

Supplementary Online Content

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eTable 1. Characteristics of Therapeutic Agents Included in the Analysis

eTable 2. Quality Score of the Research and Development Estimate for Each Therapeutic Agent

eTable 3. Median Research and Development Outlays (2018 US \$, Millions) by Product Category, Without Adjustment for Costs of Failures

eTable 4. Research and Development Costs (2018 US \$, Millions), Broken Down by Phase of Clinical Development, for All Therapeutic Agents Included in the Analysis

eTable 5. Dates of Clinical Trial Phase Changes for All Therapeutic Agents Included in the Analysis

eTable 6. Estimated Research and Development Costs (2018 US \$, Millions) for All Therapeutic Agents Included in the Analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

Appendix 1: Breakdown of results for the 63 therapeutic agents included in the analysis.

eTable 1. Characteristics of Therapeutic Agents Included in the Analysis

Brand name	Generic name	Manufacturer ^a	Route ^b	Type	ATC ^c	FIC	OR	FT	BT	PR	AA
Adcetris	brentuximab vedotin	Seattle Genetics	injection	BLA	L	1	1	1		1	1
Alunbrig	brigatinib	Ariad Pharmaceuticals	oral	NDA	L		1		1	1	1
Aristada	aripiprazole lauroxil	Alkermes Inc.	injection	NDA	N						
Beleodaq	belinostat	Spectrum Pharmaceuticals	intravenous	NDA	L		1	1		1	1
Belviq	lorcaserin hydrochloride	Arena Pharmaceuticals Inc.	oral	NDA	A	1					
Brineura	cerliponase alfa	Biomarin Pharmaceuticals	injection	BLA	A	1	1		1	1	
Copiktra	duvelisib	Infinity Pharmaceuticals	oral	NDA	L		1	1		1	1
Crysvita	burosumab-twza	Ultragenyx Pharmaceuticals Inc.	injection	BLA	M	1	1	1	1	1	
Dificid	fidaxomicin	Optimer Pharmaceuticals Inc.	oral	NDA	A			1		1	
Dupilixent	dupilumab	Regeneron Pharmaceuticals	injection	BLA	D	1			1	1	
Elzonris	tagraxofusp-erzs	Stemline Therapeutics Inc.	injection	BLA	L	1	1		1	1	
Eucrisa	crisaborole	Anacor Pharmaceuticals Inc.	other	NDA	D						
Exondys 51	eteplirsen	Sarepta Therapeutics Inc.	intravenous	NDA	M	1	1	1		1	1
Eylea	aflibercept	Regeneron Pharmaceuticals	injection	BLA	S					1	
Fanapt	iloperidone	Vanda Pharmaceuticals, Inc.	oral	NDA	N						
Firdapse	amifampridine	Catalyst Pharms	oral	NDA	N		1		1	1	
Folotyng	pralatrexate	Allos Therapeutics Inc.	intravenous	NDA	L		1			1	1
Galafold	migalastat	Amicus Therapeutics US	oral	NDA	A	1	1	1		1	1
Gattex	teduglutide	NPS Pharms Inc.	injection	NDA	A	1	1				
Hetlioz	tasimelteon	Vanda Pharmaceuticals, Inc.	oral	NDA	N		1			1	
Iclusig	ponatinib	Ariad Pharmaceuticals	oral	NDA	L		1	1		1	1
Idhifa	enasidenib	Agios Pharms Inc.	oral	NDA	L	1	1	1		1	
Imbruvica	ibrutinib	Pharmacyclics Inc.	oral	NDA	L	1	1	1	1	1	1

Brand name	Generic name	Manufacturer ^a	Route ^b	Type	ATC ^c	FIC	OR	FT	BT	PR	AA
Ingrezza	valbenazine	Neurocrine Biosciences	oral	NDA	N			1	1	1	
Juxtapid	lomitapide	Aegerion Pharmaceuticals	oral	NDA	C	1	1				
Kalbitor	ecallantide	Dyax Corp	injection	BLA	B	1	1			1	
Kengreal	cangrelor	The Medicines Company	intravenous	NDA	B						
Kerydin	tavorole	Anacor Pharmaceuticals Inc.	other	NDA	D	1					
Kevzara	sarilumab	Regeneron Pharmaceuticals	injection	BLA	L						
Kybella	deoxycholic acid	Kythera Biopharms	injection	NDA	D						
Kyprolis	carfilzomib	Onyx Therapeutics	intravenous	NDA	L		1	1			1
Libtayo	cemiplimab-rwlc	Regeneron Pharmaceuticals	intravenous	BLA	L				1	1	
Linzess	linaclotide	Ironwood Pharmaceuticals	oral	NDA	A	1					
Mepsevii	vestronidase alfa-vjbjk	Ultragenyx Pharmaceuticals Inc.	injection	BLA	A	1	1	1		1	
Mytesi	crofelemer	Salix Pharmaceuticals Inc.	oral	NDA	A	1		1		1	
Northera	droxidopa	Chelsea Therapeutics	oral	NDA	C	1	1	1		1	1
Nuplazid	pimavanserin	Acadia Pharms Inc.	oral	NDA	N				1	1	
Nuzyra	omadacycline	Paratek Pharmaceuticals Inc.	other	NDA	J			1		1	
Ocaliva	obeticholic acid	Intercept Pharms Inc.	oral	NDA	A	1	1	1		1	1
Orbactiv	oritavancin	The Medicines Company	intravenous	NDA	J					1	
Palynziq	pegvaliase-pqpz	Biomarin Pharmaceuticals	injection	BLA	A	1	1	1		1	
Praluent	alirocumab	Regeneron Pharmaceuticals	injection	BLA	C	1					
Rapivab	peramivir	BioCryst Pharmaceuticals	intravenous	NDA	J			1			
Rhopressa	netarsudil	Aerie Pharmaceuticals, Inc.	other	NDA	S	1					
Rubraca	rucaparib	Clovis Oncology Inc.	oral	NDA	L		1		1	1	1
Strensiq	asfotase alfa	Alexion Pharmaceuticals	injection	BLA	A	1	1	1	1	1	
Talzenna	talazoparib	Biomarin Pharmaceuticals	oral	NDA	L					1	
Tegsedi	inotersen	Ionis Pharms Inc.	injection	NDA	N	1	1	1		1	
Tibsovo	ivosidenib	Agios Pharms Inc.	oral	NDA	L	1	1	1		1	

Brand name	Generic name	Manufacturer ^a	Route ^b	Type	ATC ^c	FIC	OR	FT	BT	PR	AA
Trulance	plecanatide	Synergy Pharmaceuticals	oral	NDA	A						
Tymlos	abaloparatide	Radius Health Inc.	injection	NDA	M						
Ultomiris	ravulizumab	Alexion Pharmaceuticals	injection	BLA	L		1				
Varubi	rolapitant	Tesaro Inc.	other	NDA	A						
Veltassa	patiromer for oral suspension	Relypsa Inc.	oral	NDA	V						
Viberzi	eluxadoline	Furiex Pharmaceuticals Inc.	oral	NDA	A			1		1	
Viibryd	vilazodone hydrochloride	Clinical Data Inc.	oral	NDA	N						
Vimizim	elosulfase alfa	Biomarin Pharmaceuticals	injection	BLA	A	1	1	1		1	
Vitrakvi	larotrectinib	Loxo Oncology Inc.	oral	NDA	L	1	1		1	1	1
Xerava	eravacycline	Tetraphase Pharms	intravenous	NDA	J			1		1	
Xtandi	enzalutamide	Medivation Inc.	oral	NDA	L			1		1	
Zaltrap	ziv-aflibercept	Regeneron Pharmaceuticals	injection	BLA	L					1	
Zejula	niraparib	Tesaro Inc.	oral	NDA	L		1	1	1	1	
Zerbaxa	ceftolozane/tazobactam	Cubist Pharmaceuticals LLC	intravenous	NDA	J			1		1	

Acronyms: AA, accelerated approval; ATC, anatomical therapeutic chemical (classification system); BLA, biologics license application; BT, break-through therapy; FIC, first in class; FT, fast track; NDA, new drug application; OR, orphan drug; PR, priority review.

^a This is the firm that reported research and development (R&D) expenses for the therapeutic agent in question in the US Securities and Exchange filings used to produce our estimates. In almost all cases, this was the manufacturer listed on the BLA or NDA approval issued by the Food and Drug Administration (FDA).

^b Injection included intramuscular and subcutaneous; other routes included multiple, ophthalmic, and topical.

^c The anatomical therapeutic chemical classification system codes correspond to “alimentary tract and metabolism” (A), “blood and blood forming organs” (B), “cardiovascular system” (C), “dermatologicals” (D), “anti-infectives for systemic use” (J), “antineoplastic and immune-modulating agents” (L), “musculo-skeletal system” (M), “nervous system” (N), “sensory organs” (S), and “various” (V).

eTable 2. Quality Score of the Research and Development Estimate for Each Therapeutic Agent

Brand name	R&D estimate quality	Comments
Adcetris	medium	There was a co-development and marketing deal with Millennium in 2009/2010 (approval in 2011). In 1998, they licensed in the product from Bristol-Myers Squibb.
Alunbrig	high	We were able to track costs since inception, with the exception of the final 3 quarters due missing SEC filings (we extrapolated). The product was discovered internally with pre-clinical costs reported.
Aristada	high	We were able to track costs since inception.
Beleodaq	low	They licensed the product from TopoTarget in phase 3 of development, although approval based on phase 2 data; there was a license fee and subsequent milestone payments
Belviq	high	We were able to track costs since inception.
Brineura	high	We were able to track costs since inception.
Copiktra	low	There was a deal with Intellikline, Inc.; unclear if licensing or contractual fees captured. They also struck a late deal with Infinity.
Crysvita	medium	There was an unclear early licensing deal with Kyowa Hakko Kirin. The indirect includes pre-clinical costs, so we are over-estimating the development costs.
Dificid	medium	There was a late commercialization deal, as well as an early collaboration agreement in place with Par Pharmaceutical, Inc. related to the clinical development commercialization of the product. There was also a development and commercialization agreement in place with Astellas.
Dupixent	low	There was a complex deal struck between Sanofi and Regeneron which entailed milestone payments, cost sharing, and royalties.

Brand name	R&D estimate quality	Comments
Elzonris	high	We were able to track costs since inception; report small royalties due to Scott and White (medical center).
Eucrisa	high	We were able to track costs since inception.
Exondys 51	low	It was unclear how R&D costs were reported, so we had to make assumptions about cost breakdown related to Exondys over time. We also had to extrapolate 3 years of data.
Eylea	low	There was a complex deal struck between Regeneron and Sanofi/Bayer, which seems to have entailed sizable milestone payments, cost sharing, and royalties.
Fanapt	low	There was a complex deal struck between Vanapt and Novartis, which seems to have entailed milestone payments, cost sharing, and royalties. Novartis regained commercialization rights in amended agreement. In the 2009 10-K, Vanapt Pharmaceuticals stated the following: "Prior to FDA approval, all Fanapt manufacturing-related and milestone costs were included in research and development expenses."
Firdapse	low	The active ingredient was discovered in the 1970s, with research and development ongoing for a long time. There was a deal struck between BioMarin and Catalyst late in development; we conservatively assumed 100% of Catalyst's development costs were related to Firdapse.
Folotyn	high	We were able to track costs since inception. They struck a small deal with Memorial Sloan Kettering in 2004 (fees and milestone payments incurred during development were included in R&D expenses).
Galafold	high	We were able to track costs since inception. They acquired rights to develop and commercialize the therapeutic agent from Mt Sinai School of Medicine (small deal). There was a late commercialization deal with GlaxoSmithKline.

Brand name	R&D estimate quality	Comments
Gattex	high	We were able to track costs since inception. They received some funding from the Canadian government. Licensed from academic collaborator.
Hetlioz	low	They acquired the product from Bristol-Myers Squibb in late stages of development. They only started testing for the FDA-approved indication in 2010 (after years of phase 2 and 3 trials in other indications).
Iclusig	high	We were able to track costs since inception; the product was discovered internally.
Idhifa	low	There was a complex early licensing deal struck with Celgene, which seems to have entailed milestone payments, cost sharing, and royalties. We did not count the so-called reduction in R&D expenses in our estimates.
Imbruvica	medium	They entered into a collaboration and license agreement with Janssen in 2011, after a few years of phase 1 and 2 development. There was an associated reduction in R&D costs (2nd half of 2012 only), but we can still track all of the costs incurred by Pharmacyclics. It is unclear how milestone payments were reported.
Ingrezza	high	We were able to track costs since inception. There was a late commercialization deal.
Juxtapid	medium	They entered into a late licensing arrangement with the University of Pennsylvania (who had previously been donated the license by Bristol-Myers Squibb). There were small upfront fees and milestone payments, but also royalty payments (10%) on future sales.
Kalbitor	medium	There was a collaboration agreement with Genzyme Corporation; we did not deduct R&D expenses reimbursed by former joint venture
Kengreal	low	There was a complex late deal struck with AstraZeneca, which seems to have entailed milestone payments, cost sharing, and royalties.

Brand name	R&D estimate quality	Comments
Kerydin	medium	The product was discovered internally, but they later struck an “exclusive license, development and commercialization agreement” with Schering-Plough Corporation.
Kevzara	low	There was a complex deal struck between Sanofi and Regeneron which entailed milestone payments, cost sharing, and royalties.
Kybella	low	There was a complex late deal struck with Bayer, which seems to have entailed milestone payments, cost sharing, and royalties.
Kyprolis	low	They acquired the company Proteolix in 2009, including its development pipeline. It is unclear whether costs associated with acquisition of Proteolix in November 2009 are reflected in R&D expenses.
Libtayo	low	There was a complex deal struck between Sanofi and Regeneron which entailed milestone payments, cost sharing, and royalties.
Linzess	medium	They entered into co-development and marketing deals with Almirall, Astellas, and Forest Laboratories.
Mepsevii	high	We were able to track costs since inception; they licensed the product from St. Louis University for a small up-front fee and subsequent milestone payments which were recorded as R&D expenses.
Mytesi	low	The product was licensed in from Napo Pharmaceuticals at phase 3 of development; the deal included upfront payment and milestone fees (both during development and upon sales thresholds being met). It was unclear if milestone payments were recorded as indirect costs, in which case we would likely be under-estimating the costs.
Northera	low	There was a complex late licensing deal struck with Dainippon Sumitomo Pharma Co., Ltd.
Nuplazid	high	We were able to track costs since inception.

Brand name	R&D estimate quality	Comments
Nuzyra	medium	The therapeutic agent was developed in-house, but missing early data (start with 2013 phase 3 costs). We used the accumulated deficit of 197.9 million as of Dec 2014 as proxy for early development (treated as phase 1), since the company seemed focused almost entirely on Nuzyra.
Ocaliva	high	We were able to track costs since inception. There was a late commercialization deal with Sumitomo Dainippon for the Japanese and Chinese markets.
Orbactiv	medium	They acquired the rights to this product through their acquisition of Targanta Therapeutics Corporation in 2009 during late stages of development.
Palyngiq	medium	There were sizable discrepancies in R&D outlays (both total and unallocated) between years; we used amounts reported in most recent available years. In 2005, they entered into a development and commercialization agreement with Merck Serono.
Praluent	low	There was a complex late deal struck with AstraZeneca, which seems to have entailed milestone payments, cost sharing, and royalties.
Rapivab	medium	The company received support through a sizable contract with the Biomedical Advanced Research and Development Authority (part of the US Department of Health and Human Services). The contract expired in 2014. They also partnered with Shionogi & Co., Ltd., and another partner for the commercialization of the product in Japan and Israel 2014. The data we collected includes at least 2 years of pre-clinical data.
Rhopressa	high	We were able to track costs since inception.
Rubraca	medium	There was a complex deal struck with Pfizer which entailed milestone payments, cost sharing, and royalties.
Strensiq	medium	They acquired the rights to this product through their acquisition of Enobia Pharma Corporation in 2012 during late stages of development.

Brand name	R&D estimate quality	Comments
Talzenna	low	There was a late deal struck between BioMarin and Medivation in 2015.
Tegsedi	medium	The product was developed through a collaboration agreement with GSK. There were both early and late commercialization deals.
Tibsovo	low	There was an early licensing deal with Celgene which was subsequently terminated.
Trulance	high	We were able to track costs since inception. We assumed 100% of R&D costs attributable to Trulance in some years, since this seemed to be corroborated by the SEC filings. They entered into a late commercializing agreement with Ironwood Pharmaceuticals.
Tymlos	high	We were able to track costs since inception. Small early licensing deal with another entity (Ipsen).
Ultomiris	high	We were able to track costs since inception.
Varubi	medium	At a late stage, they in-licensed the exclusive worldwide rights to the therapeutic agent from OPKO Health, Inc., who in turn had acquired these rights from Schering-Plough Corporation.
Veltassa	high	We were able to track costs since inception. They entered into a late commercialization deal (outside the US) with Vifor Fresenius Medical Care Renal Pharma Ltd.
Viberzi	medium	We had to extrapolate the last 2 years due to missing SEC filings. They licensed in the product from Janssen in 2009.
Viibryd	high	There was a collaboration agreement with Merck, with all milestone payments recorded as R&D expenses.
Vimizim	high	We were able to track costs since inception.
Vitrakvi	high	We were able to track costs since inception. There was an early deal with Array, and a late commercialization deal with Bayer in 2018 (year of approval).

Brand name	R&D estimate quality	Comments
Xerava	high	We were able to track costs since inception, including costs borne by the US government (Biomedical Advanced R&D Authority and the National Institute of Allergy and Infectious Disease at the NIH).
Xtandi	medium	There were both early and late deals: They licensed the agent from the University of California at Los Angeles in 2005 (milestone payments, fees, and royalties) and an agreement with Astellas came into effect in 2009 (50/50 sharing of costs related to the development/commercialization of the agent for the US market).
Zaltrap	low	There was a complex deal struck between Sanofi and Regeneron which entailed milestone payments, cost sharing, and royalties.
Zejula	low	The product was licensed in from Merck Sharp & Dohme Corp., a subsidiary of Merck. The deal entailed an up-front fee and subsequent milestone and royalty payments.
Zerbaxa	low	There was a merger agreement with the company Calixa, through which the manufacturer acquired the rights to two development candidates. It is unclear whether costs associated with acquisition of Calixa are reflected in R&D expenses.

Acronyms: R&D, research and development.

eTable 3. Median Research and Development Outlays (2018 US \$, Millions) by Product Category, Without Adjustment for Costs of Failures^a

Characteristics	R&D costs for full sample (n=63), \$ millions [IQR]
All agents	319.3 [160.0 – 418.1]
Agent type	
Pharmacologic	309.0 [147.2 – 388.0]
Biologic	391.3 [188.1 – 792.5]
P value	.03
Therapeutic area^b	
Alimentary tract and metabolism	343.7 [160.0 – 395.6]
Anti-infective agents for systemic use	388.0 [301.2 – 461.8]
Antineoplastic and immuno-modulating agents	358.55 [180.7 – 425.1]
Nervous system	187.65 [130.5 – 326.3]
Other	236.4 [147.2 – 418.1]
P value	.51
Orphan status	
Yes	272.1 [147.2 – 384.1]
No	326.3 [195.3 – 551.9]
P value	.15
Accelerated approval	
Yes	351.2 [147.2 – 384.1]
No	309.0 [166.5 – 430.5]
P value	.94
Any expedited development or approval pathway^c	
Yes	322.1 [158.0 – 418.9]
No	312.0 [197.1 – 390.0]

Characteristics	R&D costs for full sample (n=63), \$ millions [IQR]
P value	.99
Innovativeness	
First in class	262.6 [146.2 – 418.1]
Next in class	326.3 [195.3 – 409.8]
P value	.43
Route of administration^d	
Injection	319.1 [198.3 – 602.2]
Intravenous	347.7 [155.9 – 418.1]
Oral	322.1 [143.5 – 392.8]
Other	197.1 [136.4 – 208.0]
P value	.38
Year of approval	
2009 to 2013	272.1 [139.8 – 383.4]
2014 to 2018	326.3 [167.9 – 430.5]
P value	.27

Acronyms: \$, United States dollars; FDA, Food and Drug Administration; IQR, interquartile range; R&D, research and development.

^a Total non-capitalized direct and indirect expenses incurred across all phases of development.

^b Other therapeutic areas included blood and blood forming organs, cardiovascular system, dermatologicals, musculo-skeletal system, sensory organs, and various.

^c Included accelerated approval, breakthrough therapy, fast track, orphan drug, and priority review.

^d Injection included intramuscular and subcutaneous; other routes included multiple, ophthalmic, and topical.

eTable 4. Research and Development Costs (2018 US \$, Millions), Broken Down by Phase of Clinical Development, for All Therapeutic Agents Included in the Analysis^a

Brand name	Quality of estimate	Actual R&D outlay, without success rate adjustment or cost of capital (\$, in millions)				Pre-clinical costs, with success rate adjustments and cost of capital (\$, in millions) ^b	
		Phase 1	Phase 2	Phase 3	Total	Pre-clinical (adjusted)	Share of total estimate
Adcetris	medium	89.3	95.5	178.2	363	444.7	27.3%
Alunbrig	high	9.9	243	98.1	351	95.2	8.1%
Aristada	high		47.2	281.9	329.1	38.7	5.1%
Beleodaq	low		89.4		89.4	L	
Belviq	high	74.5	136	606.5	817	916.5	26.8%
Brineura	high	42.4	220.1		262.5	515.4	45.0%
Copiktra	low	146.2	45.4	460.3	651.9	L	
Crysvita	medium	4	21.9	140.6	166.5	L	
Dificid	medium	4.2	6.9	128.7	139.8	26.3	7.0%
Dupixent	low	140.2	363.9	1615.8	2119.9	U	
Elzonris	high		167.9		167.9	U	
Eucrisa	high	29.7	49	129.3	208	U	
Exondys 51	low	17.2	166.2	234.7	418.1	103.1	7.9%
Eylea	low	112.9	89.3	790.6	992.8	L	
Fanapt	low		10.9	92.5	103.4	L	
Firdapse	low			108	108	L	
Folotyn	high	19.1	89		108.1	L	
Galafold	high	27.5	43.7	324.4	395.6	L	
Gattex	high	1.5	54.6	252.9	309	L	

Brand name	Quality of estimate	Actual R&D outlay, without success rate adjustment or cost of capital (\$, in millions)				Pre-clinical costs, with success rate adjustments and cost of capital (\$, in millions) ^b	
		Phase 1	Phase 2	Phase 3	Total	Pre-clinical (adjusted)	Share of total estimate
Hetlioz	low		77	110.1	187.1	L	
Iclusig	high	49.5	222.6		272.1	U	
Idhifa	low	22.6	47.1	15.5	85.2	238.4	50.7%
Imbruvica	medium	91.9	69.6	159.3	320.8	171.2	12.4%
Ingrezza	high	13.8	108.1	201.5	323.4	133.5	12.6%
Juxtapid	medium		18.2	88.5	106.7	L	
Kalbitor	medium	6.4	60	142	208.4	U	
Kengreal	low			312	312	L	
Kerydin	medium	30	8.2	77.1	115.3	U	
Kevzara	low	80.7		630.7	711.4	371.7	12.8%
Kybella	low		53.1	183.4	236.5	100.2	14.7%
Kyprolis	low		50.4	333.1	383.5	L	
Libtayo	low	67.3	674.4		741.7	L	
Linzess	medium	90.9	84.1	215.2	390.2	U	
Mepsevii	high	12.7	12.6	121.1	146.4	L	
Mytesi	low			73.8	73.8	L	
Northera	low			147.2	147.2	L	
Nuplazid	high	34.9	106.8	373.2	514.9	642.3	23.0%
Nuzyra	medium	205.9		255.9	461.8	L	
Ocaliva	high	28.4	23.9	299	351.3	U	
Orbactiv	medium			155.9	155.9	L	

Brand name	Quality of estimate	Actual R&D outlay, without success rate adjustment or cost of capital (\$, in millions)				Pre-clinical costs, with success rate adjustments and cost of capital (\$, in millions) ^b	
		Phase 1	Phase 2	Phase 3	Total	Pre-clinical (adjusted)	Share of total estimate
Palynziq	medium	97	145.5	600.7	843.2	13.1	0.3%
Praluent	low	92	107.7	1045.3	1245	L	
Rapivab	medium	24.2	151.3	125.8	301.3	49.4	3.3%
Rhopressa	high	13.6	24.8	98	136.4	U	
Rubraca	medium		77.2	307	384.2	L	
Strensiq	medium		160		160	L	
Talzenna	low		71.8	516.9	588.7	91.9	6.4%
Tegsedi	medium	11.3		177	188.3	U	
Tibsovo	low	256.1	174.4		430.5	447.1	18.0%
Trulance	high	7.3	87.5	253.3	348.1	9.3	0.9%
Tymlos	high	28.3	21.4	255.7	305.4	L	
Ultomiris	high	9.1	70.6	274.6	354.3	U	
Varubi	medium		23.6	173.6	197.2	L	
Veltassa	high	60.7	67.5	191.2	319.4	U	
Viberzi	medium	17.3	71.6	254.8	343.7	L	
Viibryd	high		7	146	153	L	
Vimizim	high	33.2	114.3	345.5	493	109.7	6.8%
Vitrakvi	high	15	104.2		119.2	U	
Xerava	high	31	31.6	325.3	387.9	U	
Xtandi	medium	8.8	41.3	143.6	193.7	L	
Zaltrap	low	117.4	138.2	164.1	419.7	L	

Brand name	Quality of estimate	Actual R&D outlay, without success rate adjustment or cost of capital (\$, in millions)				Pre-clinical costs, with success rate adjustments and cost of capital (\$, in millions) ^b	
		Phase 1	Phase 2	Phase 3	Total	Pre-clinical (adjusted)	Share of total estimate
Zejula	low		19.3	380.8	400.1	L	
Zerbaxa	low		279.3	628.4	907.7	L	
Mean ^c		52.9	100.8	291.6	374.1	237.8	

Acronyms: \$, dollars; L, licensed / acquired through purchase; R&D, research and development; U, unclear.

^a Phase 1 or 2 costs were not recorded if a company initiated a phase 1/2 or 2/3 trial, since those were categorized as phases 2 and 3, respectively. The costs incurred during the filing of a new drug application (NDA) or biologics license application (BLA) were included in the final phase for each drug. Under the "actual R&D outlay" section of this table, pre-clinical outlays, where captured, were recorded as part of the first phase of clinical development for a particular agent.

^b These reflected pre-clinical costs with success rate adjustments and costs of capital (10.5%), with shares calculated as % of the final estimate presented in eTable 6 (under Wong et al. (10.5%)).

^c Costs in certain phases were not recorded for some drugs since expenditures could not always be disaggregated between phases (i.e., due to licensing and phase 1/2 and 2/3 trials being treated as phases 2 and 3, respectively). For example, if a company recorded \$50 million in costs for a phase 1 trial and \$250 million in costs for a phase 2/3 trial, then it was not possible to provide the breakdown of costs for phase 2 vs 3. This was not necessary to produce the estimates in the present paper, since the whole phase 2/3 trial was treated as phase 3 trial for the purposes of clinical trial success rate adjustments, as done in previous studies of clinical trial success rates (e.g., Wong et al., Hay et al., and Thomas et al. studies presented in the paper). Wong et al., in the Methods section of their paper, explained: "We make the standard assumption that Phase 1/2 and Phase 2/3 trials are to be considered as Phase 2 and 3, respectively." The same issue arose when a drug was licensed after clinical testing had already begun, where milestone payments / license fees were taken to indirectly capture earlier costs. The phase-specific mean values presented here are based on the observed costs in eTable 5 (with "missing" observations dropped). Consequently, the mean cost across all phases (i.e., mean for the Total column) does not equal the sum of the means for each individual phase.

eTable 5. Dates of Clinical Trial Phase Changes for All Therapeutic Agents Included in the Analysis^a

Brand name	Start year	IND submission	Phase 2 start (d/m/y)	Phase 3 start (d/m/y)	NDA/BLA submission (d/m/y)	Date of FDA approval (d/m/y)	Duration (years) ^h
Adcetris	2002	27/06/06	01/02/09	01/04/10	25/02/11	19/08/11	9.6
Alunbrig	2010	28/06/11	20/09/11	26/05/16	29/08/16	28/04/17	7.3
Aristada	2010	16/07/10	01/01/10	01/12/11	22/08/14	05/10/15	5.8
Beleodaq	2010	2004	01/02/10	[Approval based on phase 2]	08/12/13	03/07/14	4.5
Belviq	2003	25/05/04	01/12/04	01/09/06	18/12/09	27/06/12	9.5
Brineura	2009	01/03/14 ^e	01/09/13	[Approval based on phase 2]	27/05/16	27/04/17	8.3
Copiktra	2012	18/08/11	01/05/13	01/11/13	02/02/18	24/09/18	6.7
Crysvita	2013	15/10/13 ^c	02/07/14	01/12/15	17/08/17	17/04/18	5.3
Dificid	2003	01/08/03	01/07/04	01/05/06	29/11/10	27/05/11	8.4
Dupixent	2009	30/06/10	01/04/12	01/09/14	29/07/16	28/03/17	8.2
Elzonris	2009	27/06/14	01/01/09	[Approval based on phase 2]	21/06/18	21/12/18	10.0
Eucrisa	2006 ^b	20/04/08	01/05/11	01/03/14	07/01/16	14/12/16	11.0
Exondys 51	2007	09/08/07	01/01/09	17/11/14	26/06/15	19/09/16	9.7
Eylea	2004	16/05/05	01/04/06	01/08/07	17/02/11	18/11/11	7.9
Fanapt	2004	2004	01/06/04	01/11/05	27/09/07	06/05/09	5.4
Firdapse	2009	14/12/10	[Licensed in phase 3]	01/06/11	28/03/18	28/11/18	9.9
Folotyn	2002	31/01/97	01/08/06	[Approval based on phase 2]	23/03/09	24/09/09	7.7
Galafold	2002 ^b	03/02/04 ^d	02/01/06	01/04/09	13/12/17	10/08/18	16.6
Gattex	1998 ^b	26/04/99 ^e	01/07/00	01/04/04	30/11/11	21/12/12	15.0

Brand name	Start year	IND submission	Phase 2 start (d/m/y)	Phase 3 start (d/m/y)	NDA/BLA submission (d/m/y)	Date of FDA approval (d/m/y)	Duration (years) ^h
Hetlioz	2004	17/05/04 ^c	01/02/04	01/08/10	31/05/13	31/01/14	10.1
Iclusig	2008	21/11/07	30/09/10	[Approval based on phase 2]	30/07/12	14/12/12	5.0
Idhifa	2011	01/07/13	27/08/13	30/12/15	30/12/16	01/08/17	6.6
Imbruvica	2005	07/10/08	01/02/11	10/12/12	28/06/13	13/11/13	8.9
Ingrezza	2008	19/07/11 ^e	01/10/10	01/10/14	11/08/16	11/04/17	9.3
Juxtapid	2005	13/04/07 ^{c,e}	01/01/05	01/12/07	28/02/12	21/12/12	8.0
Kalbitor	1998	30/04/02 ^e	01/07/00	01/12/05	23/09/08	01/12/09	11.9
Kengreal	2004	10/02/99	[Licensed in phase 3]	01/01/04	23/12/14	22/06/15	11.5
Kerydin	2004 ^b	03/10/05 ^d	01/11/05	01/12/10	26/07/13	07/07/14	10.5
Kevzara	2007	16/10/07 ^d	[Phase 2/3 treated as 3]	01/06/09	30/10/15	22/05/17	10.4
Kybella	2007	01/11/07	01/08/07	01/12/10	13/05/14	29/04/15	8.3
Kyprolis	2009	13/06/05	01/01/09	14/07/10	26/09/11	20/07/12	3.6
Libtayo	2015	10/09/15	11/05/16	[Approval based on phase 2]	28/02/18	28/09/18	3.7
Linzess	2008	14/04/08 ^c	01/11/06	01/08/08	08/08/11	30/08/12	4.7
Mepsevii	2010	10/10/14 ^e	01/11/13	01/12/14	16/03/17	15/11/17	7.9
Mytesi	2008	01/12/08 ^c	[Licensed in phase 3]	[Approval based on phase 2] ^f	05/12/11	31/12/12	5.0
Northera	2006	01/09/07	[Licensed in phase 3]	01/05/06	23/09/11	18/02/14	8.1
Nuplazid	2002	02/07/03 ^d	01/03/04	01/06/07	03/09/15	29/04/16	14.3

Brand name	Start year	IND submission	Phase 2 start (d/m/y)	Phase 3 start (d/m/y)	NDA/BLA submission (d/m/y)	Date of FDA approval (d/m/y)	Duration (years) ^h
Nuzyra	2012	Not found	[Reported costs phase 3 onwards] ^g	01/03/09	02/02/18	02/10/18	6.8
Ocaliva	2002	27/01/06	01/10/07	01/01/12	27/06/15	27/05/16	14.4
Orbactiv	2009	01/08/96	[Licensed in phase 3]	01/12/10	06/12/13	06/08/14	5.6
Palyngiq	2004	27/11/07	01/09/09	01/05/13	30/06/17	24/05/18	14.4
Praluent	2009	12/11/09	01/01/11	01/06/12	24/11/14	24/07/15	6.6
Rapivab	2004	23/11/05	01/01/07	01/09/09	19/12/13	19/12/14	11.0
Rhopressa	2010	Not found	01/03/12	01/07/14	28/02/17	18/12/17	8.0
Rubraca	2011	11/09/11	01/01/11	01/04/14	23/06/16	19/12/16	6.0
Strensiq	2012	04/06/14 ^c	01/01/12	[Approval based on phase 2]	23/12/14	23/10/15	3.8
Talzenna	2010	10/12/10 ^c	01/01/10	01/10/13	06/04/18	16/10/18	8.8
Tegsedi	2012	09/11/12	[Licensed in phase 3]	01/02/13	06/11/17	05/10/18	6.8
Tibsovo	2011	20/12/13	[Moved from phase 1 to 3]	01/04/17	21/12/17	20/07/18	7.6
Trulance	2008	02/04/08	01/02/10	13/11/13	29/01/16	19/01/17	9.1
Tymlos	2008	08/12/05	01/01/08	01/04/11	30/03/16	28/04/17	9.3
Ultomiris	2013	Not found	01/07/15	20/12/16	18/06/18	21/12/18	6.0
Varubi	2010	01/10/05 ^d	01/12/10	01/02/12	05/09/14	01/09/15	5.7
Veltassa	2007 ^b	01/12/07	01/01/11	01/02/13	21/10/14	21/10/15	8.8
Viberzi	2009	21/11/07	01/04/10	01/06/12	26/06/14	27/05/15	6.4
Viibryd	2004	21/11/97	01/09/04	01/02/06	22/03/10	21/01/11	7.1

Brand name	Start year	IND submission	Phase 2 start (d/m/y)	Phase 3 start (d/m/y)	NDA/BLA submission (d/m/y)	Date of FDA approval (d/m/y)	Duration (years) ^h
Vimizim	2005	28/12/07	01/11/08	01/02/11	29/03/13	14/02/14	8.1
Vitrakvi	2013	28/02/14	01/10/15	[Approval based on phase 2]	24/03/18	26/11/18	5.9
Xerava	2009 ^b	20/08/09	01/01/12	01/08/13	28/12/17	27/08/18	10.7
Xtandi	2005	01/02/07	23/07/07	30/09/09	21/05/12	31/08/12	7.7
Zaltrap	2004	Not found	01/09/05	01/11/07	03/02/12	03/08/12	8.6
Zejula	2012	01/09/12 ^c	01/01/12	01/06/13	01/11/16	27/03/17	5.2
Zerbaxa	2009	01/07/09	01/12/09	01/07/11	21/04/14	19/12/14	6.0

Acronyms: BLA, biologics license application; FDA, Food and Drug Administration; IND, investigational new drug [application]; NDA, new drug application.

^a These dates corresponded to the coding of the phase data in our analyses. Although these data generally were aligned with the actual start dates of phases 2 and 3 of clinical development, there were discrepancies in some cases. For example, if company X acquired the rights to a product in 2013 from company Y after the latter firm had already been conducting a phase 3 trial for two years, we would report 2013 as the start of phase 3 testing to match our collected data. All data prior to the start of phase 2 were treated as phase 1. For the date of the investigational new drug application, we relied on the date the application was filed (obtained from Drugs@FDA database). If this date was unavailable, we reported the date that the investigational new drug application was approved or opened by the FDA. In some cases, the investigational new drug application dates shown in the table relate to the application filed by the originator company, not the company that subsequently licensed the product and brought it to market. We checked dates for consistency with the Securities and Exchange Commission filings. If unclear, it was assumed that no pre-clinical costs were reflected in our estimates, regardless of dates listed in this table.

^b The start year was deduced from since inception statement in Securities and Exchange Commission filings.

^c The transfer date for the investigational new drug application.

^d Date of pre-investigational new drug application meeting, which was used as a proxy for the date of submission of the investigational new drug application (unavailable).

^e Clinical testing was conducted outside the US prior to submission of investigational new drug application.

^f All costs were treated as Phase 2.

^g We treated the amount reported “since inception” as phase 1, which is why no phase 2 date was recorded.

^h This corresponds to the total numbers of years for which we were able to collect R&D expenditures. This duration may have been lower than the actual number of years of clinical development when there were licensing arrangements, acquisition and mergers, or other collaborations between parties.

eTable 6. Estimated Research and Development Costs (2018 US \$, Millions) for All Therapeutic Agents Included in the Analysis^a

Brand name	Actual R&D outlay	Wong et al. (0.0%)	Wong et al. (7.0%)	Wong et al. (10.5%)	Wong et al. (10.5% + pre-clinical excl. licensed) ^b	Wong et al. (10.5% + pre-clinical incl. licensed) ^c	Hay et al. (10.5%)	Thomas et al. (10.5%)	Therapeutic-area -specific rates (10.5%)
Adcetris	363.0	1,185.3	1,461.2	1,627.9	2,072.2	2,072.2	2,373.4	2,527.3	6,255.2
Alunbrig	351.0	895.9	1,076.6	1,180.6	1,900.9	1,900.9	2,289.1	2,417.6	5,463.2
Aristada	329.2	579.3	692.0	755.5	1,255.3	1,255.3	1,081.1	1,109.9	994.3
Beleodaq	89.4	229.5	283.5	314.3	314.3	550.4	659.4	696.7	1,568.6
Belviq	817.1	1,893.3	2,811.5	3,422.1	4,388.1	4,388.1	5,929.3	5,171.7	3,572.8
Brineura	262.6	806.8	1,018.1	1,146.2	1,104.7	1,104.7	1,912.1	2,033.7	1,220.1
Copiktra	651.9	1,954.7	2,692.9	3,147.2	3,147.2	5,511.7	4,195.3	4,440.3	10,501.4
Crysvita	166.5	307.3	352.1	376.5	376.5	659.4	524.5	540.7	374.1
Dificid	139.8	261.5	333.7	377.8	661.6	661.6	487.7	501.5	412.9
Dupixent	2,119.8	4,568.8	5,718.5	6,419.0	11,241.7	11,241.7	9,240.1	9,659.7	6,019.3
Elzonris	167.9	442.8	519.2	564.0	987.7	987.7	1,191.8	1,259.7	2,845.3
Eucrisa	208.0	551.9	731.5	846.2	1,482.0	1,482.0	1,249.3	1,322.3	748.6
Exondys 51	418.1	915.4	1,149.3	1,297.8	2,092.3	2,092.3	2,193.0	2,306.4	1,385.2
Eylea	992.8	2,316.2	2,981.0	3,393.0	3,393.0	5,942.2	4,577.5	4,804.1	2,270.4
Fanapt	103.3	175.6	211.4	231.3	231.3	405.1	313.2	319.8	292.6
Firdapse	108.0	177.6	240.6	281.4	281.4	492.8	329.7	331.9	323.0
Folotyn	108.0	356.0	431.8	477.3	477.3	835.9	809.7	862.7	2,118.3
Galafold	395.6	855.7	1,498.6	2,015.2	2,015.2	3,529.2	2,836.2	2,974.2	2,070.9
Gattex	309.0	567.9	848.9	1,048.1	1,048.1	1,835.6	1,620.3	1,678.4	1,298.5
Hetlioz	187.0	396.9	561.8	671.2	671.2	1,175.5	1,232.3	1,291.1	1,062.4
Iclusig	272.1	899.2	988.2	1,036.2	1,814.7	1,814.7	1,773.4	1,887.1	4,588.8
Idhifa	85.2	322.4	415.6	470.6	406.7	406.7	767.5	819.7	2,051.8

Brand name	Actual R&D outlay	Wong et al. (0.0%)	Wong et al. (7.0%)	Wong et al. (10.5%)	Wong et al. (10.5% + pre-clinical excl. licensed) ^b	Wong et al. (10.5% + pre-clinical incl. licensed) ^c	Hay et al. (10.5%)	Thomas et al. (10.5%)	Therapeutic-area -specific rates (10.5%)
Imbruvica	320.9	1,095.0	1,279.0	1,383.9	2,123.8	2,123.8	1,975.5	2,105.8	5,269.2
Ingrezza	323.3	717.6	930.0	1,063.3	1,628.4	1,628.4	1,747.8	1,834.7	1,473.5
Juxtapid	106.6	190.7	231.5	255.6	255.6	447.6	383.0	394.9	255.5
Kalbitor	208.3	438.8	586.2	683.2	1,196.5	1,196.5	1,104.8	1,157.0	709.7
Kengreal	312.0	526.6	776.9	943.8	943.8	1,652.9	1,112.7	1,121.5	876.2
Kerydin	115.2	364.0	522.5	625.8	1,096.0	1,096.0	836.1	890.0	479.0
Kevzara	711.4	1,587.7	2,369.8	2,910.6	4,446.4	4,446.4	3,614.0	3,781.3	2,697.8
Kybella	236.4	450.8	593.4	683.6	1,021.7	1,021.7	1,102.2	1,143.7	746.2
Kyprolis	383.4	621.2	671.1	697.0	697.0	1,220.7	959.7	980.0	1,657.9
Libtayo	741.7	1,964.9	2,137.7	2,228.3	2,228.3	3,902.5	3,926.1	4,150.3	9,569.7
Linzess	390.0	1,235.9	1,780.4	2,134.6	3,738.4	3,738.4	3,086.8	3,285.1	1,971.8
Mepsevii	146.2	314.5	369.3	400.7	400.7	701.8	534.3	557.1	404.8
Mytesi	73.8	117.0	134.0	143.2	143.2	250.8	165.4	166.1	161.6
Northera	147.2	231.4	308.8	355.8	355.8	623.1	410.4	412.0	339.4
Nuplazid	515.0	1,163.2	2,062.7	2,787.9	3,757.6	3,757.6	4,279.9	4,503.7	3,548.8
Nuzyra	461.8	1,906.4	2,708.9	3,215.8	3,215.8	5,631.9	4,185.2	4,488.7	1,888.1
Ocaliva	351.4	724.5	932.0	1,062.6	1,860.9	1,860.9	1,404.9	1,465.8	1,053.9
Orbactiv	155.9	259.1	308.5	336.1	336.1	588.6	394.3	397.1	265.9
Palynziq	843.2	2,075.4	3,242.1	4,104.7	7,165.7	7,165.7	5,925.0	6,262.5	4,032.3
Praluent	1,245.1	2,606.2	3,126.0	3,429.6	3,429.6	6,006.3	4,583.5	4,771.0	2,862.4
Rapivab	301.2	817.6	1,230.1	1,502.0	2,544.0	2,544.0	2,628.6	2,778.1	1,259.9
Rhopressa	136.4	323.6	415.0	471.5	825.7	825.7	679.4	714.1	335.2
Rubraca	384.1	693.5	770.1	812.7	812.7	1,423.3	1,243.9	1,284.2	2,384.5

Brand name	Actual R&D outlay	Wong et al. (0.0%)	Wong et al. (7.0%)	Wong et al. (10.5%)	Wong et al. (10.5% + pre-clinical excl. licensed) ^b	Wong et al. (10.5% + pre-clinical incl. licensed) ^c	Hay et al. (10.5%)	Thomas et al. (10.5%)	Therapeutic-area-specific rates (10.5%)
Strensiq	160.0	384.4	418.8	436.7	436.7	764.8	885.1	932.8	613.9
Talzenna	588.7	1,047.7	1,284.1	1,425.4	2,335.4	2,335.4	2,044.7	2,100.6	3,684.6
Tegsedi	188.3	365.2	450.2	500.5	876.5	876.5	605.0	623.2	537.5
Tibsovo	430.5	1,856.6	2,256.2	2,486.0	3,570.8	3,570.8	3,210.9	3,449.5	10,526.4
Trulance	348.1	688.2	887.4	1,009.2	1,751.1	1,751.1	1,595.1	1,661.6	1,217.6
Tymlos	305.4	685.6	1,009.7	1,228.9	1,228.9	2,152.2	1,637.4	1,713.1	1,052.6
Ultomiris	354.1	697.9	762.4	796.6	1,395.1	1,395.1	1,183.1	1,226.3	926.6
Varubi	197.1	340.6	397.6	429.3	429.3	751.8	597.8	612.2	517.1
Veltassa	319.3	911.8	1,156.8	1,301.8	2,279.9	2,279.9	1,885.9	1,999.3	1,121.0
Viberzi	343.7	721.9	888.3	985.3	985.3	1,725.6	1,474.1	1,537.8	1,113.5
Viibryd	153.0	245.4	291.6	317.9	317.9	556.7	401.8	407.3	383.1
Vimizim	492.9	1,103.7	1,422.2	1,614.4	2,635.2	2,635.2	2,450.1	2,566.9	1,792.4
Vitrakvi	119.2	380.3	433.1	461.9	808.9	808.9	849.2	902.6	2,159.3
Xerava	388.0	850.6	1,119.9	1,287.9	2,255.5	2,255.5	1,732.5	1,807.5	943.6
Xtandi	193.5	407.5	484.9	530.1	530.1	928.4	798.5	833.1	1,718.8
Zaltrap	419.6	1,514.9	2,331.8	2,878.3	2,878.3	5,040.8	4,356.2	4,649.2	11,645.6
Zejula	400.0	665.0	756.9	807.0	807.0	1,413.3	1,021.1	1,035.9	1,591.5
Zerbaxa	907.7	1,786.3	2,132.7	2,332.2	2,332.2	4,084.4	3,928.2	4,088.7	2,128.3

Acronyms: \$, dollars; R&D, research and development.

^a Wong et al., Thomas et al., and Hay et al. refer to the sources of aggregate success rates. The therapeutic-area-specific rates were obtained from Wong et al. The percentages in parentheses refer to the cost of capital rate used in the calculations.

^b This column includes adjustments for the potential underestimation of pre-clinical costs. No imputations were performed for products licensed

after clinical development had begun, since it was assumed that licensing fees and milestone payments reflected pre-clinical costs incurred by the company that sold the rights to the product. In such cases, the results for "Wong et al. (10.5%)" and "Wong et al. (10.5% + pre-clinical excl. licensed)" were identical.

^c This column includes adjustments for the potential underestimation of pre-clinical costs but with imputations done for all products, including licensed agents. For non-licensed agents, the results shown for "Wong et al. (10.5% + pre-clinical excl. licensed)" and "Wong et al. (10.5% + pre-clinical incl. licensed)" were identical.