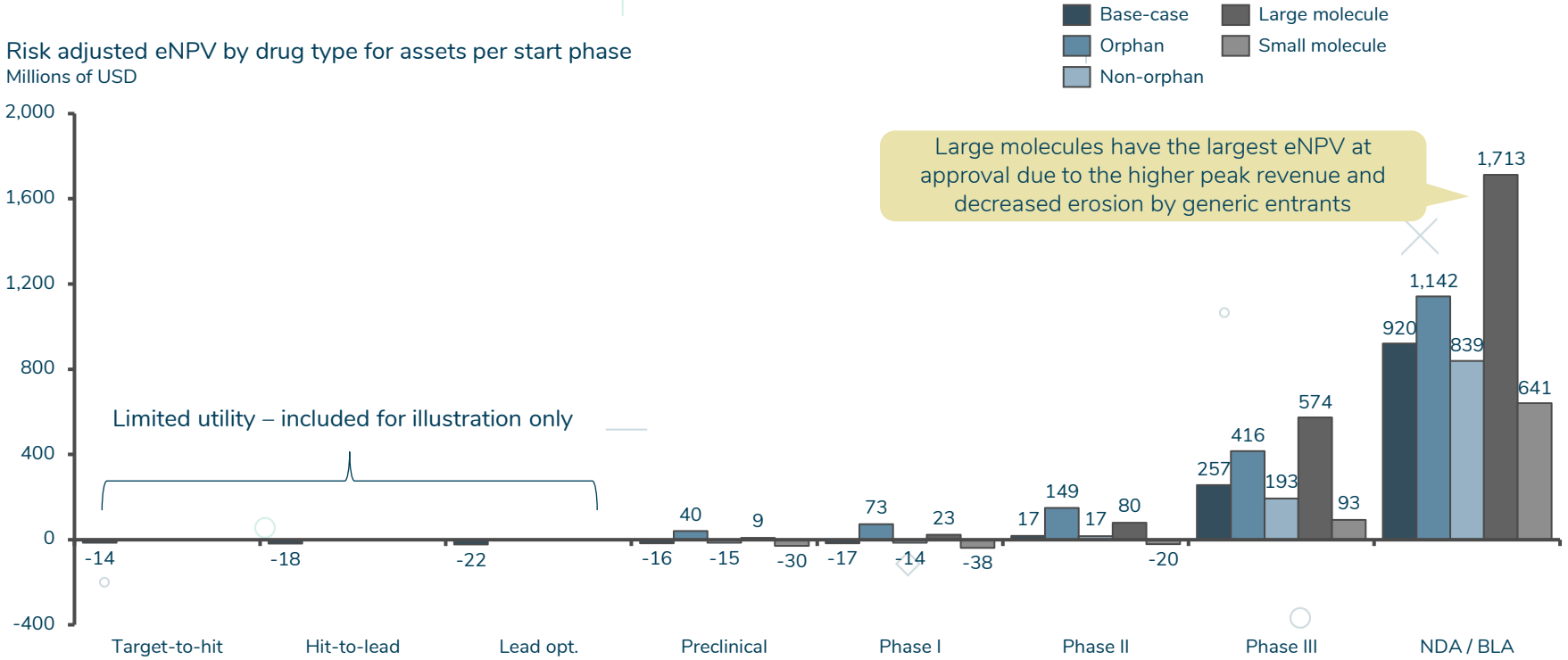
- Large molecule drugs have the highest peak revenue of all drug types, with large molecules reaching c.$945m compared to c.$610m for the base case weighted-average asset
- Since all asset types have a similar PoS to launch from Phase II onwards, large molecules have a higher Phase III and approval eNPV due to the higher expected revenues

SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Risk adjusted eNPV increases throughout clinical development, with large molecule drugs providing the highest eNPV at approval



SiRM. Strategies in Regulated Markets

L.E.K.

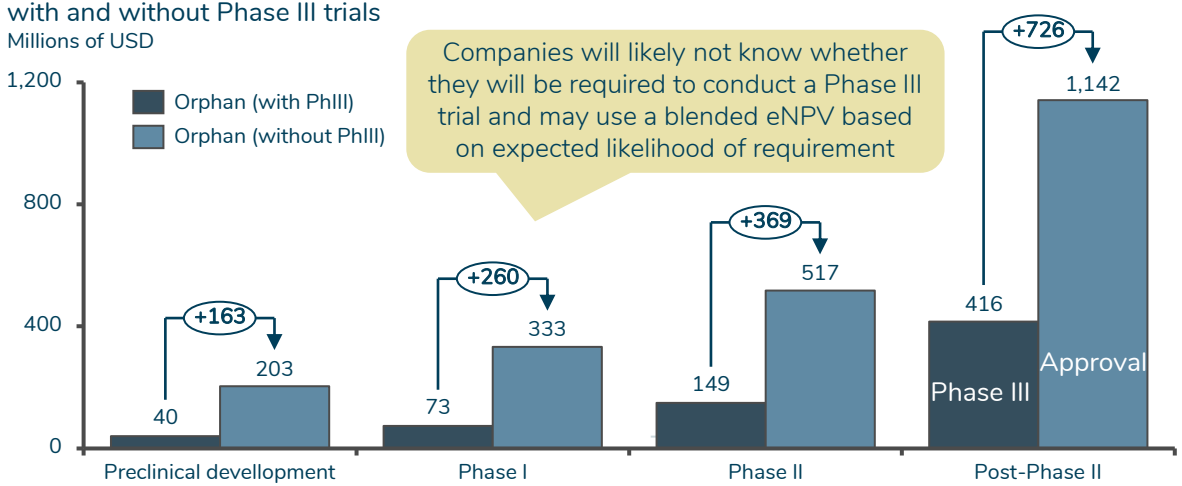
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Orphan designation allows for approval with Phase II data, and without a Phase III trial, resulting in higher eNPV throughout development

Indicative only

Risk adjusted eNPV for orphan assets per start phase, with and without Phase III trials

Millions of USD



The following assumptions were adjusted to reflect accelerated approval without Phase III

	Orphan (with PhIII)	Orphan (w/o PhIII)
Phase II PoS	69%	69%
Phase III PoS	65%	100%
Phase III duration	48 months	0 months
Phase III R&D costs	$115m	$0

Accelerated approval based on removing Phase III assumptions results is the best-case scenario; Phase II PoS may also be reduced to reflect the additional scrutiny on a pivotal Phase II trial

Time to launch from start of phase (years)				
Orphan (with PhIII)	11.5	10.5	8.5	5.5
Orphan (without PhIII)	7.5	6.5	4.5	1.5

Accelerated approval for orphan drugs based on Phase II data, thus not requiring a Phase III trial, reduces time to launch and means approval eNPV is reached 4 years earlier

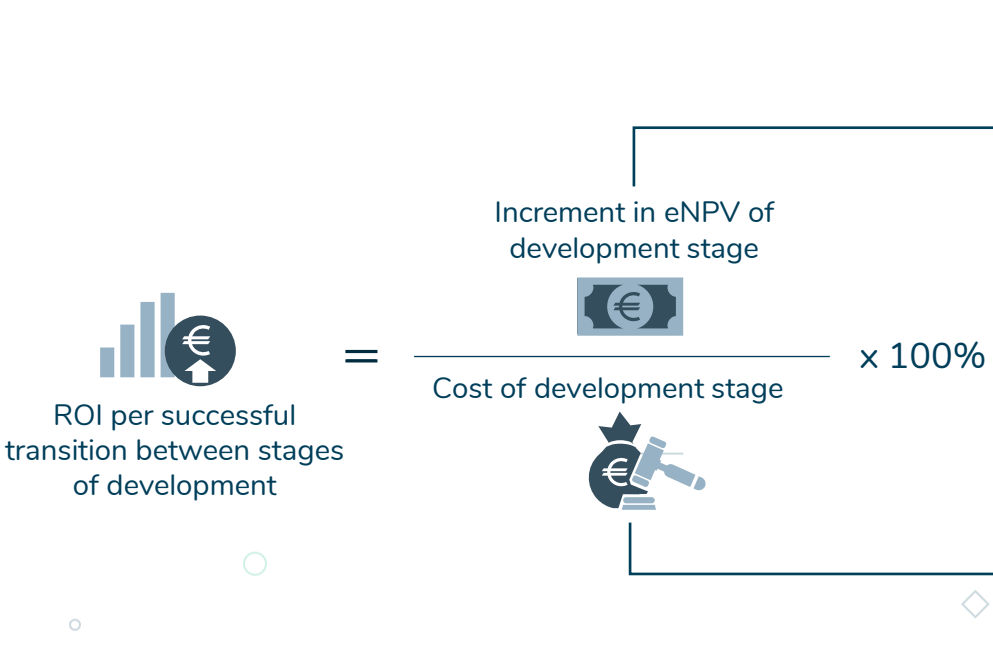
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

ROI and quantification of loss

ROI per successful stage transition is based on the increment in eNPV from the prior stage and the total stage-specific R&D cost

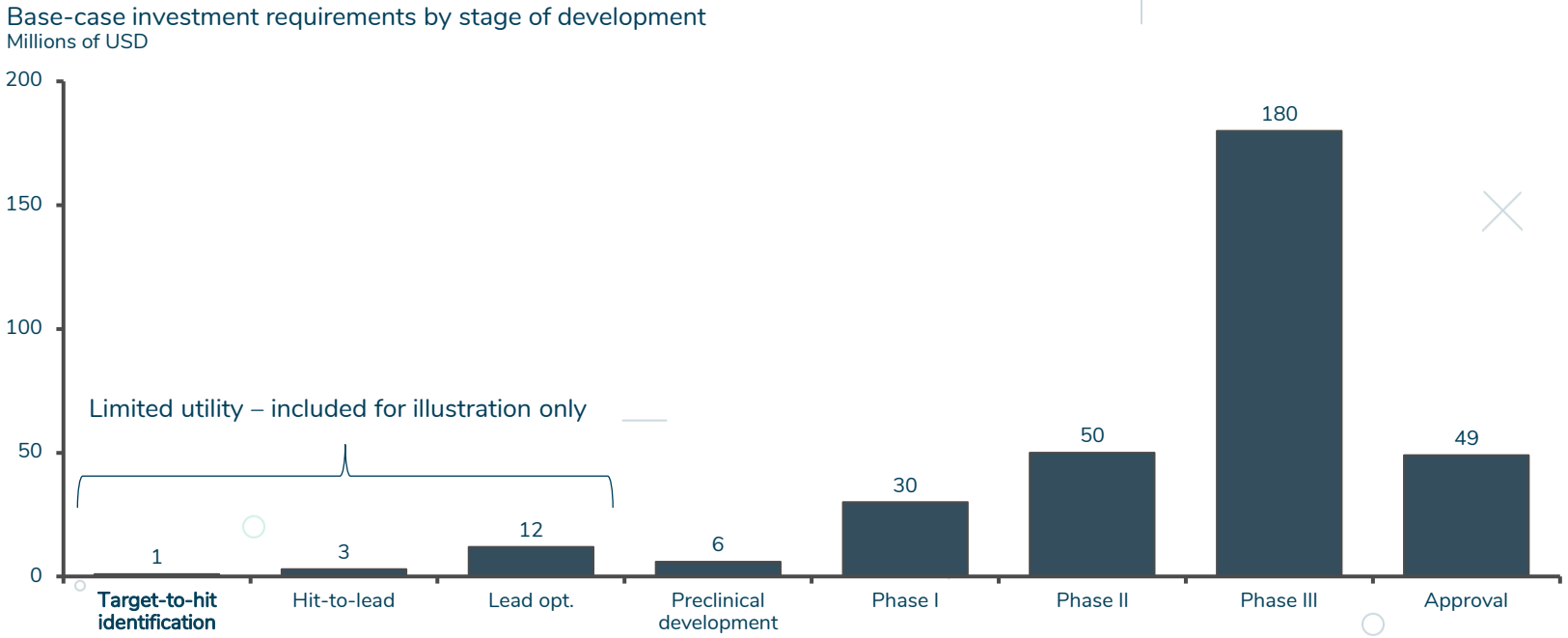


SiRM. Strategies in Regulated Markets

L.E.K.

Source: L.E.K. research and analysis

Investment requirements for each successful stage transition is the R&D costs associated with the completed phase of development

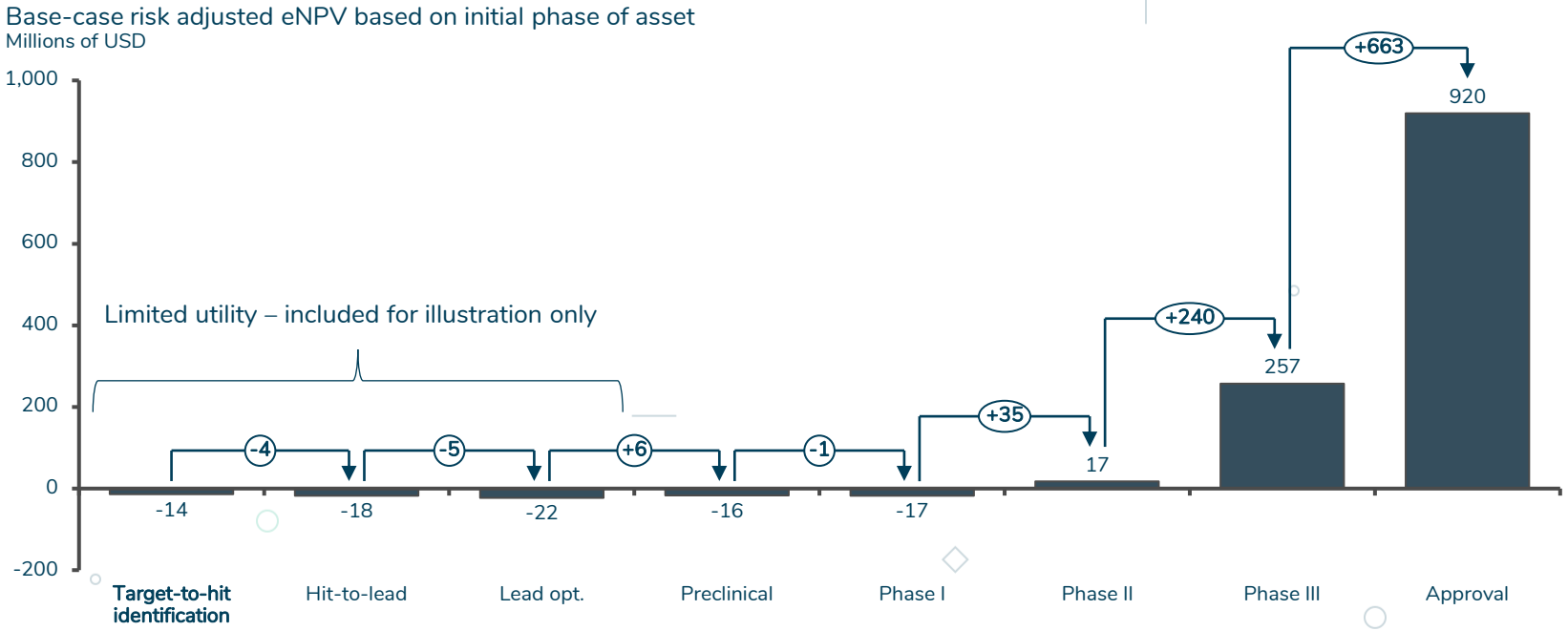


SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

For each successful stage progression, the return is calculated based on the change in eNPV compared to the prior stage



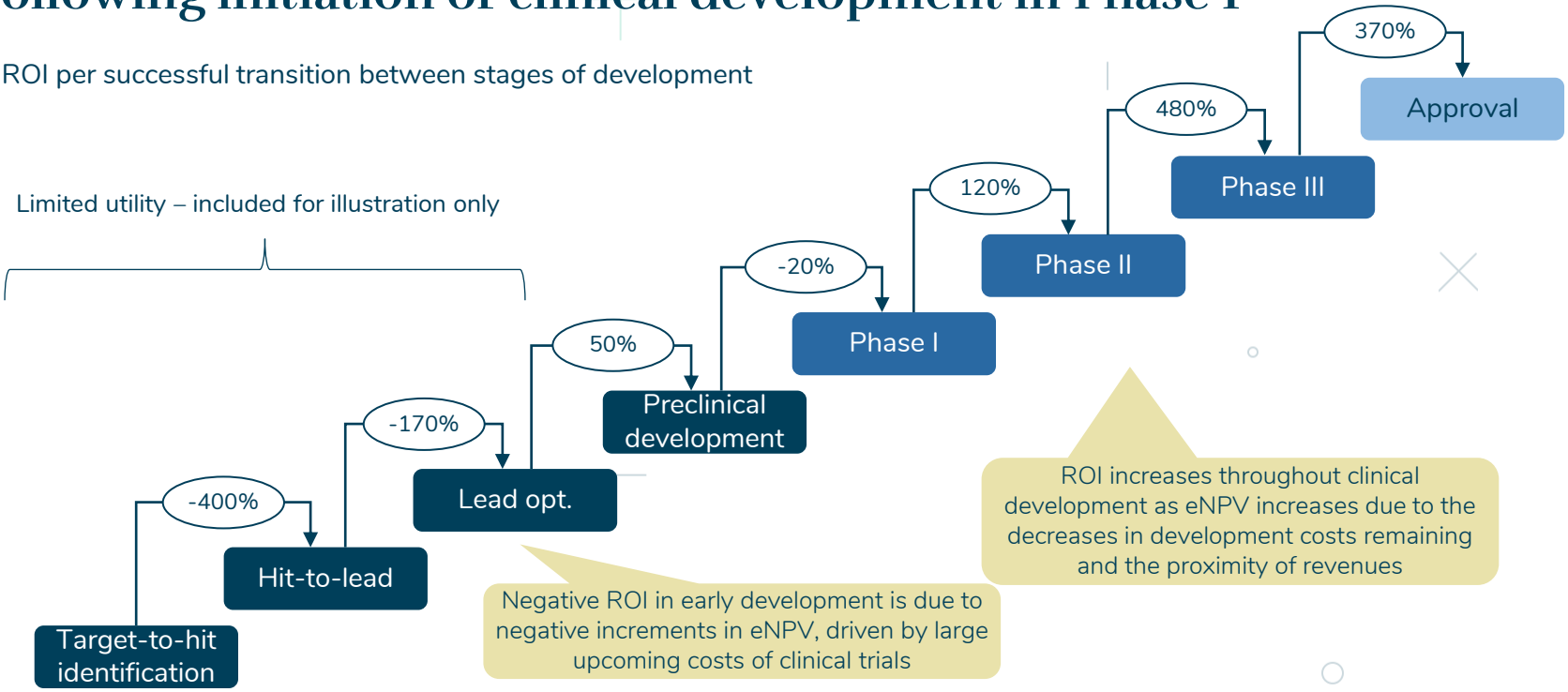
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Early development is characterized by negative ROI; ROI increases following initiation of clinical development in Phase I

ROI per successful transition between stages of development



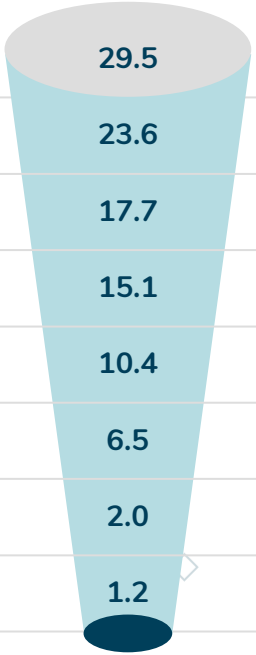
SiRM. Strategies in Regulated Markets

L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Majority of failures occur from target-to-hit identification to preclinical development, which is reflected in the lower ROI for these phases

	PoS	Cumulative PoS	Assets needed to launch 1 asset	Assets failed per stage to launch 1 asset	% of total assets failed per stage*
Target-to-hit identification	80%	3%	**29.5**	5.9	20%
Hit-to-lead	75%	4%	**23.6**	5.9	20%
Lead optimisation	85%	6%	**17.7**	2.7	9%
Preclinical dev.	69%	7%	**15.1**	4.7	16%
Phase I	63%	10%	**10.4**	3.8	13%
Phase II	31%	15%	**6.5**	4.5	15%
Phase III	58%	49%	**2.0**	0.9	3%
Approval	85%	85%	**1.2**	0.2	1%
Launched			**1**		



% of total assets failed per stage represents the numbers of assets failed per stage as a proportion of all assets entering the development funnel

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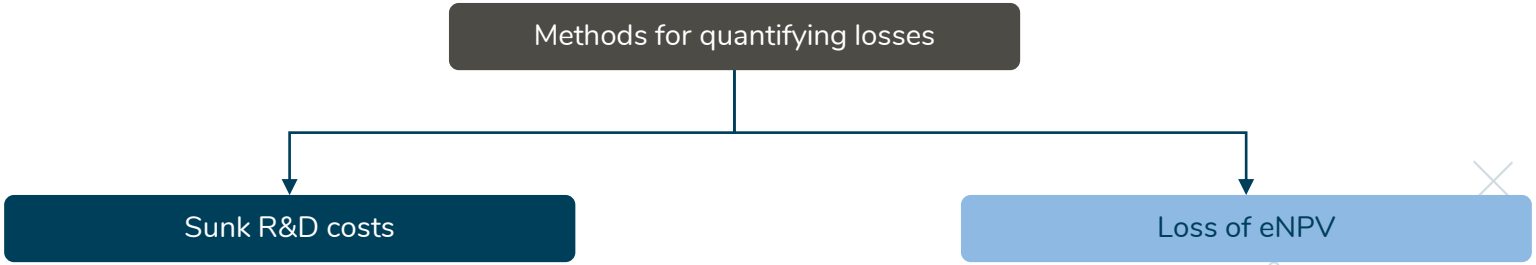
L.E.K.

Notes: *% of total assets failed per stage example: Phase I = 3.8 / 29.5 = 12.88%
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Loss associated with negative outcomes can be quantified as sunk costs or as loss of eNPV



- Sunk R&D costs represent all R&D costs incurred for an asset to date, including all earlier trial costs and the cost of the failed trial

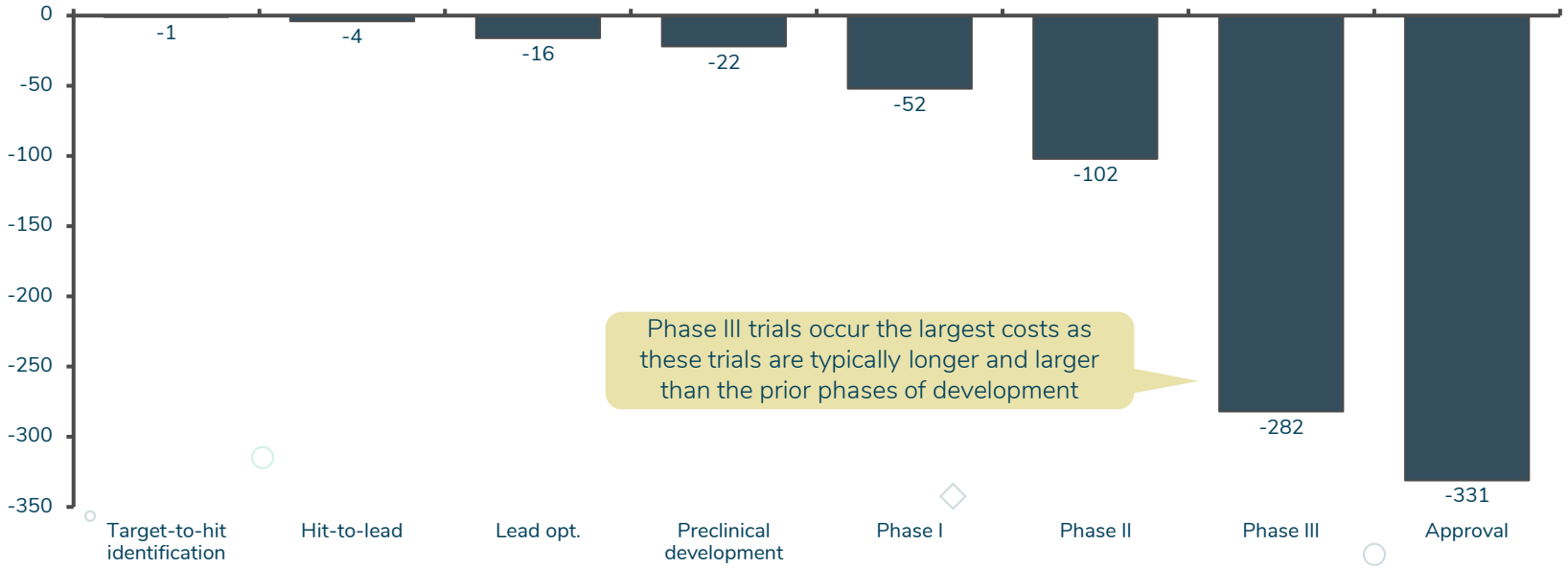
- Loss of eNPV represents the loss of eNPV of the stage of development that has failed

Source: L.E.K. research and analysis

Sunk R&D costs represent the irrecoverable expenditure and increases with each stage of development

Cumulative sunk costs associated with negative outcomes for a general asset across the development process

Millions of USD



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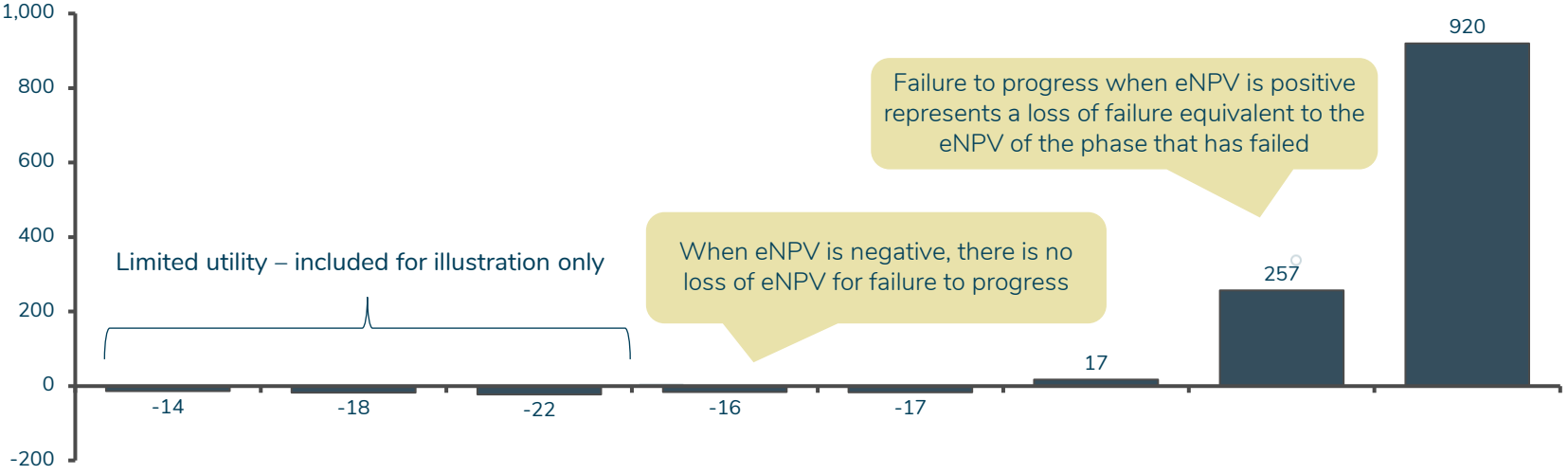
L.E.K.

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Loss of eNPV affects assets in lead opt. and clinical development, as eNPV increases with each further stage of development

Base-case risk adjusted eNPV based on initial phase of asset
Millions of USD



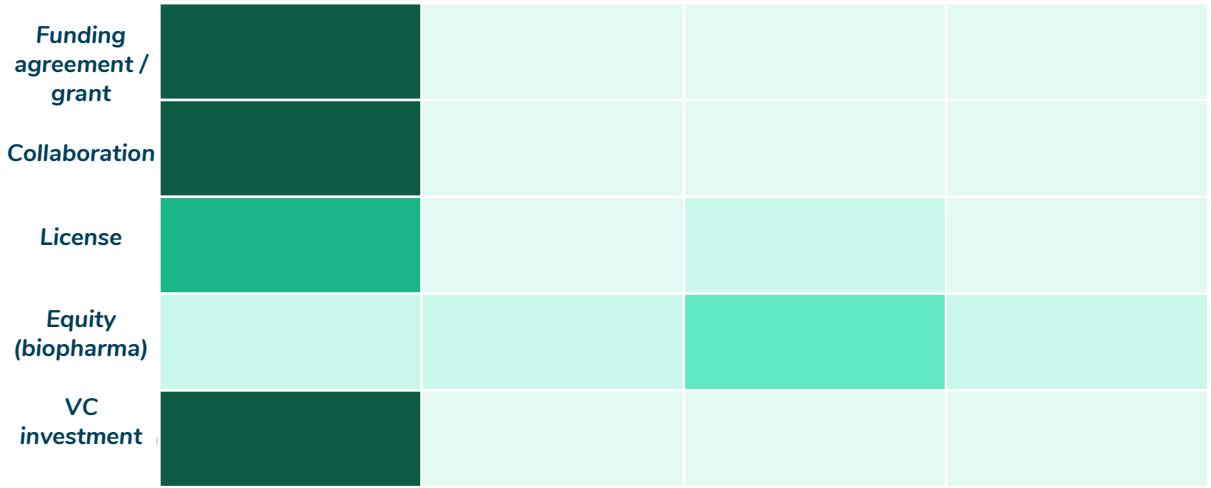
	Target-to-hit identification	Hit-to-lead	Lead opt.	Preclinical development	Phase I	Phase II	Phase III	Approval
Loss of eNPV*	0	0	0	0	0	-17	-257	-920

Note: *From failing Phase and not progressing
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Summary of R&D decision making

Different transaction types are leveraged across the development process, with equity transactions most common in Phase II

	Preclinical dev.	Phase I	Phase II	Phase III
eNPV	-16	-17	17	257
Loss of eNPV*	0	0	-17	-257
Sunk costs	-22	-52	-102	-282



Comments – number of deals

- Grants are often utilised in early pre-clinical development to stimulate academic research in non-competitive areas
- Licenses and collaborations are typically utilized in pre-clinical and early-stage clinical development because it allows big pharma companies to access the operating model and innovations of small biotech
- Asset purchases can occur in clinical development, as big pharma companies are well-placed to conduct clinical trials
- Equity investments and corporate M&A activity increases following human PoC, typically in Phase Ib and Phase II
- Venture funding uses equity investments in preclinical development and early stages of development, with divestments typically occurring post human PoC

Percentage of deals by instrument by development class** 0-15% 16-30% 31-45% 46-60% >60%

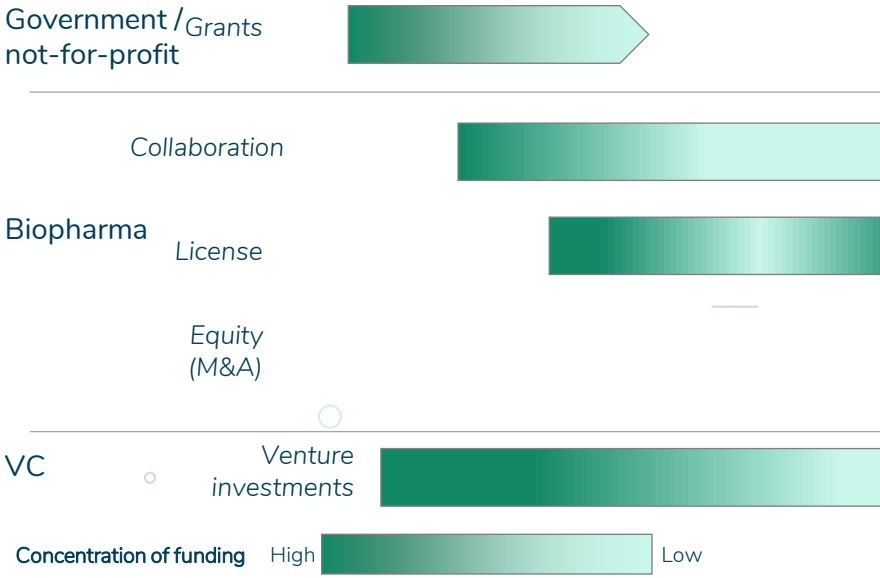
SiRM. Strategies in Regulated Markets

L.E.K.

Notes: *From failing Phase and not progressing; **Percentage based on number of deals per phase per instrument compared to total number of deals per instrument
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Lower value and lower risk investments typically occur earlier in the value chain where sunk costs are low and eNPV is negative

	Preclinical dev.	Phase I	Phase II	Phase III
eNPV	-16	-17	17	257
Sunk costs	-22	-52	-102	-282



Comments – concentration of funding

- Government's and not-for-profits are not driven by financial returns so will provide funding agreements and grants to fill a gap where eNPV is low / negative
- Collaboration is used to share expertise and risk and therefore funding is increasingly common in early development stages
- Licenses are generally either used at preclinical development phases where upcoming costs are low or after human POC where eNPV starts to become positive
- Corporate M&A is increasingly common post human POC, likely driven by increased PoS and eNPV positivity
- VCs also invest in early stages to fill a gap where eNPV is low / negative
- VCs do not typically invest based on eNPV and will aim to invest in companies with higher than average PoS

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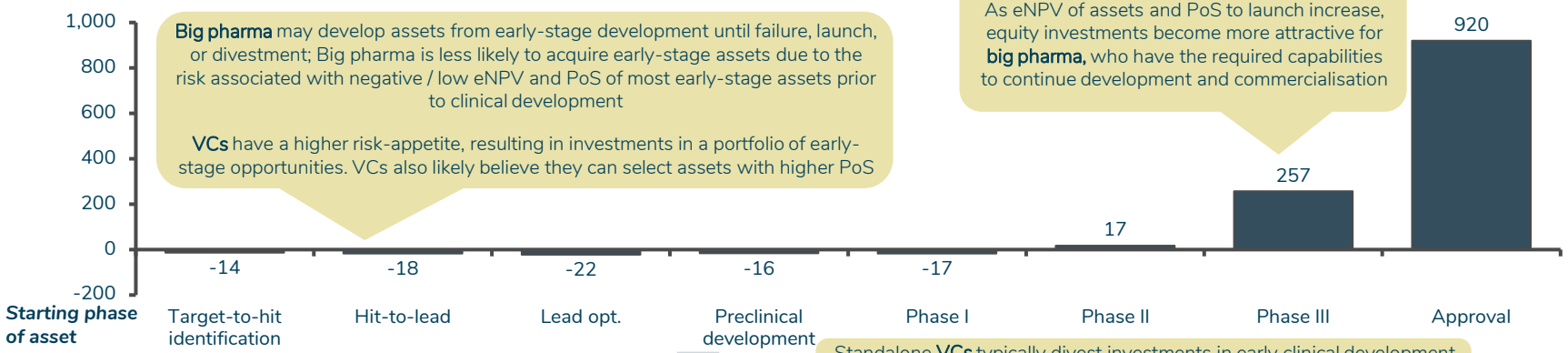
Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Investment and divestment decisions differ by funder type based on risk appetite and internal capabilities

Base-case risk adjusted eNPV at the start of the development phase, based on initial phase of asset

Millions of USD



Big pharma may develop assets from early-stage development until failure, launch, or divestment; Big pharma is less likely to acquire early-stage assets due to the risk associated with negative / low eNPV and PoS of most early-stage assets prior to clinical development

VCs have a higher risk-appetite, resulting in investments in a portfolio of early-stage opportunities. VCs also likely believe they can select assets with higher PoS

As eNPV of assets and PoS to launch increase, equity investments become more attractive for **big pharma,** who have the required capabilities to continue development and commercialisation

Standalone **VCs** typically divest investments in early clinical development due to high costs associated with late-stage clinical development, with sunk costs increasing significantly from Phase II onwards

Loss of eNPV*	0	0	0	0	0	-17	-257	-920
Sunk costs	-1	-4	-16	-22	-52	-102	-282	-331

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Note: *From failing Phase and not progressing

Source: Abrantes-Metz, Adams and Metz (2004); BioMedTracker (2016); Hay et al., (2014); Jayasundara et al., (2019); Prior L.E.K. experience; L.E.K. research, interviews, and analysis

Due to the low PoS of assets in preclinical and early development, big pharma and VCs use various risk-management techniques

Pharmaceutical companies use risk-adjusted techniques to assess risks

- Pharmaceutical companies use risk-adjusted NPV to incorporate risk into opportunity assessments

  "... When assessing opportunities, we use a risk-adjusted NPV which considers scientific risk, competitive risk, commercial risk ..."
  Head of R&D #1, big pharma (EU)

  - typically, companies will have higher risk-appetites for strategic areas and lower risk appetites for non-core areas

  "... Overall, we're willing to take a higher risk in areas that are of strategic importance to us. Our risk appetite in non-core areas is lower than for core areas..."
  Financial investor #1, big pharma BD (EU)

VCs manage risk by diversifying their portfolio across a range of metrics

- VCs have a portfolio of investments, allowing them to diversify and reduce overall risk

  "... We consider a lot of different types of risk: scientific risk, data risk, management risks, competitive risks. We look at all of those and create a balanced portfolio with different times to exit, different therapeutic areas, different molecules, different stages of development..."
  Financial investor #4, standalone VC (EU)

Biotechs and big biopharma use basic licenses and collaboration to share risks

- Basic license agreements and collaborations allow for risk-sharing, often between biotech companies and larger pharmaceutical companies

  "... Risk sharing often depends on the stage of the assets and the specifics of the deal. You can have a licensing agreement which results in risk sharing between pharma and biotech, with pharma chipping in on investment and shouldering some of the development risk..."
  Head of R&D #1, big pharma (EU)

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Source: L.E.K. research, interviews, and analysis

In R&D funding, drug developers assess scientific basis, risk-adjusted commercial potential and the ability to achieve funding

Drug developer key drivers of drug development

Scientific 'strength' and synergies

- Alignment with current strengths and supporting therapeutic area leadership is a key consideration for R&D investments

"... We typically develop a TPP and we then look at what opportunities have the required scientific backing to meet the TPP..."*
Head of R&D #1, big pharma (EU)

"...For us, it is important to have scientific leadership in certain areas, so we look for opportunities that support that..."
Head of R&D #2, big pharma (U.S.)

Commercial potential / PoS

- Commercial potential, including risk-adjusted revenues, can drive R&D investments and decisions

"... You need to consider the asset's opportunity, the sales, the time to achieve those sales..."
Head of R&D #2, big pharma (U.S.)

- For revenue generating companies, maintaining or growing the top line is critical, resulting in high investments to keep revenues stable

"... We look at opportunities and we have to consider the PoS to success. It needs to fill the gaps that we have in our pipeline..."
Financial investor #1, big pharma BD (EU)

Ability to achieve funding

- Ability to fund the required phases of development is an essential consideration driving R&D decision making

"... It is always important to think about whether we've got the money to invest. Do we have it internally? Are we able to get it externally? Funding is a really important consideration..."
Head of R&D #1, big pharma (EU)

"... Time and money are both very important, but money even more so. Do we have the money to get to market before anyone else? If we don't have internal capabilities, do we have the money to get it done externally?..."
Head of R&D #2, big pharma (U.S.)

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Notes: * TPP = target product profile
Source: L.E.K. research, interviews, and analysis

For financial investors, financial returns and timings of returns are key considerations for R&D investments

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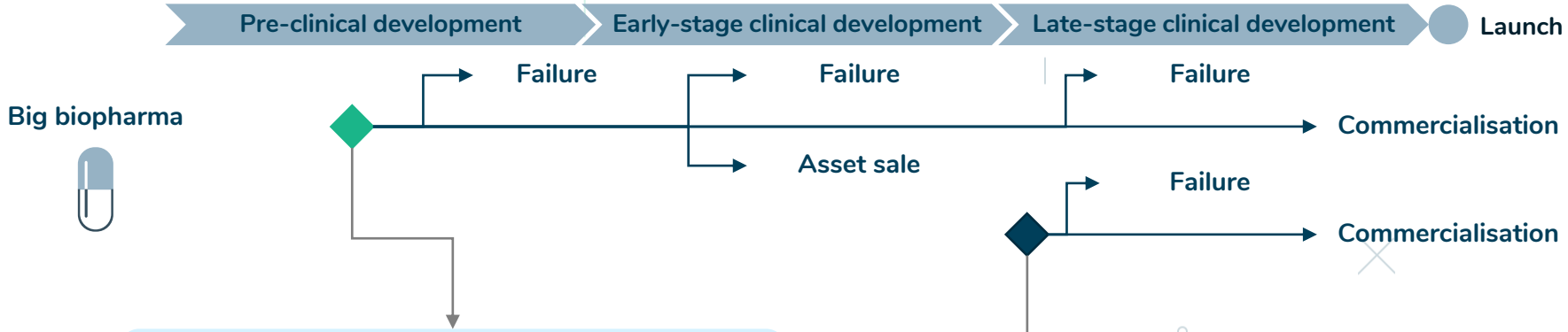
Source: L.E.K. research, interviews, and analysis

Big biopharma minimise risk by focusing on internal pre-clinical assets and late-stage external opportunities



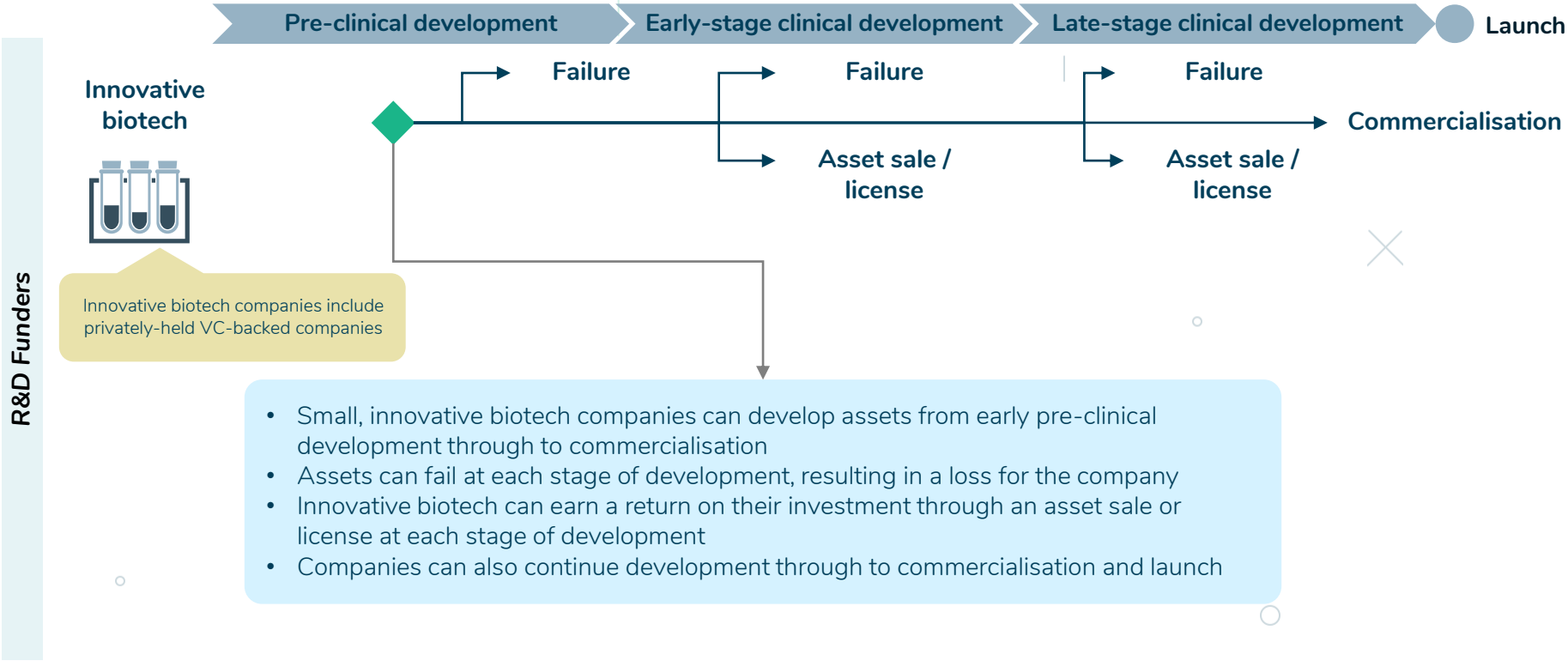
- Big biopharma can develop assets from early pre-clinical through to commercialisation
- These assets can fail at each stage of development
- Big biopharma can extract value by divesting these assets in early development if data readout suggests the asset is not efficient in core strategic areas, but shows promise in non-core areas

- Big biopharma also acquires assets entering into late-stage development
- Big biopharma is well placed to conduct late-stage clinical development assets

External investment
Internal investment

Source: L.E.K. research, interviews, and analysis

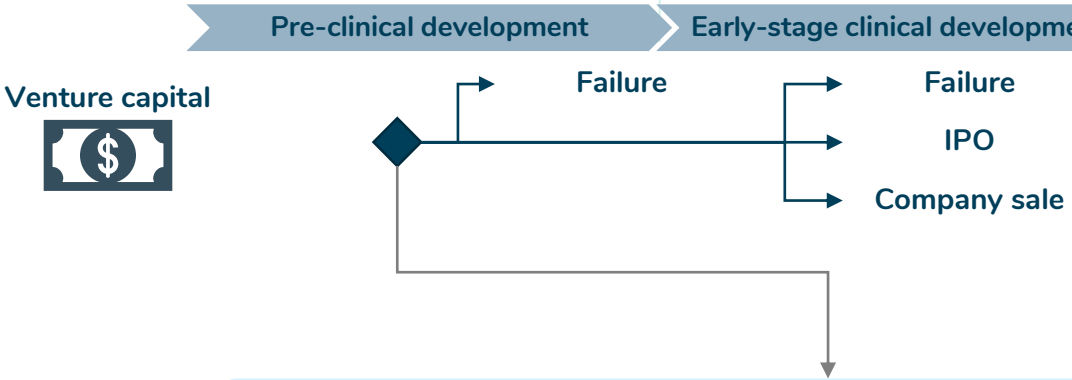
Innovative biotech can extract value at many different stages of the value chain and can ultimately go-it-alone if possible



External investment Internal investment

Source: L.E.K. research, interviews, and analysis

VCs invest in pre-clinical or early-stage companies and earn a return on investment when these companies IPO or are acquired

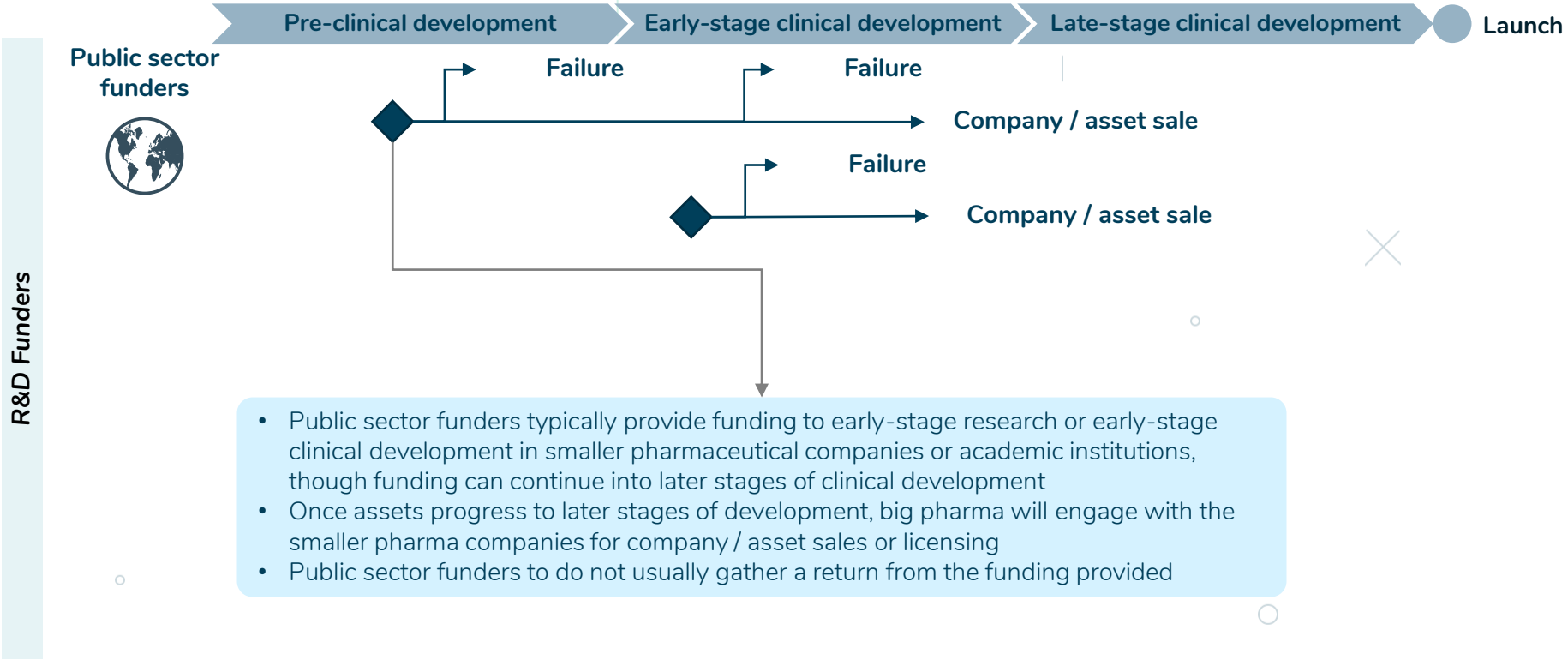


- VCs typically invest in early research opportunities
- These opportunities can fail in pre-clinical or early-clinical development
- VCs typically extract value by divesting the company through IPO or company sale
  - divestment typically occurs in early-stage clinical development, ahead of the high-cost late-stage clinical development stages, with big pharma typically better equipped to conduct late-stage clinical trials

External investment Internal investment

Source: L.E.K. research, interviews, and analysis

Public sector funders typically provide early-stage funding; funders do not necessarily earn a return from their investment

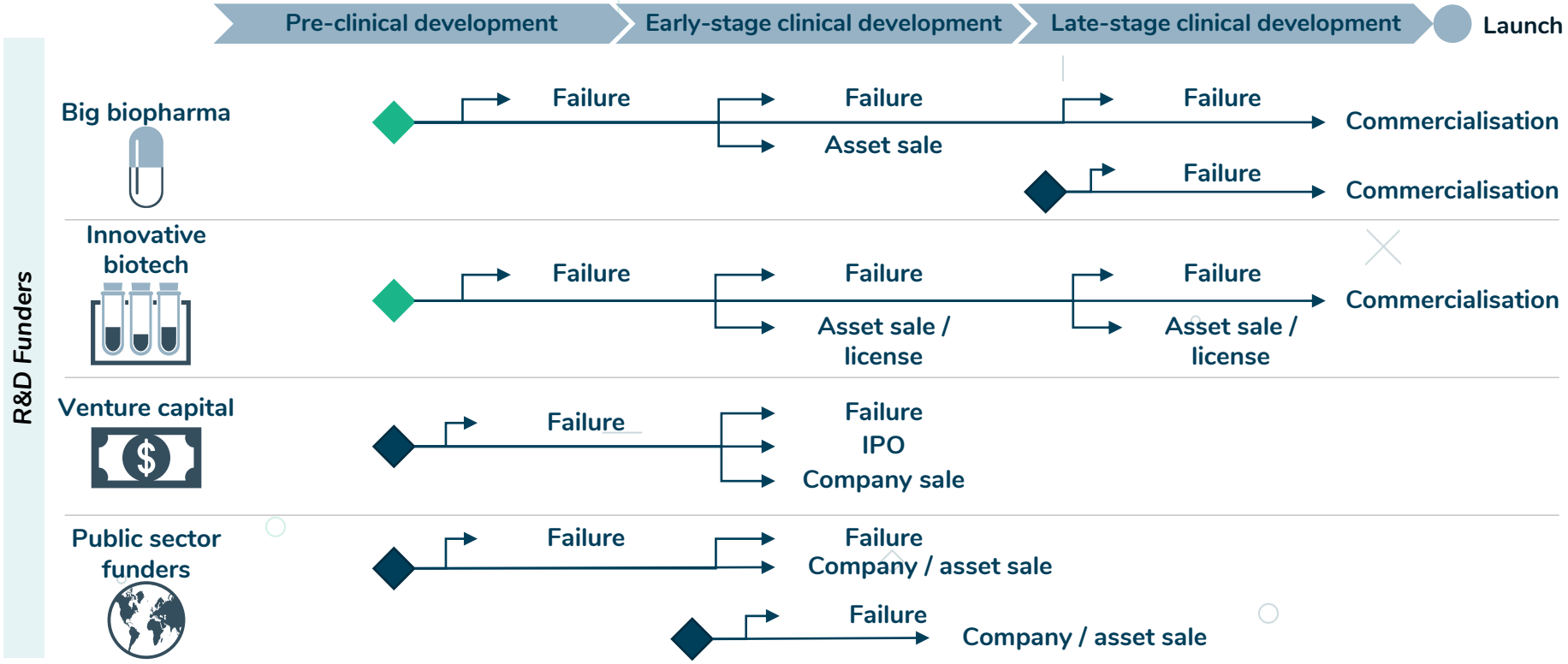


- Public sector funders typically provide funding to early-stage research or early-stage clinical development in smaller pharmaceutical companies or academic institutions, though funding can continue into later stages of clinical development
- Once assets progress to later stages of development, big pharma will engage with the smaller pharma companies for company / asset sales or licensing
- Public sector funders to do not usually gather a return from the funding provided

External investment Internal investment

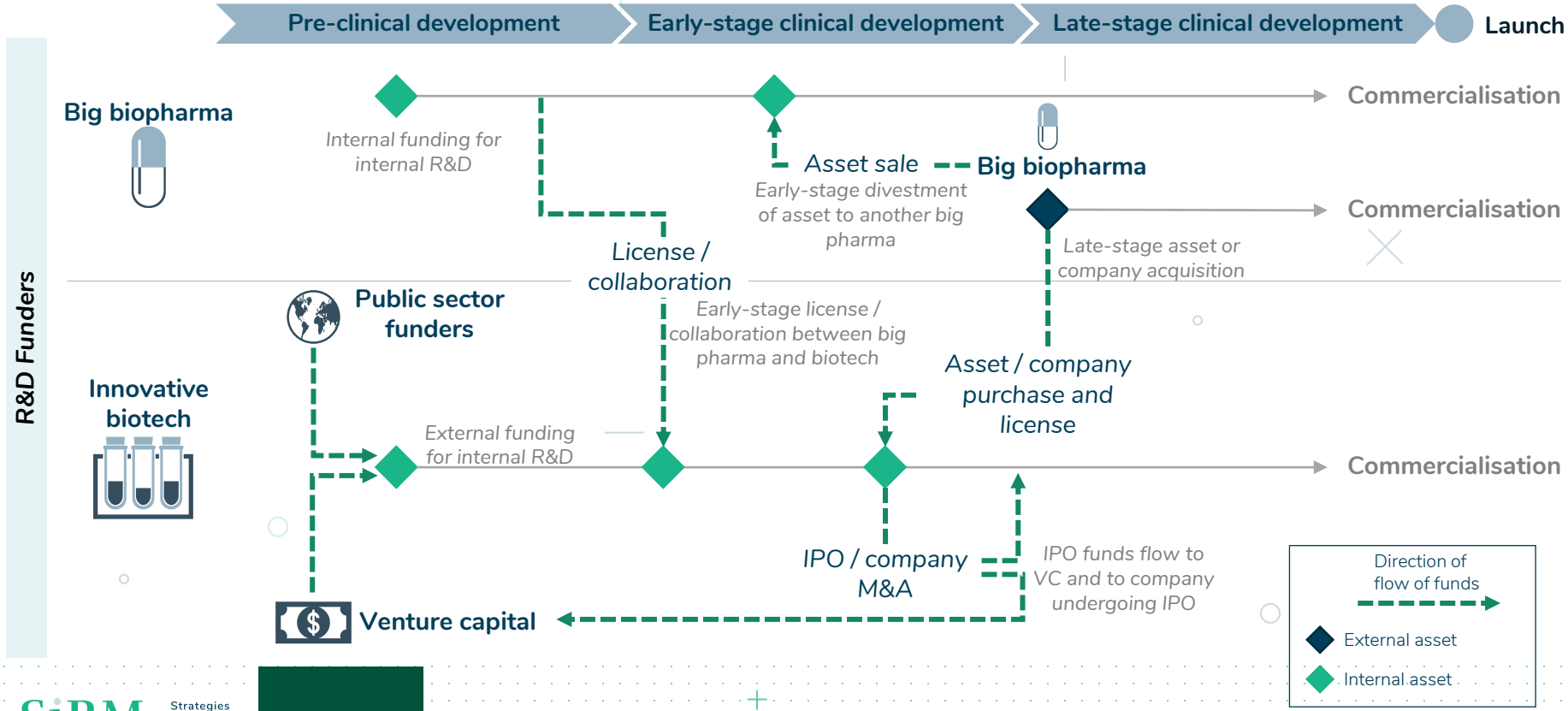
Source: L.E.K. research, interviews, and analysis

VCs and public sector funders are the main investors in early-stage external opportunities; big biopharma are the key late-stage investors



Source: L.E.K. research, interviews, and analysis

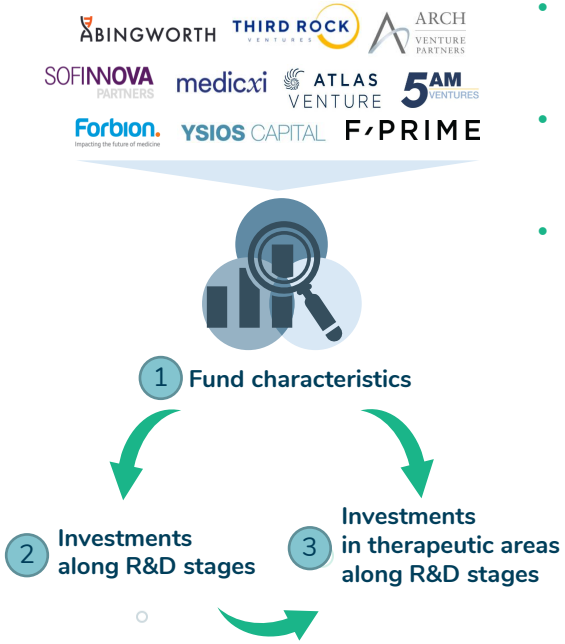
VCs, public sector funders and innovative biotech are key funders in early-stage development; big biopharma are the key late-stage players



Source: L.E.K. research, interviews, and analysis

Financial investor portfolio strategy

In light of the lack of consolidated data on venture investment across R&D stages, recent investments from 10 major LS venture firms were analysed



- While there is existing research on the characterisation of venture capital investment in biopharma by fundraising rounds, the timing of venture capital investment by phase of development is less clearly defined
- L.E.K. has analysed venture investment behavior across the R&D value chain by identifying 19 recently invested funds in 10 major life sciences venture firms located in Europe and the U.S., and analysing the investments and portfolio company characteristics of each fund
- The outcome of of this analysis is presented in three facets

1. Overall fund characteristics – size of funds, number of investments, number of portfolio companies and the percentage of non-pharma companies* in the portfolio
2. Distribution of investments by R&D stages within a fund** – the R&D stages of portfolio companies are determined by the R&D status of its lead product at the time of the deal announcement, which is then used to generate the percentage of investments in preclinical development and phase I – III within a fund
3. Distribution of investments by therapeutic area within R&D stages – the lead therapeutic area of portfolio companies are determined by that of its lead product, which is then used to generate the percentage of investments in a given therapeutic area within each R&D stage (preclinical development and phase I – III)

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Notes: *Non-pharma investments include medical technology and diagnostics, health technology, and non-life sciences investments; **Excludes non-pharmaceutical investments
Source: Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

The five European venture firms each have between $0.5-2.1bn in assets under management with total number of investments correlating to year founded

Overview of selected funds

	ABINGWORTH	SOFINNOVA PARTNERS	medicxi	Forbion. Impacting the future of medicine	YSIOS CAPITAL
Year founded	1973	1972	2016	2006	2008
Headquarters	London, United Kingdom	Paris, France	London, United Kingdom	Naarden, Netherlands	San Sebastian, Spain
Total investments	239	365	47	152	57
Exits	149	135	17	75	14
AUM* (billions of USD)	1.8	2.0	1.2	2.1	0.5
Key investment areas	Pharmaceuticals and Biotechnology**	Pharmaceuticals, Biotechnology**, Agriculture, Chemicals manufacturing	Pharmaceuticals and Biotechnology**	Pharmaceuticals and Biotechnology**	Pharmaceuticals and Biotechnology**
Stated investment stages	Seed, Early to late VC, PE Growth/ Expansion	Seed, Early to late VC, Spin-off	Seed, Early to late VC	Early to late VC	Seed, Early to late VC, Spin-off

Notes: *Asset under management; **Includes medical technology and diagnostics, and healthcare technology

Source: Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

The U.S. firms selected have higher assets under management and made a larger number of investments, each managing between $1.6-9.0bn assets

Overview of selected funds

	THIRD ROCK VENTURES	ARCH VENTURE PARTNERS	ATLAS VENTURE	5AM VENTURES	F-PRIME
Year founded	2007	1986	1980	2002	1969
Headquarters	Boston, MA	Chicago, IL	Cambridge, MA	San Francisco, CA	Cambridge, MA
Total investments	111	529	739	201	400
Exits	77	220	359	79	117
AUM* (billions of USD)	1.6	9.0	2.5	2.0	2.0
Key investment areas	Pharmaceuticals and Biotechnology**	Various	Pharmaceuticals and Biotechnology**	Pharmaceuticals and Biotechnology**	Pharmaceuticals and Biotechnology**
Stated investment stages	Seed, Early to late VC	Seed, Early to late VC	Seed, Early to late VC	Accelerator/Incubator, Seed, Early to late VC	Seed, Early to late VC

Notes: *Asset under management; **Includes medical technology and diagnostics, and healthcare technology
Source: Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

Abingworth and Sofinnova have similar fund sizes, but Abingworth invests more heavily in biopharma while Sofinnova appears more diversified

1 Overall fund characteristics - Europe

Name of Fund	Abingworth BioVentures VI	Abingworth BioVentures VII	Sofinnova Capital VII	Sofinnova Capital VIII
Fund size (millions of USD)	373	350	310	322
Investment period	2006-20	2009-21	2013-18	2016-20
No. of companies invested	19	16	12	21
No. of investments (Average investment per company)	30 (1.6)	20 (1.3)	14 (1.2)	27 (1.3)
Percentage of non-pharma* companies in portfolio	5% (MedTech)	13% (MedTech)	25% (MedTech, Software technology)	67% (MedTech, Software technology, Agriculture)

Notes: *Includes healthcare technology, medical technology and diagnostics, and non-life sciences related investments
Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

Medicxi and Forbion are both focused in biopharma investments, while Ysios has the highest number of investments per company

1 Overall fund characteristics - Europe

Name of Fund	Medicxi Growth 1	Medicxi Ventures 1	Forbion Capital Fund III	Forbion Capital Fund IV	Ysios BioFund II
Fund size (millions of USD)	300	228	207	420	142
Investment period	2017-20	2016-20	2015-18	2018-21	2010-21
No. of companies invested	11	11	13	11	21
No. of investments (Average investment per company)	12 (1.1)	13 (1.2)	15 (1.2)	11 (1.0)	34 (1.6)
Percentage of non-pharma* companies in portfolio	9% (HealthTech)	9% (MedTech)	0%	0%	38% (MedTech)

Notes: *Includes healthcare technology, medical technology and diagnostics, and non-life sciences related investments
Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

Compared to Third Rock, ARCH Venture has slightly larger fund sizes and higher industry diversification of investments

1 Overall fund characteristics – U.S.

Name of Fund	Third Rock Ventures III	Third Rock Ventures IV	Arch Venture Fund VIII + Overage	Arch Venture Fund IX + Overage
Fund size (millions of USD)	516	616	560	690
Investment period	2013-19	2016-20	2013-19	2017-20
No. of companies invested	15	17	66	11
No. of investments (Average investment per company)	33 (1.5)	22 (1.3)	100 (1.5)	11 (1.0)
Percentage of non-pharma* companies in portfolio	20% (MedTech, Diagnostics)	18% (MedTech, Bio-manufacturing)	39% (MedTech, Diagnostics, HealthTech, Agriculture, Bio-manufacturing)	27% (MedTech, Veterinary care)

Notes: *Includes healthcare technology, medical technology and diagnostics, and non-life sciences related investments
Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

Atlas Ventures, 5AM Ventures and F-Prime share similar fund sizes, but F-Prime focuses more on non-pharma investments

1 Overall fund characteristics – U.S.

Name of Fund	Atlas Venture Fund XI	Atlas Venture Fund X	5AM Ventures V	5AM Ventures VI	F-prime Life Sciences Fund VI	F-prime Healthcare Fund V
Fund size (millions of USD)	350	280	285	350	400	400
Investment period	2018-20	2016-18	2016-20	2017-20	2017-20	2016-20
No. of companies invested	13	25	17	5	11	14
No. of investments (Average investment per company)	13 (1.0)	30 (1.2)	24 (1.4)	5 (1.0)	12 (1.1)	21 (1.5)
Percentage of non-pharma* companies in portfolio	8% (MedTech)	12% (Media and Infrastructure)	29% (MedTech, Electronics, Software technology)	60% (MedTech)	100% (MedTech, Diagnostics, HealthTech, Software technology)	64% (MedTech, Software technology, Education)

Notes: *Includes healthcare technology, medical technology and diagnostics, and non-life sciences related investments
Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

For EU investors the majority of pharma investments occur at preclinical development stages

2 Distribution of investments by R&D stages within a fund

Select funds from European venture firms	Pharma companies per fund	Development stage of companies at first investment			
		Drug discovery / Preclinical dev.	Phase I	Phase II	Phase III
Abingworth BioVentures VI	18	56%	17%	11%	17%
Abingworth BioVentures VII	14	29%	29%	36%	7%
Sofinnova Capital VII	9	33%	22%	44%	0%
Sofinnova Capital VIII	7	29%	43%	14%	14%
Medicxi Growth 1	10	60%	0%	40%	0%
Medicxi Ventures 1	10	80%	10%	10%	0%
Forbion Capital Fund III	13	54%	23%	23%	0%
Forbion Capital Fund IV	11	55%	18%	18%	9%
Ysios BioFund II	13	62%	8%	23%	8%

Percentage of total investments in the same fund: 0-20% | 21-40% | 41-60% | 61-80% | 81-100%

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Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

U.S. venture firms selected invested even more heavily in the preclinical stages, with most funds conducting 60-100% of first investments at this stage

2 Distribution of investments by R&D stages within a fund

Select funds from U.S. venture capital firms	Pharma companies per fund	Development stage of companies at first investment			
		Drug discovery / Preclinical dev.	Phase I	Phase II	Phase III
Third Rock Ventures III	12	83%	8%	8%	0%
Third Rock Ventures IV	14	100%	0%	0%	0%
Arch Venture Fund VIII + Overage	40	73%	8%	18%	3%
Arch Venture Fund IX + Overage	8	75%	13%	13%	0%
Atlas Venture Fund XI	12	67%	25%	8%	0%
Atlas Venture Fund X	22	95%	5%	0%	0%
5AM Ventures V	12	75%	8%	8%	8%
5AM Ventures VI	2	50%	0%	0%	50%
F-prime Life Sciences Fund VI	0	Not applicable*			
F-prime Healthcare Fund V	5	100%	0%	0%	0%

Percentage of total investments in the same fund: 0-20% | 21-40% | 41-60% | 61-80% | 81-100%

Note: *This fund was fully invested in non-therapeutics

Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

U.S. funds analysed tend to be bigger and more focused on preclinical development investments, possibly due to access to capital and earlier IPOs

Access to capital is greater in the U.S. compared to Europe

- The U.S. venture firms selected had larger fund sizes than their European counterparts, which is likely due to the more active R&D ecosystem and higher availability of capital in the U.S.
  - EU investors note that some funders require their capital to be invested into companies in their own countries, which may contribute to more fragmented funding and small fund sizes

"... Some clients have local mandates which limits the geography we can target investments in..."
Former Venture Advisor, European corporate venture capital firm

U.S. investors may be less risk-adverse

- U.S. venture funds analysed had a higher percentage of investments made in drug discovery / preclinical development stages, which may be due to higher investor risk appetite

"...The wilingness to deploy risk capital in the U.S. is much larger..."
Partner, U.S. standalone venture capital firm

EU companies typically IPO later in development

- In the EU, investors also invest mostly at preclinical development stages but with more clinical-stage investments, they note there are more clinical-stage pre-IPO companies in the EU to invest upon
  - EU companies often have to balance investor interests when deciding which market to IPO in, which can result in delay in IPO
  - some investors may also have mandates on trading funds and hence EU companies are motivated to IPO later to capture maximum investments available given capital contraints
- Given later IPOs, EU VCs have to wait longer for ROI which makes them more risk averse

"...Local mandates can also apply to when companies go public, which means companies may not necessarily be trading at the most profitable market when they IPO, so they are more likely to wait until it's favorable..."
Former Venture Advisor, European corporate venture capital firm

Source: L.E.K. interviews, research and analysis

Across EU and U.S. funds, Oncology remains the main TA for investment across all R&D stages, followed by neurology, immunology and nephrology

3 Distribution of investments by TA within a development stage

Development stage	Drug discovery / Preclinical development	Phase 1	Phase 2	Phase 3
No. of investments	157	29	36	10
Cardiovascular				
Dermatology				
Endocrinology				
Hematology				
Hepatology				
Immunology				
Infectious Diseases				
Musculoskeletal				
Nephrology				
Neurology				
OBGYN				
Oncology				
Ophthalmology				
Otorhinolaryngology				
Psychiatry				
Pulmonology				
Rare Diseases*				
Gastroenterology				

Some rare diseases are classified in their primary therapeutic areas

Percentage of total investments in the same phase: 0-10% | 11-20% | 21-30% | 30-40%

Note: *Does not include musculoskeletal diseases

Source: Clinicaltrials.gov; Company annual reports and press releases; Pitchbook; L.E.K. research and analysis

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Investors diversify investments to avoid risk of multiple failures in a portfolio

Venture firms control risk by diversifying different aspects of investments

- In order to limit risk, venture investors often diversify investments through R&D stages (either different stages within drug discovery / preclinical or in clinical development stages), modalities, therapeutic areas, potential returns and assessment of probabilty of success

  "…In the portfolio, we create diversity and balance of risk through investing in different stages, with different time to exit, differences in risks and subsequently the expected returns. We also look at the type of drug and their likelihood to succeed…"

  Partner, European standalone venture capital firm

Venture firms may invest in adjacent industries based on capability

- Whether a venture firm chooses to invest outside of the biopharma space depends on individual firms' strategy and capabilities; common adjacencies for life sciences venture firms are:
  - medical technology (e.g., cardiac devices) and diagnostics (e.g., cancer detection)
  - healthcare technology (e.g., digital health, healthcare logistics)
  - bio-manufacturing (e.g., recombinant proteins)
- These investments have different risk / reward profiles and reduce reliance on a single sector (biopharma)

Source: L.E.K. interviews, research and analysis

Venture firms may invest at late-preclinical development stages to minimise risk of failure and incorporate some clinical-stage investments with higher PoS

To minimise risk, firms may invest in late-preclinical development stages

- For preclinical development investments, venture firms may invest at late stages of preclincial development (e.g., after lead optimisation) to maximise probability of success while controlling for investment costs

"…The sweet spot for maximising returns from is around series A, or preclinical development. The majority of private capital is deployed at late preclinical development or early clinical stages, afterwards R&D costs become significantly more costly and companies rely on public capital / licensing agreements …"
Partner, U.S. standalone venture capital firm

Funds may invest in clinical-stage assets to benefit from higher PoS and shorter time to exit

- Venture investment timing is focused around preclinical development stages, but there will typically be a minority of clinical-stage investments in a fund; these investments are made as a risk diversification strategy – clinical stage assets typically carry higher PoS and a shorter time to exit

"…We also invest in a small number of phase I assets. They are pricier but with higher PoS, so they may be more likely to succeed. You also benefit from a shorter time to exit as we typically exit at phase IIb…"
Former Venture Advisor, EU corporate venture capital firm

Clinical-stage investments are more costly

- However, based on the higher transactional value of clinical-stage investments, firms require increasing levels of comfort in their investment

"…When we make clinical-stage investments, we have to be very confident, and that relies on our expertise. Modality is also important, for example clinical trial costs for small molecules are less than biologics…"
Partner , EU standalone venture capital firm

Source: L.E.K. interviews, research and analysis

Reinvestments based on milestones are used to lower capital commitment, but reinvestments at clinical stages or after exits are less common

VCs may make multiple investments in the same company within the same fund

- As a derisking strategy, companies may make several investments in the same company; this is typically done by multiple investments within the same fund
- Some investors have a total investment budget for a company but stagger the amount invested in each series and only continue to invest when companies fulfill development milestones

"…We set a total amount of investment based on our ROI multiple and the expected asset value at exit. But then we spread this capital across different series based on the risk of investing at each series…"
Former Venture Advisor, European corporate venture capital firm

Clinical stage reinvestments in companies through different funds are less common, especially after a complete exit

- Venture firms may use reinvestments in companies from previous funds to derisk their larger clincial-stage investments, but this is not as common
  - among all the investments made in later clinical stage assets (Phase 2 / 3) in the funds analysed, only c.13% were reinvestments in companies from previous funds
- In the previous exit, venture firms have increased the valuation of the company, which makes subsequent investments more costly with potentially less favorable ROIs

"…It's all about the value we can create when the company progresses to the next period, and we will have done most of the groundwork at the first holding period already…"
Partner, U.S. standalone venture capital firm

Source: L.E.K. interviews, research and analysis

Despite Oncology being a main R&D driver, venture firms typically focus on 2-3 therapeutic areas and diversify investments by modality / disease

Investments are largely focused on oncology

- Across selected funds in Europe and U.S., there is a significant oncology focus as this comprises the majority of current R&D pipeline (e.g., due to scientific developments like immuno-oncology, high unmet need etc.)

"...Oncology is a primary focus within R&D..."
Associate Director R&D, multinational biopharma

Venture firms focus on 2-3 therapeutic areas to spread investment risk

- Venture firms typically have 2-3 therapeutic areas they focus on in order to diversify investments and risks; oncology, immunology, neurology and rare diseases are named as the most attractive therapeutic areas currently

"...Our investments are focused around the main therapeutic areas of our parent company, of which there are a few, so our investments are also diversified in that manner..."
Former Venture Advisor, EU corporate venture capital firm

"...We have expertise in oncology, neuroscience and rare diseases..."
Partner, U.S. standalone venture capital firm

Investments are also diversified in core therapeutic areas by drug mechanism and diseases

- To diversify risk within the same therapeutic area, venture firms make investments on therapies with different mechanisms of action or therapies targeting different diseases

"...Within our core TAs, we take a balanced view of the portfolio which means making related but differentiating investments. We consider factors such as time to exit, target diseases and class of drug..."
Partner, EU standalone venture capital firm

Source: L.E.K. interviews, research and analysis

5. Drug developer corporate finance

Accounting principles

Big biopharma and biotechs focus on re-investment of funds in R&D; with excess, big biopharma will retain funds to shareholders

Big pharma

Innovative biotech

R&D re-investment

- Big biopharma companies typically re-invest c.20% of revenues in R&D, recorded as R&D expenses on the income statement the following year as expenses are incurred
  - Big biopharma companies have an average operating margin, after R&D expenses, of c.30%
  - R&D is essential to continue developing products and ensure stable or growing revenues in the future

"... Most big pharma would typically reinvest about 10-20% of revenues in R&D because it is essential to keep the pipeline moving and develop new products for launch..."
Financial investor #1, big pharm BD (EU)

- Small, innovative biotech companies are likely to re-invest as much of their revenues as possible in R&D, resulting in relatively high R&D expenses on the income statement

"... For biotechs, you see companies doubling down on R&D. You're seeing more investment in R&D because there is a need to for innovation for these companies. For these types of companies, it is all about investing in R&D..."
Head of R&D #2, big pharma (U.S.)

Internal cash retention

- Once sufficient re-investment is made in R&D, companies will typically retain cash for potential investments, which is recorded as a current asset on the balance sheet

- Small biotech companies are usually focused on re-investing for internal growth rather than engaging in external acquisitions

Returns to investors

- Funds are returned to shareholders through consistent dividends, of c.40-85% of operating profit, or opportunistic share buy-backs

"... Companies are doubling down on R&D investments. But if they still have funds remaining after R&D in a specific year, they may do an opportunistic share buy-back ..."
Accounting expert #2, big pharma (U.S.)

- Small companies with lower, less stable revenues are unlikely to pay dividends to shareholders

"... Smaller companies usually don't pay dividends because their income is usually lower, and less consistent and reliable..."
Accounting expert #2, big pharma (U.S.)

SiRM. Strategies in Regulated Markets

L.E.K.

Source: Ledley et al, (2020); L.E.K. research, interviews, and analysis

L.E.K. has used a selection of large, medium, and small pharmaceutical companies to assess accounting and dividend policies

L.E.K. assessed 10 years worth of financial statements for the selected large, medium, and small pharmaceutical companies, alongside supplementary primary and secondary research, to identify accounting practices, dividend policies, and share buy-back policies

Large companies

- L.E.K. selected five of the top ten pharmaceutical companies to analyse accounting and dividend policies for big pharma

Medium companies

- UCB and Incyte were selected as mid-sized, U.S. and EU pharma to identify differences between large and medium pharma

Small companies

- Adaptimmune and Circassia were selected as recently IPO-ed companies to assess dividend policy in small companies

Please note: the following slides summarise L.E.K.'s understanding of accounting policies but do not provide a comprehensive guide to accounting treatment of all potential types of transactions and exceptions

Source: L.E.K. research, interviews, and analysis

The income statement presents a company's revenues and expenses over a defined period of time

Illustrative income statement

In thousands of euro	Note	2020
Continuing operations		
Revenue[c, d]	8	102,860
Cost of sales[e]	9(C)	(55,432)
Gross profit		47,428
Other income	9(A)	893
Selling and distribution expenses[e]	9(C)	(18,322)
Administrative expenses[e]	9(C)	(17,732)
Research and development expenses[e]	9(C)	(1,109)
Impairment loss on trade receivables and contract assets[f]	32(C)(ii)	(200)
Other expenses	9(B)	(996)
Operating profit[g]		9,962
Finance income[d]		1,131
Finance costs[h]		(1,883)
Net finance costs	10	(752)
Share of profit of equity-accounted investees, net of tax	24	1,141
Profit before tax		10,351
Income tax expense	14	(3,178)
Profit from continuing operations		7,173
Discontinued operation		
Profit (loss) from discontinued operation, net of tax[i]	7	379
Profit for the period		7,552

- The income statement, also known as the statement of profit and loss (P&L) or statement of earnings, summarises a company's revenues and expenses over a period of time, known as the reporting period
  - the reporting period is usually a one-year period and does not need to align with the country's tax year
- Income statements can include four measures of profitability:
  - gross profit: reflects a company's efficiency at using its variable materials (such as labour and supplies) to generate revenue, and is calculated as revenue less cost of goods sold
  - operating profit: reflects a company's total earnings from core business operations, excluding the deduction of interest and tax, and is calculated as gross profit less SG&A and R&D expenses
  - Profit before tax: consists of the profit remaining after all operating expenses, interest, and depreciation are deducted
  - net earnings (profits from continuing operations): represents the income remaining after all expenses are deducted
- Internal R&D costs, and the cost of out-sourcing R&D will be accounted for as expenses between gross profit and operating profit
- Acquisitions of assets or companies initially appear on the balance sheet
  - depreciation, the decrease in value of an asset due to wear-and-tear over time, is an expense on the income statement in the years following acquisition

Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

The balance sheet provides snapshot of a company's assets, liabilities and equity at a specific point in time

Illustrative balance sheet

In thousands of euro	*Note*	31 December 2020	31 December 2019 Restated[*b]
Assets			
Property, plant and equipment[d]	21	**28,490**	33,230
Intangible assets and goodwill	22	**6,226**	4,661
Biological assets	16	**4,698**	4,025
Investment property[d]			
Equity-accounted investees			
Other investments, including c			
Deferred tax assets			
Employee benefits			
Non-current assets[f]			
Biological assets			
Inventories[g]			
Contract assets[h]			
Other investments, including c			
Current tax assets			
Trade and other receivables			
Prepayments[i]			
Cash and cash equivalents			
Assets held for sale			
Current assets[f]			
Total assets			

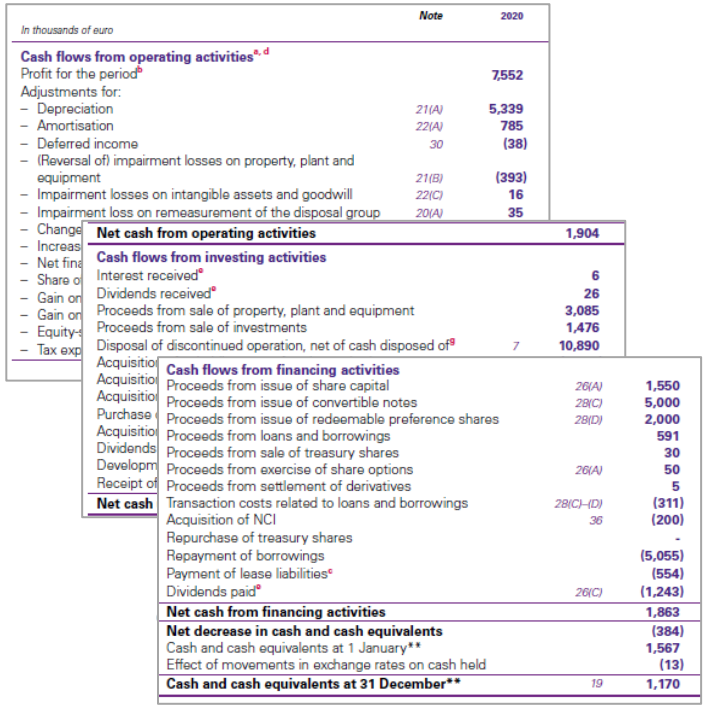
Equity		
Share capital		**14,979**
Share premium		**4,777**
Reserves		**1,219**
Retained earnings		**20,443**
Equity attributable to owners of the Company	26	**41,418**
Non-controlling interests	35	**3,804**
Total equity		**45,222**
Liabilities		
Loans and borrowings[j]	28	**23,758**
Employee benefits	13	**912**
Trade and other payables[k]	29	**290**
Deferred income	30	**1,424**
Provisions	31	**1,010**
Deferred tax liabilities	14	**549**
Non-current liabilities[f]		**27,943**
Bank overdraft	19	**334**
Current tax liabilities		**4,751**
Loans and borrowings[j]	28	**5,347**
Employee benefits	13	**20**
Trade and other payables[k,l]	29	**24,013**
Contract liabilities	8	**160**
Deferred income	30	**-**
Provisions	31	**660**
Liabilities directly associated with the assets held for sale	20	**4,410**
Current liabilities[f]		**39,695**
Total liabilities		**67,638**
Total equity and liabilities		**112,860**

- The balance sheet, also known as the statement of financial position, shows a company's assets, liabilities and shareholders equity at a specific point in time, which is usually the end of the reporting period covered by the income statement
- The underlying principle of the balance sheet is that a company's assets are equal to the company's liabilities and shareholder's equity
- Assets on the balance sheet include current assets (cash or other assets expected to be converted into cash within the year) and non-current assets (assets expected to be held for longer than a year)
  - assets can be tangible, which means they have monetary value and physical form, or intangible, which means they have monetary value but no physical form
  - tangible assets include property, plant, and equipment
  - intangible assets include patents, trademarks, and copyrights
- Similarly, liabilities are categorized as current liabilities (with payments due within the year) and non-current liabilities (financial obligations not due within the year)
- Shareholders equity represents the amount of money that would be returned to shareholders if all the company's assets were sold and debts were paid
- In an acquisition, all of the assets and liabilities of the acquired company are added to the balance sheet of the parent company at their fair value
  - fair value is generally defined as the price received to sell an asset, or paid to transfer a liability, in an arms-length transaction between market participants
  - the purchase price in excess of the fair value of assets acquired is accounted for as goodwill (an intangible asset)

Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

The cash flow statement shows the cash in- and out-flows over a specific period of time

Illustrative cash flow statement



In thousands of euro	Note	2020
Cash flows from operating activities[a, d]		
Profit for the period[b]		7,552
Adjustments for:		
– Depreciation	21(A)	5,339
– Amortisation	22(A)	785
– Deferred income	30	(38)
– (Reversal of) impairment losses on property, plant and equipment	21(B)	(393)
– Impairment losses on intangible assets and goodwill	22(C)	16
– Impairment loss on remeasurement of the disposal group	20(A)	35
Net cash from operating activities		1,904
Cash flows from investing activities		
Interest received[e]		6
Dividends received[e]		26
Proceeds from sale of property, plant and equipment		3,085
Proceeds from sale of investments		1,476
Disposal of discontinued operation, net of cash disposed of[g]	7	10,890
Cash flows from financing activities		
Proceeds from issue of share capital	26(A)	1,550
Proceeds from issue of convertible notes	28(C)	5,000
Proceeds from issue of redeemable preference shares	28(D)	2,000
Proceeds from loans and borrowings		591
Proceeds from sale of treasury shares		30
Proceeds from exercise of share options	26(A)	50
Proceeds from settlement of derivatives		5
Transaction costs related to loans and borrowings	28(C)–(D)	(311)
Acquisition of NCI	36	(200)
Repurchase of treasury shares		-
Repayment of borrowings		(5,055)
Payment of lease liabilities[c]		(554)
Dividends paid[e]	26(C)	(1,243)
Net cash from financing activities		1,863
Net decrease in cash and cash equivalents		(384)
Cash and cash equivalents at 1 January**		1,567
Effect of movements in exchange rates on cash held		(13)
Cash and cash equivalents at 31 December**	19	1,170

- The cash flow statement illustrates the amount of cash, or cash equivalents, entering and leaving a company during a period of time, equivalent to the period of time used for the income statement
- The cash flow statement is split into cash from operating activities, cash from investing activities, and cash from financing activities
- Cash flow from operating activities represents the in- and outflow of any cash regarding the running of the core business, such as receipts from sales of goods, payments to suppliers, income tax payments, and employee salary payments
  - R&D costs that are expensed in the income statement are accounted for in the cash flow from operating activities
- Cash flow from investing activities includes any cash flows related to purchase or sale of an asset, a company, or marketable securities
- Cash flow from financing activities represents cash flows from investors or banks, as well as cash paid to shareholders
  - dividend payments and repurchasing of shares are categorized as financing activities
- In an acquisition, the consideration paid in the acquisition would be accounted for in cash flow from investing activities and any loans acquired to fund the acquisition would be accounted for in cash flow from financing activities

SiRM. Strategies in Regulated Markets

L.E.K.

Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

Transactions in the pharmaceutical industry can typically be classified as corporate M&A, asset purchase, or basic license / collaboration

Accounting treatment of acquisitions and partnerships is broadly consistent across company types, with the potential exception of very small, innovative companies

Common transactions in pharmaceutical companies

Corporate M&A

- Corporate M&A is a transaction in which an acquirer obtains control of another business
- Control can be obtained by acquiring the target company outright, or by acquiring majority of voting rights

Asset purchase

- An asset purchase is a transaction in which an asset, or group of assets, is transferred for consideration
- The acquirer does not gain control of the target company

Basic license / collaboration

- A basic license involves transfer of rights to an asset with an ongoing business relationship between licensor / licensee
- Collaborations involve companies sharing risks and rewards of an asset depending on the developmental and commercial success of the asset in question

Notes: *Milestone payments are recorded as R&D expenses for pre-regulatory approval assets and as COGS for post-regulatory approval assets
Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

In corporate M&A, assets and liabilities of the target company are added to the balance sheet of the acquirer

General accounting policies

Balance sheet considerations:

- All assets of the target company are added to the acquiring company's balance sheet at fair value in the year of acquisition
- Intangible R&D assets, such as protocols and data, are reported as in-process R&D intangible assets
- Difference between fair value of assets and purchase price is recorded as goodwill
- Future milestone payments are recorded as liabilities or intangible assets

Income statement considerations:

- R&D costs incurred after completion of the acquisition form part of the company's internal R&D costs and are accounted for in the company's income statement

Cash flow statement considerations:

- Consideration paid upfront for the acquisition is accounted for in cash flow from investing activities
- Any cash flow from loans or other financing required for the acquisition are accounted for in cash flow from financing activities

Milestone payments

- Milestone payments are recorded at fair value as a contingent consideration intangible asset or as a liability
  - fair value of milestone payments takes into consideration the likelihood of meeting milestones and requiring payment

- Companies can usually elect to treat milestones as intangible assets or liabilities depending on the contract terms
  - future royalty payments are typically seen as part of the value of the asset, and are therefore reported as intangible assets

- If the milestone is reported as an intangible asset, payment of the milestone results in an amortisation cost on the P&L
- If the milestone is reported as a liability, payment results in an R&D expense or COGS on the P&L

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Notes: *Milestone payments are recorded as R&D expenses for pre-regulatory approval assets and as COGS for post-regulatory approval assets
Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

In asset purchase, the asset is added to the acquirer's balance sheet; the income statement is unchanged until the transaction is complete

General accounting policies

Balance sheet considerations:

- The asset acquired is added to the balance sheet of the acquiring company with the value deemed to be the purchase price
- If a group of assets is acquired, the purchase price is allocated to the assets based on the relative fair value of each asset
- Unlike with company acquisitions, goodwill is not recognized on the acquisition of assets
- Future milestone payments are recorded as liabilities or intangible assets

Income statement considerations:

- R&D costs incurred after completion of the acquisition form part of the company's internal R&D costs and are accounted for in the company's income statement

Cash flow statement considerations:

- Consideration paid upfront for the acquisition is accounted for in cash flow from investing activities
- Any cash flow from loans or other financing required for the acquisition are accounted for in cash flow from financing activities

Milestone payments

- Milestone payments are recorded at fair value as a contingent consideration intangible asset or as a liability
  - fair value of milestone payments takes into consideration the likelihood of meeting milestones and requiring payment
- Companies can usually elect to treat milestones as intangible assets or liabilities
  - future royalty payments are typically seen as part of the value of the asset, and are therefore reported as intangible assets
- If the milestone is reported as an intangible asset, payment of the milestone results in an amortisation cost on the P&L
- If the milestone is reported as a liability, payment results in an R&D expense or COGS on the P&L

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L.E.K.

Notes: *Milestone payments are recorded as R&D expenses for pre-regulatory approval assets and as COGS for post-regulatory approval assets
Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

In licenses and collaborations, upfront payments are expensed to the income statement; licenses are recorded as intangible assets

General accounting policies

Balance sheet considerations:

- Since no assets are acquired, collaborations do not typically add assets to the company's balance sheet
- In a licensing agreement, the license is recorded as an intangible asset on the balance sheet
- Potential milestone payments are recorded as liabilities at their fair value

Income statement considerations:

- Upfront payments to collaborative partners for pre-regulatory approval assets are recorded as R&D expenses
- Royalties paid to collaborative partners are expensed as COGS
- Royalties received from collaborative partners are recorded as other income

Cash flow statement considerations:

- Consideration paid upfront for the acquisition is accounted for in cash flow from operating activities
- Any cash flow from loans or other financing required for the acquisition are accounted for in cash flow from financing activities

Milestone payments

- Milestone payments to partners for pre-regulatory approval assets are accounted as R&D expenses

- Milestone payments for post-regulatory approval assets are accounted as cost of products sold / COGS

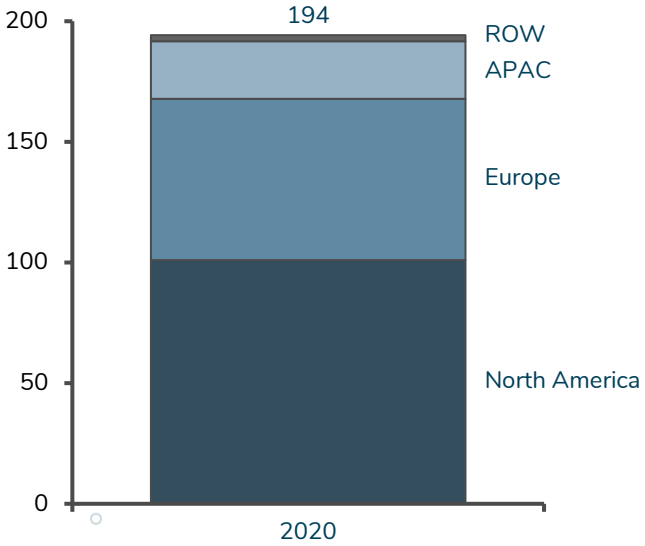
SiRM. Strategies in Regulated Markets

L.E.K.

Notes: *Milestone payments are recorded as R&D expenses for pre-regulatory approval assets and as COGS for post-regulatory approval assets
Source: Grant Thornton; PwC; KPMG; L.E.K. research, interviews, and analysis

L.E.K. believes EvaluatePharma R&D spend data presented in sub-report A is reflective of real R&D spend by companies

Global Private sector R&D spend by Region (Company HQ)* EvaluatePharma (2020)
Billions of USD



Data from sub-report A

- The R&D spend presented in sub-report A is based on EvaluatePharma data
- EvaluatePharma data is based on the R&D expenses reported in each company's annual reports and P&L
  - items reported as "exceptional R&D expenses" are disclosed separately and not included in EvaluatePharma's R&D spend
  - exceptional R&D expenses do not include upfront payments in equity investments, corporate M&A, or asset purchases
  - exceptional items were typically used to report upfront costs of licensing agreements, but are not often used in this way anymore, with licensing upfront costs incorporated in standard R&D expenses

"... 5-10 years ago, you would see companies using exceptional R&D expenses for their upfront licensing costs. However, nowadays it is usually included in the R&D expense, with a footnote explaining what is included..."
Accounting expert #3, former Deloitte U.S.

- Based on L.E.K.'s analysis of accounting policies, equity transactions and asset purchases are not reported in R&D expenses on the P&L
  - only upfront costs of basic licenses and milestone payments can appear under R&D expenses on the P&L

L.E.K. believes EvaluatePharma R&D spend reflects actual R&D spend, including basic licenses, and is not affected by M&A, equity transactions, and asset purchases

Notes: * c.5% of companies per year could not be allocated to a region – the remaining R&D spend has been allocated proportionally to the rest of global spend
Source: EvaluatePharma; Eikon; Orbis; clinicaltrials.gov; L.E.K. research and analysis

Johnson and Johnson's M&A resulted in acquisition of tangible and intangible assets, as well as milestone liabilities

Johnson & Johnson

Illustrative deals

	AURIS	XBiotech
Description of transaction	• In 2019, J&J acquired Auris Health Inc., a privately held developer of robotic technologies with an FDA-cleared platform	• In 2020, J&J acquired bermekimab, an investigational compound, along with certain employees from XBiotech
Upfront & milestone payments	• Upfront payment: $3.4bn (net of cash acquired)* • Milestone payments: up to $2.35bn	• Upfront payment: $0.8bn • Milestone payments: undisclosed milestone payments for certain commercialisation authorisations
Accounting treatment	• J&J accounted for this transaction as a business combination, resulting in additions to the balance sheet, but no additions to the income statement until the acquisition was complete • The main intangible assets consisted of IPR&D* ($3bn), goodwill ($2bn), and marketable securities ($0.2bn)** • $1.8bn of liabilities were recorded, which includes the fair value of the milestone payments* • In 2020, J&J recorded other income of $1.1bn due to the reversal of the contingent consideration related to certain milestones that are not expected to be met	• J&J accounted for this transaction as a business combination with the fair value of the acquisition allocated primarily to non-amortizable intangible assets • The main intangible asset was IPR&D ($0.8m fair value when applying a probability of success factor that ranged from 20% to 60%)

SiRM. Strategies in Regulated Markets

L.E.K.

Notes: *IPR&D = in-process R&D; ** The fair value recorded in the balance sheet is not necessarily equal to the upfront amount + milestones as milestone payments are recorded at fair value, taking into consideration PoS (55-95% in the Auris Health acquisition)
Source: Johnson & Johnson annual reports; L.E.K. research, interviews, and analysis

Pfizer's upfront payment for Nexium was recorded as an R&D expense with further royalty payments as COGS

	ARRAY BIOPHARMA	*Illustrative deals* Nexium (esomeprazole magnesium)
Description of transaction	• In 2019, Pfizer acquired Array, a commercial stage biopharmaceutical company focused on treatment of cancer and other diseases of high unmet need	• In 2012, Pfizer entered into an agreement with AstraZeneca for the exclusive global OTC rights for Nexium
Upfront & milestone payments	• Upfront payment: $48 per share in cash ($10.9bn, net of cash acquired) • Milestones: undisclosed milestones for pipeline of assets	• Upfront payment: $250m • Milestones: up to $550m
Accounting treatment	• The main intangible assets consisted of goodwill ($6.1bn), IPR&D ($2.8bn), developed technology rights ($2bn), and licensing agreements ($1.5bn) • $157m in payments to Array employees for the fair value of previously unvested stock options was recorded as restructuring charges	• The upfront payment of $250m was recorded as a R&D expense in the income statement when incurred • In 2014, Nexium OTC was launched in the U.S., resulting in the payment of $200m product launch milestones • Further royalty payments will be reported on the income statement as cost of goods sold

Source: Pfizer annual reports; L.E.K. research, interviews, and analysis

Acquisitions of AveXis and Ziarco are recorded on the balance sheet; post-acquisition R&D costs are expensed on the income statement

Illustrative acquisitions

	NOVARTIS / AveXis	ZIARCO
Description of transaction	• In 2018, Novartis acquired AveXis, a clinical stage gene therapy company through a tender offer to purchase all outstanding common stock	• In 2017, Novartis acquired Ziarco group, a privately held company focused on the development of novel treatments in dermatology
Upfront & milestone payments	• Upfront payment: $8.7bn • Milestones: None announced	• Upfront payment: $325m • Milestones: up to $95m
Accounting treatment	• The identifiable assets recorded on the balance sheet were intangible assets ($8.5bn), other assets ($0.3bn) and goodwill ($1.5bn) • Deferred tax liabilities of $1.6bn were also recorded on the balance sheet • R&D costs incurred after completion of the acquisition were expensed to the R&D expenses on the income statement	• The total purchase consideration was $420m, consisting of the $325m up front payment and the net present value of the $95m milestone payments due to Ziarco shareholders • The transaction resulted in net identifiable assets of $395m, including the net present value of milestones, and $25m of goodwill

Source: Novartis annual reports; L.E.K. research, interviews, and analysis

Sanofi's corporate M&A is recorded on the balance sheet; acquisition-related costs are expensed on the income statement

Illustrative acquisitions

	SANOFI	synthorx	PRINCIPIA BIOPHARMA
Description of transaction	• In 2019, Sanofi acquired all of the outstanding shares of Synthorx, a clinical-stage biotech focused on cancer and autoimmune diseases		• In 2020, Sanofi acquired all the outstanding shares of Principia, a late-stage biopharmaceutical company focused on autoimmune diseases
Upfront & milestone payments	• Upfront payment: €2.2bn ($68 per share) • Milestones: None		• Upfront payment: €3.2bn ($100 per share) • Milestones: None
Accounting treatment	• Acquired assets recorded on the balance sheet were intangible assets (€2.4bn, including goodwill of €0,93bn) and other assets (€0.04bn) • A deferred tax liability of €0.27bn was recorded on the balance sheet as well • Cash flow from this investment was reported in the cash flow from investing activities		• Acquired assets recorded on the balance sheet were intangible assets (€2.5bn), cash & cash equivalents (€186m), and goodwill (€913m) • Liabilities recorded were deferred tax liability (€437m) and other liabilities (€38m) • Acquisition related costs of €13m were expensed to the income statement as "other expenses"

Source: Sanofi annual reports; L.E.K. research, interviews, and analysis

Roche records corporate M&A according to the accounting policies, with directly attributable acquisition costs recorded as G&A expenses

Illustrative acquisitions

	flatiron	Spark THERAPEUTICS
Description of transaction	• In 2018, Roche acquired Flatiron Health, a privately owned U.S. company focused on the curation and development of real-world evidence for cancer research	• In 2019, Roche acquired Spark Therapeutics, a public company that discovers, develops, and delivers gene therapies
Upfront & milestone payments	• Upfront payment: $1.6bn • Milestones: None	• Upfront payment: $4.8bn • Milestones: None
Accounting treatment	• Upfront costs were allocated to tangible and intangible assets, with $1.1bn of goodwill recorded on the balance sheet • Directly attributable transaction costs of CHF 3m were reported as general and administration expenses in the income statement • In the 9 months following the acquisition to the end of the accounting period, Flatiron Health contributed CHF 56m to revenues	• Purchase price was allocated to tangible and intangible assets, with $4.5bn recorded as goodwill on the balance sheet • Directly attributable transaction costs of CHF 25m were reported in general and administration expenses in the income statement

Source: Roche annual reports; L.E.K. research, interviews, and analysis

UCB's corporate M&A are accounted for on the balance sheet, with milestone payments adjusted for likelihood and timing of payments

Illustrative acquisitions

	ENGAGE THERAPEUTICS	Ra Pharma
Description of transaction	• In 2020, UCB acquired Engage Therapeutics, a privately held company developing treatments for people living with epilepsy	• In 2020, UCB completed the acquisition of Ra Pharma, a clinical-stage biopharma company focused on serious diseases of the immune system
Upfront & milestone payments	• Upfront payment: €125m • Milestones: up to €145m	• Upfront payment: $2.3bn ($48 per share) • Milestones: None
Accounting treatment	• The fair value of the contingent consideration recorded on the balance sheet was calculated to be €88m based on the likelihood and timing of achieving the milestones • A payment of €3m was paid by UCB to engage Therapeutics to settle transaction costs, which was not considered part of the acquisition cost and was recorded as other expenses in the income statement	• The fair value of certain intangible assets were calculated based on 26 year cash flow forecasts and 12.5% discount rate • Majority of the purchase price was allocated to goodwill (€2.05bn) on the balance sheet • Acquisition related costs of €95m have been recorded under other expenses in the income statement

Source: UCB annual reports; L.E.K. research, interviews, and analysis

Upfront payments in Incyte's collaboration with MorphoSys were recorded as R&D expenses in the income statement

	Incyte	*Illustrative acquisitions*
	ARIAD	morphosys
Description of transaction	• In 2016, Incyte acquired ARIAD's European operations, as well as the license to develop and commercialise Iclusig in Europe and selected countries	• In 2020, Incyte entered into a collaboration and license agreement with MorphoSys for the worldwide development and commercialisation of MOR208
Upfront & milestone payments	• Upfront payment: $140m • Milestones: up to $135m in future milestones and additional tiered royalties	• Upfront payment: $750m • Milestones: up to $740m in development milestones and up to $315 in commercialisation milestones, as well as additional tiered royalties
Accounting treatment	• The upfront payment to ARIAD was recorded in research and development expenses in the income statement • Future royalty payments will be expensed as COGS in the income statement as revenues are earned	• The upfront payment of $750m was recorded in research and development expenses in the income statement • Milestone payments will be expensed to research and development expenses as payments are made

Source: Incyte annual reports; L.E.K. research, interviews, and analysis

Dividend payments

Companies use consistent dividend policies to attract stable investors

Companies use dividends to attract specific types of investors

- Regular dividends typically attract long-term, stable investors, with the investor relations team influencing the dividend policy based on the strategy to diversify the company's investor base

"... Many big biopharma companies use dividends to attract a stable investor base. Investor relations is often involved in developing the dividend policy because they use this to ensure they have a diversified investor base..."
Accounting expert #2, big pharma (U.S.)

Dividend per share should be kept stable to retain investors

- Once a company initiates dividend payments, investors expect dividend per share to remain stable or grow at a consistent rate, usually to offset inflation
  - An unstable dividend policy can lead to an unstable investor base

"... Once you initiate a dividend, you set an expectation that this dividend won't stop because you are now attracting a certain investor base that you do not want to lose. So once you start a dividend, you can't stop..."
Accounting expert #2, big pharma (U.S.)

Small-to-medium sized companies are less likely to use dividends

- Smaller companies with less predictable annual income are less likely to announce dividends, due to the need to continue the policy for the long-term

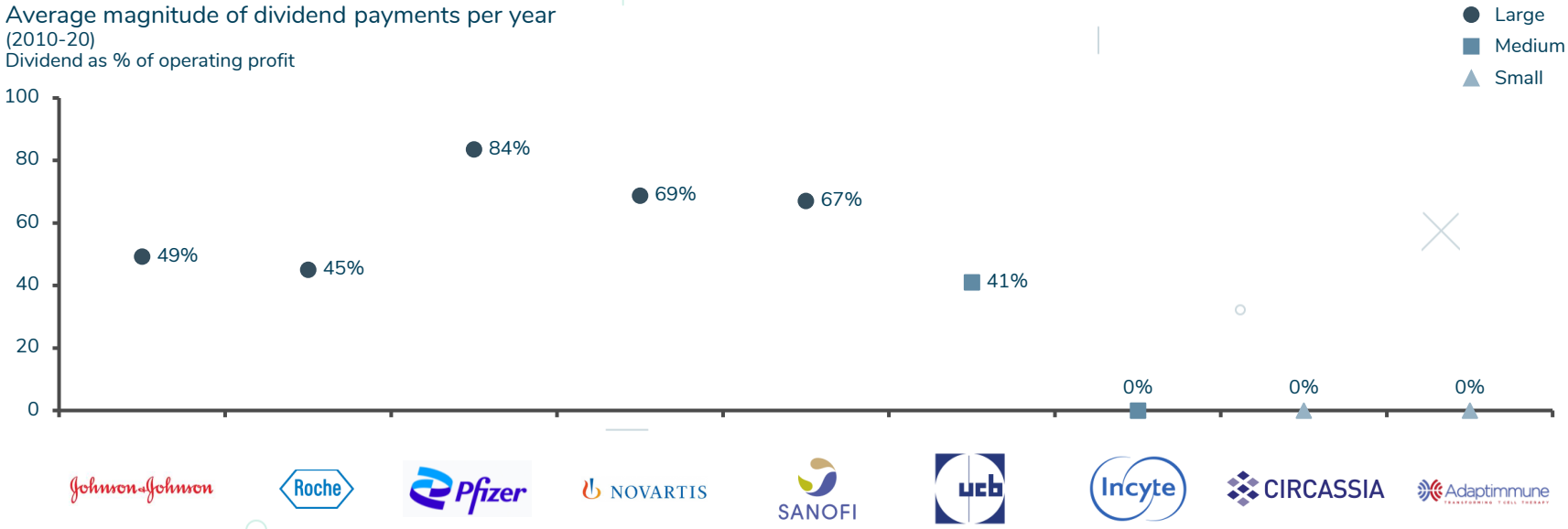
"... When you're a small company, you have an unpredictable stream of income. You don't want to put pressure on your company by committing to a dividend policy..."
Accounting expert #2, big pharma (U.S.)

Dividends can be unattractive due to double-taxation

- Dividends can be considered as a less efficient manner to provide returns to shareholders due to double taxation
  - Earnings, which will ultimately be used to pay dividends, are taxed at a corporate level
  - Investors are taxed on the dividend they receive

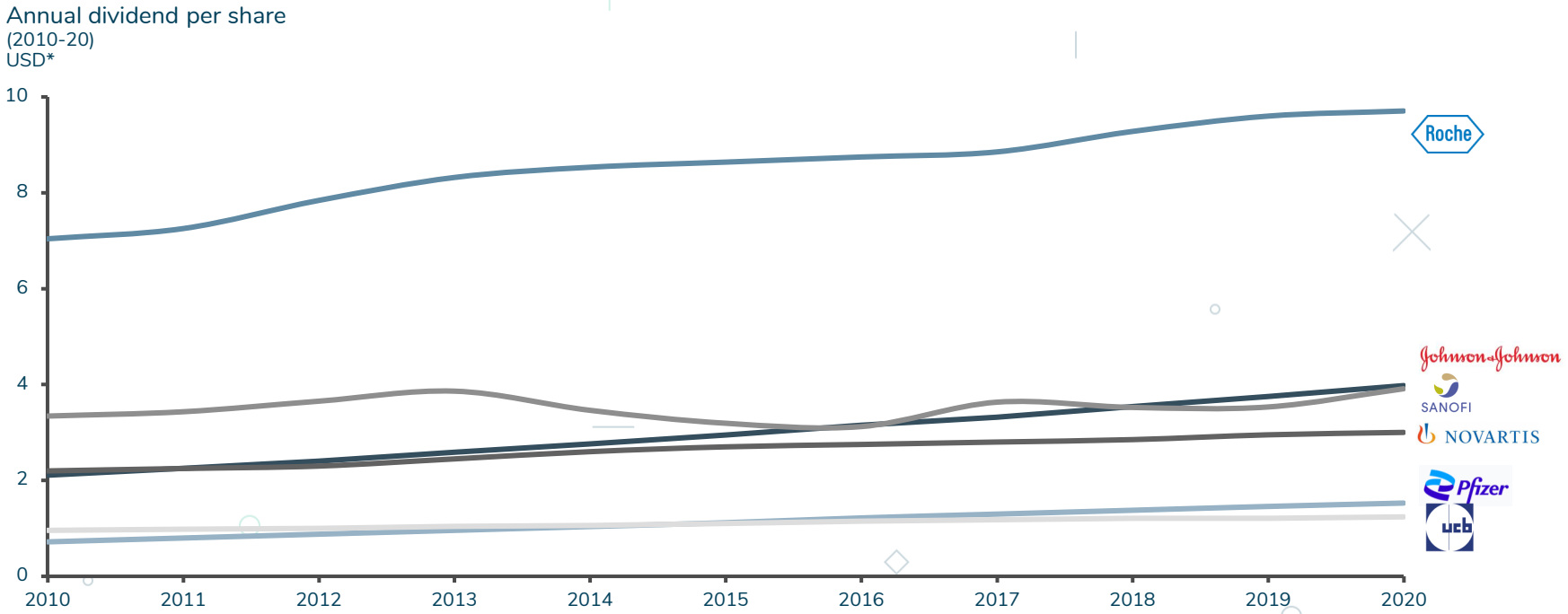
Source: L.E.K. research, interviews, and analysis

Large companies typically offer annual or quarterly dividends; smaller companies often do not distribute dividends



Source: Company websites and annual reports; L.E.K. research, interviews, and analysis

Companies aim to have stable growth in annual dividends per share pay-outs



Notes: * Roche dividend per share is reported in CHF and shown here in 2020 USD constant currency
Source: Company websites and annual reports; L.E.K. research, interviews, and analysis

Share buy-backs

Share buy-backs are a flexible, tax efficient alternative to dividends to return capital to shareholders

Share buy-backs are a more flexible way to return capital to shareholders than dividends

- Share buy-backs are seen as opportunistic, rather than systematic like dividends, providing companies with a flexible way to return capital to investors

  "... Unlike dividends, share buy-backs are seen as opportunistic. Initiating a share buy-back doesn't mean that you have to continue doing that going forward..."
  Accounting expert #2, big pharma (U.S.)

- Share buy-backs are often used when companies have excess funds in a given year which are not required for R&D investments

  "... You might have a company that has already invested a lot in R&D and they have excess cash. Investing further in R&D or even in other investment opportunities may not provide good bang-for-your-buck. In those cases, it can be good to initiate a share buy-back..."
  Accounting expert #2, big pharma (U.S.)

Companies can use share buy-backs to offset undervalued stock

- When a company believes their shares are undervalued, a share buy-back can be used to demonstrate the shares have value and to signal to the market

  "... If you think your shares are undervalued, initiating a share buy-back can be a good way to show the market that these shares are worth more, and create more confidence in the market..."
  Accounting expert #2, big pharma (U.S.)

Share buy-backs are usually more tax efficient than dividends

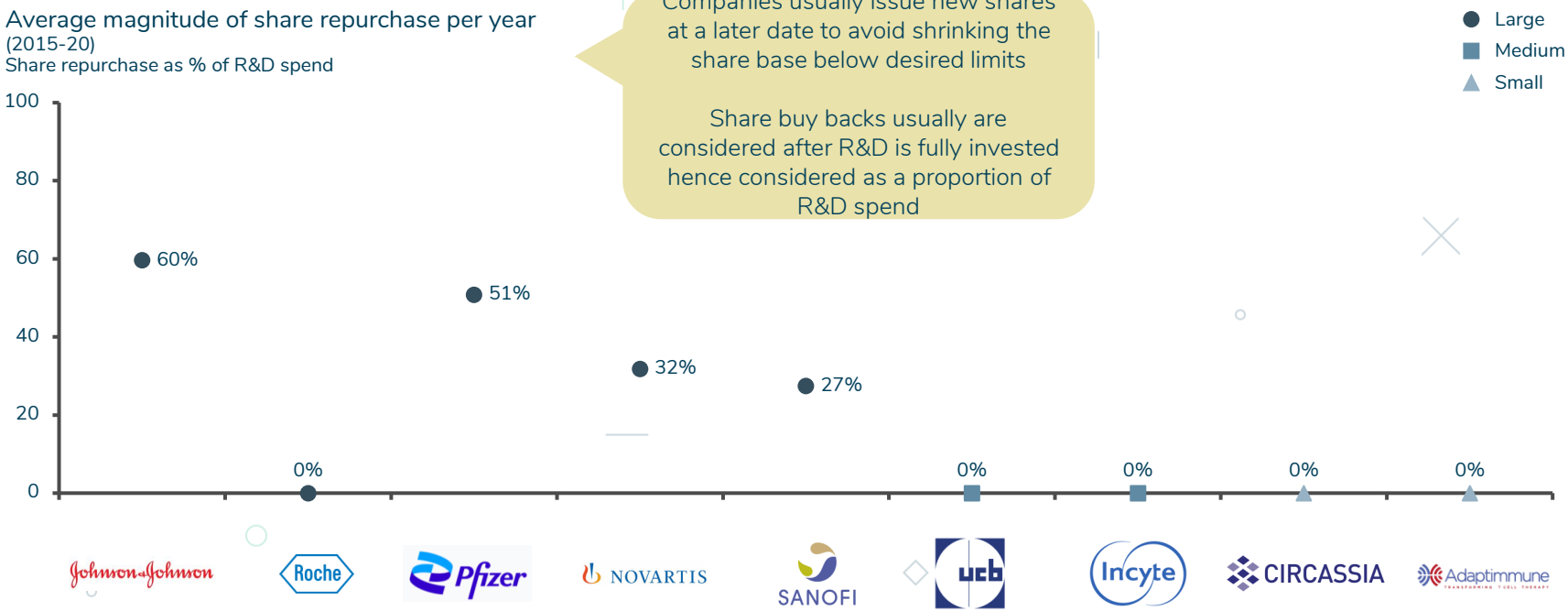
- Share buy-backs are a more tax efficient alternative to dividends because they are not exposed to the same double taxation as dividends

  "... With dividends, you pay corporation tax and income tax on the same dollar. With share buy-backs, you avoid this double taxation..."
  Accounting expert #2, big pharma (U.S.)

Source: Company websites and annual reports; L.E.K. research, interviews, and analysis

There is variation in share repurchase policies across companies and company types

Average magnitude of share repurchase per year
(2015-20)
Share repurchase as % of R&D spend



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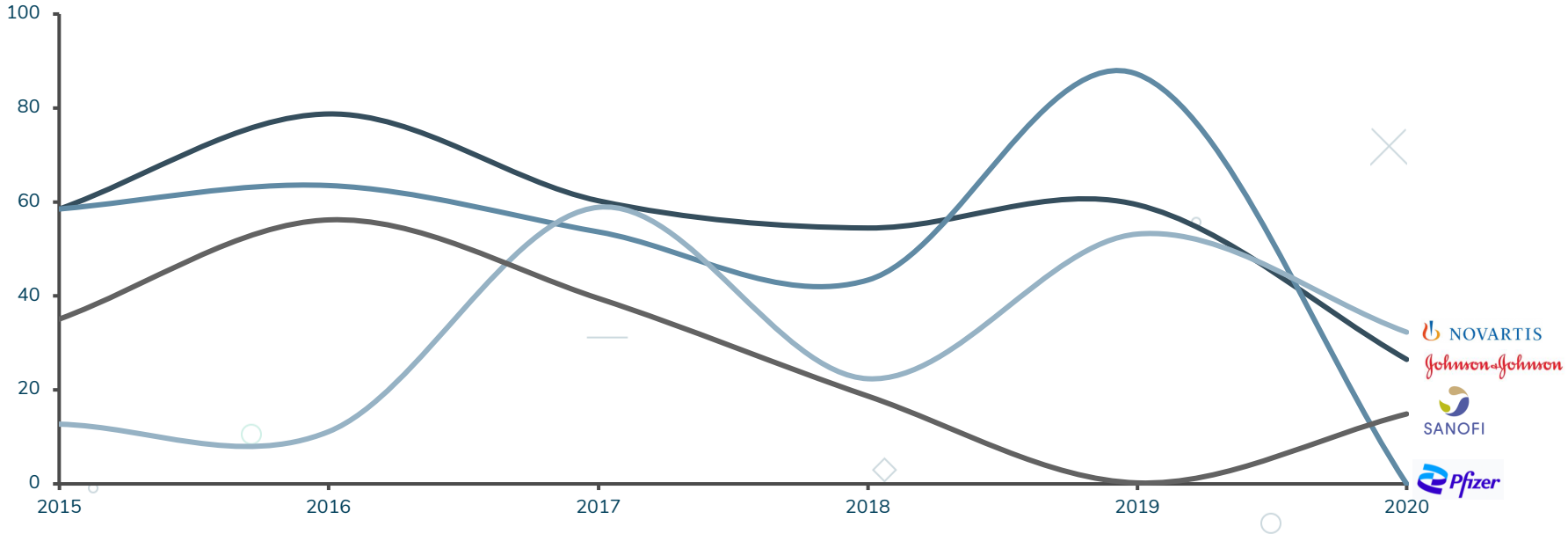
Source: Company websites and annual reports; L.E.K. research, interviews, and analysis

Share buy-backs are opportunistic, resulting in year-on-year variation in magnitude of share buy-backs

Magnitude of share repurchase per year
(2015-20)
Share repurchase as % of R&D spend



Source: Company websites and annual reports; L.E.K. research, interviews, and analysis

Johnson & Johnson initiated a share buy-back in 2018 following a decrease in share price of c.10% following a negative Reuters report

Johnson & Johnson

Company announcement of share buy-back

- On December 17th 2018, Johnson & Johnson announced a repurchase of up to $5bn of the company's common stock

"Based on our continued strong performance and, more importantly, the confidence we have in our business going forward, the Board of Directors and management team believe that the company's shares are an attractive investment opportunity. Our strong cash flow enables us to simultaneously return value to shareholders through our regular quarterly dividend and share repurchases, while at the same time continuing to deploy capital that will further strengthen our robust enterprise pipeline and drive long-term growth."

Alex Gorsky, Chairman and Chief Executive Officer in December 17, 2018 statement

Market considerations at the time

- On December 14th 2018, Reuters published an investigative piece entitled "Johnson & Johnson knew for decades that asbestos lurked in its Baby Powder", causing Johnson & Johnson share prices to decrease by c.10% in 2 days representing a loss of c.$40m in market value
- Johnson & Johnson's share prices increased by c.1% following the announcement of the share buy-back
- An article in Reuters following the announcement noted that the share repurchase was part of a range of efforts to increase investor confidence
  - in addition to the share buy-back, Johnson & Johnson stated they did not hide information regarding the safety of talc and they took out a full-page ad in the New York Times stating "If we had any reasons to believe our talc was unsafe, it would be off our shelves"

Source: Johnson & Johnson website and annual reports; Reuters; L.E.K. research, interviews, and analysis

Pfizer paused its share repurchase programme to increase funds available for internal R&D and external M&A

Company announcement of share buy-back

- Following several years of share repurchases, in January 2020, Pfizer announced they were not conducting any share buy-backs this year
- In the Q4 earnings call, Pfizer CEO Albert Bourla announced the pause in share buy-backs was, in part, to allow for increased investment in internal R&D and external business development opportunities

"[the pipeline will be augmented] with mid stages R&D programs through targeted bolt on business development opportunities… M&A is a very important part of our strategy. And as I just alluded before, this is why we are not diluting our firepower with share purchases right now. Because we do believe that we can create significant value with the right strategic moves"

Albert Bourla in Q4 earning call in January 2020

Market considerations at the time

- Analysts noted earnings fell short of Wall Street expectations due to higher-than-expected operating costs and lower-than-expected sales on certain drugs
- Investing in R&D and M&A, rather than announcing a share repurchase programme, was seen as an opportunity to bolster the pipeline and develop additional products

Source: Pfizer website and annual reports; Reuters; L.E.K. research, interviews, and analysis

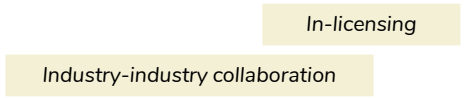
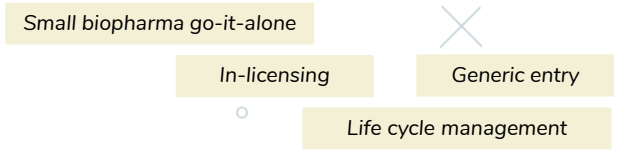
6. Case studies

The case studies show different development archetypes are mostly combined

Drug	Development	Archetype
Kalydeco*	• Vertex developed in-house with financial support from Cystic Fibrosis Foundation	Industry / NGO collaboration Biopharma in-house
Zolgensma*	• Avexis in-licensed rights to use ReGenX's rAAV9 vectors to develop SMA therapies; Avexis took Zolgensma through to phase III before being acquired by Novartis	Asset in-licensing Big pharma M&A Biotech go-it-alone
Darzalex	• Genmab took Darzalex through to phase I before Janssen entered a co-development agreement and then in-licensed the product	Small biopharma go-it-alone In-licensing Industry-industry collaboration
Luxturna	• Children's Hospital of Philadelphia (CHOP) took Luxturna through to phase III before spinning out Spark who took it through to market before being acquired by Roche; Novartis in-licensed ex-U.S. rights	Academia go-it-alone In-licensing Biotech go-it-alone M&A
Keytruda	• Merck & Co. acquired Schlering-Plough and inherited Keytruda; Merck & Co took Keytruda through development and to market	Big pharma M&A Big pharma in-house
Yescarta	• Kite collaborated with National Cancer Institute for preclinical development; then carved out the relevant IP and took Yescarta through to phase II before being acquired by Gilead	Biotech – Academia collaboration Big pharma M&A Biotech go-it-alone

*Additional interviews were conducted to characterise the decision-making rationale behind key investment events in Kalydeco and Zolgensma's R&D.
Source: L.E.K. interviews, research and analysis

Two additional case studies demonstrate examples of R&D failure and the life cycle evolution of a less innovative / non-orphan therapy

Case study	Development	Archetype
Galapagos Pharma	• Galapagos had strong revenue growth due to upfront payments after signing two major contracts with Gilead, but three of its key pipeline assets have either failed in late-stage clinical trials or to get FDA approval in 2020-21	
Aripripazole	• Discovered by Otsuka Pharma in 1992, the first aripiprazole therapy Abilify was launched in 2002 and maintained commercial success through indication expansion and reformulation; generics and reformulations were introduced in 2015, some of which have improved dosing schedules	

Source: L.E.K. interviews, research and analysis

The Kalydeco case study is a rare example of commercially successful industry-NGO collaboration with ROI for stakeholders involved

Drug	Development	Archetype
Kalydeco	Vertex developed in-house with financial support from Cystic Fibrosis Foundation (CFF)	*Industry / NGO collaboration* *Biopharma in-house*

Summary

- The Kalydeco case study is a rare, and likely most successful, example of a funding program by not-for-profits / NGOs that resulted in the discovery of the first disease-modifying therapy for cystic fibrosis (CF), and significant return on investment for both R&D funders and executors

Development progression

- Cystic Fibrosis Foundation (CFF) directed funding towards biopharma for discovering therapies for CF and partnered with Aurora Bioscience, which was acquired by Vertex Pharma
- Vertex Pharma significantly increased investment in Kalydeco after phase I success, reshifting the company's strategic focus from virology to cystic fibrosis
- CFF assisted with patient access on top of providing funding, which helped Kalydeco to become a blockbuster drug

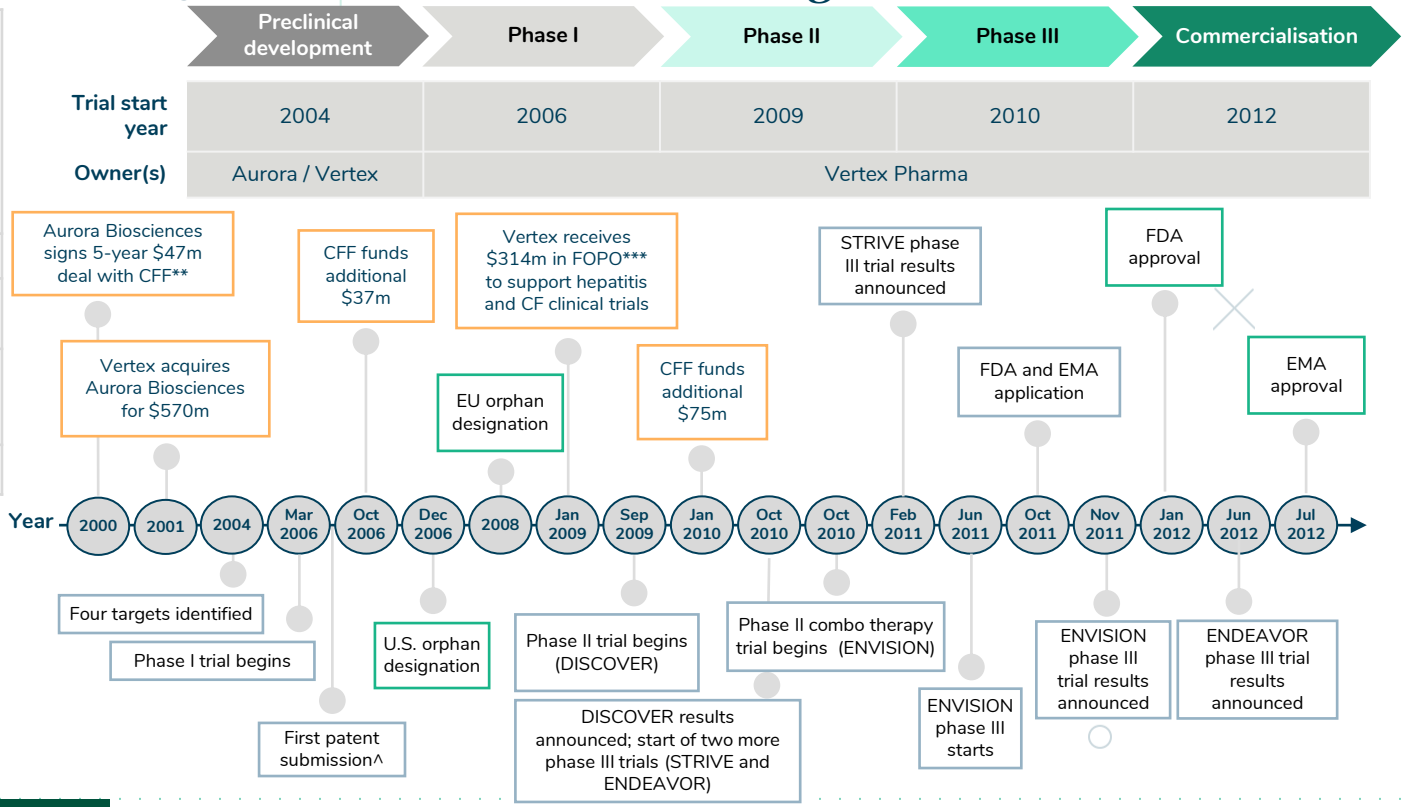
Stakeholder returns

- Kalydeco's commercial success significantly benefited both CFF and Vertex Pharma financially – CFF sold royalty rights for Kalydeco in a $3.3bn deal and reinvested in CF research; Vertex grew to be the market leader in CF therapeutics
- Strategically, CFF and Vertex have since entered additional R&D agreements for CF therapies; the relationship continues to be synergistic based on the two parties' leadership status in the CF therapeutic space

Notes: *Also known as Cystic Fibrosis Foundation Therapeutics (CFFT) until 2017
Source: L.E.K. interviews, research and analysis

Kalydeco is an oral therapy used to treat cystic fibrosis, first approved for treating patients with G511D mutation in the CFTR* gene

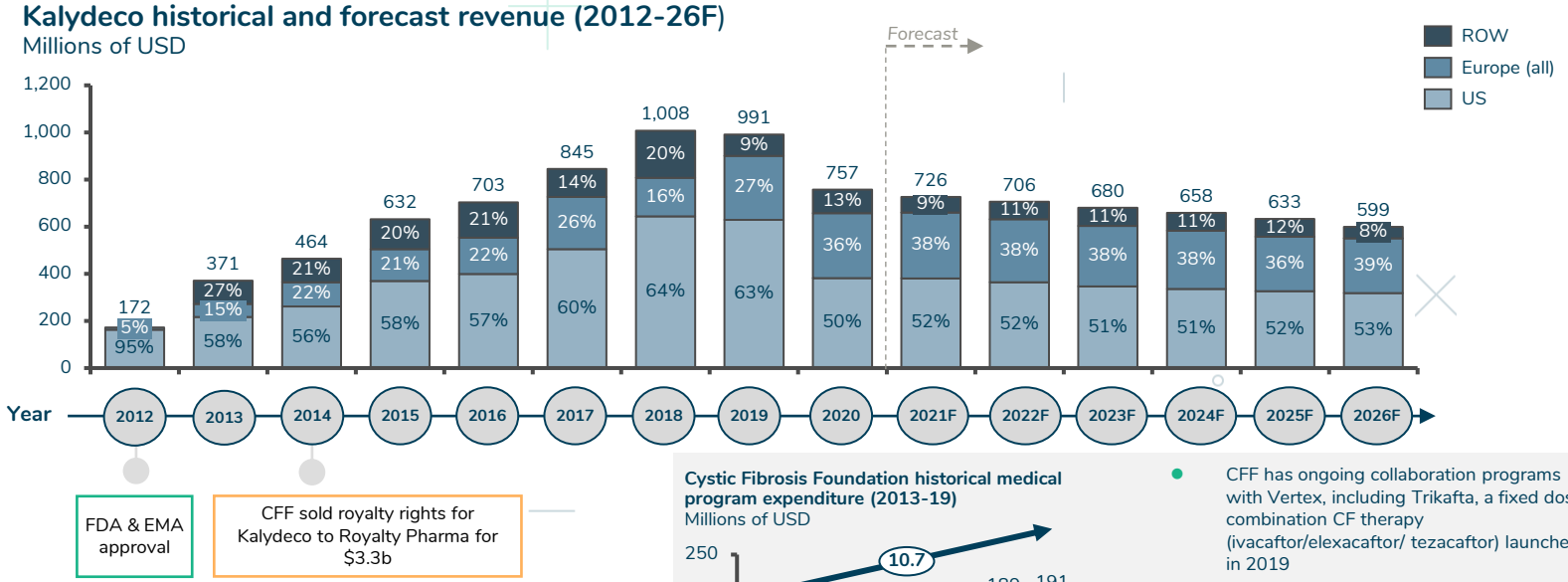
Name (INN)	Kalydeco (ivacaftor) 
Owner	Vertex Biopharma
Origination	Small / medium biopharma
Route to market	Industry / NGO collaboration / M&A, biopharma in-house
Funding	NGO ; Public offering

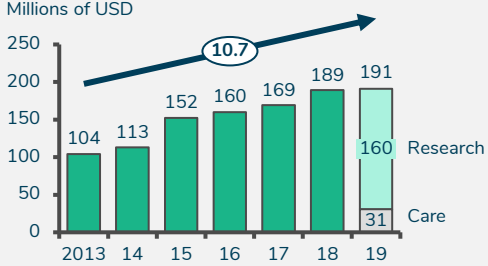


Notes: ^WO2006002421A2; *Cystic fibrosis transmembrane conductance regulator; **Cystic Fibrosis Foundation Therapeutics; ***Follow-on public offering

Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

In 2014, CFF signed a $3.3b deal with Royalty Pharma to sell its royalty rights to Kalydeco, which CFF reinvests in ongoing research programs





- CFF has ongoing collaboration programs with Vertex, including Trikafta, a fixed dose combination CF therapy (ivacaftor/elexacaftor/ tezacaftor) launched in 2019
- CFF's funding has increased at a CAGR of 11%; it plans to allocate $500m of funding from 2019-2024 to Path to a Cure, a research initiative for all subgroups of CF patients to receive treatment and ultimate cure

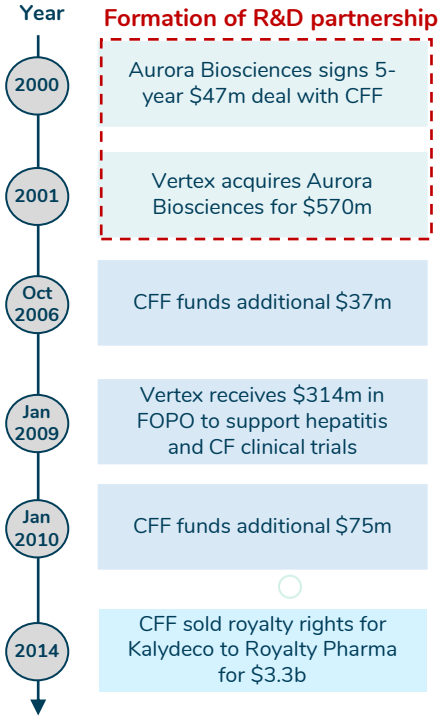
Transactions and agreements
Development milestones
Approval / designations

Year	Indication approved^
2012	G551D mutation in the CTFR gene
2014	10 mutations in the CTFR gene
2017	Identified mutation(s) in the CTFR gene

Note: ^FDA approval dates
Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Kalydeco's R&D began with CFF funding Aurora Biosciences for disease modifying therapies in CF, which was then acquired by Vertex Pharma

Kalydeco – Key strategic events



CFF funded disease modifying therapy R&D in pharma for higher financial returns and partnered up with Aurora

- In the late 1990s, there were only a few therapies that treat the symptoms of cystic fibrosis (CF), and the Cystic Fibrosis Foundation was looking to support the development of disease-modifying therapies
  - major pharmaceutical companies were focused in the development of blockbuster drugs for indications with high disease prevalence, and had little interest in CFF's proposal
- CFF wanted to make strategic investments in pharma companies specifically aimed at cystic fibrosis therapy development, which had a higher return on investment potential than funding academic research
  - in 2000, CFF partnered with biotech company Aurora Biosciences to identify disease-modifying molecules based on Aurora's capabilities in high throughput screening

Vertex acquired Aurora but did not invest heavily in CF franchise due to virology focus

- Vertex Pharma acquired Aurora Biosciences in 2001 with a strategic aim to expand its drug discovery program to additional gene families
- Up until 2009, Vertex's strategy was heavily focused on virology as it prepared to bring its first therapeutic asset, Incivek for the treatment of hepatitis C, to market
  - the cystic fibrosis franchise was overlooked as it was inherited from Aurora Biosciences and did not fit with Vertex's virology portfolio

"…Although we had the virology and CF franchises, the company was really just focused on virology. The CF franchise was seen more as inherited from Aurora…"
Former VP managed markets, Vertex Pharma

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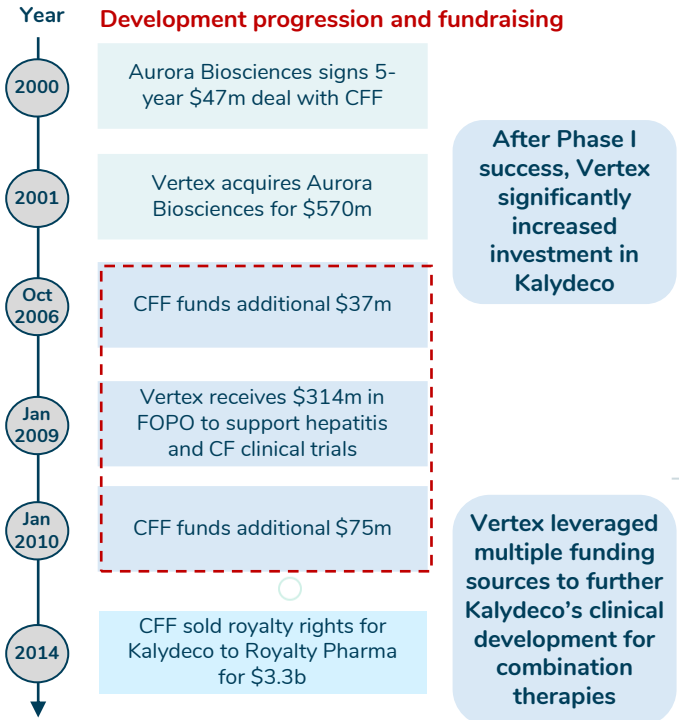
Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

After Phase I success and potential for combination therapy, Vertex increased investment in Kalydeco, leveraging multiple sources of capital

Kalydeco – Key strategic events



- When Kalydeco entered phase I trials in 2006, additional funding was required to advance its research, and hence CFF funded an additional $37m, and would eventually commit an additional $75m in 2010
- In 2009, positive phase I results from Kalydeco encouraged Vertex to invest more into building R&D and commercialisation capabilities for the cystic fibrosis franchise
  - the company had accumulated significant deficit since its founding, the capital required for the forward-looking R&D and commercialisation costs of Incivek and Kalydeco motivated Vertex to raise $314m in a public offering
  - the company also restructured its research and sales forces significantly to achieve a more balanced focus across the two franchises

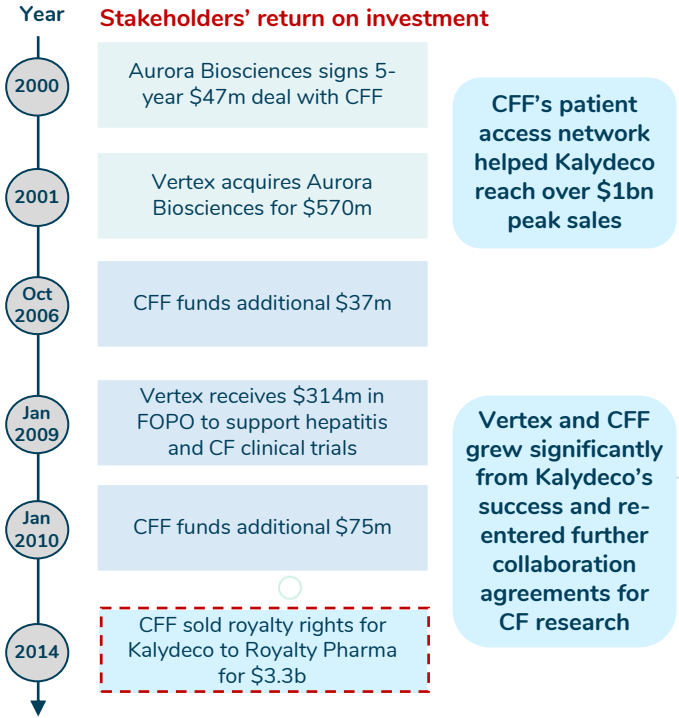
"…We underwent a huge internal restructuring in 2009 to increase our focus on CF and to build out commercialisation capabilities for both Kalydeco and Incivek. The offering was required at that time to get us to the capital to implement these changes…"
Former VP managed markets, Vertex Pharma

- In 2009-2011, Vertex decided to shift most of its revenue on Kalydeco's R&D upon discovering that by combining Kalydeco with other therapeutic agents it can significantly expand the treatable patient population
  - on top of funds raised from the offering in 2009, Vertex divested some of its pipeline assets and leveraged Incivek's sales revenue to support multiple phase II / III trials aimed at CF patients with different mutations
  - Vertex's hepatitis C drug Incivek was shortly outcompeted by Gilead's Harvoni post-launch, which further strengthened Vertex's R&D efforts in the CF franchise

Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Synergistic partnership between CFF and Vertex helped Kalydeco reach >$1bn peak sales, and new agreements have been made to further CF R&D

Kalydeco – Key strategic events



- Vertex and CFF's partnership was beneficial from both research funding and market access perspectives
  - CFF worked closely with Vertex on Kalydeco's market access – CFF has close relationships to c.150 cystic fibrosis centres worldwide and also has in-house pharmacy benefit management strategies to maximise patient access
  - this has facilitated Kalydeco to reach over $1bn peak sales in 2018

"…Kalydeco would not achieve the same commercial success without the CFF's distribution network, we worked closely on getting Kalydeco to all eligible patients …"
Former VP managed markets, Vertex Pharma

- Vertex was able to reinvest Kalydeco's sales revenue into developing other therapies for cystic fibrosis and is now a leader in the therapeutic space; it has faced limited competition, which has allowed it to maximise revenue / profits
- While the majority of Kalydeco's revenue went to Vertex, CFF also achieved significant financial gains from Kalydeco's royalty which it has sold to reinvest in cystic fibrosis research
- CFF has entered further research agreements with Vertex; given Vertex's present status as the lead therapeutic company in CF, and CFF's patient access network and growth in funding, the relationship continues to be synergistic

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Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

The Zolgensma case study shows how partnerships and licenses at different stages of development can be leveraged to bring an asset to market

Drug	Development	Archetype
Zolgensma	Avexis in-licensed rights to use ReGenX's rAAV9 vectors to develop SMA therapies; Avexis took Zolgensma through to phase III before being acquired by Novartis	Asset in-licensing; Big pharma M&A; Biotech go-it-alone

Summary

- The Zolgensma case study shows how a biotech company fundraises to progress Zolgensma's development and how being acquired by Novartis was beneficial for both Zolgensma's commercialisation and Novartis's strategy to enter gene therapy

Development progression

- AveXis assembled its R&D infrastructure for spinal muscular atrophy (SMA) through in-licensing academic research, platform technology, and hiring the suitabe experts for its management team
- AveXis issued four public offerings, totalling c.$1bn, to support Zolgensma's R&D; late-stage funding was more substantial and involved institutional investors
- During Zolgensma's phase III development, AveXis was acquired by Novartis for $8.7bn

Stakeholder returns

- Acquiring AveXis helped Novartis gain relevant expertise and pipeline assets in cell and gene therapy, which led them to become one of the leaders in the therapeutic area
- Zolgensma benefited from Novartis's reputation in neurology and commercialisation infrastructure, which increased its competitiveness against Biogen and Roche
- ReGenX successfully out-licensed its SMA viral vectors in a $260m deal

Source: L.E.K. interviews, research and analysis

Zolgensma is a first-in-class, one-time gene therapy for treatment of spinal muscular atrophy (SMA) type I

Name (INN)	Zolgensma (onasemnogene abeparvovec) 
Owner	Novartis
Origination	Small / medium biopharma
Route to market	Transactional (in-licensing, company M&A)
Funding	VC ; IPO ; Big pharma internal

	Preclinical development	Phase 1	Phase 2	Phase 3	Approval
Trial start year	2013 (estimated)	2014		2017	2019
Owner	ReGenX / AveXis	AveXis		AveXis / Novartis	Novartis

- **2013** — ReGenX raises $8m VC funding for drug discovery using its NAV* technology
- **Apr 2014** — AveXis in-licenses rights to use ReGenX's rAAV9** vectors to develop SMA therapies
- **Sep 2014** — AveXis raises $10m in series C
- **Jan 2015** — Start of phase I/II trial (START)
- **Jun 2015** — U.S. orphan designation
- **Sep 2015** — EU orphan designation
- **Feb 2016** — AveXis raises $65m in series D
- **Sep 2016** — AveXis $98m IPO
- **Oct 2016** — AveXis $128m FOPO
- **Apr 2017** — U.S. breakthrough therapy designation
- **Jun 2017** — AveXis / ReGenX $260m deal – AveXis now has exclusive global rights for all NAV vectors for SMA
- **Dec 2017** — AveXis $271m FOPO
- **Jan 2018** — AveXis $432m FOPO
- **Jan 2018** — START phase II data announced
- **May 2018** — Phase II trial starts (STRONG)
- **Oct 2018** — Novartis acquires AveXis for $8.7b
- **Dec 2018** — EMA application
- **Apr 2019** — First readout of STR1VE phase III data
- **May 2019** — FDA approval
- **May 2020** — EMA conditional marketing approval

Year – 2013 | Apr 2014 | Sep 2014 | Jan 2015 | Jun 2015 | Sep 2015 | Feb 2016 | Sep 2016 | Oct 2016 | Apr 2017 | Jun 2017 | Dec 2017 | Jan 2018 | Jan 2018 | May 2018 | Oct 2018 | Dec 2018 | Apr 2019 | May 2019 | May 2020

- Preclinical data announced^
- START phase I data announced
- Start of three phase III trials*** (REACH, STR1VE, SPR1NT)
- FDA application

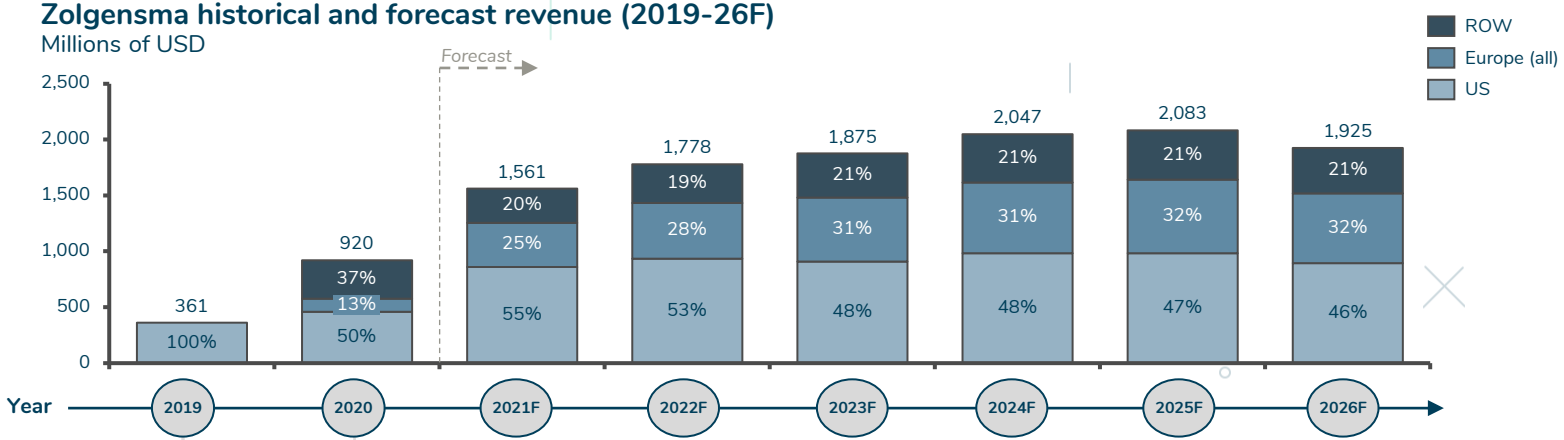
Transactions and agreements
Development milestones
Approval / designations

Notes: ^Patent information not available; *Next-generation adeno-associated virus vector; **Recombinant adeno-associated virus type rh 9; *** REACH (aged 6 month – 18 year old), STR1VE (START's follow-on trial, aged <6 months), SPR1NT (aged <6 weeks)
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

ReGenX received $84m for the use of its vector technology for Zolgensma which is projected to reach peak revenue of $2.1b in 2025

Zolgensma historical and forecast revenue (2019-26F)

Millions of USD



FDA approval

EMA approval

ReGenX to receive $3.5m from Zolgensma's approval

ReGenX received $80m from Zolgensma's $1b sales milestone

Year	Indication approved^
2019	Pediatric SMA patients (<2 years) with biallelic mutations in SMN1* gene

Transactions and agreements

Development milestones

Approval / designations

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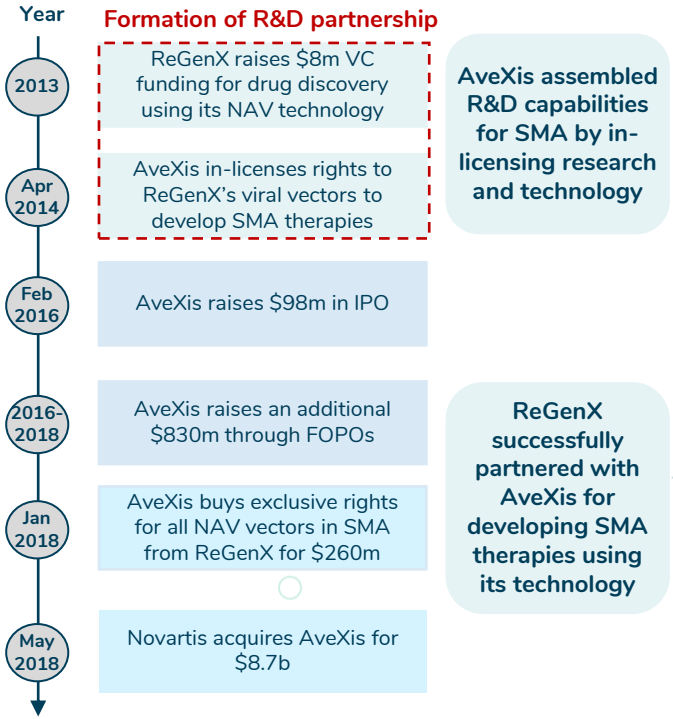
Note: *Survival motor neuron 1; ^FDA approval dates

Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Zolgensma's R&D infrastructure was assembled from ReGenX's technology, AveXis's executive team and Nationwide Children Hospital's research

Zolgensma – Key strategic events



AveXis assembled R&D capabilities for SMA by in-licensing research and technology

- AveXis was founded in 2012 after the restructuring of a biotech company that provides cryogenic storage of stem cells, with a focus on development therapies in rare diseases
- With SMA as one of its first therapeutic focuses, AveXis assembled the R&D infrastructure required from in-licensing research outcomes from the Nationwide Children's Hospital in 2013 and rights to ReGenX's viral vectors in 2014

ReGenX successfully partnered with AveXis for developing SMA therapies using its technology

- ReGenX, a gene therapy biotech company, had developed its NAV viral vector technology platform and was actively seeking drug discovery partners to share both cost and risk of development
  - it had achieved early success through partnerships with other biopharma for rare diseases (e.g., haemophilia B, XLMTM* and Pompe disease)
- In 2014, ReGenX approached AveXis for partnership as SMA's genetic mutation was well understood and potentially could be solved through protein expression; the two parties successfully struck a deal for AveXis to use ReGenX's viral vectors to develop SMA therapies

"…We are pleased to be formally collaborating with AveXis which has assembled a world class team of scientific and clinical experts in SMA, led by Brian Kaspar, Ph.D. and his colleagues at Nationwide Children's Hospital…"
Ken Mills, CEO of ReGenX, 2014

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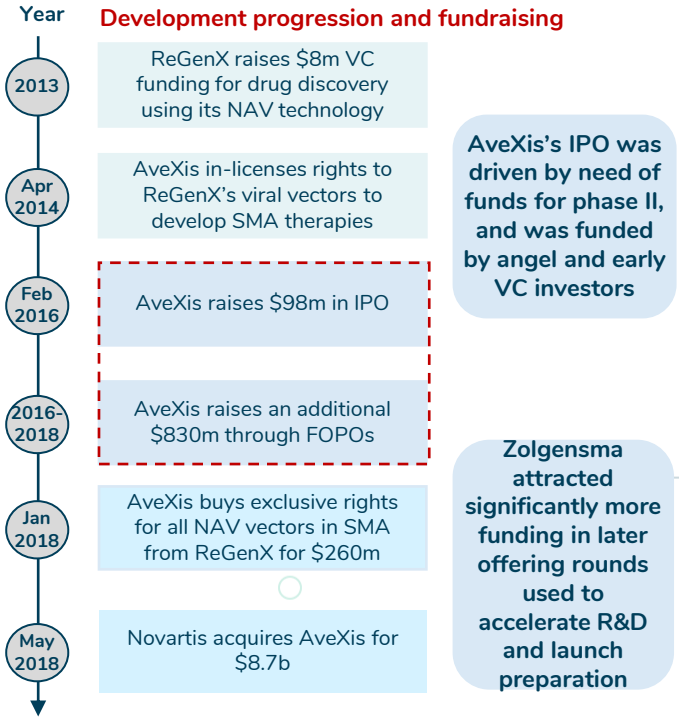
Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Zolgensma was funded by a series of public offerings which attracted a variety of investors as the asset progressed through development stages

Zolgensma – Key strategic events



AveXis's IPO was driven by need of funds for phase II, and was funded by angel and early VC investors

Zolgensma attracted significantly more funding in later offering rounds used to accelerate R&D and launch preparation

- Public sector funding (e.g., Nationwide Children's Hospital, National Institute of Neurological Disorder and Stroke) were important to Zolgensma at earlier stages but were starting to be insufficient at late phase I trials
- AveXis's IPO was driven by the need to fundraise for phase II trials and address questions around the therapy's long-term efficacy through these studies

  "…There was public funding but not enough – we had to IPO. We chose to do it around phase I to get more investor confidence by showing some preclinical development and preliminary phase I data …"
  Former VP Commerical Operations, AveXis

- After Zolgensma's positive phase I outcomes, subsequent offering rounds generated significantly more capital as investors gained confidence in Zolgensma's launch potential
  - institutional investors (e.g., VC / private equity) also played a role and they were confident in making bigger investments based on Zolgensma's development progression

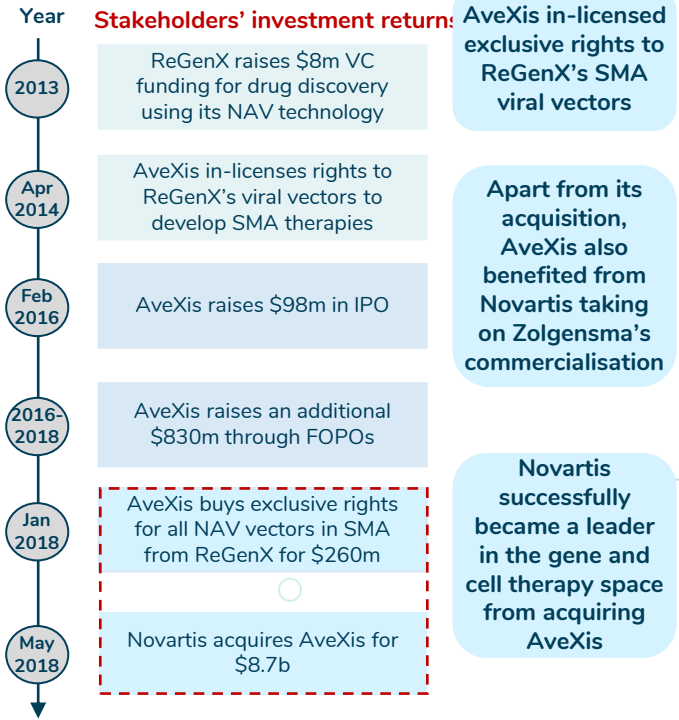
  "…In later rounds investors were more confident and made bigger investments. We also attracted more institutional investors such as RA Capital…"
  Former VP Commercial Operations, AveXis

- Zolgensma allocated capital towards accelerating manufacturing scale-up, R&D progression and to set up commercialisation infrastructure; AveXis was under time pressure to launch the therapy in light of competitors Biogen's Spinraza and Roche's Enrysdi

Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Novartis helped Zolgensma's commercialisation in the competitive SMA space and gained leadership status in gene and cell therapy

Zolgensma – Key strategic events



- ReGenX successfully out-licensed rights to its NAV vectors in SMA to AveXis in a $260m deal
  - it has so far received c.$140m in direct payments and c.$84m in milestones and this remains one of ReGenX's most successful licensing deals thus far
- Apart from being acquired by Novartis at a significant valuation, AveXis also benefited from the merger from Novartis's commercialisation capabilities which has benefited Zolgensma's revenue outcome
  - Novartis is one of the therapeutic leaders in neurology and invested significantly in commercialisation and market access of Zolgensma

"...Novartis is big in neuroscience and it was good for Zolgensma to stand on the giant's shoulders, especially given how competitive the SMA space is, and with competition from Biogen and Roche..."
Former VP Commercial Operations, AveXis

- Novartis had little expertise in the cell and gene therapy space before acquiring AveXis, but this acquisition has led to Novartis becoming one of the leaders in this therapeutic space by acquiring both the company's experts and pipeline assets
  - AveXis has been restructured to become Novartis Gene Therapies which is the leading unit for gene and cell therapy in the organisation
- Apart from Zolgensma, Novartis also acquired other pipeline assets for treating Rett Syndrome and amyotrophic lateral sclerosis from AveXis

"...The acquisition also made a lot of sense to Novartis. They acquired the relevant expertise alongside several pipeline programs and became a leader in the space..."
Former VP Commercial Operations, AveXis

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Source: Biomedtracker; Company press release; Cortellis; Cystic Fibrosis Foundation; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Darzalex is the first-in-class anti-CD38 biologic, first approved in the treatment of refractory multiple myeloma

Name (INN)	Darzalex (daratumumab) 
Owner	Janssen (Johnson and Johnson)
Origination	Small / medium biopharma
Route to market	Industry-industry collaboration, transactional (in-licensing)
Funding	Big pharma internal

	Preclinical development	Phase I	Phase II	Phase III	Commercialisation
Trial start year	2008	2011	2013	2014	2015
Owner	Genmab	Genmab / Janssen	Janssen		

Year — 2006 · 2008 · 2011 · Aug 2012 · May 2013 · Jul 2013 · Sep 2013 · Jun 2014 · Oct 2014 · Dec 2014 · Feb 2015 · Jul 2015 · Mar 2016 · Nov 2015 · Mar 2016 · May 2016 · Jun 2016 · Apr 2017

- Preclinical development studies begin
- First patent submission^
- Genmab announces preclinical development data; starts phase I trial
- Janssen in-licenses and enters co-development agreement with Genmab's Darzalex for $1.2bn
- U.S. orphan and breakthrough therapy designation
- EU orphan designation
- Phase II trial starts (SIRIUS)
- Phase III trial starts (POLLUX)
- Janssen in-licenses rights to develop five assets, including Darzalex using Halozyme Therapeutics' Enhanze platform
- Phase III trial starts (CASTOR)
- Phase III trial starts (ALCYONE)
- Phase II results announced
- EMA application
- FDA application
- FDA approval
- EMA conditional marketing approval
- EMA approval
- Phase III (POLLUX) data announced
- Phase III (CASTOR) data announced

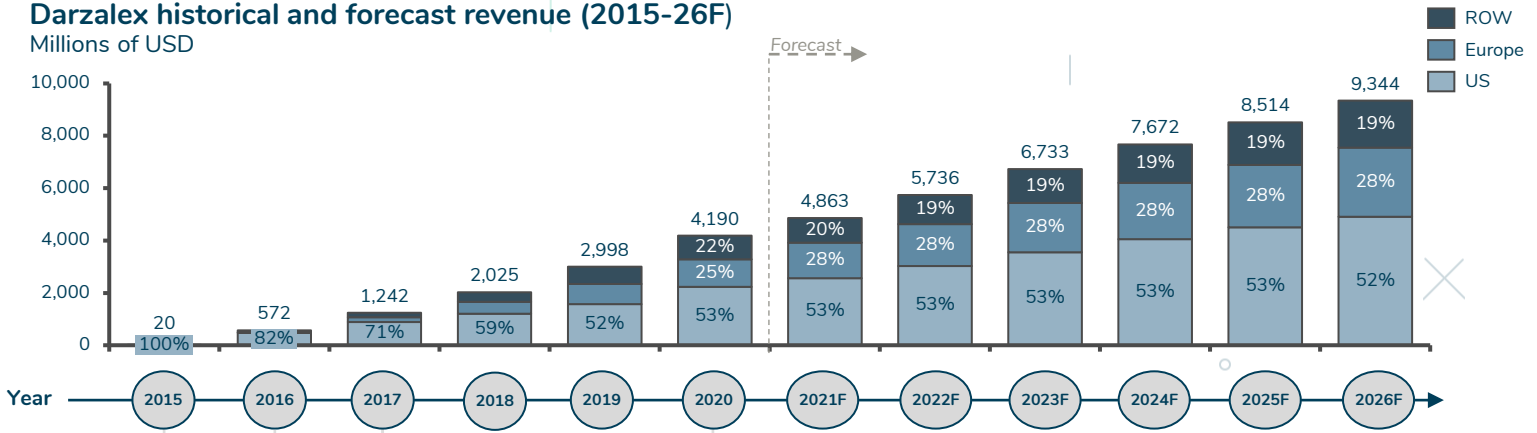
Transactions and agreements
Development milestones
Approval / designations

Note: ^US7828673B2; *Janssen to fully fund Genmab to finish phase I/II trials fully funded by Janssen and Janssen to take over subsequent development
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Darzalex is expected to achieve $9.3b sales worldwide by 2026, driven by launch of a SubQ formulation and possible additional indications

Darzalex historical and forecast revenue (2015-26F)

Millions of USD



FDA approval

EMA approval

SubQ phase III trial (COLUMBA) initiated

Janssen enters collaboration trials with Genentech, Amgen and BMS for combination therapy in multiple cancer indications*

Darzalex Faspro - SubQ formulation approved

Halozyme received $45m in milestone payments for subQ launch

Year	Indication approved^
2016	Monotherapy for double refractory multiple myeloma
2017	Combination with dexamethasone and lenalidomide or bortezomib
2018	Combination with pomalidomide and dexamethasone

Transactions and agreements

Development milestones

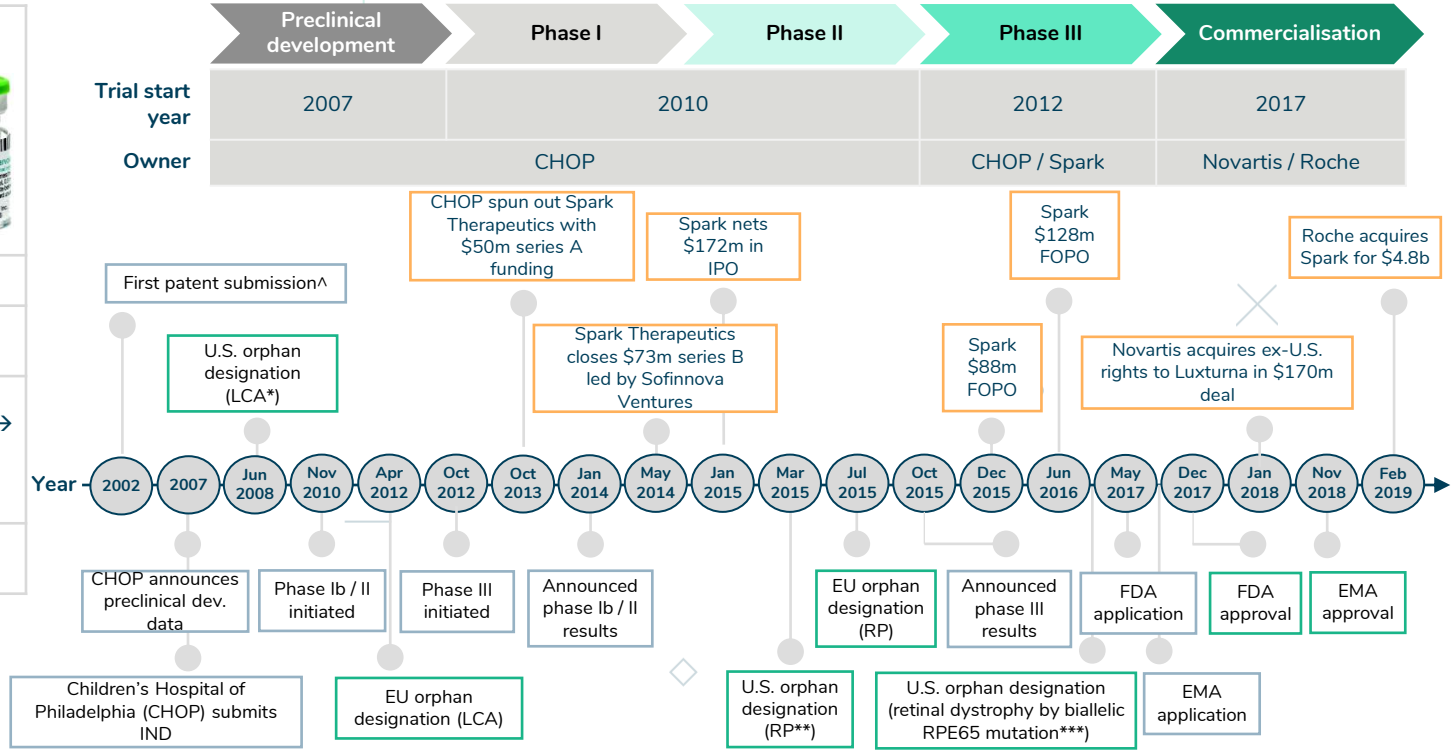
Approval / designations

Note: *Janssen / Genentech for daratumumab / atezolizumab combo therapy in myeloma and solid tumours, Janssen / Amgen for daratumumab / carfilzomib / dexamethasone combo therapy in myeloma, Janssen / BMS for daratumumab / nivolumab combo therapy in blood and solid tumours; ^FDA approval dates

Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Luxturna is the first one-time gene therapy for patients with vision loss associated with a confirmed biallelic RPE65 mutation

Name (INN)	Luxturna (voretigene neparvovec) 
Owner	Roche
Origination	PRG / NGO / Academic spinout
Routes to market	Small / medium biopharma go it alone → Transactional (in-licensing, company M&A)
Funding	VC ; IPO ; Big pharma internal



Transactions and agreements

Development milestones

Approval / designations

Note: ^WO2002082904A2; *Leber's congenital amaurosis; **Retinitis pigmentosa; ***Adeno-associated viral vector type 2 expressing human recombinant retinal pigment epithelial 65KDa protein gene for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations

Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

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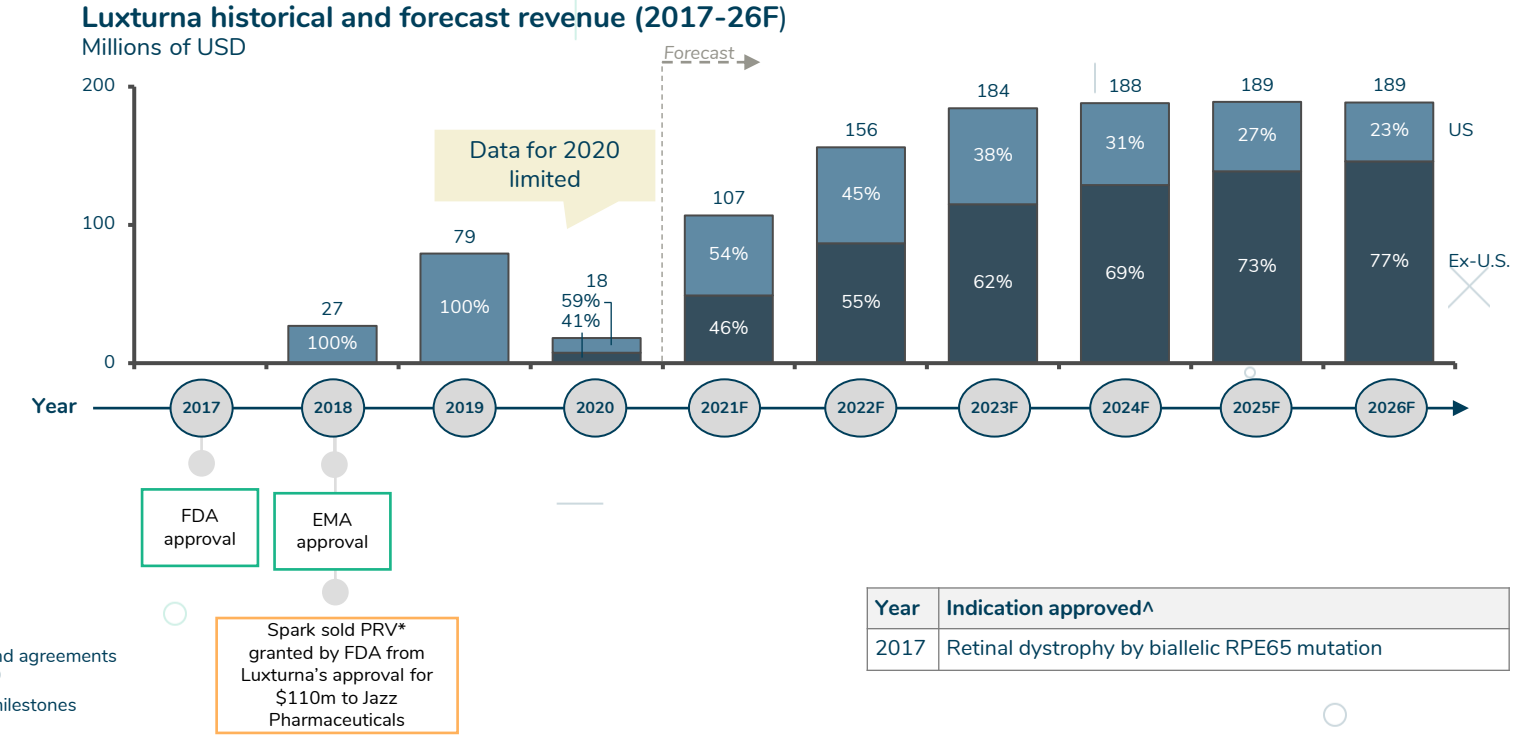
Luxturna is expected to reach $189m global sales in 2026; Spark sold PRV* from Luxturna's approval for $110m to fund pipeline research



Year	Indication approved^
2017	Retinal dystrophy by biallelic RPE65 mutation

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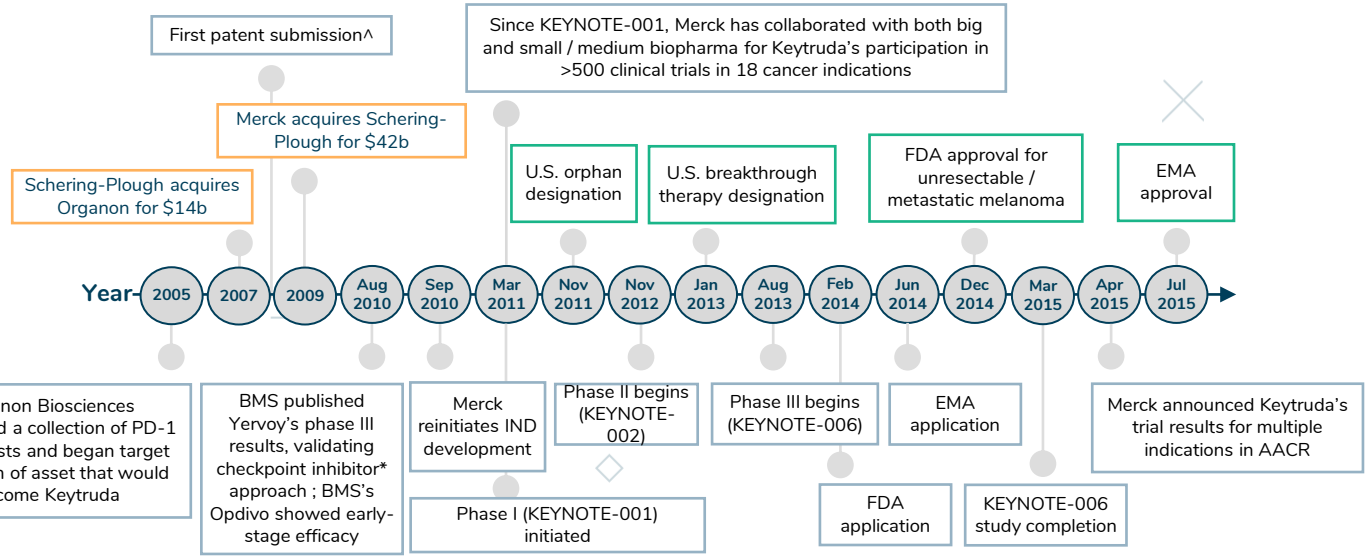
Notes: * Priority Review Voucher; ^FDA approval dates
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Keytruda is an anti-PD1 immunotherapy first approved for treating melanoma; it has since been approved in numerous other indications

Name (INN)	Keytruda (pembrolizumab) 
Owner	Merck & Co.
Origination	Small medium biotech
Routes to market	Transactional (Company M&A) → Big pharma in-house
Funding	Big pharma internal

	Preclinical development	Phase I	Phase II	Phase III	Commercialisation
Trial start	2010	2011	2012	2013	2014
Owner	Organon / Merck & Co.	Merck & Co.			



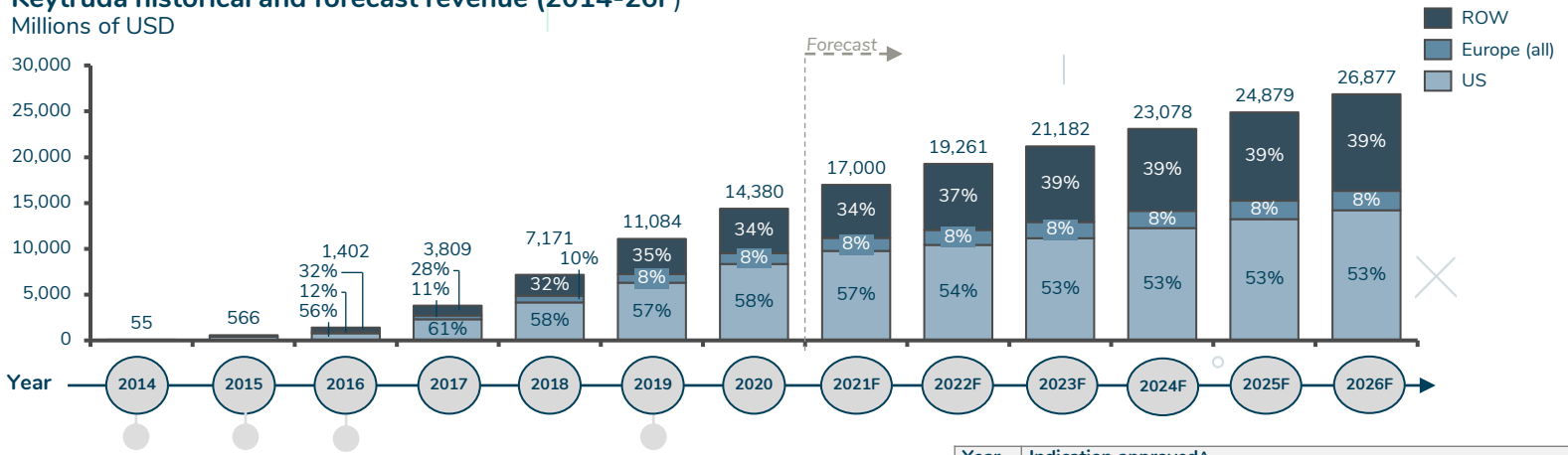
- Transactions and agreements
- Development milestones
- Approval / designations

Notes: ^US8354509B2; *Yervoy, a CTLA-4 inhibitor, was the first checkpoint inhibitor approved for cancer treatment. Checkpoint inhibitors counteract immune-cell disempowerment by inhibiting the same checkpoints also used in programmed death (PD-1) inhibitors, such as Keytruda and Opdivo

Source: Alexander (2016); Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Keytruda sales is expected to increase to $26.9b in 2026; LifeArc has twice divested portions of Keytruda's royalty for a total of $1.5b

Keytruda historical and forecast revenue (2014-26F)
Millions of USD



FDA 1st approval

EMA 1st approval

DRI Capital acquires LifeArc*'s royalty on Keytruda for $150m

CPPIB** acquires LifeArc's royalty on Keytruda for $1.3b

- CPPIB views investing in Keytruda as a means to provide stable, long-term cash flow into the fund
- This transaction also made LifeArc one of UK's leading medical research not-for-profits by size of investment assets

Year	Indication approved^
2014	Melanoma
2015	NSCLC
2016	Head and neck
2017	Hodgkin lymphoma, colorectal, bladder / urothelial, gastric
2018	B-cell diffuse lymphoma, cervical, liver, Merkel cell carcinoma
2019	MSI-H^^, renal, oesophageal, endometrial
2020	TMB-H^^^, cutaneous squamous cell, triple negative breast cancer

Transactions and agreements

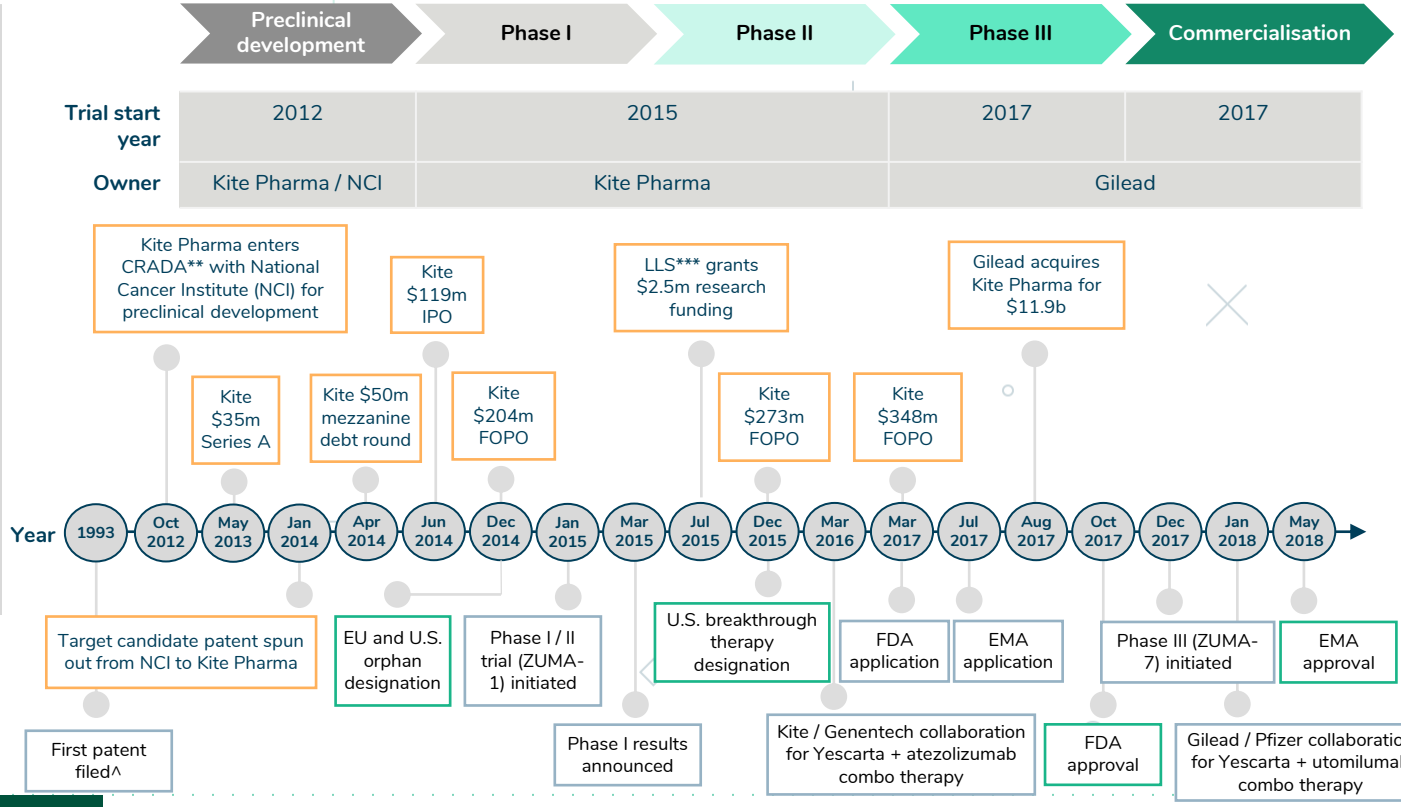
Development milestones

Approval / designations

Note: *Formerly known as MRC Technology, LifeArc receives royalties on Keytruda sales because it contributed to the humanisation of the antibody pembrolizumab in 2007; **Canadian Pension Plan Investment Board; ^FDA approval dates; ^^Microsatellite instability-high; ^^^Tumour mutational burden-high;
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Yescarta is a CD-19* directed, chimeric antigen receptor T-cell (CAR-T) therapy approved for refractory non-Hodgkin's Lymphoma

Name (INN)	Yescarta (axicabtagene ciloleucel) 
Owner	Gilead
Origination	PRG / NGO / Academic spinout
Routes to market	Small medium biopharma go it alone → Transactional (Company M&A)
Source of funding	VC ; IPO ; Big pharma internal

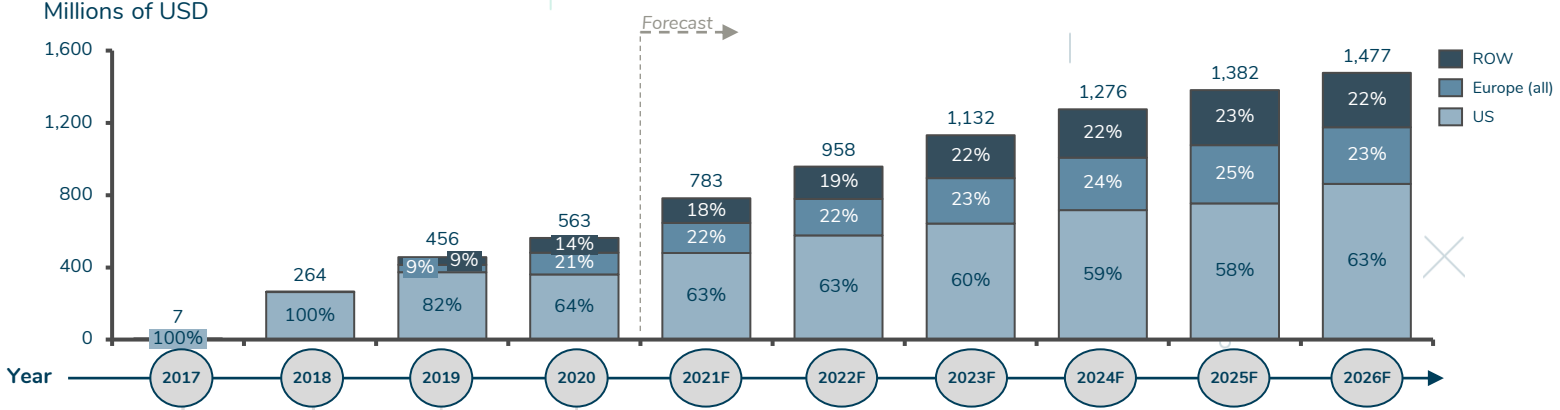


Note: ^US7741465B1; *Custer of Differentiation 19, biomarker for B lymphocytes; **Cooperative research and development agreement, ***Leukaemia and Lymphoma society
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Yescarta is forecast to reach $1.5b sales in 2026; Gilead has partnered with Genentech, Pfizer and Kiniksa Pharma for combo therapies

Yescarta historical and forecast revenue (2017-26F)

Millions of USD



FDA Approval

EMA Approval

Phase III (ZUMA-7) initiated

Gilead / Kiniksa Pharma collaboration for Yescarta + mavrilimumab combo therapy

Gilead / Pfizer collaboration for Yescarta + utomilumab combo therapy

Gilead announced Phase III (ZUMA-11) preliminary results

Year	Indication approved^
2017	Refractory non-Hodgkin Lymphoma - diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Transactions and agreements

Development milestones

Approval / designations

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Note: ^FDA approval dates

Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

The Galapagos case study shows how failures in R&D can occur, even at late-clinical stages when PoS is relatively high resulting in substantial losses

Case study	Development	Archetype
Galapagos Pharma	Galapagos had strong revenue growth due to upfront payments after signing two major contracts with Gilead, but three of its key pipeline assets have either failed in late-stage clinical trials or to get FDA approval in 2020-21	*In-licensing* *Industry-industry collaboration*

Summary

- The Galapagos case study shows how three of its assets have experienced undesirable R&D outcomes, either through trial termination or inability to obtain approval in key geographies

Development progression

- GLPG-1972, developed for the treatment of osteoarthritis, failed at phase II trial due to failure to meet trial endpoints
- GLPG-1690, developed for the treatment of idiopathic pulmonary fibrosis, failed at phase III due to dissatisfactory safety-risk profile
- Filgotinib, developed for the treatment of rheumatoid arthritis, obtained approval in EU and Japan but not in U.S., due to concerns over testicular toxicity

Stakeholder returns

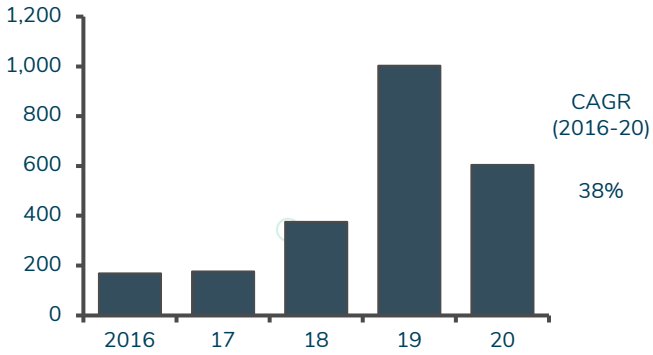
- Return on R&D investments can be negative for stakeholders when R&D failure or failure to launch in key geographies occurs; these events are more common in preclinical development stages but can also happen to late-stage assets with larger sunk costs
- Galapagos, Gilead and likely other licensing partners involved in developing these three assets suffered losses; there may be ways to repurpose these therapies for other diseases to recoup losses, but this has not yet happened

Source: L.E.K. interviews, research and analysis

Galapagos has historically relied on public offerings as its source of capital; revenue has increased in recent years from major contracts with Gilead

Company	Galápagos
Description	Specialty pharma focused on discovery and development of small molecules with novel modes of action
Founded	1999
HQ	Mechelen, Belgium
Revenue (2020)	$606m

Galapagos Pharma – Historical revenue (2016-20)
Millions of USD



Major investments*	Year	Major corporate events
	1999	Galapagos was founded as a joint venture between two biopharma companies, Crucell (now Janssen Vaccines) and Tibotec
Galapagos raises $22m through private funding	2002	
Galapagos raises $28m through public offering in Amsterdam and Brussels stock exchange	2005	
GSK invests $6m equity in Galapagos	2007	
Follow-on public offering rounds see Galapagos raise an additional total of $192m	2006-2013	Galapagos divests CRO** business units BioFocus and Argenta to Charles River Laboratories for $84m
	2014	Galapagos signs filgotinib in-licensing deal with Gilead for $725m
Galapagos raises $310 through U.S. public offering	2015	
	2019	Galapagos signs 10-year R&D agreement with Gilead for $5.1bn
	2020	Galapagos divests CRO business unit Fidelta to Selvita for $36m

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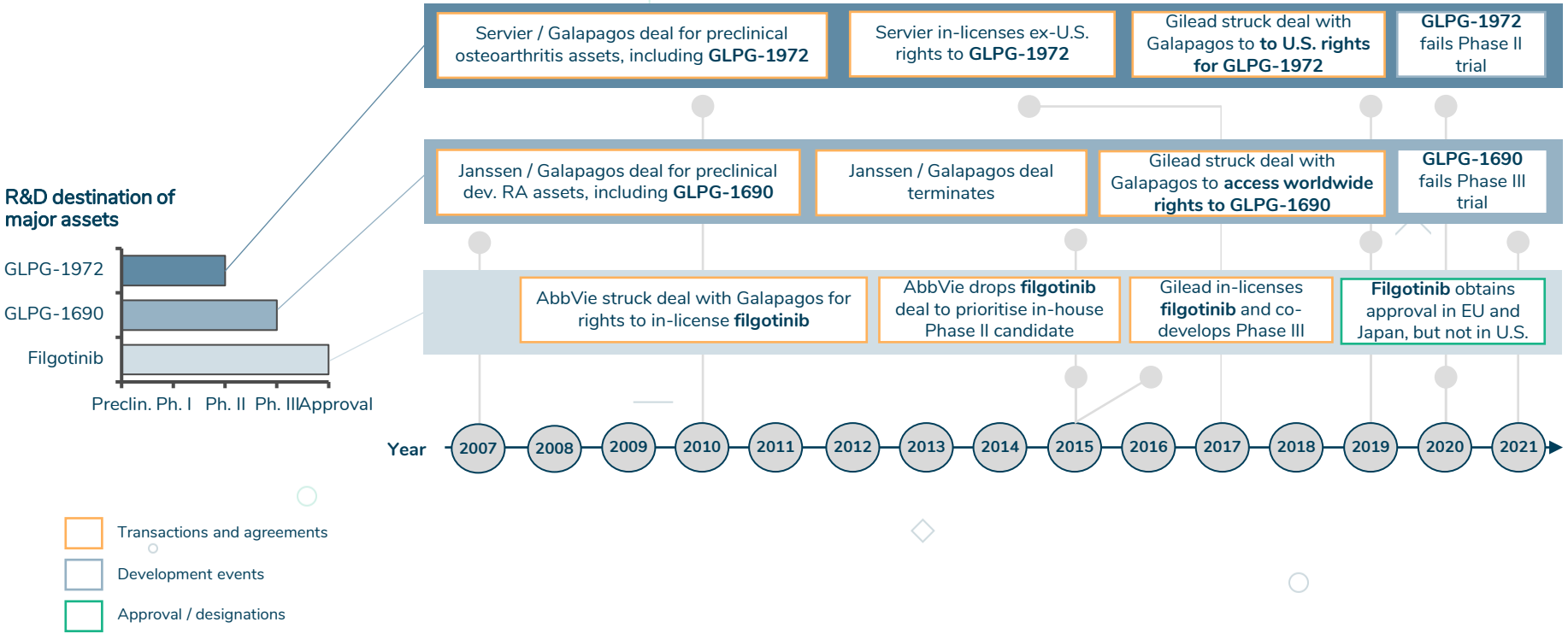
Note: *Investments through public offerings raises capital but do not contribute to the company's revenue; **Contract research organisation
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Galapagos Pharma experienced dissatisfactory late-stage trial outcomes for three assets, resulting in R&D termination / inability to obtain FDA approval



Note: *Rheumatoid arthritis; **Pharmaceuticals and Medical Devices Agency
Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

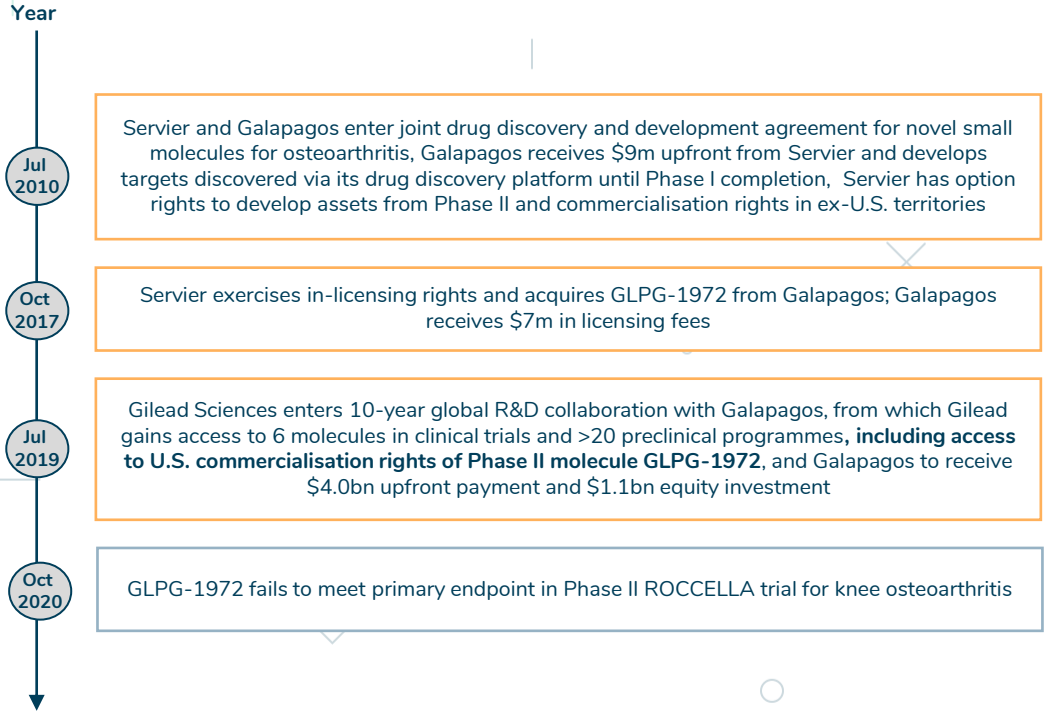
Despite R&D partnerships with Servier and Gilead Sciences, Galapagos was not able to bring GLPG-1972 to market as it failed phase II trials

Name (INN)	GLPG-1972/201086 (Aldumastat)
Mechanism of action	Oral metalloproteinase inhibitor
Target disease	Osteoarthritis
Status	Discontinued (Phase II)
Current Owner	Galapagos (U.S.), Servier (ex-U.S.)
R&D funders	Servier, Galapagos, Gilead
Origination	Galapagos Pharma
Route to market	Transactional (In-licensing)

Transactions and agreements

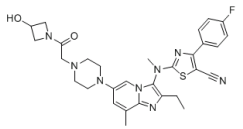
Development events

Approval / designations



Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Galapagos was also unable to bring GLPG-1690 to market based on phase III outcomes, despite investment from Janssen and Gilead

Name (INN)	GLPG-1690 (Ziritaxestat) 
Mechanism of action	Oral cyclooxygenase inhibitor
Target disease	Idiopathic pulmonary fibrosis
Status	Discontinued (Phase III)
Current Owner	Galapagos
R&D funders	Janssen, Galapagos, Gilead
Origination	Galapagos Pharma
Route to market	Transactional (In-licensing)

Transactions and agreements

Development events

Approval / designations

Year

Oct 2007 — Janssen enters research alliance agreement with Galapagos for obtaining future option rights to exclusively license up to 12 small molecule programs from internally identified targets for the treatment of rheumatoid arthritis, and Galapagos to receive upfront payment of $21m

Mar 2015 — Janssen contract agreement terminated and Galapagos regains rights to three clinical trial molecules including Phase II molecule GLPG-1690

Jul 2019 — Gilead Sciences enters 10-year global R&D collaboration with Galapagos, from which Gilead gains access to 6 molecules in clinical trials and >20 preclinical programmes**, including Phase III molecule GLPG-1690**, and Galapagos to receive $4.0bn upfront payment and $1.1bn equity investment

Feb 2021 — Galapagos and Gilead discontinued GLPG-1690's ISABELA phase III trial in IPF due to dissatisfactory benefit-risk profile, based on recommendations from IDMC*

Note: *Independent Data Monitoring Committee

Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Gilead invested $725m in filgotinib, but its sales potential is likely to be limited as it was not able to obtain FDA approval

Name (INN)	Jyseleca (filgotinib) 
Mechanism of action	Oral JAK inhibitor
Indication	Rheumatoid arthritis
Status	Launched (EU and Japan) FDA approval rejected (U.S.)
Current Owner	Galapagos (U.S. and Europe), Gilead (ROW) Eisai (Japan)
R&D funders	Galapagos, Abbvie, Gilead
Origination	Galapagos Pharma
Route to market	Transactional (In-licensing)

Transactions and agreements

Development events

Approval / designations

Year

- **Feb 2012** — AbbVie and Galapagos struck deal to develop and commercialise filgotinib, with AbbVie paying $150m upfront and gains exclusive rights to in-license program for $200m after Phase II completion, and take over Phase III development and commercialisation rights
- **Aug 2015** — AbbVie declines to license filgotinib after Phase II trial completion as it decided to advance its in-house JAK inhibitor, ABT-494 to Phase III in RA; all rights to filgotinib reverted back to Galapagos
- **Dec 2015** — Galapagos and Gilead enter partnership to codevelop filgotinib from Phase III onwards and Galapagos to receive $300m licensing fee and $425m equity investments upfront
- **Oct 2020** — Filgotinib is approved by EMA and PMDA* for the treatment of rheumatoid arthritis in adults who have responded inadequately or are intolerant to one or more DMARDs
- **Oct 2020** — Following filgotinib's NDA submission, FDA requested data from Phase III trials and expressed concerns regarding the drug's safety profile, particularly around testicular toxicity; Gilead decides not to pursue FDA approval of filgotinib for RA
- **Jan 2021** — Gilead and Galapagos amends agreement on filgotinib, with Galapagos to resume all rights and costs on development, manufacturing and commercialisation rights in Europe, and Gilead to maintain ROW rights, and own co-commercialisation rights in Japan with Eisai

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Source: Biomedtracker; Company press release; Cortellis; EMA; FDA; PharmaProjects; L.E.K. research and analysis

The aripiprazole case study shows the drug discovery and commercialization in a competitive space of a NME, and strategies to maximise revenue

Case study	Development	Archetype
Aripripazole	Discovered by Otsuka Pharma in 1992, the first aripiprazole therapy Abilify was launched in 2002 and maintained commercial success through indication expansion and reformulation; generics were introduced in 2015, some of which have improved dosing schedules	*Small biopharma go-it-alone* *In-licensing* *Generic entry* *Life cycle management*

Summary

- The aripiprazole case study shows how a new molecular entity (NME) is discovered and commercialised, and shows life cycle management strategies by the originator company to defend itself against generic entry

Development progression

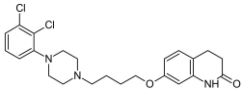
- Aripiprazole was discovered by Otsuka Pharma, a Japanese biopharma company, who partnered with Bristol Myers-Squibb to launch its first product Abilify globally
- Otsuka expanded Abilify's indication in neurology multiple times, and reformulated Abilify as a long-acting injectable (Abilify Maintena), to capture maximum revenue
- Alternative aripiprazole-based drugs, such as Aristada, an injectable with longer inter-dose duration, were launched

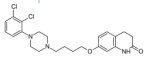
Stakeholder returns

- Abilify's life cycle management strategies enabled it to achieve a peak sales of $6.2bn in 2013
- Generic entry 2015 lowered Abilify's revenue since 2015, which is partially offset by Abilify Maintena as it is projected to achieve >$1bn peak sales in 2023

Source: L.E.K. interviews, research and analysis

Aripiprazole is a non-innovative oral atypical antipsychotic used to treat schizophrenia and bipolar disorder, which entered a competitive market

Name	Aripiprazole 
Branded products	• Abilify • Abilify Mycite • Abilify Maintena • Aristada • Aristada Initio
Originator	Otsuka Pharma
Origination	Small / medium biopharma
Route to market	Transactional (in-licensing)
Funding	Big pharma internal

	Abilify	Abilify Mycite	Abilify Maintena	Aripiprazole generics (various)	Aristada	Aristada Initio
						
INN (ROA)	Aripiprazole (oral)	Aripiprazole (oral)	Aripiprazole (intramuscular)	Aripiprazole (oral)	Aripiprazole lauroxil (intramuscular)	Aripiprazole lauroxil (intramuscular)
Description	First aripiprazole product	Aripiprazole with digital IEM* sensor for dose tracking	Once-a-month long acting injectable	Oral aripiprazole generics	Prodrug of aripiprazole with longer coverage duration, given once every 6-8 weeks	One-time dose that reduces oral aripiprazole supplement-ation to 1 day when starting Aristada treatment
Owner	Otsuka Pharma, Bristol Myers-Squibb			Hetero Labs, Teva, Alembic Pharma, Torrent Pharma**	Alkermes Pharma	
Launch Year	2002	2012	2013	2015	2015	2018
Available geography	Worldwide	U.S.	Worldwide	Worldwide	Worldwide	U.S.

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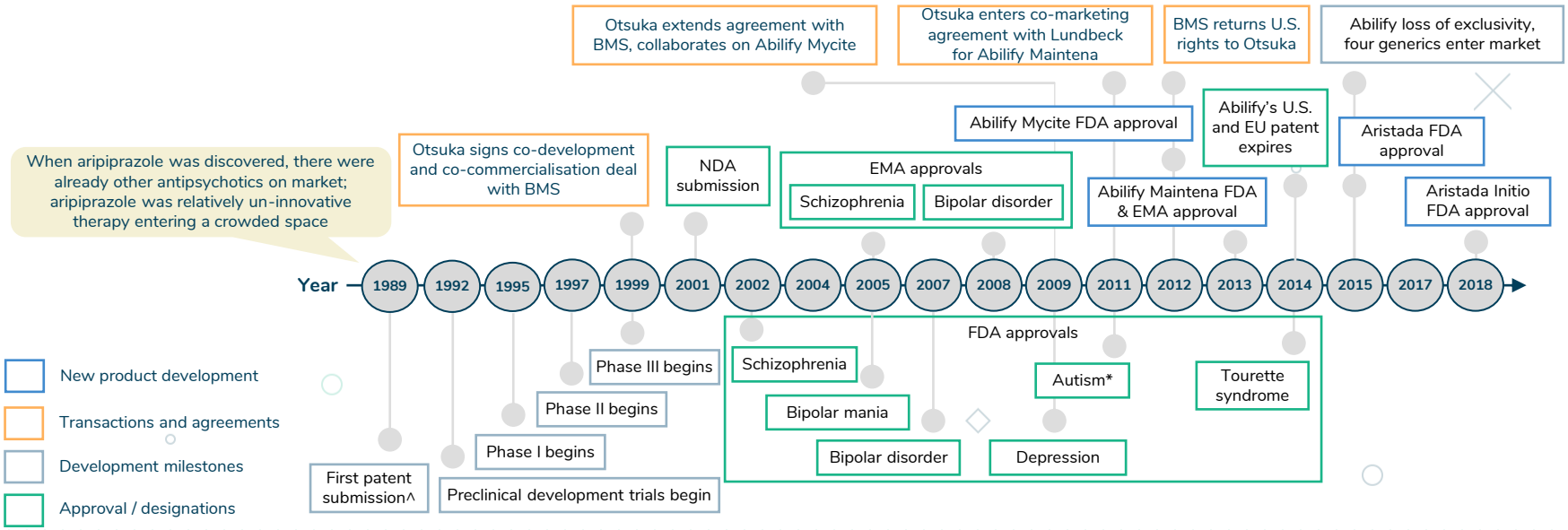
Note: *Ingestible Event Tracker; **Non-exhaustive
Source: Biomedtracker; Clinicaltrials.gov; Company press release; EMA; Evaluate Pharma; FDA; PharmaProjects; L.E.K. research and analysis

Aripiprazole was discovered by Otsuka who entered a co-development agreement with BMS to launch Abilify, the first aripiprazole drug

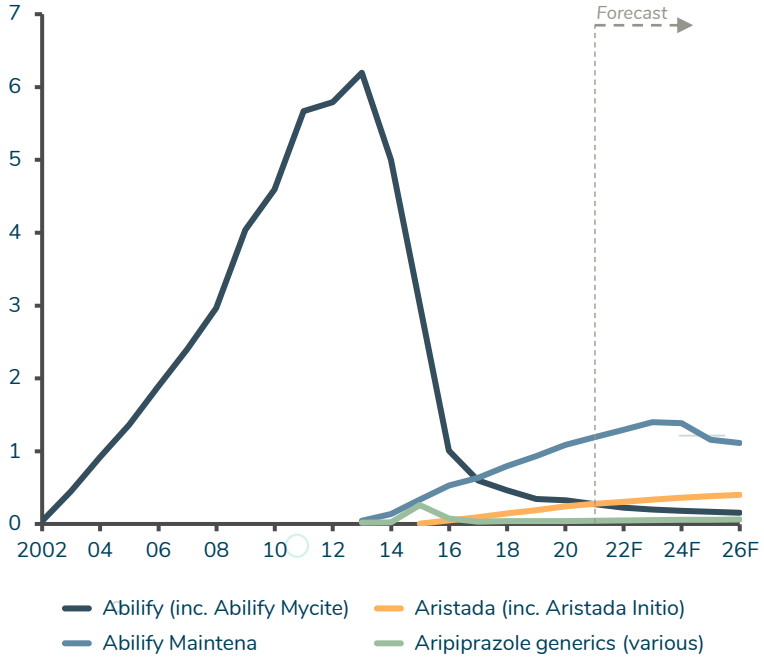
R&D timeline (first product)	Preclinical dev.	Phase I	Phase II	Phase III	Commerciali -sation	Reformulation launch	Loss of exclusivity
Start year	1992	1995	1997	1999	2002	2009, 2012	2015
Owner(s)	Otsuka Pharma			Otsuka Pharma + Bristol Myers Squibb			



Notes: ^US5006528A; *Treats irritability associated with autism
Source: Biomedtracker; Clinicaltrials.gov; Company press release; EMA; FDA; PharmaProjects; L.E.K. research and analysis

Abilify achieved peak sales of $6.2bn in 2013; revenue has significantly declined due to generic entry, but was partially offset by Abilify Maintena

Global revenue of aripiprazole products (2012-26F)
Billions of USD



- Since its launch in 2002, Abilify has successfully expanded its treatment indications to achieve peak sales of $6.2bn in 2013
- Anticipating Abilify's U.S. and EU patent expiry in 2014, Abilify launched the Abilify Maintena, a once-monthly injectable; which was shown to achieve higher patient compliance rates compared to daily oral treatments and is projected to achieve peak sales of $1.4bn in 2023
- Abilify's revenue has significantly declined since 2015 due to its loss of exclusivity, after which at least four generics were launched
- Despite Aristada's superior dosing frequency compared to Abilify, it achieved relatively lower global sales (projected $0.4bn in 2025) due to three factors
  - Abilify Maintena was launched two years before Aristada and had secured most of its target patient population
  - Abilify Maintena benefited from Abilify's brand reputation
  - Abilify Maintena is available in U.S. and EU, while Aristada was only approved in the U.S.

SiRM. Strategies in Regulated Markets

L.E.K.

Note: *Treats irritability associated with autism
Source: Biomedtracker; Clinicaltrials.gov; Company press release; EMA; FDA; PharmaProjects; Yan et al., 2018; L.E.K. research and analysis

Appendix

The following methodology has been used to calculate the drug-type specific R&D costs, PoS, and phase duration (1/2)

Overall methodology

$$\text{Base-case assumption} = \left(\frac{\text{\# of small molecule assets in published literature}}{\text{\# of total assets in published literature}} \times \text{L.E.K. eNPV small molecule assumption}\right) + \left(\frac{\text{\# of large molecule assets in published literature}}{\text{\# of total assets in published literature}} \times \text{L.E.K. eNPV large molecule assumption}\right)$$

Process

1. Calculate ratio between large and small molecule assumptions from literature

$$\text{Ratio} = \frac{\text{Large molecule assumption in published literature}}{\text{Small molecule assumption in published literature}}$$

2. Use ratio to solve for L.E.K.'s small molecule assumption

$$\text{Base-case assumption} = \left(\frac{\text{\# of small molecule assets in literature}}{\text{\# of total assets in literature}} \times \text{L.E.K. eNPV small molecule assumption}\right) + \left(\frac{\text{\# of large molecule assets in literature}}{\text{\# of total assets in literature}} \times \text{L.E.K. eNPV small molecule assumption} \times \text{Ratio}\right)$$

3. Use L.E.K.'s small molecule assumption to solve for L.E.K.'s large molecule assumption

$$\text{L.E.K. eNPV large molecule assumption} = \text{L.E.K. eNPV small molecule assumption x ratio}$$

The following methodology has been used to calculate the drug-type specific R&D costs, PoS, and phase duration (2/2)

Example calculation – R&D cost, Phase I

1. Calculate ratio between large and small molecule assumptions from literature

$$\text{Ratio} = \frac{24}{26}$$

2. Use ratio to solve for L.E.K.'s small molecule assumption

$$\$30\text{m} = \left(\frac{87}{106} \times \text{L.E.K. eNPV small molecule Ph I cost assumption}\right) + \left(\frac{19}{106} \times \text{L.E.K. eNPV small molecule Ph I cost assumption} \times \frac{24}{26}\right)$$

$$\text{L.E.K. eNPV small molecule Ph I cost assumption} = \$30.4\text{m} = \$30\text{m (rounded)}$$

3. Use L.E.K.'s small molecule assumption to solve for L.E.K.'s large molecule assumption

$$\text{L.E.K. eNPV large molecule Ph I cost assumption} = \$30.4\text{m} \times \frac{24}{26} = \$28\text{m (rounded)}$$

Data from study

Number of small molecules	87
Number of large molecules	19
Small molecule cost	$26m
Large molecule cost	$24m

Disclaimer

Standard Disclaimer (1 of 2)

NON-DISCLOSURE RULES AND LIABILITY DISCLAIMER

To: The Ministry of Health, Welfare and Sport, Parnassusplein 5, 2511 VX The Hague, Netherlands (the “Client")

Project Study into financial ecosystem of medicine development: L.E.K. Draft Report dated 5th November (the "Draft Report")

1. **Introduction**

1.1 This Draft Report has been prepared by L.E.K. Consulting LLP ("L.E.K." or "we") at the request of the Client which is contemplating [description of work carried out] (the "Project").

1.2 This Draft Report is for the sole benefit and use of the Client. This Draft Report has been prepared to address the interests and priorities of the Client and not the interest or priorities of any third party.

1.3 This Draft Report must be construed in the context in which it was prepared including the constraints relating to availability of time and information, the quality of that information, the instructions agreed with the Client and our assumptions and qualifications, in each case, as more fully set out in this Draft Report.

2. **Disclosure**

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3.4 This Draft Report shall be governed by the laws of England.

REPORT CONTEXT

Attention: The following points of context are directed at third parties receiving this Draft Report with, or without, our permission.

1. Our principal task has been to analyse and present data on **financial ecosystem of medicine development**. This Draft Report is intended to assist the Client in understanding and evaluating those issues.
2. This Draft Report is not intended as a recommendation to proceed or not to proceed with the Project which decision requires consideration of a broader range of issues and is a commercial decision for the Client and the other Project participants to make entirely at their own risk.
3. This Draft Report has been prepared from and includes information received from the Client, and other publicly available information sources. The provenance, authenticity, completeness and accuracy of this information may not have been verified. We did not complete such verification and cannot confirm that such verification has been completed by a third party before L.E.K. received this information. L.E.K. makes no representation and gives no warranty, in either case express or implied, as to the provenance, authenticity, accuracy or completeness of such information.
4. This Draft Report has been prepared under time constraints and is not exhaustive or based on all available information relating to its subject matter. This Draft Report does not reveal the matters which would have been identified by unrestricted investigation and research.
5. The interests and priorities of persons other than the Client are not known to us and have not been considered in the preparation of this Draft Report. Consequently, if you are not the Client, the issues addressed in this Draft Report and the emphasis given to them may not fully or adequately address the issues of interest or relevance to you and your role in the Project.
6. Save for reliance on such matters by the Client as permitted under the letter of engagement, L.E.K. makes no representation and gives no warranty, guarantee or other assurance that all or any of the assumptions, estimates, projections or forecasts set out in this Draft Report are accurate, reasonable or will materialise or be realised and nothing contained in this Draft Report is or should be construed or relied upon as a promise as to the future.
7. This Draft Report is based on the information of which we were aware at the time this Draft Report was prepared. The occurrence of change after the date of issue of this Draft Report affecting this Draft Report is a risk accepted by all parties receiving this Draft Report. Unless otherwise agreed in writing with you, L.E.K. is not obliged to update this Draft Report after its date of issue for your benefit or obliged to advise you of the availability of information not previously available even where we learn of information which if known at the time of preparation of this Draft Report would have lead us to vary the content of this Draft Report.
8. Your reference to this Draft Report is not a substitute for the investigations you would ordinarily undertake or those investigations that you would be recommended to make given your involvement in or in connection with the Project.
9. Your acceptance of this Draft Report is in replacement of all Draft Reports you may have received from us in connection with Project Study into financial ecosystem of medicine development.