SCRIP
CITELINE COMMERCIAL

26 Jan 2023 | **Analysis**

10 Clinical Trials To Watch Out For In 2023

Line Extensions To The Fore In 2023

by Alex Shimmings

Scrip surveys the Phase III clinical trial readout landscape and picks 10 of the more interesting studies set to report in 2023, with a few added extras. AstraZeneca, Novo Nordisk, Novartis and Roche feature heavily.

The European majors are set to dominate 2023 in terms of high-profile clinical trials readouts and it will be a year where studies of new indications of marketed drugs become more important than ever before.

Looking particularly strong on the clinical catalyst front are *AstraZeneca PLC*, *Novo Nordisk A/S* and *Novartis AG*, which all have $5bn-$6bn's worth of peak potential readouts this year. Also making the list are *Roche Holding AG*, *Pfizer Inc.*, *Eli Lilly and Company*, *GSK plc*, *Sanofi*, *Merck KGaA* and *Bayer AG*.

Analysts at Credit Suisse in a recent note estimated that about 40% of 2023's global pivotal trial value would come from drugs already approved in a different disease setting, as compared with the previous five-year average of 24%. Line extensions historically have a higher chance of success (about 80%) but have less impact on investor sentiment, they noted.

Here, *Scrip* highlights 10 of the more critical Phase III datasets due to report in 2023, in rough chronological order.

CLICK TO READ MORE:

SCRIP
CITELINE COMMERCIAL

Sanofi's CARMEN-LC03 Study Of Tusamitamab Ravtansine In NSCLC (1st Half)

One of a number of antibody-drug conjugates (ADCs) in late-stage development, the French major Sanofi's tusamitamab ravtansine (SAR408701) is the most advanced to target CEACAM5. CEACAM5, or anti-carcinoembryonic antigen-related cell adhesion molecule 5, is a member of the CEA family of proteins which plays a key role in cell migration, cell invasion, and cell adhesion, and is overexpressed by a variety of cancer cell types.

Topline data from the Phase III CARMEN-LC03 study in CEACAM5-positive second- and third-line non-small cell lung cancer (NSCLC) patients are due in the first half (prior chemotherapy and checkpoint inhibition). It has two primary endpoints: improvement of progression-free survival (PFS) compared with docetaxel up to 15 months and improvement in overall survival (OS) compared with docetaxel up to two years.

Tusamitamab has previously reported an overall response rate (ORR) of 20% in CEACAM-5 high (≥2+ intensity in more than 50% of tumor cells) but this fell to 7% in patients with moderate

CEACAM-5 expression (⩾2+ intensity in 1-50% of tumor cells). CARMEN-LC03 is enrolling CEACAM-5 high patients.

Analysts at J.P. Morgan said in a recent note that they expected the ADC to show a PFS benefit over docetaxel in this setting, though anticipate the data for AstraZeneca/Daiichi-Sankyo's TROP2-targeted ADC datopotamab deruxtecan (see below) will look numerically stronger than the French firm's product in all-comers, "potentially limiting the opportunity for Sanofi." They put peak sales of tusamitamab at €0.9bn.

The candidate was advanced under a development and commercialization agreement between Sanofi and *ImmunoGen, Inc.* formed in 2014.

Also to look out for from Sanofi:

-
  - Sarclisa (isatuximab) IMROZ Phase III readout in first-line multiple myeloma in patients ineligible for transplant, which should provide an indication of the competitive profile for Sarclisa in this setting compared with Johnson & Johnson's Darzalex (daratumumab).
  - Fitusiran (with Alnylam) full Phase III data from the ATLAS program for hemophilia in Q4

Back To Top

AstraZeneca/Daiichi Sankyo's TROPION-LUNG01 study Of Datopotamab Deruxtecan In NSCLC (1st Half)

The first Phase III readout for *Daiichi Sankyo Co., Ltd.* and AstraZeneca' second ADC offering, datopotamab deruxtecan, is due in the first half from the TROPION-LUNG01 study in second-line (and beyond) NSCLC with or without actionable genomic alterations.

Datopotamab, which targets TROP2, is also in late-stage development for use in breast cancer (both triple-negative and HR-positive/HER2-negative) and follows the two firms' blockbuster HER2-targeting ADC Enhertu (trastuzumab deruxtecan).

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is widely

expressed in several types of solid tumors, including NSCLC. While TROP2 is expressed across all lung cancer subtypes, the highest expression is seen in adenocarcinoma (64%) and squamous cell carcinoma (75%) cases (the most common forms of NSCLC).

No TROP2-directed therapies are currently approved for the treatment of patients with NSCLC, but *Gilead Sciences, Inc.* already has the first TROP2-targeting ADC, Trodelvy (sacituzumab govitecan), on the market for second-line or later locally advanced or metastatic triple-negative breast cancer (TNBC), and as a later-line therapy for locally advanced or metastatic urothelial cancer. It is also being tested in the Phase III EVOKE-01 study in metastatic NSCLC but this lags about a year behind TROPION-LUNG01.

Analysts at Deutsche Bank are positive, saying in a recent note, "As regards to thoughts into TL01, we continue to expect a win, though … we are not expecting Enhertu-like HRs against chemo in second-line NSCLC." They see peak sales of datopotamab in the region of $3.3bn in second-line NSCLC.

"If TL01 is positive, it is likely to unlock the debate around real first-line potential, based on the TL07/TL08 studies, which we expect to read out in the 2024-25 timeframe," they added.

Also to look out for from AstraZeneca:

-
  - Imfinzi (durvalumab) in AEGEAN in neoadjuvant NSCLC, EMERALD-2 in hepatocellular carcinoma, and ADRIATIC in SCLC (H1)
  - Tagrisso (osimertinib) in LAURA Stage III unresectable NSCLC (H2)
  - Enhertu in DESTINY-Breast-06 in second-line HER2-low breast cancer (H2)
  - Camizestrant SERENA-6 in first-line HR-positive metastatic breast cancer patients with ESR1 mutations (H2)

Back To Top

GSK's DREAMM-8 and DREAMM-7 Studies Of Blenrep In Second-Line Multiple Myeloma (1st Half)

GSK's blockbuster hopes for the BCMA-targeting Blenrep (belantamab mafodotin) took a hit when the product was taken off the US market late last year at the US Food and Drug Administration's request after the drug failed to show significant PFS benefits in the Phase III DREAMM-3 confirmatory study. (Also see "*Blenrep US Withdrawal Is A Big Blow To GSK's Blockbuster Hopes*" - Scrip, 22 Nov, 2022.)

Blenrep was conditionally approved in the US in August 2020 for relapsed/refractory multiple myeloma, and later that same month by the European Medicines Agency, based on response rates in the DREAMM-2 study, for patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent. The drug was the first BCMA-targeting agent to gain approval in myeloma, but eye toxicity concerns had already contributed to a modest launch trajectory – it only reached £36m ($42.8m) in revenues in the third quarter of 2022.

The product's future now rests largely on data from DREAMM-7 and DREAMM-8, both due in the first half where, along with efficacy ocular, toxicity will be a key consideration.

DREAMM-8 is a head-to-head trial of Blenrep plus pomalidomide and dexamethasone (Pd) versus bortezomib plus Pd in patients who have received at least one prior therapy including lenalidomide.

DREAMM-7, meanwhile, is an open-label study combining the drug with bortezomib and dexamethasone and comparing it to *Johnson & Johnson*'s CD38-directed cytolytic antibody Darzalex with bortezomib and dexamethasone in relapsed/refractory patients who have received at least one prior therapy. Both studies are expected to read out in the first half of 2023.

While much of Blenrep's commercial potential lies in the earlier lines of therapy being tested in these two studies and success here would unearth a lot of value, expectations are not high following the failure of DREAMM-3.

Also to look out for from GSK:

- Depmokimab Phase III data completion in December
- Pentavalent (MenABCWY) meningitis vaccine Phase III data

Back To Top

Novartis's NATALEE Study Of Kisqali In Early-Stage Breast Cancer (2nd Half)
Novartis is aiming for best-in-class status with its CDK4/6 inhibitor Kisqali (ribociclib) as it takes aim at Pfizer's market-leading Ibrance (palbociclib) and seeks to catch up with Lilly's Verzenio (abemaciclib) in the early-stage breast cancer setting.

Kisqali is approved by the FDA in combination with an aromatase inhibitor or fulvestrant as an initial endocrine therapy or following disease progression on ET for the treatment of HR+/HER2- advanced or metastatic breast cancer. It first reached the market in 2017 and is now the only CDK4/6 inhibitor with an overall survival benefit in first-line HR+/HER2- advanced breast cancer.

NATALEE is looking to bring Kisqali to early-stage patients. Novartis is testing it as an adjuvant therapy in HR+/HER2- early breast cancer, potentially opening up a new tranche of patients for the product. The study has passed its first interim analysis at 70% of events and a second interim analysis (at 85% of events) is expected in the first half; final analysis is due in the second half.

Analysts at Bank of America said in a recent note that they were somewhat reassured by the study's continuation past its first interim analysis since Pfizer's similar study of Ibrance, PALLAS, failed for futility at 67% of events. Verzenio's monarchE study in high-risk HR+/HER2- early breast cancer was stopped for efficacy at 83% of events, setting the bar for Kisqali, but the analysts see the failure to stop NATALEE at the first interim analysis as likely due to immature OS data. (Also see "*Early Adjuvant Results A Major Boost For Verzenio*" - Scrip, 17 Jun, 2020.) (Also see "*Pfizer's Hopes For Ibrance In Adjuvant Breast Cancer Fall With PALLAS*" - Scrip, 1 Jun, 2020.) (Also see "*ESMO: A Tale Of Two CDK 4/6 Inhibitors With monarchE Success and Failure For PALLAS*" - Scrip, 21 Sep, 2020.)

They describe NATALEE as an $6bn-$8bn opportunity for Kisqali, out of their total peak sales forecast for the drug of $10bn.

Also to look out for from Novartis:

- Sabatolimab Phase III readout in myelodysplastic syndromes and acute myeloid leukemia
- Iptacopan Phase III readout in IgA/C3 glomerulopathy

Back To Top

SCRIP
CITELINE COMMERCIAL

Novo Nordisk's SELECT CVOT Study Of Wegovy In Obesity (Mid-Year)

Recent advances in the obesity field are expected to mature in 2023, with Lilly's GLP1/GIP agonist Mounjaro (tirzepatide) chasing down Novo Nordisk's GLP1 analogue, Wegovy (semaglutide injection 2.4mg), in this indication.

Mounjaro has already prevailed in a head-to-head study against semaglutide (Ozempic) in diabetes, and Lilly has made noises about conducting a similar comparative trial in obesity.

In the meantime, Novo has much riding on the 17,500-patient SELECT cardiovascular outcomes study of Wegovy, along with the OASIS 1 study of oral semaglutide (see below) to shore up its semaglutide franchise.

Having now gotten past the manufacturing issues that plagued Wegovy following its launch in the US in 2021 (based on weight loss data from the SETP Phase III study), success in the CVOT study should allow the drug to unlock its potential in a vast and underserved market by loosening payors' purse strings.

As analysts at Guggenheim Securities said, "In our view, SELECT-COVT represents D-Day (demarcation day) for reimbursement and further transformation of the obesity market. We believe a positive CV outcome benefit in SELECT likely will be the first meaningful step toward broadening reimbursed access to GLP-1/incretin medications."

> ***Novo Nordisk Committed To Advancing In Cardiovascular***
>
> By Kevin Grogan
>
> 20 Sep 2022
> The Danish major's head of development tells *Scrip* that as cardiovascular disease is very closely related to obesity and diabetes, Novo Nordisk has the expertise to thrive in the former.
>
> *Read the full article here*

The study has continued beyond its interim analysis and the analysts are highly convinced that SELECT-CVOT will ultimately succeed at the final analysis, due mid-year. They put peak Wegovy sales at around $11.4bn.

Also to look out for from Novo Nordisk:

-
  - Oral semaglutide OASIS 1 Phase III data in obesity

- Semaglutide Phase III STEP data in heart failure with preserved ejection fraction

Back To Top

Lilly's TRAILBLAZER-ALZ2 Study Of Donanemab In Early Alzheimer's Disease (Mid-Year)

Lilly is set to have a busy year with four possible product launches in the offing, one of which is its potential Alzheimer's therapy, donanemab. The N3pG amyloid-ß targeting product had been poised to follow the recent approval and launch of *Eisai Co., Ltd.*/*Biogen, Inc.*'s Leqembi (lecanemab), after Lilly initiated a rolling biologics license application (BLA) to the FDA in late 2022, but the agency has just issued a complete response letter due to the limited number of patients with at least 12 months of drug exposure data in the Phase II TRAILBLAZER-ALZ clinical trial. (Also see "*US FDA Rejects Lilly's Bid For Donanemab Accelerated Approval In Early Alzheimer's*" - Scrip, 19 Jan, 2023.)

But Lilly had already intimated that it would not approach the Centers for Medicare and Medicaid Services about reimbursement until it had the results from the Phase III TRAILBLAZER-ALZ2 study in early disease. It now plans that these data will form the basis of a filing for traditional approval shortly after the topline results are in, due mid-year.

The data will be important to Lilly's future, noted analysts at Guggenheim. "We view [TRAILBLAZER-ALZ-2] as mission critical for Lilly to deliver +10% returns," they said in a recent note.

But hopes are high for TRAILBLAZER-ALZ2's success, and with some Alzheimer's drugs now reaching the market the ground is prepared for more comprehensive coverage: analysts at J.P. Morgan said in a 17 January note that they are expecting full reimbursement in late 2023/early 2024.

Lilly Does Not Expect A Quick Medicare Coverage Decision For Donanemab

By Mandy Jackson

15 Dec 2022

Donanemab may receive accelerated approval for Alzheimer's disease in early 2023, but Lilly will not approach CMS about Medicare coverage until mid-year when it has Phase III data – and even then does not expect a quick decision.

The product could also have a dosing advantage over Leqembi as it is given intravenously every four weeks as compared with Leqembi's every-two-week iv dosing, but subcutaneous versions of both products are in development.

Read the full article here

Lilly's other possible launches this year are the BTK inhibitor pirtobrutinib for mantle cell lymphoma, the IL-23-targeting mirikizumab for ulcerative colitis and the IL-13 inhibitor lebrikizumab for atopic dermatitis.

Also look out for from Lilly:

- ◦ Mounjaro (tirzepatide) SURMOUNT-2/3/4 data in obesity (mid-year)

Back To Top

Pfizer's Phase III Study Of Its mRNA Influenza vaccine Flu vaccine PF-07252220 (2nd Half)

Pfizer started the first Phase III efficacy study of an mRNA-based flu vaccine, PF-07252220, last September and results of the 25,000-patient US trial are expected mid-year. The quadrivalent modified RNA (modRNA) influenza vaccine candidate forms part of a 2018 worldwide collaboration and license agreement with *BioNTech SE*.

PF-07252220's Phase III trial is just one of a number of readouts for non-COVID mRNA vaccines expected this year: others include Phase I data for Pfizer's self-amplifying mRNA flu vaccine PF-07845104, Phase I data for GSK's monovalent mRNA flu vaccine GSK4382276A and Phase I/II data for Sanofi's respiratory syncytial virus vaccine.

Analysts from Cowan recently pointed to the potential for mRNA-based vaccines to significantly disrupt traditional vaccine markets, adding that Pfizer estimates its mRNA vaccine portfolio has annual revenue potential in the region of $10bn-$15bn.

They said the fact that mRNA vaccines for COVID-19 have shown comparable or better efficacy than traditional recombinant protein vaccines, and that the initial data for PF-07252220 showed promising cellular and humoral immune responses were reasons for optimism for the project.

However, they also noted that increased reactogenicity seen with COVID mRNA vaccines might make them unsuitable for non-pandemic vaccine markets. Furthermore, they pointed out that the PF-07252220 study has not been able to take advantage of the main putative advantages of mRNA vaccines for flu – namely, the ability to react quickly to changing viral strains due to their fast manufacturing – as it is using the same 2022-23 Northern Hemisphere strains as current culture based/recombinant flu vaccines, as recommended by the World Health Organization.

Also to look out for from Pfizer:

- ◦ Ibrance PATINA data HR+/HER2+ breast cancer Phase III data

Back To Top

Roche/Sarepta's EMBARK Study Of Gene Therapy SRP-9001 For Duchenne Muscular Dystrophy (2nd Half)

Data from the EMBARK Phase III study of Roche and *Sarepta Therapeutics, Inc.*'s gene therapy for Duchenne muscular dystrophy, SRP-9001 (delandistrogene moxeparvovec), are due in October but an approval decision should come well before then: the FDA has decided to review the drug's data early via a priority review and has set a PDUFA date of 29 May.

Sarepta had originally expected the FDA to wait for the Phase III study results before considering an approval of SRP-9001 and EMBARK has been recast as a post-approval confirmatory trial.

The study is fully enrolled with 125 patients aged four-seven, an age group in which muscle deterioration has begun but individuals are still able to walk. Its primary endpoint is change from baseline in the North Star Ambulatory Assessment total score to gauge how disability has progressed at week 52.

Analysts at Cantor Fitzgerald said in a recent note that they believed DMD was

A Duchenne Breakthrough Awaits In 2023 - But Risks Remain For Sarepta And US FDA

By Andrew McConaghie

06 Dec 2022
The FDA and Sarepta have had a controversial history with the accelerated approvals of the firm's earlier drugs for Duchenne muscular

the next rare disease opportunity poised for major growth, based on expectations of continued demand for existing therapies such as *PTC Therapeutics, Inc.*'s Translarna (ataluren), as well as the approach of SRP-9001. This therapy, they say, could potentially treat most of the ambulant DMD population, which Sarepta already dominates. Then there is the opportunity to advance therapies towards commercialization for non-ambulant patients, "where a vast unmet need remains."

dystrophy – but the company's investigational gene therapy, SRP-9001, now under a priority review, could be a genuine breakthrough.

Read the full article here

Pfizer's gene therapy fordadistrogene movaparvovec is also in Phase III testing in the CIFFREO study, but the company experienced a delay in enrolling patients in the US due to a clinical hold implemented by the FDA after the death of a non-ambulatory patient in a Phase Ib study in late 2021. (Also see "*Spotlight On High Doses Again After Pfizer Duchenne Gene Therapy Death*" - Scrip, 22 Dec, 2021.) That hold has since been lifted and the CIFFREO trial remains underway, with results due in 2024.

Also to look out for from Roche:

- Tiragolumab SKYSCRAPER-01 OS data in first-line NSCLC PD-1 high patients
- Crovalimab Phase III data in PNH
- Tecentriq Phase III data in adjuvant squamous cell carcinoma of the head and neck (SCCHN), peri-adjuvant NSCLC, hepatocellular carcinoma and triple-negative breast cancer
- Alecensa adjuvant ALK+ NSCLC Phase III interim data

Back To Top

Bayer's OASIS Study Of Elinzanetant For Menopause Vasomotor Symptoms (2nd Half)

One investigational drug of four products that Bayer is banking on to bring in a total of €12bn in peak sales is its non-hormonal menopause drug for vasomotor symptoms, elinzanetant.

The first results from its Phase III OASIS study program are expected in the second half of 2023.

Elinzanetant, which came with the September 2020 acquisition of the UK's *KaNDy Therapeutics Ltd.* inhibits both the neurokinin-1 and 3 receptors. This dual mechanism of action, which potentially reduces hyperactivity of the kisspeptin, neurokinin B and dynorphin neuronal circuit involved in thermoregulation, could give the drug an advantage over *Astellas Pharma, Inc.*'s more advanced rival fezolinetant, an oral neurokinin-3 receptor antagonist which is under priority review at the US FDA, with a decision expected by 22 February. (Also see "*Menopause Drug A Priority For Astellas*" - Scrip, 18 Aug, 2022.)

Treatment options for menopausal symptoms are limited as the current standard of care, hormone therapy, is not an option for many due to contraindications or personal preference. Elinzanetant, in contrast, demonstrated significant and rapid improvement in vasomotor symptoms in Phase II studies and was well-tolerated. Consensus peak sales forecasts for elinzanetant are more than €1bn. (Also see "*Bayer Backs Hot Flashes Drug For Blockbuster Status*" - Scrip, 9 Nov, 2021.)

Bayer's other blockbuster hopes are the anti-androgen therapy Nubeqa (darolutamide) in prostate cancer, its non-steroidal mineralocorticoid receptor antagonist Kerendia (finerenone) in kidney disease and the once-daily oral Factor XIa inhibitor asundexian in stroke prevention.

Bullish Bayer Highlights Four Future Blockbusters

By Kevin Grogan

11 Jan 2023

The German group has shone a light at the J.P. Morgan Healthcare Conference on its new launched drugs Nubeqa and Kerendia, plus its late-stage candidates asundexian and elinzanetant, as it prepares for life after patent expiries on Xarelto and Eylea.

Read the full article here

Back To Top

Merck KGaA's Phase III EVOLUTION RMS 1&2 Trials Of Evobrutinib in Multiple Sclerosis in (4th Quarter)

BTK inhibitors are set to be the next big battleground in multiple sclerosis, with a number of candidates in late-stage development. These are led by Merck KGaA's evobrutinib and Sanofi's tolebrutinib, with Roche and Novartis close behind with fenebrutinib and remibrutinib,

respectively.

It looks likely that Merck's EVOLUTION RMS 1&2 Phase III trials of evobrutinib in relapsing MS will be first up to report sometime in the last quarter of 2023, but still neck and neck with the Phase III readout for Sanofi's tolebrutinib.

BTK is expressed by B-cells and myeloid cells, both of which are considered drivers of MS, but the BTK inhibitors in development are highly selective and only target certain B-cells, which could improve the safety profile compared with CD20-targeting monoclonal antibodies, Roche's Ocrevus (ocrelizumab) and Novartis' Kesimpta (ofatumumab).

Additionally, the BTK inhibitors can cross the blood-brain barrier so they can inhibit both the B-cells and the microglia that drive disease progression in MS.

The data for both products should give an idea of how big this class could be and within it, who can take what share, said analysts at UBS in a note earlier this month.

"Despite there being a feasible theoretical justification for BTK inhibition, and both tolebrutinib and evobrutinib showing an effect on disease activity in Phase II, questions remain about the role the class will play in MS treatment and when potential differentiation could be shown."

BTK Inhibitors Are The Next Big Race In MS

By Jessica Merrill

09 Jun 2022
BTK inhibitors are in late-stage development for multiple sclerosis, with Merck KgAA and Sanofi in the lead and Roche and Novartis close behind.

Read the full article here

The analysts added that it was not clear whether BTKs will have moderate or high efficacy, if they will provide any unique benefits or if their use might be restricted due to liver toxicity.

For Merck, if successful, evobrutinib alongside its other main upcoming Phase III readout for xevinapant in head and neck cancer, should help the company weather the upcoming patent expiry for its older MS drug Mavenclad (cladribine).

Also to look out for from Merck KGaA:

- TrilynX Phase III trial of xevinapant in locally advanced squamous cell carcinoma of the head and neck

SCRIP
CITELINE COMMERCIAL

Back To Top