Market movers and shakers

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Key Upcoming Trial Results
Key Upcoming Regulatory Dates
Top Gains (Past Month)
Top Losses (Past Month)
Market Moving Events

September 2016

Welcome to the latest issue of Evaluate's Calendar of Events newsletter, your monthly digest of upcoming events in the industry. Each issue highlights key clinical and regulatory events, as well as providing you with detailed analysis of some of the biggest moving events over the last month and opinion from EP Vantage.

This month's edition features a look at **Amgen's Humira Biosimilar ABP 501**, **Karyopharm Therapeutics Myeloma product Selinexor** and the **CAR-T market**.

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Key Upcoming Trial Results

Company/Product	Event NPV ($m)	Event NPV % of Mkt Cap	Event	End Date	2022 Consensus Sales Forecast ($m)
Phase III Trial Results					
Northwest Biotherapeutics – DCVax-L	899	2342%	Phase III Trial Results for DCVax-L in Glioblastoma Multiforme	30/09/16	600
Novavax – RSV F Vaccine	1243	64%	Phase III Trial Results for RSV F Vaccine for Respiratory Syncytial Virus	30/09/16	845
Array BioPharma – Encorafenib	310	62%	Phase III Trial Results for Binimetinib/ Encorafenib for BRAF-mutant melanoma	30/09/16	136
Retrophin – Sparsentan	349	59%	Phase II/III Trial Results for Sparsentan for Focal Segmental Glomerulosclerosis (FSGS)	30/09/16	285
Aerie Pharmaceuticals – Roclatan	217	41%	Phase III Trial Results for Roclatan for Glaucoma	30/09/16	402
Phase II Trial Results					
Karyopharm Therapeutics – Selinexor	616	240%	Phase II Trial Results for Selinexor for Relapsed or Refractory Multiple Myeloma	30/09/16	439
Enanta Pharmaceuticals – ABT-493	445	104%	Phase IIb Trial Results for ABT-493 in combination with ABT-530 for Hepatitis C treatment	30/09/16	
Kite Pharma – KTE-C19	1604	56%	Phase I/II Trial Results for KTE-C19 for Non-Hodgkin lymphoma (NHL)	30/09/16	1332
Medivation – Talazoparib	452	3%	Phase II Trial Results for Talazoparib for second line Ovarian Cancer	30/09/16	165
Bayer – Copanlisib	979	1.1%	Phase II Trial Results for Copanlisib for Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphoma	30/09/16	259
Bayer – Vericiguat	825	0.9%	Phase IIb Trial Results for Vericiguat for Chronic heart failure	30/09/16	190
Shire – SHP610	357	0.6%	Phase IIb Trial Results for SHP610 for Sanfilippo Syndrome	30/09/16	86

September sees the expected read out of phase II Trial Results for Selinexor for Relapsed or Refractory Multiple Myeloma. Dogged by safety issues earlier in the year as news that dosing in an AML trial called Sopra had to be lowered to 60mg owing to higher than expected rates of sepsis, has led to shares falling 39% in the second quarter this year. However, on August 30th shares rose 37% with news that the company was going to present top line data for Selinexor and announced plans to expand the trial; analysts at Jefferies upgrade ratings to a "buy" from a "hold". Selinexor has consensus forecasts of $439 million in 2022.

Key Upcoming Regulatory Dates

Company/Product	Event NPV ($m)	Event NPV % of Mkt Cap	Event	End Date	2022 Consensus Sales Forecast ($m)
US Product Approval					
Amgen - ABP 501	6287	5%	FDA Decision Date (BsUFA) on ABP 501 for moderate-to-severe plaque Psoriasis and Rheumatoid Arthritis	06/09/16	810
EU Product Approval					
Astellas Pharma – Xtandi	19011	58%	EMA Decision Date (Type II Variation) on Xtandi for metastatic castration-resistant Prostate Cancer	30/09/16	4658
Medivation – Xtandi	4587	34%	EMA Decision Date (Type II Variation) on Xtandi for metastatic castration-resistant Prostate Cancer	30/09/16	
Exelixis – Cometriq	1191	47%	EMA Decision Date on Cabometyx for second line Renal Cell Carcinoma	30/09/16	487
Eisai – Lenvima	2356	14%	EMA Decision Date on Kisplyx in combination with Everolimus for Renal Cell Carcinoma	30/09/16	960
Johnson & Johnson – Stelara	14880	4.5%	EMA Decision Date (Type II Variation) on Stelara for Crohn's disease	30/09/16	4527
Shire – Natpara	1568	2.7%	EMA Decision Date on Natpara for Hypoparathyroidism	30/09/16	658

Amgen's Humira Biosimilar – ABP 501 is set to receive FDA approval this month. Early in July the FDA's advisory committee voted 26 – 0 in favour of the product, following studies that showed the product met its primary goals in demonstrating clinical equivalence to Humira. The product is set to take on AbbVie's giant in the anti TNF market, Humira, which has 2022 forecast sales of $13.645 billion in 2022.

Top 5 Gains (Past Month)

Event Date	Company/Product	Change %	Market Cap ($m)	Event Type
24/08/16	Nymox Pharmaceutical – NX-1207	83.1%	93	24 Aug: Company reports positive long-term phase III data for prostate cancer treatment fexapotide.
17/08/16	Auris Medical – Keyzilen	39.3%	52	17 Aug: Shares volatile ahead of upcoming phase III data for lead drug AM-101 for the treatment of acute tinnitus.
16/08/16	Syros Pharmaceuticals – SY-1425	36.1%	92	16 Aug: Company states in its Q2'16 earnings release on 15 Aug that its phase II trial for AML treatment SY-1425 is on track for Q3'16.
04/08/16	Ocular Therapeutix – Dextenza	34.0%	35	4 Aug: FDA states that company's corrective actions on its filing for ocular pain treatment Dextenza have addressed the agency's concern.
02/08/16	Advaxis – MNE Research Project	30.8%	90	2 Aug: Company grants Amgen WW rights to its cancer immunotherapy treatment ADXS-NEO for $40m upfront, a $25m purchase of company stock by Amgen, up to $475m in milestone, and additional royalties.

Top 5 Losses (Past Month)

Event Date	Company/Product	Change %	Market Cap ($m)	Event Type
18/08/16	Auris Medical – Keyzilen	-59.8%	74	18 Aug: Company's lead drug Keyzilen (AM-101) for the treatment of tinnitus misses its co-primary efficacy endpoints in a phase III trial.
18/08/16	Cerulean Pharma – CRLX101	-56.2%	33	17 Aug [post market]: Company's renal cell carcinoma treatment CRLX101 misses primary endpoint in a phase II trial. 18 Aug: Leerink Swann downgrades rating to "market perform" from "outperform".
15/08/16	Aurinia Pharmaceuticals – Luveniq	-54.8%	64	15 Aug: Company's lupus nephritis treatment voclosporin meets primary endpoint in a phase IIb trial however, 13 deaths and a higher overall rate of serious adverse events are reported in both voclosporin groups.
23/08/16	Acrux – Axiron	-43.1%	51	23 Aug: A US district court rules against company and partner Eli Lilly in a patent lawsuit related to testosterone deficiency therapy Axiron, invalidating its patents and allowing generic versions into the market.

EP vantage
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MARKET MOVING EVENTS

Upcoming Events – Biogen holds on to Lingo, and pivotal data for Nanobiotix

Further data from Biogen's anti-Lingo-1 antibody opicinumab are expected at next month's Ectrims meeting. The project failed its phase II in relapsing multiple sclerosis, but with Biogen noting an unexpected response with the middle doses the group does not look to be ditching it just yet.

Meanwhile Nanobiotix is awaiting interim data from the pivotal trial of its radiation amplification technology NBTXR3 in soft tissue sarcoma, which if positive could enable a European approval filing.

Clinging on

Biogen's shares fell 13% when it reported the failure of opicinumab's Synergy trial in June, with the MAb missing both the primary and secondary endpoint (No bingo for Lingo, June 8, 2016).

On its second-quarter results call Biogen said the results produced a bell-shaped curve, with efficacy lost at the highest dose, but middle doses showing signals of efficacy. The anti-Lingo MAb had been tested at 3mg/kg, 10mg/kg, 30mg/kg and 100mg/kg versus placebo, concurrently with Avonex.

Further analysis is expected on September 16 at the Ectrims conference in London, and the results could determine the next steps for the drug. A phase I study recently started in healthy volunteers using opicinumab produced by two different manufacturing processes, a signal that the asset is not dead and buried yet.

Ectrims will also separately see the keenly awaited presentation of data from Novartis's phase III Expand trial of siponimod, toplined yesterday, one of the first studies specifically recruiting secondary progressive MS patients to show a positive result.

Biogen's most valuable R&D project, aducanumab, is high risk given that it targets Alzheimer's disease, and its MS franchise looks to be hitting a plateau, so clinging on to opicinumab might be a wise move (Biogen needs to fill pipeline or rethink strategy, July 22, 2016).

Nanoparticles

Interim phase II/III data on Nanobiotix's NBTXR3 in soft tissue sarcoma (STS) will appear this quarter and if it is positive the French group ought to be able to file for CE mark approval, the European regulatory path for medical devices, according to Edison analysts. Approval itself could follow by the end of the year, giving Nanobiotix its first marketed product.

NBTXR3 is a nanoparticle radio-enhancer injected directly into tumours. Upon exposure to ionising radiation, such as X-rays, the hafnium oxide contained in the nanoparticles amplifies the dose of energy delivered to the tumour. The theory is that this increases the efficacy of radiotherapy, keeping the effect localised so as to limit damage to healthy tissue.

The STS study has enrolled 156 patients and is testing NBTXR3 plus radiation against radiation alone; the primary endpoint is complete pathologic response, a measure of tumour necrosis, and secondary endpoints include safety, tumour volume changes and surgical resection rates.

The interim look will include data on the first 104 patients in the trial, with the final analysis of all 156 enrolled patients due by the end of this year.

Stifel analysts point to data in head and neck cancer as being promising for NBTXR3's chances of approval in STS. The phase I/II trial in head and neck is still ongoing, but initial data from seven evaluable patients – there are 10 in the study – showed a reduction of more than 50% in tumour volumes in patients aged over 65 with advanced cancers. But this is a tiny sample size, and the trial was uncontrolled and open-label.

Nevertheless, Stifel gives the asset an 80% chance of success in STS and forecasts peak global sales of €250m ($283m) in this indication

Project	Study	Trial ID
Opicinumab	Synergy	NCT01864148
NBTXR3	-	NCT02379845

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FEATURE ARTICLES

A day of soul-searching for CAR-T bulls

Smart investors who had been wondering why, after making a huge splash about CAR-T in 2012, Novartis had grown so reticent about it over the past year or so got their answer today: the Swiss group is disbanding its cell and gene therapy unit.

The company is insisting that this is merely procedural, and that its CAR-T projects will simply be folded into the broad organisation. But the fear is that without a dedicated unit cell therapies will no longer be championed at Novartis, which coupled with yesterday's scathing initiations on Juno and Kite by the bank BTIG should make CAR-T bulls pause for thought.

As it stands of course, timelines for the leading three CAR-T projects remain unchanged, and Novartis's CTL019 is to be filed in the US next year, after Kite's KTE-C19 and before Juno's JCAR015. With the prospect of pivotal data from Kite and Novartis at December's ASH meeting there is still plenty to play for.

But news that Novartis is disbanding the cell therapy unit, broken today by Endpoints, will rock the sector. A Novartis spokesperson confirmed that the 280 of the 400 staff involved would be redeployed, with the remainder likely being let go.

Novartis remains committed to its lead CAR-T programmes, and does not agree that they will now be sidelined, the spokesperson told EP Vantage, insisting that the move reflected broader changes at the group. But without its own dedicated business unit CAR-T risks being deprioritised, and follow-on projects could fail to gain traction with R&D heads.

Novartis/Penn CAR-T projects

Project	Target	Indication	Trial ID
CTL019	CD19	Paediatric ALL	NCT02435849
CTL119	CD19	Paediatric ALL	NCT02228096
CART - BCMA	BCMA	Multiple myeloma	NCT02546167
CART22 cells	CD22	ALL	NCT02588456
CART - EGFRvIII EGFRvIII	Glioblastoma	NCT02209376	NCT01864148
CART - meso	Mesothelin	Various	NCT02388828

Certainly this is a big U-turn for the field and for Novartis, which four years ago gave the University of Pennsylvania cash to build a cell therapy lab in return for rights to CTL019, which Penn had until then been struggling to fund, and declared itself at the forefront of cancer cell therapy.

But over the past year Novartis has scarcely made more than a passing mention of CAR-T during quarterly updates. Meanwhile, Juno has struggled with patient death-related CAR-T study halts, while the Penn group has suggested switching away from CTL019 to the humanised CTL119 to overcome the problem of poor persistence (Therapy focus – How do you solve a problem like CAR-T relapse?, December 22, 2015).

A separate development has been the recent launch of Penn's own cell therapy spinout, Tmunity Therapeutics, by the same team that pioneered CTL019, headed by Dr Carl June. Tmunity is focused on T regulatory cells and engineered T-cell receptors, and there is no suggestion yet of it straying into CAR-T, likely for IP reasons.

But its formation coincides with Novartis's growing reticence on CAR-T, and in the longer term it could be seen as a vehicle that might take back any CAR-T assets that are cut loose by the Swiss group.

Asked about Tmunity the Novartis spokesperson said the group's collaboration was with Penn, and that it continued to work under its terms to advance CAR-T therapies.

The bear case

Before the Novartis news emerged CAR-T bulls had already had to digest yesterday's initiations by BTIG on Kite with a hold rating, and on Juno with a sell, adding to simmering doubts about Juno's JCAR015 even though its latest safety scare had been resolved quickly.

In a savage analysis of the sector BTIG's Dane Leone said Juno was behind the competition, and Kite, while clearly out in front, had generated limited data. With 2020 sales forecasts of $738m for KTE-C19 and $482m for JCAR015 /JCAR017 BTIG said it was $185m and $217m respectively below Street consensus.

The analysts also said anti-CD19 bispecific antibodies like Blincyto, and Johnson & Johnson /Macrogenics' MGD011, were an underappreciated threat – an argument EP Vantage has made separately (EHA – CAR-T has Blincyto breathing down its neck, June 13, 2016). Juno and Kite opened off 7% and 5% respectively this morning.

MGD011 could soon grow in prominence if data on it are reported at ASH, which could also see Zuma-1 trial results from Kite and pivotal CTL019 data. With ASH still over three months away it is already shaping up to be one of the most important healthcare meetings of 2017.

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ANALYSIS

Therapy focus – Clinging to options in Friedreich's ataxia

Before the end of the year phase III results are expected from the most advanced pipeline project Actimmune, for the inherited neuromuscular disorder Friedreich's ataxia. This interferon developed by Horizon Pharma has been on the market for two other genetic disorders for over a quarter-century.

As is often the case with rare diseases clinical setbacks in Friedreich's have been rife, but delving into the pipeline sees private and larger companies such as Shire and Abbvie hoping to make headway (see table). Targets include decreasing oxidative stress or increasing levels of the missing protein, while gene therapy is at its very early stages.

Mutated gene

Friedreich's ataxia (FA) is an inherited neurodegenerative disease that causes progressive damage to the nervous system, caused by a mutation in the gene encoding the frataxin protein necessary for proper mitochondrial function.

It leads to degeneration of the peripheral nerves and spinal cord, resulting in difficulties walking and impaired sensory functions. Heart disorders such as atrial fibrillation, along with type 1 diabetes, can affect patients, but the disease does not affect cognitive function.

Symptoms typically appear between the ages of 5 and 15 years, and the average life expectancy is 37. With a lack of medical treatments patients are monitored for symptom management and offered occupational therapy.

Santhera's idebenone received conditional market approval as Catena for FA in Canada back in 2008, but was removed from the market five years later because of a subsequent clinical trial failure (Catena once again Santhera's downfall, May 20, 2010).

Actimmune is the most advanced candidate in the pipeline, and is marketed for the chronic granulomatous disease and severe malignant osteopetrosis. In animal models of FA it has increased frataxin levels.

A phase III trial, Steadfast, completed enrolment in May having recruited 90 patients aged 10-25 who will receive Actimmune or placebo three times a week for 26 weeks. The primary endpoint is the change from baseline in neurological outcome as measured by a modified version of the FA rating scale (FARS).

A phase II trial in 12 patients showed improvements in FARS scores but could not demonstrate a clear relationship to changes in frataxin levels. Actimmune was well tolerated with no serious adverse events. It has orphan drug designation for FA and fast-track status.

Despite being such an elderly drug it has forecast sales of $745m in 2022, according to consensus from EvaluatePharma, with $249m expected in FA. Last year sales were $107m. It is holding off biosimilar competition for now, thanks to its composition of matter patent, though this expires in 2022.

Protein target

Also trying to increase frataxin levels are projects from Jupiter Orphan Therapeutics and Biomarin. Jupiter's JOT101 is a proprietary formulation of resveratrol, a natural compound present in grapes and red wine, and in January the company signed a licensing agreement with the Murdoch Children's Research Institute in Australia.

An open label phase I/II trial in 24 patients was carried out by Murdoch. This found no effect on frataxin levels, but improvements were observed in neurological function in the high-dose group. Gastrointestinal side effects were common.

Biomarin is further behind, having acquired Repligen's HDAC inhibitor programme in 2014. Repligen completed a phase I Italian trial with oral RG2833, which at high doses caused an increase in frataxin mRNA, a measure of gene expression. Little news has emerged since then, but the Freidreich's Ataxia Research Alliance website notes that Biomarin is identifying follow-on versions.

Status	Project	Company	Pharma Class	Trial ID
Phase III	Actimmune	Horizon Pharma	Interferon gamma	NCT02415127 OLE NCT02593773 Safety extension NCT02797080 Phase II NCT01965327
Phase II	EPI-743	Edison Pharmaceuticals	NADPH quinone oxidoreductase 1 modulator	NCT01962363 NCT01728064
	Epicatechin	Cardero Therapeutics	Mitochondria targeted therapy	NCT02660112
	Omaveloxolone	AbbVie/Reata Pharmaceuticals	Nuclear factor erythroid derived 2 activator	MOXIe study NCT02255435
	JOT101	Jupiter Orphan Therapeutics	Sirtuin activator	Murdoch Children's Research Institutie trial NCT01339884
	Nicotinamide	Imperial College London	Vitamin B3	NCT01589809
	RT001	Retrotope	Free radical scavenger	NCT02445794
Phase I	Oxigon/SHP622	Shire	Beta-amyloid aggregation inhibitor	NCT01898884
	RG2833	BioMarin Pharmaceutical/Repligen	Histone deacetylase inhibitor	-

Another popular area of development in FA is looking at decreasing oxidative stress or increasing mitochondrial function. Bigger pharma companies, including Abbvie and Shire, are active here.

Reata's omaveloxolone is an activator of Nrf2, a protein whose signalling is impaired in FA, resulting in an impairment of antioxidant defence mechanisms. The MOXIe phase II/III study started enrolling last year and aims to recruit 56 patients aged 16-40. Oral omaveloxolone, also known as RTA 408, is pitted against placebo in the dose-escalation study.

Reata completed its $61m IPO in May, and while shares have since risen 35% the company had to float at a 27% discount to its announced price. Abbvie's involvement stems from historic Abbott licensing agreements, and Abbvie now shares omaveloxolone development costs with Reata.

Meanwhile, Shire gained SHP622, also known as Oxigon, through its acquisition of Viropharma, which licensed rights from Intellect Neurosciences. In a phase Ib trial completed in July last year in 55 adults with FA SHP622 was well tolerated, but there were no clinically meaningful differences between treatment and placebo. According to Shire's half-year report the group is determining a path forward for the programme.

Small private companies including Edison Pharmaceuticals and Retrotope are also investigating oxidative damage as a target in FA.

Root cause

Gene therapies feature in preclinical trials, but this area has struggled to make headway in many disorders.

Voyager Therapeutics signed a $100m deal with Sanofi last year over four early-stage gene therapy assets, including one in FA. The company completed its $70m IPO towards the end of the year. Agilis Biotherapeutics and Adverum Biotechnologies are also in the space. The latter, once known as Avalanche Biotechnologies, suffered a huge setback when its wet AMD gene therapy failed.

While gene therapy remains a long way off perhaps Horizon's candidate can be the success the space so desperately needs.

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