As a supplement to our well-known quarterly outlook report, Biomedtracker is pleased to present a longer-term look at some key late-stage drugs projected to hit the market in 2022. These drugs represent new drug classes, major changes to standards of care, and/or large market opportunities across the wide range of indications covered by Biomedtracker and Datamonitor Healthcare.

The information in this presentation, including likelihood of approval (LOA) ratings and upcoming catalysts, is up to date as of April 2021.

More details about each drug can be viewed instantly on Biomedtracker by clicking the icon.
## Contents

This report covers the following indications:

- **Allergy**  
  Pruritus

- **Autoimmune/Immunology (A&I)**  
  Crohn's Disease  
  Myasthenia Gravis (MG)  
  Psoriasis  
  Ulcerative Colitis (UC)

- **Cardiovascular**  
  Cardiomyopathy - Hypertrophic  
  Chronic Heart Failure – Preserved Ejection Fraction (Chronic HFpEF)

- **Dermatology**  
  Alopecia Areata  
  Burn Injury  
  Wrinkles  
  Vitiligo

- **Endocrine**  
  Diabetes Mellitus, Type II  
  Menopause (including HRT)  
  Non-Alcoholic Steatohepatitis (NASH)  
  Osteoporosis/Osteopenia

- **Hematology**  
  Hemophilia A and B  
  Thalassemia

- **Infectious Diseases (ID)**  
  Clostridium Difficile-Associated-Diarrhea/Infection (CDAD/CDI)  
  Seasonal Influenza Vaccines  
  Cytomegalovirus (CMV) Infection  
  Fungal Infections - Non Systemic  
  Dengue Fever  
  HIV/AIDS  
  HIV Prevention

- **Metabolic**  
  Epidermolysis Bullosa  
  hATTR Amyloidosis with Polyneuropathy  
  Menkes Disease and TK2 Deficiency  
  Niemann-Pick Disease  
  Pyruvate Kinase Deficiency  
  Wilson's Disease

- **Neurology**  
  Fragile X Syndrome  
  Postsurgical Pain  
  Seizure Disorders (Epilepsy)

- **Obstetrics/Gynecology (Ob/Gyn)**  
  Endometriosis  
  Uterine Fibroids

- **Oncology**  
  Bone Marrow & Stem Cell Transplant  
  Cervical Cancer  
  Cervical Dysplasia  
  Chronic Lymphocytic Leukemia (CLL)  
  Chronic Myelogenous Leukemia (CML)  
  Diffuse Large B Cell Lymphoma (DLBCL)  
  Follicular Lymphoma (FL)  
  Gastric Cancer  
  Mantle Cell Lymphoma (MCL)  
  Marginal Zone Lymphoma (MZL)  
  Melanoma  
  Multiple Myeloma (MM)  
  Myelofibrosis (MF)  
  Myelodysplastic Syndrome (MDS)  
  Non-Small Cell Lung Cancer (NSCLC)  
  Ovarian Cancer  
  Peripheral T-Cell Lymphoma (PTCL)  
  Post-Transplant Lymphoproliferative Disease  
  Prostate Cancer  
  Uveal Melanoma

- **Ophthalmology**  
  Wet AMD

- **Psychiatry**  
  Bipolar Disorder  
  Schizophrenia  
  Major Depressive Disorder

- **Renal**  
  Alport Syndrome  
  Focal Segmental Glomerulosclerosis (FSGS)  
  Immunoglobulin A (IgA) Nephropathy

- **Respiratory**  
  Asthma

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Click to jump directly to any of the disease groups

- Allergy  
- A&I  
- CV  
- Dermatology  
- Endocrine  
- Hematology  
- ID  
- Metabolic  
- Neuro  
- Ob/Gyn  
- Oncology  
- Ophthalmology  
- Psychiatry  
- Renal  
- Respiratory
Allergy
**Pruritus**

Dupixent is a monoclonal antibody directed against the interleukin (IL)-4 receptor alpha subunit, which blocks signaling from both IL-4 and IL-13. It is approved for atopic dermatitis, asthma, and chronic rhinosinusitis (CR) with nasal polyposis. Dupixent sales have grown since its first approval in 2017 with worldwide sales reaching $4.3 billion in 2020. Dupixent is currently in Phase III development for additional dermatological indications including pruritus (see below), chronic spontaneous urticaria (2022 submission), chronic inducible urticaria-cold (2022 submission) and bullous pemphigoid (2023 submission). Phase III development is also active for eosinophilic esophagitis (2022 submission) as well as a number of respiratory indications including Type 2 COPD, CR without nasal polyposis, and allergic fungal rhinosinusitis, all of which are expecting regulatory submissions in 2023. Two identical Phase III trials evaluating Dupixent in patients with prurigo nodularis, inadequately controlled on topical prescription therapy are expected to read out at the end of the year and, if the results are positive, regulatory submissions can be expected in 2021 with possible approval in late 2022. There is currently no standard of care for prurigo nodularis.

*Tags: Label Expansion (New Indication); Practice Changing*
RINVOQ | ABBV | LOA: ABOVE AVERAGE

Crohn’s Disease

Rinvoq (upadacitinib) is being positioned to become a first-in-class Janus Kinase (JAK) inhibitor for moderate-to-severe Crohn’s disease (CD). The drug offers a distinct mechanism of action and convenient oral route of administration beyond the current treatment armamentarium. Notably, AbbVie has extensive commercial resources and marketing experience with Humira (adalimumab), and is positioning Rinvoq as its next-generation product since Humira will face biosimilar competition in the US from 2023. AbbVie expects regulatory submissions for Rinvoq for CD in 2022, following the release of pivotal Phase III clinical trial data from its induction and maintenance studies (Clinicaltrials.gov identifier: NCT03345836 and NCT03345823). Datamonitor Healthcare forecasts blockbuster potential for Rinvoq in the Crohn’s disease market with peak sales of $1.3bn across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) by 2030.

Rinvoq is competing against fellow JAK inhibitor Jyseleca (filgotinib) in the pipeline. Jyseleca has performed well in Phase II clinical trials for CD and is being positioned to address unmet needs by targeting inadequate responders to biologic and conventional therapies as well as perianal fistulizing CD. Conversely, the benefit/risk profile of the higher 200mg Jyseleca dose has been called into question by the US Food and Drug Administration (FDA), which threatens the drug’s success. The JAK inhibitor class has been associated with venous thromboembolism events and pulmonary embolism issues which have previously caused the FDA to reject higher doses of these drugs. Nevertheless, Rinvoq has already overcome this hurdle and is marketed for the treatment of rheumatoid arthritis, whereas Jyseleca is yet to be approved for any indications in the US. For CD, it is anticipated that Rinvoq will be the first-to-market, novel JAK inhibitor and this will provide a competitive edge over Jyseleca that will facilitate uptake.

Tags: Label Expansion (New Indication), Potential Blockbuster, Practice Changing
ULTOMIRIS | ALXN | LOA: SAME AS AVERAGE

Myasthenia Gravis (MG)

Alexion's Ultomiris is a second generation, longer acting, anti-C5 monoclonal antibody developed as a follow-on to Alexion's blockbuster Soliris. Ultomiris' once every eight weeks dosing reinforces its clinical attractiveness and provides it with a competitive advantage over Soliris' biweekly dosing. This is favored both by patients and payers who benefit from reduced infusion costs and has helped drive conversion of patients from Soliris to Ultomiris in Ultomiris' first two approved indications, the ultra rare diseases paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome.

Soliris was approved in 2017 for adults with generalized MG (gMG) who are anti-acetylcholine receptor (AchR) antibody-positive, but its high-price has largely limited its use to treatment refractory patients. Ultomiris' Phase III trial is comparing Ultomiris to placebo in complement-inhibitor-naïve patients with gMG. Results from the trial are expected in Q4 2021 and Alexion expects to submit a sBLA at the end of 2021 with a possible approval/launch in late 2022. Out of a total of 60-80K total US gMG patients, Soliris is used to treat 5-8K patients. Alexion expects Ultomiris to be used in ~20K US gMG patients. While Ultomiris sales amounted to ~$1.1 billion in 2020, the expected approval for gMG has led to consensus forecasts of ~$2.5 billion for 2023. Ultomiris is also in Phase III development for a second neurological condition, neuromyelitis optica spectrum disorder, with a possible approval in late 2023.

Ultomiris may face competition from UCB's zilucoplan, a peptide based C5 inhibitor that is designed for once-daily subcutaneous self-administration. RAISE is a Phase III trial comparing zilucoplan to placebo in patients with gMG. Results are expected in Q4 2021 with an NDA submission in early 2022 and possible approval in early 2023.

Tags: Label Expansion (New Indication)
Psoriasis

BMS’ oral TYK2 inhibitor deucravacitinib has demonstrated efficacy in psoriasis patients similar to that of TNF-α inhibitors, which should drive potential uptake among patients averse to injectables, assuming pricing will ultimately compete with biosimilars. TYK2 is a member of the JAK family, but as an allosteric inhibitor deucravacitinib is differentiated as highly selective for TYK2.

By highlighting the uniqueness of the mechanistic approach, BMS hopes to avoid the black box warning and lab monitoring that accompanies even JAK1 selective inhibitors. This may prove difficult, though, as two venous thromboembolism events were seen in deucravacitinib-treated patients in the pivotal POETYK PSO-1 and -2 trials. Regardless, with deucravacitinib demonstrating superiority to PDE4 inhibitor Otezla, BMS is going into the potential launch with sights set on making deucravacitinib the number one oral brand in psoriasis.

Tags: First Approval, Potential Blockbuster

Psoriasis

Tapinarof is a once-daily steroid-free therapeutic aryl hydrocarbon receptor modulating agent (TAMA). This potential first-in-class treatment formulated as a desirable cream would provide a novel topical option for physicians and patients. Currently, corticosteroids and vitamin D derivatives are the preferred topical agents in psoriasis, however, long-term use of topical steroids is limited by the risk of skin atrophy. Although tapinarof fared well against placebo in the Phase III PSOARING 1 and 2 studies in psoriasis patients, the lack of an active comparator may limit the drug’s potential. Dermavant expects an NDA submission in mid-2021.

Tags: First Approval, New Drug Class
**Autoimmune/Immunology**

**RINVOQ | ABBV | LOA: ABOVE AVERAGE | 🗷**

**Ulcerative Colitis**

Rinvoq (upadacitinib) has generated impressive efficacy data in its pivotal Phase III U-ACHIEVE and U-ACCOMPLISH trials (Clinicaltrials.gov identifier: NCT02819635 and NCT03653026) in refractory, moderate-to-severe ulcerative colitis (UC) patients and is set to expand the market as a convenient once-daily, oral treatment option. With its likelihood of approval (LOA) at 11% above average, we expect a smooth road to approval by the US Food and Drug Administration following a planned supplemental New Drug Application in 2021. Datamonitor Healthcare forecasts Rinvoq to attain $1.4bn in peak sales for UC across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) by 2030.

Rinvoq is part of the emerging oral Janus Kinase (JAK) inhibitor class. Aside from Rinvoq, there is only one other marketed drug of the same class, Xeljanz (tofacitinib), which has been available in the US since 2018. Although it is difficult to compare across trials, the ~21–29% clinical remission (adapted Mayo Score) over placebo at week 8 in Rinvoq's pivotal trials appears very competitive versus other marketed and pipeline therapies, including fellow JAK inhibitor Xeljanz (~10–13% clinical remission over placebo at week 8 in the OCTAVE Induction 1 and 2 trials [Clinicaltrials.gov identifier: NCT01465763 and NCT01458951]). Interviewed Key Opinion Leaders in the gastroenterology space have voiced their enthusiasm towards Rinvoq and would like to prescribe it to more patients than Xeljanz as well as earlier in the treatment paradigm. Further to this, AbbVie has extensive commercial resources and marketing experience with Humira (adalimumab). The company is aligning Rinvoq as its next-generation product to defend its market share in anticipation of biosimilar adalimumab's entry in the US in 2023.

Tags: Label Expansion (New Indication), Potential Blockbuster

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**KEY POTENTIAL DRUG LAUNCHES IN 2022 (AS OF APRIL 2021)**
Cardiovascular
Cardiovacular

MAVACAMTEN | BMY | LOA: ABOVE AVERAGE | ⬤

Cardiomyopathy - Hypertrophic

Mavacamten is an allosteric inhibitor of myosin that reduces heart contractility for patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). In that condition, the thickened and stiff walls of the heart lead to obstruction of outflow, and paradoxically, the degree of obstruction can depend on the contractile force. Mavacamten's Phase III trial in patients with symptomatic oHCM showed a significant increase in the proportion of patients with a composite outcome, which consisted of both symptomatic (NYHA functional class) and functional (peak VO2) measures. The difference in responders was moderate (37% versus 17%), but over double the number of patients in the treatment group (65%) achieved improvement of one NYHA class, compared to 31% placebo, and encouragingly, 50% of treated patients achieved class I NYHA status, meaning they are no longer symptomatic, compared to 21% placebo. In addition, 74% of treated patients compared to 21% on placebo achieved a left ventricular outflow tract (LVOT) peak gradient below 50mmHg (the threshold for surgery), an endpoint likely to be of particular interest for payers, and 57% versus 7% had a reduced LVOT gradient to below 30mmHg, which is no longer considered obstructive according to diagnostic guidelines. On safety, a few patients did have reduced ejection fractions below 50%, which required temporary discontinuation of therapy, but this was also seen in the placebo group.

There are currently no drugs specifically approved for oHCM, and in the US, mavacamten has both orphan and breakthrough designations, with a PDUFA in January 2022. European filings are expected this year as well. While standard-of-care includes generic drugs with negative inotropic properties (beta-blockers, calcium channel blockers, and for combination therapy, disopyramide), a number of patients are still symptomatic or may require surgical intervention. The vast majority of patients in mavacamten’s Phase III trial were already on such medications.

Tags: First Approval, New Drug Class, Practice Changing, Potential Blockbuster
# Cardiovascular

## Chronic Heart Failure - Preserved Ejection Fraction (Chronic HFpEF)

Jardiance and Farxiga are SGLT-2 inhibitors that were initially approved for diabetes, but in cardiovascular outcomes trials (CVOTs), were found to have benefits generally in heart failure outcomes, leading to initiation of pivotal HF studies. Farxiga is already approved for HF with reduced ejection fraction (HFrEF), and Jardiance has an upcoming PDUFA for that from of HF as well. Both are also being tested in HFpEF, with pivotal trial data expected this year, so depending on the timing and type of regulatory review, approvals may come in 2022. However, chances for the drugs are mixed, and there is limited outcomes data in this segment. In the HFpEF subgroup of Farxiga’s diabetes CVOT, DECLARE-TIMI58, the drug led to a more modest, but still good, benefit on hospitalization for HF versus placebo than in the subgroup with HFrEF (hazard ratio of 0.72 compared to 0.64). However, unlike the subgroup with HFrEF, Farxiga showed no benefit on CV death, and actually had a numerical increase. The numbers of patients in these subgroups were small and they were not separately randomized, so the data are fairly tentative. Jardiance has negative data from a smaller functional trial in HFpEF, EMPERIAL-Preserved, where it failed to show an improvement in exercise ability. However, it likewise failed to show an improvement in exercise ability in a similar HFrEF functional trial, yet still showed a benefit on hospitalization for HF in an HFrEF outcomes trial, EMPORER-Reduced, which has been submitted for a label expansion. The drugs are already blockbusters, with renal benefits as well, but if the data are strong, HFpEF indications could still expand sales substantially, especially since Entresto, the first drug with an approval for HFpEF in the US, has somewhat weak data.

Interestingly, the SGLT-1/2 inhibitor Zynquista had a trial, SOLOIST, in patients stabilized after worsening HF, where it actually had numerically stronger results in the HFpEF than HFrEF subgroup, though there were far fewer HFpEF patients and the confidence intervals were wide. Lexicon is planning a broad filing including both groups this year, so it too could be approved for HFpEF patients in 2022. The data also raise hope that Jardiance and Farxiga will have positive outcomes in their larger, specific HFpEF trials. We have not included Zynquista as a highlighted drug, as it is so late to the market and likely to lag these other treatments. There’s a possibility, though, that Zynquista could have a broad HF approval, and the HFpEF trials of Jardiance and Farxiga fail. That could bolster its prospects, though there could be skepticism about its effects in HFpEF, without a larger, dedicated trial.

**Tags: New Drug Class, Practice Changing**
Dermatology
Dermatology

**Alopecia Areata**

Incyte and Eli Lilly recently announced positive updated results from both of their Phase III trials (BRAVE-AA1 and BRAVE-AA2) which evaluated the efficacy and safety of their Janus kinase (JAK) inhibitor, baricitinib, in adult patients with severe alopecia areata. In both trials, a statistically significant proportion of patients in the treatment arm achieved the primary endpoint of scalp hair regrowth compared to placebo across two different doses (2mg and 4mg) over 36 weeks.

Based on these results, Eli Lilly plans to submit a supplemental New Drug Application (sNDA) to the FDA for baricitinib in alopecia areata in the second half of 2021, followed by submissions to other regulatory agencies around the world. This potential approval would expand Incyte's Olumiant franchise outside of rheumatoid arthritis where it has been approved since 2018.

*Tags: Label Expansion (New Indication)*

**Vitiligo**

Incyte's ruxolitinib, which targets Janus kinase 1 and 2, is already approved in oral form as Jakafi by the US FDA for graft vs. host disease, polycythemia vera, and myelofibrosis. In the near term, Incyte is expecting a PDUFA decision for ruxolitinib cream for the potential treatment of atopic dermatitis on June 21, 2021. An expected 2022 approval for ruxolitinib cream in vitiligo, therefore, would expand the drug's label and has the potential to add significant revenue to Incyte's ruxolitinib franchise.

At present there are no products specifically approved to improve vitiligo in the US: treatment is with off-label topical treatments including steroids and calcineurin inhibitors, narrowband UVB phototherapy, surgical transplantation or depigmentation (skin bleaching). All of these have drawbacks, whether they be unwanted side effects or inconvenience, and although around 3-6.5 million people in the US and 75-150 million people worldwide are thought to be affected by the disease, the large majority go untreated.

*Tags: Label Expansion (New Indication); Practice Changing; Potential Blockbuster*
Dermatology

**DAXI | RVNC | LOA: ABOVE AVERAGE | ↪**

**Wrinkles**

DAXI is a next-generation, injectable neurotoxin that integrates Revance’s proprietary, purified botulinum toxin type A molecule with the patented TransMTS peptide technology.

DAXI met all primary and secondary endpoints in both Phase III trials SAKURA 1 and 2 and demonstrated an impressive six-month median durability which should allow patients to be treated twice a year versus three to four times a year with currently approved botulinum toxins. DAXI’s attractive durability gives it enough differentiation from currently approved therapies to capture a significant proportion of the wrinkles market.

In addition to cosmetic uses, Revance is developing DAXI for therapeutic indications such as cervical dystonia and neuromuscular spasm and spasticity, increasing DAXI’s commercial prospects further.

*Tags: Practice Changing*

**NEXOBRID | VCEL | LOA: ABOVE AVERAGE | ↪**

**Burn Injury**

NexoBrid is a topically administered eschar removal agent that consists of a mixture of enzymes extracted from the stem of the pineapple plant and has been approved in Europe since 2012 for the treatment of burn injuries. Results from the US Phase III study (DETECT) demonstrated very strong statistical significance in the primary endpoint of incidence of complete eschar removal compared to gel vehicle (93.3% vs. 4%, respectively). Similar significance was demonstrated in each secondary endpoint comparing NexoBrid to standard of care showing shorter times to achieving complete eschar removal, lower incidence of surgical eschar removal, lower blood loss, and a much-improved score at 12 months on the modified Vancouver Scar Scale.

Confidence in this drug is high since ahead of NexoBrid’s PDUFA date on June 29, 2021, the Office of the Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services, has accepted the first shipment of NexoBrid as part of its mission to build national preparedness for public health emergencies.

*Tags: First Approval in US; Practice Changing*
Endocrine
Endocrine

**TIRZEPATIDE** | LLY | LOA: ABOVE AVERAGE |

**Diabetes Mellitus, Type II**

Tirzepatide is expected to be the first GIP/ GLP-1 co-agonist approved, for Type 2 diabetes. The GLP-1 agonist class is of course well known and has seen strong growth recently. Phase III results for tirzepatide showed better glycemic control and weight loss than the highest currently approved dose of the most effective GLP-1 agonist, Ozempic, albeit with some tradeoff in side effects, and suggest that high doses of tirzepatide may still have modest advantages over Novo Nordisk's Ozempic 2mg, which may also be approved in 2022. Comparisons with Ozempic's 2.4mg dose in obesity are complex, given different weight loss in obese diabetics versus non-obese, and that dose of Ozempic also had fairly high rates of GI side effects. Tirzepatide will face some barriers, though. Its titration period could be somewhat of a hassle for patients, and unlike Ozempic, it does not yet have a cardiovascular indication. Novo Nordisk also hopes to see substantially more weight loss combining Ozempic with an amylin analog which the company is developing for obesity. Finally, tirzepatide is an injectable, and like the injectable GLP-1 agonists, will be facing competition from Rybelsus, the first oral GLP-1 agonists, and potentially other oral candidates in the pipeline. Still the drug could well become a blockbuster, though a large portion of its sales may be from cannibalizing Lilly’s own Trulicity.

*Tags: New Drug Class, Potential Blockbuster*
Endocrine

FEZOLINETANT | ASTELLAS | LOA: ABOVE AVERAGE | 🔄

Menopause (including Hormone Replacement Therapy [HRT])

Fezolinetant is a once-daily, oral neurokinin 3 (NK3) receptor antagonist, which acts upon specific neurons that control body temperature to mimic the effects of estrogen making it amenable to treating menopause-related vasomotor symptoms (MR-VMS). The drug is being studied in the pivotal Phase III SKYLIGHT clinical trial program for the treatment of moderate-to-severe MR-VMS. Positive top-line results from the SKYLIGHT 1 and 2 trials (Clinicaltrials.gov identifier: NCT04003155 and NCT04003142) were announced in January and February 2021 with minimal details released. For both trials, Astellas reported that the 30mg and 45mg doses met the co-primary endpoints, namely, the frequency and severity of vasomotor symptom (VMS) at both week 4 and 12. In this way, Astellas has satisfied the four US Food and Drug Administration (FDA)-recommended co-primary endpoints. Detailed results have only been released for fezolinetant’s Phase II trial in MR-VMS (Clinicaltrials.gov identifier: NCT03192176). Despite the high placebo response (55% reduction), the reduction in VMS frequency from baseline to week 12 was still larger for the once-daily (75.1%-77.9%) fezolinetant regimens (30mg, 60mg, and 120mg).

Overall, fezolinetant’s prospects appear positive and its likelihood of approval for MR-VMS is 6% above average. The drug is attractive as a novel, non-hormonal alternative to the standard-of-care hormonal therapies that may be associated with increased risks of breast cancer and venous thromboembolic events. The relevance of modulating neurokinin signalling to regulate dynorphin (KNDy) neuron activity in the thermoregulatory pathway is also being tested by NT-814 in KaNdy Therapeutics’ Phase IIb SWITCH-1 trial (Clinicaltrials.gov identifier: NCT03596762). Advantageously, fezolinetant is on track to reach Phase III faster than its competitor NT-814, as the latter is expected to initiate Phase III investigations in 2021.

Tags: First Approval, New Drug Class, Practice Changing
Endocrine

**OCALIVA | ICPT | LOA: ABOVE AVERAGE | 📌**

**Non-Alcoholic Steatohepatitis (NASH)**

While US approval has been delayed by the surprise receipt of a Complete Response Letter (CRL) in June 2020, Ocaliva (obeticholic acid) is likely to be the first therapy approved for the treatment of NASH in 2022 if Intercept resubmits an NDA in late 2021, though its monopoly will be short-lived and it will face fierce competition from pipeline therapies with more promising risk/benefit profiles (eg resmetirom, semaglutide, lanifibranor, and efruxifermin). There are currently no disease-specific approved therapies for NASH, and the disease represents a significant unmet need due to its high clinical and economic burden on healthcare systems and the large prevalent population. Indeed, NASH is expected to become the leading indication for liver transplant in the US in the next few years, increasing the urgency of finding an efficacious therapy.

Ocaliva was the first therapy to display a significant (but modest) increase in the percentage of patients achieving an improvement in fibrosis with no worsening of NASH vs placebo in the pivotal REGENERATE trial, though it had a weaker impact on NASH resolution without worsening of fibrosis, which did not reach statistical significance in the primary intent-to-treat analysis of F2/F3 patients at 18 months. Efficacy was also greatest with the higher 25mg dose, but this triggered pruritus in 51% of recipients, which is a significant drawback vs other pipeline therapies with improved tolerability profiles. In addition, Ocaliva was associated with LDL-C increases which could be problematic in patients with pre-existing dyslipidemia or CV risk factors, and could require concomitant use of statins in patients not already receiving them. Notably, the FDA's initial CRL was issued because the agency was concerned that Ocaliva's risk/benefit profile was not strong enough for widespread use in the NASH population, as well as concerns over the over the reliability of NASH surrogate endpoints and their correlation with improvements in clinical outcomes, thus Intercept is gathering additional longer-term efficacy and safety data from the pivotal REGENERATE trial to include in its NDA resubmission in late 2021.

*Tags: First Approval, New Drug Class, Practice Changing*
ABALOPARATIDE-TD | RDUS | LOA: SAME AS AVERAGE |  

Osteoporosis/Osteopenia

The current market size for anabolic therapies in severe osteoporosis is limited by the use of daily injectables in the majority of patients, which results in poor patient compliance and persistence, thereby reducing sales potential. Radius Health is currently developing a daily administered transdermal patch of abaloparatide, which is expected to drive broader uptake of anabolic therapies in patients who wish to avoid injectable drugs, as well as cannibalizing the share of the existing subcutaneous formulation of abaloparatide (Tymlos). If priced comparably to the current price of injectable Tymlos, which is already competitive with Forteo (teriparatide) and biosimilar versions of teriparatide, the abaloparatide transdermal patch is expected to emerge as the leading anabolic therapy. The patch will face competition from Amgen’s injectable Evenity (romosozumab), which is only administered once-monthly, though there are lingering concerns over increased risk of CV events with the latter which currently precludes uptake in patients with pre-existing CV risk factors. Should an ongoing pivotal trial comparing the transdermal patch against injectable Tymlos yield positive results in H2 2021, approval and launch could occur in H2 2022.

Tags: Practice Changing
Hematology

**BIVV 001 | SNY | LOA: SAME AS AVERAGE**

Hemophilia A

Amunix’s proprietary XTEN technology has been utilized to extend BIVV 001’s half life beyond what was previously achieved by extended half-life (EHL) factor VIII (fVIII) products such as Eloctate and Adynovate. The fusion protein consists of recombinant fVIII, which is fused to the D’D3 domain of VWF via an IgG Fc and two XTEN polypeptides. So far, Phase I/IIa trials have shown that the XTEN modification increases the half-life of fVIII by three- to four-fold, from 13.2 hours for standard recombinant fVIII to 42.5 hours for BIVV 001 in the higher dose group. Even more impressively, patients achieved fVIII activity within the normal range (50-150%) for four days following infusion and remained at reasonable levels by day 7 (17%). Given that current replacement factors have troughs as low as 1-3%, a trough of 17% is a substantial improvement. Together these pharmacokinetic data from early-stage trials indicate that the BIVV 001 will have a weekly dosing schedule as opposed to the bi-weekly schedule needed for EHL products. Although BIVV 001 has the potential to be a best-in-class fVIII product, its uptake will be limited by competition with Hemlibra which benefits from a superior two-week dosing regimen and a more convenient subcutaneous route of administration. Nonetheless, with the hemophilia market continuing to expand, if priced competitively BIVV 001 will likely capture significant market share away from older fVIII products. In particular, there are strong opportunities in the on-demand segment of the market, given that Hemlibra is used for prophylaxis only. Having captured some market share from recombinant fVIII and EHLs, BIVV 001 is projected to achieve blockbuster sales, however, competition with the current market-leader, Hemlibra, and the anticipated launch of gene therapies will lead to intense competition.

Assuming positive results in the Phase III XTEND-1 trial, expected in January 2022, current timeline indicate the drug will gain approval in H2 2022 with a potential launch at the end of 2022. The Phase III trial will evaluate the efficacy and safety of BIVV 001 as both an on-demand and prophylaxis therapy, with patients receiving on-demand treatment for 26 weeks before switching to a 26 weeks of prophylaxis. The primary endpoint will be a reduction in annualized bleed rate, while secondary endpoints will more comprehensively cover bleed rates and types, as well as fVIII activity and a physician assessment. Approval and launch in the EU is not expected until 2023/24.

**Tags:** Potential Blockbuster

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**KEY POTENTIAL DRUG LAUNCHES IN 2022 (AS OF APRIL 2021)**
Hematology

FITUSIRAN | SNY | LOA: BELOW AVERAGE

Hemophilia A/B

Fitusiran, a first-in-class RNAi targeting antithrombin, is being investigated for the treatment of all hemophilia A and B patients with or without inhibitors. The drug benefits from a favorable once every two-month dosing, delivered by subcutaneous injection, a larger patient population, and strong efficacy data in Phase II trials. However, Fitusiran has been plagued with safety concerns which will likely prevent its uptake following its planned 2022 launch. While clinical trials have shown that the drug is efficacious with a median ABR of 1.08, which is in line with other drugs in the space, there were serious safety concerns after one patient died as a result of an intracranial blood clot in Phase II trials. Despite amendments to safety protocols, there was a second adverse thrombotic event, albeit non-fatal, which led to the FDA placing a second clinical hold on the drug in November 2020. Since then, the FDA has agreed with a lower dosing regimen of 50mg every two months as opposed to its original monthly dosing.

A reduction in the dosing to once every two months will likely reduce the drug’s efficacy, and therefore it is critical that Fitusiran achieves a clean safety and efficacy profile, comparable to the standard of care, in its upcoming Phase III data-readout. Although Fitusiran will not stand competition in the hemophilia A space, it has market potential for hemophilia B patients with inhibitors.

Tags: First Approval, New Drug Class
Hematology

**AMT-061 | QURE | LOA: ABOVE AVERAGE | 🟢**

**Hemophilia B**

With the US FDA lifting the clinical hold on AMT-061 in April 2021, UniQure's gene therapy remains on track for 2021 BLA filing and is set to become the first-to-market gene therapy in the hemophilia space. The drug has shown impressive efficacy in Phase IIb trials and from interim data of its Phase III HOPE-B trial. In the HOPE-B trial, a single infusion of AMT-061 increased mean factor IX (fIX) activity from 1.2% to 37.2%, reduced annualized bleed rate (ABR) to a projected 0.8 bleeds per year, and reduced reliance on replacement fIX by 96%. Importantly, current estimates indicate UniQure's hemophilia B gene therapy will be durable for over five years, based on long-term data on the former product, AMT-060, and two-year data on AMT-061.

Gene therapies offer a substantial advancement in the dosing schedule compared to the current standard of care, recombinant fIX and extended half life fIX products (twice and once weekly-dosing schedules, respectively). The launch of gene therapies will lead to a shift in the treatment paradigm for severe hemophilia B patients, although uptake will be initially muted given patient and physician hesitation.

Tags: First Approval, Potential Blockbuster, New Drug Class, Practice changing

**PF-06838435 | PFE | LOA: ABOVE AVERAGE | 🟢**

**Hemophilia B**

Like competitor AMT-061, Pfizer’s PF-6838435 has shown impressive efficacy data with an ABR below 1. Importantly, PF-06838435 has the advantage of having four years of long-term safety and efficacy data, whereas UniQure's long-term data is based on its AMT-060 product, which did not use the high activity Padua fIX variant. In the Phase I/II trial 15 participants received a single infusion of the gene therapy, encouragingly fIX activity was stabilized across the four years, with a mean steady-state fIX activity of 22.8%, 26.5% 23.3% & 29.1% at years 1, 2, 3 & 4, respectively. Though this is lower than the target range of 50-150%, fIX activity of 20-49% correlates with substantial clinical improvement. Phase III data, after one-year-post infusion, will be needed to provide some insight into the relative efficacy of these therapies.

Pfizer’s latest Q1 update indicates that its gene therapy has completed patient enrollment and initiated the lead-in phase of the study, with interim 26-week data expected to read out towards the end of 2021. Assuming 26- and 52-week data are positive, Pfizer will gain approval of its gene therapy within a year of the launch of UniQure's AMT-061.

Tags: First Approval, Potential Blockbuster, New Drug Class, Practice changing
Hematology

**ZYNTEGLO** | BLUE | LOA: ABOVE AVERAGE | 📚

### Thalassemia

Zynteglo is the most advanced gene therapy for transfusion-dependent beta-thalassemia, with an ongoing rolling BLA in the US and conditional approval already in the EU. It has shown quite good results, with high percentages of patients transfusion free, after good increases in hemoglobin, though the trials are still ongoing as only a limited number of patients have been followed long enough for the primary endpoint. Preliminary results were somewhat stronger in Non-beta0/beta0 than beta0/beta0, but they have been quite good in both.

The drug has hit a couple roadblocks, however. Completion of the rolling BLA has been delayed due to the need to submit data on release assays before the FDA reviews the drug. Moreover, due to a case of acute myeloid leukemia (AML) and a second case of myelodysplastic syndrome (MDS) in sickle cell anemia, the company needs to assuage concerns about risks in beta-thalassemia with the FDA and, for renewal of conditional approval in the EU, the EMA. In fact, the company paused marketing for beta-thalassemia in Europe (it has also discontinued marketing in Germany, though that is due to reimbursement issues). Prospects are somewhat hopeful, as the diagnosis of the second case of MDS has now been revised to transfusion-dependent anemia and tests have suggested that the case of AML was not due to the therapy, but more details could come out and it remains to be seen how regulators view the issue.

The delays have allowed competition to heat up, with Vertex hoping to accelerate development of CTX001, which uses CRISPR/Cas9 gene editing for more precise insertion of the gene, to mitigate potential concerns about oncogenesis.

*Tags: New Drug Class, Practice Changing, Potential Blockbuster*
Infectious Disease
Infectious Disease

SER-109 | MCRB | LOA: ABOVE AVERAGE | 📊

**Clostridium difficile-Associated Diarrhea/Infection (CDAD/CDI)**

SER-109 is a microbiome-modulating therapy in Phase III development for the prevention of C. difficile infection in patients with a history of recurrence. It consists of the purified spores of approximately 50 bacterial species normally found in the human gut and aims to restore the ‘good’ gut microflora following standard of care antimicrobial therapy to prevent recolonization by C. difficile. Seres Therapeutics is expected to file for the therapy’s approval in late 2021 or early 2022, paving the way for it to become the first microbiome therapeutic approved for the prevention of C. difficile, addressing a major unmet need that prophylactic vaccine approaches have thus far failed to do, though Pfizer’s vaccine (PF-06425090) may yet generate positive data from its ongoing Phase III CLOVER trial in 2021. SER-109 could also face near-term competition from Rebiotix’s rival microbiome therapy, RBX2660, which has demonstrated positive Phase II data and is expected to report topline data from the pivotal PUNCH CD3 trial in 2021.

In the Phase III ECOSPOR III study, in which patients who had completed acute antimicrobial treatment for C. difficile infection were randomized to receive SER-109 or placebo, SER-109 showed a statistically significant and clinically meaningful reduction in C. diff recurrence at 12-weeks post treatment (16.7% recurrence rate with SER-109 vs 47.8% with placebo), and a favorable safety profile. However, given the study only enrolled 182 patients, the FDA has requested that Seres conduct the open-label ECOSPOR IV extension study to enrol more patients and meet the threshold of 300 patients required for the safety database. The study is currently enrolling patients, and we wait an update from the company on when the target enrolment has been met.

*Tags: New Drug Class, Practice Changing*
Infectious Disease

MARIBAVIR | TAK | LOA: ABOVE AVERAGE |

Cytomegalovirus (CMV) Infection (Antiviral)

Maribavir is a novel class of antiviral (UL97 kinase inhibitor) that aims to address an unmet need for additional treatment options in hematopoietic or solid organ transplant patients with either wild type or refractory CMV infection. Maribavir has already achieved promising results in patients with CMV infection that is refractory to current treatment options (ganciclovir, valganciclovir, foscarnet, or cidovir) in the Phase III SOLSTICE trial, where 56% of maribavir-treated patients achieved confirmed CMV clearance by week eight vs only 24% on investigator-assigned therapies. In addition, maribavir showed a reduced rate of neutropenia vs valganciclovir/ganciclovir (2% vs 25%) and a reduced rate of acute kidney injury vs foscarnet (2% vs 19%), positioning it as the new standard of care in this high unmet need setting.

Phase III data in wild-type CMV patients are not yet available but are expected by the end of H1 2021, and if maribavir can demonstrate non-inferior efficacy to current standard of care antivirals, this should be sufficient for approval in the first-line setting, though it will be competing in a highly genericized space. An NDA submission for both settings is expected in Q3 2021, paving way for approval in H1 2022.

Tags: Practice Changing, New Drug Class
Infectious Disease

TAK-003 | TAK | LOA: ABOVE AVERAGE

Dengue Fever – Vaccines and Treatments

TAK-003 is a second-generation live-attenuated vaccine and is expected to supersede Sanofi’s Dengvaxia, which has been a commercial failure after post-approval safety issues and a requirement for pre-vaccination serostatus screening prevented rollout in routine immunization programs of dengue endemic markets. Phase III TIDES data indicate that TAK-003 is efficacious regardless of serostatus (Dengvaxia lacks efficacy in seronegative/previously uninfected individuals) and no concerning safety signals have been identified thus far, which makes it a much more attractive candidate for national immunization programs, since parallel serostatus screening programs are not required. Importantly, this also places TAK-003 in a position to establish a monopoly in the lucrative traveler market, given that Dengvaxia’s inconvenient dosing schedule and lack of efficacy in seronegative individuals effectively preclude its use in this setting. Additional advantages include TAK-003’s favorable two-dose schedule (0 and 3 months), which will likely have a higher compliance rate than Dengvaxia’s three-dose regimen (0, 6, 12 months), and its wider target age range (4–16 years), which will address the unmet need of providing an immunization strategy for younger children.

However, TAK-003 could ultimately face competition from TV-003 and/or TV-005; formulations of a rival live-attenuated vaccine that are being developed in single-dose schedules. TV-003 is currently being investigated in a Phase III trial in Brazil with topline results expected in H2 2021, thus it could reach the Brazilian market in late 2022, where it will be produced domestically by the Butantan Institute and likely marketed at a much lower price than TAK-003. The vaccine has been licensed to Merck & Co in the US, Canada, China, Europe, and Japan, and various other developers in India, the Middle East, and Asia-Pacific markets (Biological E, Medigen Biotechnology, Panacea Biotec, Serum Institute of India, and Vabiotech) with the goal of facilitating cheaper domestic production in key endemic markets.

Tags: Potential Blockbuster, Practice Changing
Infectious Disease

OTESECONAZOLE | MYCOVIA | LOA: ABOVE AVERAGE |

**Fungal Infections – Non-Systemic**

Oteseconazole is a small molecule inhibitor of lanosterol demethylase (CYP51), an enzyme involved in the synthesis of fungal cell wall sterols. Due to its more selective and higher affinity binding to CYP51, it has the potential for improved efficacy and reduced risk of side effects compared to the current standard of care azoles (eg fluconazole), which have off-target effects on the human CYP450 enzyme. Oteseconazole is expected to become the first approved antifungal for the treatment of recurrent vulvovaginal candidiasis (RVVC) in early 2022, following an anticipated NDA submission in Q2 2021.

The NDA filing will be based on compelling data from the pivotal VIOLET and ultraVIOLET studies, which collectively showed that oteseconazole was non-inferior to fluconazole in the resolution of symptoms for the acute treatment of RVVC, but greatly superior to placebo in reducing the likelihood of recurrence following acute treatment (91-96% reduction across the studies). Current management of RVVC comprises of retreatment with an induction period of fluconazole for 10–14 days, followed by an extended six-month treatment period, but some recurrent infections are resistant to fluconazole, and rates of resistance are increasing, thus oteseconazole will address a major unmet need for additional treatment options.

*Tags: First Approval, Practice Changing*
Lenacapavir is a first-in-class long-acting viral capsid inhibitor which will initially be approved for the treatment of heavily treatment-experienced patients with multi-class resistance in 2022, an area of unmet need where novel therapies are required to allow patients to construct a regimen capable of inducing stable virologic suppression. Lenacapavir will compete in this setting with ViiV Healthcare's twice-daily oral Rukobia, but we expect lenacapavir's six-monthly SQ dosing will allow it to become the leading therapy in salvage patients, who are likely to have more complex regimens with higher pill burdens and may struggle to adhere to daily oral pills. In addition, lenacapavir is also being investigated in combination with other antiretroviral agents in the treatment-naive and maintenance settings, with results from the Phase II CALIBRATE trial expected in H2 2021. In March 2021, Gilead and Merck & Co formed a partnership to develop a dual-combination of islatravir/lenacapavir as long-acting oral (LAO - likely once-monthly) and long-acting injectable (LAI - likely every six months) regimens, and we believe these regimens could surpass traditional once-daily three drug regimens as the future standard of care, though the LAO and LAIs will be launched in 2025 and 2027 at the earliest.

Tags: Potential Blockbuster, New Drug Class
Infectious Disease

VOCABRIA | GSK | LOA: ABOVE AVERAGE | 🟢

HIV Prevention

Vocabria is a long-acting injectable formulation of cabotegravir under development by ViiV Healthcare for use in MSM, transgender women, and cisgender women. Following a five-week oral lead-in period and two initial injections separated by four weeks, cabotegravir is dosed bimonthly thereafter, addressing a major unmet need for additional treatment options capable of improving adherence to therapy.

Vocabria is expected to become the market leader following its anticipated US and EU approvals in late 2021/early 2022 because it showed superiority to Truvada in reducing the risk of HIV acquisition in the HPTN 083 trial in MSM and transgender women. Similarly, in the HPTN 084 trial in cisgender women, cabotegravir demonstrated superiority to Truvada on the same endpoint. However, Vocabria will face pricing pressure from generic Truvada, and its pricing will need to reflect this. Key drawbacks for Vocabria include its requirement for physician administration due to its IM formulation, which will be viewed as inconvenient by some patients, and will also pose a logistical hurdle to primary care physicians due to a greatly increased number of appointments required. The latter is a key disadvantage compared to Merck & Co's once-monthly oral islatravir, which while requiring more frequent dosing, would avoid the need to visit a physician.

Tags: Potential Blockbuster, Practice Changing
Infectious Disease

**NANOFLU** | NVAX | LOA: ABOVE AVERAGE |

**Seasonal Influenza Vaccines**

NanoFlu is a first-in-class seasonal influenza nanoparticle vaccine which has demonstrated superior immunogenicity to Sanofi’s Fluzone and Fluzone HD and aims to address an unmet need for vaccines capable of providing superior protection in the elderly. NanoFlu’s hemagglutinin (HA) antigen is produced via a cell-based process and thus avoids the risk of egg-adaptation mutations which are thought to impair the effectiveness of vaccines produced by the more laborious egg-based manufacturing process. In addition, NanoFlu includes Novavax’s proprietary Matrix-M adjuvant, which boosts immunogenicity, particularly cellular responses, which may provide another avenue for differentiation from established competitors. Having achieved positive Phase III results, we expect that Novavax will file a BLA in the US in H2 2021, paving way for approval in time for the 2022/23 influenza season.

Topline results from a Phase III head-to-head study against standard dose Fluzone (standard dose) in the elderly showed superior immunogenicity with NanoFlu against both well-matched and antigenically drifted H3N2 strains, suggesting it could improve upon the poor vaccine effectiveness currently observed in this key risk group. In addition, earlier Phase II comparisons against Fluzone HD showed that NanoFlu induced statistically significantly increased antibody titers against H3N2 strains, and this comparison is particularly important given Fluzone HD is the current standard of care in the elderly, not standard dose Fluzone. These positive immunogenicity data position NanoFlu as a strong competitor for Fluzone HD, Flublok, and Fluad (the vaccines preferentially used in the elderly due to evidence of improved effectiveness), but its uptake will be hinge on the outcome of a planned post-approval confirmatory efficacy study, as some physicians/payers will not be willing to infer that superior immunogenicity necessarily results in improved real-world protection.

*Tags: New Drug Class*
Metabolic
Epidermolysis Bullosa

Filsuvez is a topical herbal formulation including triterpenes, which are believed to stimulate keratinocytes to migrate to the site of wounds and mature into epithelial skin cells, thus assisting in wound closure. It has the potential to be the first ever therapy approved to promote wound closure in patients with recessive dystrophic epidermolysis bullosa (RDEB), a debilitating genetic disease in which the skin is very fragile and prone to blistering, scarring, and thickening in response to minor trauma or friction. Filsuvez is currently under review by the FDA and EMA, with US and EU launches expected in Q4 2021 and Q1 2022, respectively.

The regulatory filings for Filsuvez are supported by data from the pivotal EASE trial, in which Filsuvez was shown to significantly accelerate wound closure vs placebo in patients with RDEB (79% of enrolled patients), but it had no discernible effect on patients with dominant dystrophic epidermolysis bullosa or junctional epidermolysis bullosa. Somewhat disappointingly for Amryt, Filsuvez did not significantly increase the percentage of wounds with complete closure, nor did it significantly reduce itching, or pain associated with dressing changes, which will hamper payers’ perception of its value, but will not prevent approval.

Tags: First Approval, Practice Changing, New Drug Class
Epidermolysis Bullosa

D-Fi is currently in a race with rival topically-administered gene therapy, B-VEC, to become the first gene therapy approved for the treatment of RDEB in 2022, potentially addressing an unmet need for an indication with no currently approved therapies.

D-Fi comprises autologously-derived fibroblasts that are genetically modified ex-vivo using a lentiviral vector to express a functional COL7 gene. The modified fibroblasts are then injected intradermally into wound sites in patients suffering from recessive dystrophic epidermolysis bullosa (RDEB) with the aim of achieving wound closure. By modifying fibroblasts ex-vivo, integration of the viral genome into off-target cells is avoided and repeat dosing becomes possible.

Earlier Phase I/II data showed that 63% of wounds treated with D-Fi achieved complete wound closure vs 0% in the placebo arm, thus we have high hopes for the therapy given the same primary endpoint (proportion of wounds that achieve complete closure by week 24) is being used in the ongoing intra-patient placebo-controlled Phase III DEFI-RDEB study that is expected to report results later this year, paving the way for approval in 2022.

Tags: Practice Changing, New Drug Class

Epidermolysis Bullosa

Beremagene geperpavec (B-VEC) has the potential to be the first gene therapy approved for DEB in 2022, though it will compete with rival gene therapy, D-Fi, which is also expected to yield pivotal trial data this year. B-VEC is a non-integrating, replication-incompetent HSV-1 that has been engineered to deliver a functional human COL7 gene directly to dividing and non-dividing skin cells in patients with dystrophic epidermolysis bullosa (DEB). The gene therapy is applied topically once-weekly, and is safe for repeat dosing because the virus does not integrate into the human genome, leading to transient transgene expression.

Topline results are expected from the pivotal GEM-3 study in Q4 2021, which is evaluating the potential of B-VEC to promote complete wound closure vs placebo in 30 DEB patients receiving once-weekly treatments. Patients act as their own control, with each patient having at least one pair of matched wounds that will be treated with B-VEC and placebo, respectively. Earlier data from a Phase I/II study found that 90% of wounds (9/10) treated with B-VEC had fully closed by day 120 of treatment, and the only wound that didn’t close (which had previously been open for four years) did achieve closure after re-administration of B-VEC, providing a promising proof of concept.

Tags: Practice Changing, New Drug Class
Hereditary Transthyretin (hATTR) Amyloidosis With Polyneuropathy (Familial Amyloid Polyneuropathy)

Vutrisiran is Alnylam’s next generation siRNA for treating ATTR amyloidosis. An NDA was recently submitted for hATTR with polyneuropathy, and if it receives priority review, the PDUFA will be mid-December, so the bulk of its launch will be in 2022. The drug is also in a pivotal trial for ATTR with cardiomyopathy — either hereditary or wild type — but that is not expected to complete for a few years. While Alnylam’s first approved drug for hATTR with polyneuropathy is quite effective, it must be given intravenously every three weeks, with premedication to prevent infusion-related reactions. Vutrisiran in contrast is given subcutaneously every three months, which will of course be much more convenient for patients, though it is still anticipated that the drug will be given by health providers, which in the US would allow reimbursement under the medical rather than pharmacy benefit, with consequent advantages in some segments. Ionis does have a subcutaneous option for hATTR with polyneuropathy on the market, but it is a weekly injectable with black box warnings for side effects, necessitating frequent monitoring, so has lagged in the market. Ionis’s next generation drug, AKCEA-TTR-LRx, could be more of a competitor, and is currently undergoing clinical trials, though it will have monthly dosing, which will also mean it is more likely to be reimbursed under the pharmacy benefit.

While a number of hereditary patients have both polyneuropathy and cardiomyopathy symptoms, the hereditary market is much smaller than that for wild-type ATTR cardiomyopathy, so an additional future cardiomyopathy indication for vutrisiran will substantially expand the potential market. There is also already an oral medication approved for ATTR cardiomyopathy, Pfizer’s Vyndaqel/Vyndamax, but the hope is that vutrisiran may be even more effective. In addition, as noted above, reimbursement for vutrisiran could be an advantage in some segments.

*Tags: New Drug Class, Practice Changing, Potential Blockbuster*
Metabolic

**CUTX-101** | **SENTYL/FBIO** | LOA: ABOVE AVERAGE | **MT1621** | **ZGNX** | LOA: ABOVE AVERAGE

**Metabolic – General (Menkes Disease and Thymidine Kinase 2 (TK2) Deficiency)**

CUTX-101 for Menke's disease and MT1621 for TK2 deficiency are both drugs for ultra-rare orphan conditions that arose from academic programs, with pivotal data that involves comparison of survival in patients treated at academic centers for a number of years to that from natural history studies. Neither condition has an approved treatment, so the drugs are important additions, though sales expectations remain somewhat limited.

Menke's disease, an X-linked recessive disorder, is caused by mutations in genes coding for the copper-transport protein. To bypass this, CUTX-101 is a subcutaneous injectable formulation of copper histidinate, intended to improve tolerability due to a physiological pH, bypass the low oral absorption of copper, and provide higher bioavailability to cells. The drug has breakthrough status from the FDA. Chances of approval are bolstered by the fact that the primary investigator of the pivotal cohort data is an authority in the field at the NIH. Median survival for patients starting the treatment early in the NIH cohorts was substantially longer than untreated historical controls. There could of course be questions whether the groups were comparable, though both were required to have severe pathogenic mutations and the difference in survival was striking. In addition, the investigator has noted in that past that response depends on whether the particular genetic defect permits some residual copper transport, though early treatment also helps, except for connective tissue disorders. It should be noted, though, that some providers are already using related formulations made at compounding pharmacies.

For TK2 deficiency, MT1621 involves a combination of deoxynucleosides to bypasses the defective enzyme. A retrospective chart-review study covering a number of academic centers found a substantial improvement in survival for both early and late age of onset (younger onset have a more rapid mortality), compared to natural history. Since a portion of untreated patients do survive longer term, more information is needed on the comparability of the patients. There were also examples of patients who regained motor milestones, though a substantial minority did not improve, but only remained stable. In addition, per a prior publication, a number of patients remain fairly disabled despite treatment, but it was unclear how early treatment was started. At the FDA's request, the company also initiated a study looking for any other patients worldwide who have been treated with nucleosides, to see if the data is supportive, though they do not expect many additional patients.

*Tags: First Approval, Practice Changing*
Metabolic

OLIPUDASE ALFA | SNY | LOA: ABOVE AVERAGE

Niemann-Pick Disease Type B

Olipudase alfa is expected to become the first therapy approved for the treatment of Niemann-Pick disease type B in H1 2022 following planned US/EU regulatory submissions in H2 2021. Niemann-Pick disease type B is a progressive genetic disease caused by mutations in the SPMD1 gene, which regulates the production of the lysosomal enzyme acid sphingomyelinase. Acid sphingomyelinase converts the lipid sphingomyelin into ceramide, but mutations causing a deficiency of the enzyme lead to the accumulation of sphingomyelin in cells. This in turn causes cell death, which impairs the function of several tissues and organs including the brain, lungs, spleen, and liver. As olipudase alfa does not cross the blood-brain barrier, it is only being developed for Niemann-Pick disease type B, the milder juvenile non-neuronopathic form.

Olipudase alfa has generated promising results in the Phase II/III ASCEND study in which 36 patients were randomized to receive either olipudase alfa biweekly intravenous injections or placebo for 52 weeks. At 52 weeks, olipudase alfa significantly improved lung function by 22% from baseline compared to 3% for patients receiving placebo, and spleen volume was significantly reduced by 39.5% compared with a 0.5% increase in the placebo arm, meeting both co-primary endpoints as specified by the EMA. However, in the US, the spleen volume endpoint was combined with the SRS, a patient-reported outcome measurement that evaluates symptoms associated with an enlarged spleen, and puzzlingly, there was no change in the SRS with active treatment vs placebo, thus olipudase alfa failed this endpoint by the FDA's standard. Nevertheless, the trial protocol specified that only one of the primary endpoints had to be met for the trial to be considered a success, meaning that Sanofi can still seek US approval based on the significant improvement in lung function alone.

Tags: First Approval, New Drug Class, Practice Changing
MITAPIVAT | AGIO | LOA: ABOVE AVERAGE

Pyruvate Kinase Deficiency

Mitapivat is a potentially first in class pyruvate kinase (PK) agonist positioned to fulfil a major unmet need in transfusion-resistant PK deficient patients. Pyruvate kinase deficiency (PKD) is a rare and hard-to-treat form of anemia with no approved pharmaceutical therapies. Regular transfusions are needed in more severe cases, to which many patients fail to respond.

Readouts from the ACTIVATE (NCT03559699) and ACTIVATE-T (NCT03548220) established solid evidence for both hemoglobin response and an alleviation of anemia disease burden in approximately 40% of patients, over half of whom no longer needed transfusions. This marks a major improvement in the prospects for many sufferers of PKD and Agios intends to proceed with a regulatory submission for mitapivat by the end of 2021.

With most patients still failing to respond, PKD is likely to remain hard to treat in many cases. A possible explanation for these individuals' failure to respond is the compound heterozygosity of PKD, which is controlled by four PK isoenzymes in the PKLR gene. Nevertheless, the absence of any other approved pharmaceutical treatments will ensure high demand for such a novel disease-altering therapy.

*Tags: New drug class, First approval, Practice changing*
**Metabolic**

**WTX101 | ALXN | LOA: ABOVE AVERAGE | 🔄**

**Wilson's Disease**

WTX101 (bis-choline tetrathiomolybdate) is a new class of copper chelating agent for the treatment of Wilson's disease that is expected to yield positive Phase III data in Q2 2021, paving the way for approval in early 2022. WTX101 directly strips excess copper from metallothionein in hepatocytes and then binds serum albumin to form stable complexes that are excreted via the bile. This rapid and direct hepatic decoppering mode of action differs from currently available copper chelating agents (D-penicillamine or trientine di/tetrahydrochloride), which form unstable complexes with copper that is loosely bound to albumin ('free copper') and can inadvertently mobilize copper in the blood, thereby inadvertently facilitating redistribution to the CNS and transiently worsening neurological symptoms initially in some patients. In addition, the existing copper chelating agents are unable to cross the blood brain barrier and are ineffective against neurological manifestations of the disease. They also require multiple daily doses and must be taken on an empty stomach which leads to suboptimal adherence, thus WTX101’s unique mode of action and more convenient dosing schedule (once-daily) could address significant unmet needs.

Phase II data for WTX101 have been promising and showed rapid reductions in free copper levels that were accompanied by significant reductions in mean UWDRS disability scores (a measure of neurological impairment) from baseline to week 72 in newly-diagnosed patients, though the study did not have a placebo control arm for ethical reasons. Notably, the ongoing Phase III FOCuS includes a standard of care comparator arm that will provide critical insights into WTX101’s relative efficacy (both on free copper reductions and clinical scoring systems for hepatic/disability/neurological statuses) and safety. If positive, Alexion is expected to submit an NDA in Q3 2021, which would likely receive priority review given the drug’s fast track status.

*Tags: New Drug Class*
Neurology
Fragile X Syndrome

Although top-line results from Zynerba’s CONNECT-FX trial were disappointing and Zygel failed to meet primary and secondary endpoints in the full analysis set, additional analyses in patient subgroups indicated that FMR1 methylation status may be used to identify responder patients. Updated results demonstrated a statistically significant response in the treatment arm compared to placebo on multiple measures including the primary endpoint in the FMet group where patients have at least 90% methylation of the FMR1 gene.

Fragile X syndrome has a severe unmet need, with no approved therapies available for the condition. The pipeline of fragile X candidates is extremely narrow, with the next most promising asset, Ovid Therapeutics’ OV101, trailing at the Phase II stage. A potential approval in this indication would provide a much-needed therapeutic option for patients and would boost Zygel’s developmental program in a number of other indications including autism and epilepsy disorders.

Tags: First Approval, Practice Changing
ZYNRELEF | HRTX | LOA: ABOVE AVERAGE

**Postsurgical Pain**

Zynrelef is a combination local analgesic agent of bupivacaine and the NSAID meloxicam, utilizing Heron’s Biochronomer extended-release technology. The drug is designed to slowly release bupivacaine and meloxicam locally at the site of the surgery over 3-5 days. In the Phase III studies EPOCH 1 and 2 which evaluated patients undergoing bunionectomy and herniorrhaphy, respectively, statistically significant reductions in pain intensity compared to placebo were achieved. It is highly encouraging that the study met its aim in increasing the proportion of opioid-free patients and these data support its potential integration into the treatment algorithm as a new adjunctive to diminish opioid prescriptions.

Zynrelef was approved in Europe in September 2020 for postoperative pain from small-to-medium surgical wounds in adults. Although Heron received a complete response letter in June 2020, the developer has addressed the concerns all of which were non-clinical. A second FDA review is expected on May 12, 2021.

*Tags: First Approval in US*
Neurology

GANAXOLONE | MRNS | LOA: ABOVE AVERAGE | ➤

Seizure Disorders (Epilepsy)

Ganaxolone would be unprecedented as a novel US Food and Drug Administration (FDA)-approved treatment for Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) if the FDA responds positively to Marinus Pharmaceuticals’ planned New Drug Application, which should be filed in mid-2021. The company is also pursuing a pre-marketing authorization application (MAA) meeting with the European Medicines Agency (EMA) during H1 2021. CDD is a debilitating, rare genetic epilepsy, which causes both early-onset of epileptic seizures/spasms and severe impairment of neurodevelopment impacting cognitive, motor, speech, and visual function. Ganaxolone's promising efficacy in underserved children and young adults with CDD- as demonstrated through its pivotal, Phase III Marigold trial (Clinicaltrials.gov identifier: NCT03572933)- satisfies critical unmet need. Exceptionally, ganaxolone elicited a significant 32.2% median reduction in 28-day major motor seizure frequency, compared to a 4.0% reduction for those receiving the placebo, achieving the trial’s primary endpoint (p=0.002).

Given ganaxolone's valuable potential to treat this serious and rare condition, the FDA granted a Rare Pediatric Disease (RPD) Designation in July 2020. If Marinus successfully secures approval for ganaxolone in CDD, then the RPD Designation would award the company a priority review voucher for use in a subsequent marketing application. In December 2020, Marinus Pharmaceuticals launched an expanded access program (EAP) enabling CDD patients who were at least 2 years of age and experiencing uncontrolled seizures to receive ganaxolone. This importantly lays the foundation for patient access to the drug and allows more patients and physicians to establish familiarity with ganaxolone. In light of the stark absence of treatment options for CDD patients, we anticipate ganaxolone to be welcomed with strong uptake in this niche population.

Tags: First Approval, New Drug Class, Practice Changing
Obstetrics/Gynecology
Endometriosis

Orgovyx (relugolix combination pill [relugolix 40 mg plus estradiol 1.0 mg and norethindrone acetate 0.5 mg]) is an oral, once-daily, small molecule, gonadotropin-releasing hormone (GnRH) receptor antagonist, which has produced robust pivotal data from its Phase III SPIRIT clinical trial program in women with pain associated with endometriosis. Although it is difficult to compare across trials, once-daily Orgovyx in the pivotal SPIRIT 1/2 trials produced a lower dysmenorrhea responder rate over placebo at 6 months (Clinicaltrials.gov identifier: NCT03204318 and NCT03204331) versus 200mg twice-daily Orilissa (AbbVie’s elagolix) in its Phase III Solstice and Violet PETAL trials (~44.8–47.6% versus ~49–56%) (Clinicaltrials.gov identifier: NCT01931670 and NCT01620528). With respect to non-menstrual pelvic pain responder rates over placebo at 6 months versus 200mg Orilissa in its Phase III pivotal trials, Orgovyx in the SPIRIT 1/2 trials reached a slightly higher rate at ~18.9–23.4% versus ~19–21%. In the ovulation inhibition study, all women achieved ovulation inhibition and restoration after finishing Orgovyx treatment and, on average, women returned to ovulation within one cycle (23.5 days). This is an important distinguishing factor as suppression of ovulation/resting the ovary is a critical step in ensuring that target estrogen levels are met. Furthermore, statistically significant reductions in opioid use have been reported with Orgovyx, which is particularly pertinent in light of the opioid crisis in the US.

Distinctly, Myovant Sciences is the only company developing a GnRH antagonist that will have dedicated observational bone density data, both in untreated women with uterine fibroids and endometriosis. At week 24, mean changes in bone mineral density from baseline were -0.70% versus 0.21% and -0.78% versus 0.02% in the Orgovyx and placebo groups of the SPIRIT 1 and 2 trials, respectively. Notably, compared to relugolix monotherapy, the rate of bone mineral density reduction was decreased with the relugolix combination pill. In its Phase III EM-I and EM-II trials (Clinicaltrials.gov identifier: NCT01620528 and NCT01931670), 200mg twice-daily Orilissa showed a ~3.01–3.05% decrease in bone mineral density, which limits its use to 6 months. Based on Orgovyx’s positive data, its likelihood of approval is 12% above average and Myovant plans to file a supplemental New Drug Application for endometriosis to the US Food and Drug Administration in the first half of 2021.

Tags: Label Expansion (New Indication)
Obstetrics/Gynecology

**YSELTY | OBSV | LOA: ABOVE AVERAGE | 🌐**

**Uterine Fibroids**

Although Yselty (linzagolix) is poised to enter the uterine fibroids market as the third oral gonadotropin-releasing hormone (GnRH) receptor antagonist, after AbbVie’s Orilissa (elagolix) and Myovant’s Orgovyx (relugolix), Yselty remains a highly competitive prospect as it has produced impressive pivotal clinical trial data. Although it is challenging to compare between trials, numerically, Yselty’s responder rate data appear favorable versus fellow GnRH receptor antagonists (responders were defined as patients with menstrual blood loss volume of ≤80mL and ≥50% reduction from baseline in menstrual blood loss volume). The pooled responder rate for Yselty (200mg once-daily + add-back therapy [ABT]) in the PRIMROSE 1 and PRIMROSE 2 trials was 84.7%, while Orgovyx (40mg once-daily + ABT) in the LIBERTY 1 and LIBERTY 2 trials as well as Orilissa (300mg twice-daily + ABT) in the ELARIS UF-1 and ELARIS UF-2 trials had pooled responder rates of 72.2% and 72.3%, respectively. Furthermore, Yselty has demonstrated a reasonable safety and tolerability profile. In the lumbar spine, which is the most critical anatomical site in the FDA’s view, there was a 1.1-2.3% loss in bone mineral density, which is within the range of other clinical trials. Marinus representatives expect that most obstetricians and gynecologists would not be overly concerned about the amount of bone loss as a 2.2% mean loss over 52 weeks with the 100mg dose falls within the error measurements of dual-energy X-ray absorptiometry (DEXA). Encouragingly, in the PRIMOSE 1 trial, the incidence of hot flashes occurring in >5% of women was comparable across all treatment arms (6.7% placebo, 6% linzagolix 100mg, 6.5% linzagolix 200mg + ABT).

In November 2020, ObsEva submitted a Marketing Authorization Application in the EU for Yselty to treat endometriosis. A parallel New Drug Application will be filed in the US in H121. Half of the hysterectomies performed annually in the US are due to uterine fibroids, and Yselty is highly attractive as an oral alternative to surgery that causes infertility. ObsEva is developing the lower dose to offer another therapy option to produce partial estrogen suppression in women who do not wish to or cannot take ABT. According to ObsEva’s research, ~20% of women do not want to take ABT. In the US, fibroids are more prevalent in the African American population. This population is also associated with a higher body mass index (BMI) distribution (~54% with a BMI that is >30) and a higher risk of cardiovascular disorders, and cannot take ABT. Thus, an additional low-dose option without ABT distinguishes ObsEva’s uterine fibroid program compared to competitors that have only investigated oral GnRH antagonists with ABT.

*Tags: First Approval, Practice Changing*
Oncology
Oncology

**LN-145 | IOVA | LOA: ABOVE AVERAGE | 📌**

### Cervical Cancer

Iovance’s autologous cell therapy product derived from patient tumor-infiltrating lymphocytes (TILs), LN-145, has demonstrated strong results in recurrent, metastatic or persistent cervical cancer patients and could reach the market in 2022 to help fill an unmet need for effective regimens in a hard-to-treat segment. LN-145 carries Breakthrough and Fast Track designations in the US that will speed up a potential approval. Iovance also confirmed with the FDA in a 2019 meeting that the innovaTIL-04 study may be sufficient for approval pending full results.

LN-145’s strong efficacy should outweigh tolerability concerns. In the innovaTIL-04 study, LN-145 demonstrated an impressive 11% CRR, 44% ORR, and 85% DCR in pretreated, advanced cervical cancer patients who have few treatment options. Patients also responded quickly to treatment with a 2.4-month mean time to best response. The duration of response was not yet reached after 7.4 months. However, tolerability may limit its potential as 96.3% of patients experienced at least one grade 3/4 adverse event, including relatively high rates of grade 3/4 hematologic side effects.

Tags: New Drug Class

**VGX-3100 | INO | LOA: ABOVE AVERAGE | 📌**

### Cervical Dysplasia

Before the end of 2021, Inovio Pharmaceuticals plans to file for regulatory approval of DNA vaccine candidate VGX-3100 for the treatment of cervical dysplasia caused by HPV 18 and 16. However, additional data and longer follow-up are needed to confirm utility.

Topline results from Phase III REVEAL 1 trial presented in March 2021 show VGX-3100 has a positive tolerability profile, but the efficacy appears somewhat marginal. It achieved histopathological regression of HSIL combined with virologic clearance of HPV-16 and/or HPV-18 at week 36, but only just. The percentage of responders was 23.7% (31/131) in the treatment group, versus 11.3% (7/62) in the placebo group (p=0.022). It failed in the ITT group, which included only eight additional patients classified as non-responders due to a lack of data. It will be important to see longer-term follow-up, as well as data from the Phase III REVEAL 2 trial to determine whether VGX-3100 can be protective against recurrence. This would place VGX-3100 at an advantage over relatively simple surgical and ablative procedures that can still have high rates of HPV-associated recurrence.

Tags: New Drug Class, Practice Changing
Oncology

ZOLBETUXIMAB | ASTELLAS | LOA: AVERAGE | 21

Gastric Cancer

Astellas’ experimental drug candidate zolbetuximab is a monoclonal antibody against isoform 2 of claudin 18 (claudin 18.2), a cell adhesion molecule involved in the formation of tight junctions in epithelial cells. Where claudin-18.2 is present as a tumor-specific marker, cancerous tissue may be destroyed by the drug through antibody-dependent cellular cytotoxicity. In zolbetuximab’s primary indication of gastric cancer, late-stage investigations are underway in the Phase III GLOW (NCT03653507) and SPOTLIGHT (NCT03504397) studies, which test the antibody as first-line therapy for HER2-negative disease in combination with the CAPOX and FOLFOX chemotherapy regimens, respectively. Approximately 20% of gastric adenocarcinomas overexpress HER2, whereas 70% express claudin-18.2, potentially granting zolbetuximab access to a large section of the patient population. Moreover, treatment options for first-line HER2-negative disease remain sparse; the recently approved CheckMate 649 regimen of frontline Opdivo and chemotherapy, though a hugely important development in the setting, is largely confined to PD-L1+ (CPS ≥ 5) tumors.

Results from the Phase II FAST (NCT01630083) trial were very promising, with claudin-18.2-positive patients who received zolbetuximab and chemotherapy showing marked PFS and OS improvements compared to chemotherapy alone. If the impending readouts from GLOW and SPOTLIGHT are able to replicate this benefit, zolbetuximab may find a large and profitable niche in first-line gastric cancer, particularly among weakly immunogenic patients who would respond poorly to PD-1 antibodies such as Opdivo. Largely for this reason, the FDA has granted the agent orphan drug designation. With Astellas expecting a regulatory submission by early 2022, zolbetuximab is a strong candidate for a first-in-class 2022 launch. Claudin-18.2 is a possible target in a variety of solid tumors beyond gastric adenocarcinomas. Notably, the isoform is also expressed in approximately 50% of pancreatic cancers, where zolbetuximab is now in early-phase development. A successful launch in gastric cancer would be a positive step towards expanding the drug to other indications.

Tags: New Drug Class, First Approval, Potential Blockbuster
Melanoma

Iovance Biotherapeutics's Contego, a ready-to-infuse autologous cell therapy product containing tumor-infiltrating lymphocytes (TILs), is poised to become the first TIL therapy approved after demonstrating excellent results in the registrational Phase II innovaTIL-01 study. In the pivotal cohort, Contego demonstrated an overall response rate (ORR) of 32.4% and a disease control rate (DCR) of 72.1% in heavily pretreated advanced melanoma patients, the majority of whom had already progressed on both a PD-1 inhibitor and a CTLA-4 inhibitor. Furthermore, Contego has previously been granted Regenerative Medicine Advanced Therapy (RMAT) designation, Fast Track status, and orphan drug designation as a treatment for advanced melanoma.

After Iovance and the FDA were not been able to agree on the required potency assays to fully define Contego, which is required as part of a BLA submission, the BLA submission for Contego is now expected in 2021.

Tags: New Drug Class, First Approval

Melanoma

OncoSec is developing TAVO, a DNA plasmid coding for IL-12 that is delivered intratumorally via electroporation, in combination with Keytruda for the treatment of unresectable or advanced melanoma that is refractory to PD-1 inhibitors. TAVO is designed to induce local expression of IL-12, which OncoSec believes will increase the effectiveness of checkpoint inhibitors by converting immunologically suppressed “cold” tumors into T-cell inflamed “hot” tumors.

Results from the first 21 patients in the Phase IIb KEYNOTE-695 study showed that the combination demonstrated preliminary efficacy in a heavily pretreated patient population. In the US, TAVO has previously been granted both Fast Track status and orphan drug designation as a treatment for advanced melanoma.

Although TAVO will compete with Contego, the high unmet need and lack of effective therapies in this treatment setting mean that an approval would be a lucrative commercial opportunity. OncoSec intends to submit a BLA for the accelerated approval of for TAVO in the US in 2021 or early 2022.

Tags: New Drug Class, First Approval
Oncology

ILARIS | NVS | LOA: BELOW AVERAGE

Non-Small Cell Lung Cancer

Originally approved for autoimmune disorders, Novartis’s IL-1β monoclonal antibody Ilaris is now being investigated as a treatment for NSCLC in both the adjuvant and first-line setting. Novartis initiated a broad development program for Ilaris in NSCLC after a subgroup analysis from the Phase III CANTOS study in atherosclerosis showed that it reduced lung cancer incidence and mortality.

Despite the recent failure of the Phase III CANOPY-2 testing Ilaris in the second-line post-checkpoint inhibitor setting, Novartis is hoping that Ilaris may demonstrate synergy with first-line standard of care Keytruda and platinum doublet chemotherapy in the Phase III CANOPY-1 trial. Top-line results from the trial are expected by the end of the year, with a filing expected to follow shortly after if the data are positive.

Tags: Label Expansion (New Indication), New Drug Class

MRTX849 | MRTX | LOA: ABOVE AVERAGE

Non-Small Cell Lung Cancer

In development by Mirati Therapeutics, KRAS G12C inhibitor MRTX849 is in line to become the second KRAS inhibitor approved for NSCLC. In the Phase I/II KRYSAL study, the cohort of pretreated NSCLC patients with a KRAS pg.G12C mutation who received 600mg MRTX849 daily demonstrated an overall response rate (ORR) of 45% and a disease control rate (DCR) of 96%. Based on these data, Mirati Therapeutics plans on filing a New Drug Application for adagrasib for the second-line or later treatment of patients with KRAS p.G12C mutated NSCLC in the second half of 2021.

An approval would set up competition between the drug and Amgen’s Lumakras (sotorasib), which has demonstrated similar efficacy results and has a PDUFA date in August 2021. The competition between these two KRAS inhibitors will likely come down to both the relative risk/benefit profiles and which drug enters the market first.

Looking ahead, Mirati has initiated broad development programs for adagrasib-based combinations in both NSCLC and CRC.

Tags: First Approval, Potential Blockbuster
POZIOTINIB | SPPI | LOA: ABOVE AVERAGE

Non-Small Cell Lung Cancer

Spectrum Pharmaceuticals plans to submit an NDA by the end of 2021 for pan-HER inhibitor poziotinib based on data from Cohort 2 of the registrational Phase II ZENITH20 trial, which tested the efficacy of poziotinib in previously treated NSCLC patients with HER2 exon 20 insertion mutations. In Cohort 2, an intent-to-treat analysis showed a confirmed objective response rate (ORR) of 27.8%, with a median-progression free survival of 5.5 months and a duration of response of 5.1 months. The FDA recently granted poziotinib Fast Track designation based on these data.

While Enhertu, Daiichi Sankyo’s antibody-drug conjugate, is also being evaluated in this patient population, its development is lagging behind poziotinib’s. Given that approximately 2-4% of NSCLC patients have HER2 exon 20 insertion mutations, competition could be fierce between these two drugs and the first therapy to market will likely have the advantage.

Tags: Label Expansion (New Indication), New Drug Class

JEMPERLI | GSK | LOA: SAME AS AVERAGE

Ovarian Cancer

Glaxo Smith Kline’s Jemperli is poised to become the first PD-1/PD-L1 inhibitor approved for ovarian cancer patients. Top-line results from the registrational Phase II MOONSTONE study, which is testing the combination of Jemperli and PARP inhibitor Zejula in the platinum-resistant setting, are expected in the second half of 2021. Since treatment for platinum-resistant/refractory ovarian cancer is largely palliative and there are limited treatment options, an approval in this setting would be a lucrative commercial opportunity.

The combination of Jemperli and Zejula is also being tested in the Phase III FIRST study for the treatment of advanced ovarian cancers in both the first-line and first-line maintenance settings. A future label expansion into the more lucrative first-line setting would increase the overall commercial potential of Jemperli, although it will likely have to compete with the other checkpoint inhibitors in development for this treatment setting.

Tags: New Drug Class, Label Expansion (New Indication)
**Oncology**

**LUTETIUM 177LU-PSMA-617 | NVS | LOA: ABOVE AVERAGE | 📈**

**Prostate Cancer**

Novartis plans to submit US and EU regulatory filings for Lutetium 177LU-PSMA-617 in metastatic castration-resistant prostate cancer (mCRPC) before the end of 2021. Submission will be based on results from the pivotal Phase III VISION trial for heavily pretreated mCRPC patients. Initial results from March 2021 show Lutetium 177LU-PSMA-617, when added to physician's choice of treatment, improved both PFS and OS over physician's choice of treatment alone. This is an area of unmet need in the indication and a survival improvement over standard options could change the treatment paradigm in the mCRPC setting and provide a novel strategy for treating late-stage prostate cancer. This would also make Lutetium 177LU-PSMA-617 the first PSMA-directed radioligand approved in the prostate cancer space. Novartis plans to eventually expand development of the molecule to earlier lines of treatment, further increasing its commercial outlook in this indication.

*Tags: First Approval, New Drug Class*

**LYNPARZA | AZN | LOA: SAME AS AVERAGE | 📈**

**Prostate Cancer**

AstraZeneca is investigating poly (ADP-ribose) polymerase (PARP) inhibitor Lynparza in the first-line setting of mCRPC patients in the Phase III PROpel study as part of a combination with abiraterone against placebo plus abiraterone. Improved progression and/or survival outcomes over standard abiraterone in the first-line setting could be practice changing, particularly if a benefit is seen in a biomarker unrestricted manner. Approval based on PROpel would also move Lynparza earlier in the paradigm, significantly increase the available patient population, and likely generate strong sales. Topline results from PROpel and a subsequent regulatory filing are expected in H2 2021.

This expansion would also further differentiate Lynparza from competing PARP inhibitor Rubraca which is available in previously treated, BRCA-mutant mCRPC patients. Rubraca was being studied in the Phase III CASPAR study as a first-line treatment for mCRPC but this trial was suspended in March 2021.

*Tags: Label Expansion (Existing Indication), Practice Changing*
Oncology

ERLEADA | JNJ | LOA: SAME AS AVERAGE | 🔗

Prostate Cancer

Johnson & Johnson continues to aggressively develop next generation AR inhibitor Erleada and is attempting to expand its use beyond the nmCRPC and metastatic hormone-sensitive patient segments. Before the end of 2021, a supplementary NDA filing is expected based on the Phase III ATLAS study testing Erleada in high-risk, localized or locally advanced patients receiving radiation therapy. An expansion into these patients could drive significant revenues as this is a relatively untapped segment. However, late-phase data for next-generation therapies in the localized setting are lacking and concerns over the clinical and financial toxicity of early and prolonged prescribing, as well issues with sequencing these therapies as patients progress through the algorithm, could create challenges.

Tags: Label Expansion (Existing Indication), Practice Changing

ERY-ASP | ERYP | LOA: ABOVE AVERAGE | 🔗

Prostate Cancer

ERY-ASP (GRASPA) has shown promising signs of activity as a second-line treatment for pancreatic cancer patients, an area of significant need, and could reach the market and improve outcomes for these patients by 2022. In a Phase IIb study, ERY-ASP in combination with chemotherapy improved median PFS to 4.4 months compared to 1.6 months with chemotherapy alone and improved median OS to 6.0 months compared to 2.0 months with chemotherapy alone. Topline results from the pivotal Phase III TRYbeCA-1 trial testing a similar patient group are expected in Q4 2021. Regulatory filings based on TRYbeCA-1 are also expected by the end of 2021.

ERY-ASP consists of L-asparaginase entrapped into human homologous red blood cells, which attack the altered metabolism of asparagine and glutamine in cancer cells when administered.

Tags: New Drug Class
Uveal Melanoma

Tebentafusp is a bispecific t-cell engager (BiTE) whose development marks a significant innovation in cancer therapeutics. The agent simultaneously binds to lymphocyte CD3 receptors and gp100 antigens expressed on cancers cells, thereby physically bringing T-cells to tumor cells in a mechanism entirely novel to solid tumor indications. The Phase III IMCgp100-202 trial (NCT03070392) showed a one-year OS of 73% in uveal melanomas treated with tebentafusp compared to 58% in those receiving the current standard-of-care – typically off-label immune checkpoint inhibitors such as Keytruda. These findings are of course significant in uveal melanoma, a rare disease with no approved treatments, but also of major importance for the development of next-generation immunotherapies as a whole.

With BiTEs still largely an experimental field of immuno-oncology (Blincyto, also specific to CD3, remains the only such drug in circulation and is wholly confined to leukemia), IMCgp100-202 provides the first late-stage clinical data showing clear superiority to PD-(L)1 inhibitors in solid tumors. Demonstrating such a benefit over the current immunotherapy standard-of-care for many diseases is sure to generate significant interest throughout the immuno-oncology space.

Though gp100 is specific to melanomas, the technology used to manufacture tebentafusp can be easily tweaked to synthesise a similar fusion protein targeting CD3 and a tumor-associated antigen specific to another disease. A regulatory submission for the breakthrough drug is expected in 2021 and its subsequent performance will be closely monitored by physicians and developers alike.

Tags: First Approval, Potential Blockbuster
Oncology

OMIDUBICEL | GMDA | LOA: ABOVE AVG

Bone Marrow Transplant and Stem Cell Transplant

Gamida’s omidubicel is an advanced cell therapy being investigated for use in allogeneic hematopoietic (bone marrow) stem cell transplants for patients with hematologic malignancies, such as blood cancers. Omidubicel uses the company's proprietary NAM technology, to enrich umbilical cord blood (UCB) for stem cells, which is hypothesized to improve the time and rate of engraftment. In a pivotal Phase III trial, the cell therapy achieved the primary endpoint of a reduction in the time to neutrophil engraftment, from 22 days for untreated UCB to 12 days with treatment. Additionally, the cumulative incidence of neutrophil engraftment was higher at 96% for omidubicel versus 88% for comparator, with a much quicker pace of recovery. In addition to meeting the primary endpoint, the therapy met all secondary endpoints including an improvement in platelet engraftment at day-42, a reduction in the rate of infection and an increase the number of days spent hospitalized after transplant.

Platelet recovery by day 42, another component of the hematopoietic system, was almost doubled in the omidubicel arm (55% vs 28%, p=0.028). These results indicate that the accelerated recovery is not limited to neutrophils but has a broader clinical benefit on the recovery of the hematopoietic system. In line with accelerate neutrophil recovery, the rate of bacterial and fungi infections, a potentially life-threatening implication in bone marrow transplant (BMT) patients, who are immunologically comprised, was substantially lower in the omidubicel arm (37% vs 57%, p=0.027). The final secondary endpoint, a change in the number of days spent in hospital, was also met, with patients treated with omidubicel spending 60.5 days out of hospital compared to 48 days for the comparator. The company has emphasized the commercial benefit of spending 12.5 fewer days in hospital, which it predicts will lead to a saving of $112,500.

Given the difficulties in sourcing donors for traditional BMT, omidubicel provides a more ready alternative to mismatched donors with comparable efficacy. In the company's recent conference call, company officials highlighted the positive support they had received from physicians who had scored it highly based on safety, efficacy and logistical criteria. The company expects to capture 18% of the US patient market share or 2,000 patients, with omidubicel being priced at a similar price to CAR-T therapies ($373,000 - $475,000). This would lead to US sales of close to $1bn within three years of launch.

Tags: First Approval, Potential Blockbuster, Practice Changing
Chronic Lymphocytic Leukemia (CLL)/Mantle Cell Lymphoma (MCL)

Imbruvica, a Bruton’s tyrosine kinase (BTK) inhibitor, and Venclexta, an inhibitor of the anti-apoptotic protein BCL-2 are two blockbuster drugs that are being developed as new combinations for CLL and MCL. In CLL, monotherapy with Imbruvica is the preferred front-line therapy while Venclexta combined with the anti-CD20 rituximab is the preferred regimen for patients who relapse after a BTK inhibitor. Long-term follow-up data from the RESONATE-2 trial showed 70% PFS at five years, marking Imbruvica as a transformative first-line therapy. While Imbruvica is highly effective at controlling disease, the best responses are typically partial remissions, and patients must remain on treatment to maintain disease control. GLOW is a Phase I/II trial evaluating a fixed-length regimen (Imbruvica monotherapy for three cycles followed by Imbruvica + Venclexta for 12 cycles) for newly diagnosed CLL patients. Results from GLOW will be released at EHA 2021 and are expected to lead to a regulatory submission in 2021 and a supplementary approval in 2022. However, even if approved, this regimen is unlikely to be practice changing over the near term as physicians will want to see long term follow up data before it is widely adopted.

In November 2013, Imbruvica received accelerated approval as a second-line or later treatment for MCL based on ORR data. A Phase III trial, RAY, confirmed Imbruvica’s efficacy by showing superior PFS and ORR rates when compared to Torisel, which is approved in the EU but not the US for MCL. Venclexta has shown single agent activity for MCL but is not yet approved for this indication. Two Phase III trials, SYMPATICO and SHINE are expected to read out in 2021. SYMPATICO is comparing Imbruvica + Venclexta to Imbruvica alone in second-line or later MCL. If the data are positive, a regulatory submission is expected in early 2022 followed by a possible approval in late 2022. If approved, this combination could become the new standard of care for patients who fail first-line chemotherapy. SHINE is comparing Imbruvica combined with bendamustine and rituximab to bendamustine + rituximab in patients ≥ 65 with newly diagnosed MCL. A regulatory submission is expected in late 2021, followed by a possible approval in 2022. If approved, this combination could become the new standard of care for older, newly diagnosed patients.

Tags: Label Expansion (Existing Indication and New Indication), Practice Changing (MCL)
Oncology

TG-1303 | TGTX | LOA: ABOVE AVERAGE

Chronic Lymphocytic Leukemia (CLL)

TG-Therapeutics TG-1303 is a combination of Ukoniq, a PI3K delta inhibitor, and ublituximab, an anti-CD20 antibody. Ukoniq is dosed once daily, while other oral, approved PI3K inhibitors are dosed twice daily. Ukoniq also inhibits CK1 epsilon, a potential regulator of Treg count and function, which may improve its safety profile. Ublituximab has been glycoengineered for enhanced potency and is further differentiated by its shorter infusion times compared to other approved antibodies in this class. TG Therapeutics has completed a BLA submission for TG-1303 for first-line and R/R CLL, and an approval decision is expected by March 2022.

The BLA submission is supported by the UNITY-CLL trial which enrolled first-line and second-line or later CLL patients and compared TG-1303 to Gazyva combined with chlorambucil. While the Ukoniq combination reported a longer PFS (32 months vs 18 months), the comparator is no longer widely used in CLL. As such, the 38-month median PFS for first-line patients can be compared to historical data for Imbruvica monotherapy, which reported a 70% PFS for first-line patients at 60 months (median PFS was not reached). Similarly, while the Ukoniq combination reported PFS of 19.5 months for relapsed/refractory patients, Venclexta combined with rituximab had a PFS of 53.6 months for such patients in the MURANO trial. If approved, the Ukoniq combination will mostly likely be used in the third-line or later setting where it will compete with Zydelig and Copiktra with safety as the differentiator (see below).

Immune-mediated adverse events such as colitis and pneumonitis are of particular concern for PI3K inhibitors. The Ukoniq combination reported grade 3/4 colitis in 3.4% of patients, which is lower than the 12% seen for Copiktra. The Zydelig FDA label warns that fatal and/or serious diarrhea/colitis occurred in 14–20% of patients. The Ukoniq combination reported grade 3/4 pneumonitis in 2.9% of patients, which is slightly lower than what was seen for Zydelig (4%) or Copiktra (5%). Finally, the 16.5% rate of discontinuation for the Ukoniq combination is seen as favorable.

Tags: First Approval (ublituximab), Label Expansion (New Indication for Ukoniq)
Chronic Myelogenous Leukemia (CML)

Currently approved inhibitors of the BCR-ABL1 tyrosine kinase mainly target the ATP binding pocket, and approximately half of clinical resistance to these CML agents is due to mutations in this pocket, such as T315I. T315I is reported in 20% of patients with mutations and is associated with resistance to all approved tyrosine kinase inhibitors (TKIs) except Iclusig. In contrast, asciminib targets a different region of the kinase, the myristoyl pocket. In ABL1, this pocket binds the myristoylated N-terminus resulting in autoinhibition, however, the myristoylated N-terminus is lost in the BCR-ABL1 fusion. Binding of asciminib to the myristoyl pocket restores autoinhibition and this novel mechanism is proposed to increase asciminib’s specificity and safety relative to other TKIs.

A pivotal Phase III trial, ASCEMBL, compared asciminib head-to-head with Bosulif in patients with Philadelphia chromosome-positive CML in chronic phase (Ph+ CML-CP) previously treated with two or more TKIs. While Bosulif, a second-generation TKI, is approved for earlier lines including newly diagnosed CML-CP, it is viewed less favorably than Sprycel and Tasigna, and so is often relegated to third-line or later CML. Results from ASCEMBL, demonstrate that, at 24 weeks, asciminib nearly doubled the major molecular response (BCR-ABL1 transcript ≤0.1% of baseline) rate compared to Bosulif (25.5% vs. 13.2%). Grade ≥3 adverse events (AEs) occurred in 50.6% and 60.5% of patients treated with asciminib and Bosulif, respectively. Treatment discontinuation due to AEs in the asciminib arm was 5.8% compared to 21.1% for patients taking Bosulif. However, the trial used the 500 mg dose of Bosulif and was designed before the recognition that a 400 mg dose is safer. It is likely that a 400 mg dose would have reported fewer treatment discontinuations.

Asciminib has been granted Breakthrough Therapy designation by the FDA for (i) the treatment of adult patients with Ph+ CML-CP, previously treated with two or more TKIs and (ii) treatment of adult patients with Ph+ CML-CP harboring the T315I mutation. An NDA is expected to be submitted in Q2 2021.

Tags: First Approval, Practice Changing
Oncology

ENZASTAURIN | DENOV| LOA: SAME AS AVERAGE | 

Diffuse Large B-Cell Lymphoma (DLBCL)

Enzastaurin is a first-in-class inhibitor of PKC beta, which is involved in the AKT and MAPK signaling pathways. It has been studied in more than 3,000 patients across a range of solid and hematological tumor types. Enzastaurin was originally developed by Eli Lilly and acquired by Denovo after a failed Phase III trial for DLBCL. The Eli Lilly trial, PRELUDE, evaluated enzastaurin as maintenance therapy following R-CHOP frontline therapy. Denovo’s retrospective analysis of the PRELUDE trial showed that a germline biomarker, Denovo Genomic Marker 1 (DGM1), was associated with longer OS in enzastaurin-treated patients. DGM1 is a polymorphism on chromosome 8 adjacent to TRPS1, a transcription factor that plays a central role in cell cycle control and tumor development. The Denovo Phase III trial, ENGINE, will evaluate enzastaurin combined with R-CHOP in treatment naive, high-risk subjects with DLBCL. Patients in the treatment arm who respond (CR or PR) will receive enzastaurin as maintenance therapy for up to 2 years. The primary endpoint is OS in patients who possess the DGM1 biomarker. Results from ENGINE are expected in Q4 2021 and if positive, could lead to approval in late 2022.

Tags: First Approval, New Drug Class

POLIVY | RHHBY | LOA: SAME AS AVERAGE | 

Diffuse Large B-Cell Lymphoma (DLBCL)

Roche’s Polivy is an antibody-drug conjugate targeting CD79b. In June 2019, Polivy in combination with bendamustine plus rituximab received accelerated approval for the treatment of third-line or later DLBCL. POLARIX is a Phase III trial comparing Polivy combined with R-CHP (rituximab plus cyclophosphamide, doxorubicin and prednisone) to R-CHOP (R-CHP supplemented with vincristine) in patients with previously untreated DLBCL. R-CHOP has been the standard of care for first-line DLBCL since 2006 and while there have been several Phase III trials looking at new drugs and combinations for this setting, they have not been successful.

Results for the Polaris primary endpoint of PFS are expected in H2 2021 and, if positive, could lead to a sBLA in Q4 2021 and approval in late 2022. Polivy has the potential to become a new standard of care for first-line DLBCL but that may depend on also showing an improvement in overall survival (a secondary endpoint). Other therapies being evaluated for first-line DLBCL include Monjuvi, an anti-CD19 antibody being evaluated in combination with Revlimid + R-CHOP in the Phase III trial frontMIND (results expected in 2024).

Tags: Label Expansion (Existing Indication), Practice Changing
Diffuse Large B-Cell Lymphoma (DLBCL)

Supported by single-arm trials, Yescarta, Kymriah and Breyanzi were approved for third-line or later DLBCL in October 2017, May 2018 and February 2021, respectively. While these CD19 directed autologous CAR-T therapies are seen as potentially curative, Yescarta is differentiated by its higher efficacy and faster manufacturing time and so is used in more patients. Kymriah is differentiated by its improved safety and is used for older patients. Breyanzi, which has the best safety profile of the three and an efficacy that is comparable to Yescarta, is just starting to penetrate the DLBCL market.

BELINDA, ZUMA-7, and TRANSFORM are Phase III trials evaluating Kymriah, Yescarta and Breyanzi, respectively, in second-line DLBCL patients eligible for transplant. In the treatment arm of these trials, patients are treated with lymphodepleting chemotherapy + CAR-T therapy while in the comparator arm, they are treated with several cycles of platinum-based immunochemotherapy followed, in responding patients, by high-dose chemotherapy + autologous stem cell transplant. In BELINDA, patients have the option of receiving platinum-based chemoimmunotherapy prior to lymphodepleting chemotherapy + Kymriah.

Results for the primary endpoint of event-free survival from BELINDA and ZUMA-7 are expected in H1 2021 and if the results are positive, regulatory submissions are expected in H2 2021. TRANSFORM has an expected primary completion date of January 2024. Moving CAR-T therapy to earlier lines may result in healthier CAR-T cells, improve response rates and avoid the toxicity associated with standard chemotherapy. However, stem cell transplant has the advantage of physician familiarity and is potentially curative. Physicians will likely want to see long-term survival data for CAR-T therapy before it can replace transplant. A supplementary approval for second-line DLBCL would also expand the pool of patients eligible for CAR-T therapy and is expected in late 2022 for Kymriah and Yescarta.

Tags: Label Expansion (Existing Indication), Practice Changing
Follicular Lymphoma (FL)

Roche’s mosunetuzumab is a bispecific antibody that targets CD20 on B cells and CD3 on T cells simultaneously. In July 2020, mosunetuzumab was granted Breakthrough Therapy Designation by the FDA for third-line or later FL. A Phase I/II trial, GO29781, is enrolling several cohorts including a cohort of third-line or later FL patients. At ASH 2020, updated data from this cohort showed that 8 cycles of mosunetuzumab resulted in an ORR of 68% and a CR rate of 50% in 62 patients. The median duration of response was 20.4 months for all 42 responders and the median PFS was 11.8 months. Consistently high CR rates were seen in high-risk populations including those with double refractory disease (55% CR in 33 patients), PI3K inhibitor refractory patients (78% CR in 9 patients) and those who received prior CAR-T therapy (50% CR rate in 4 patients). Roche has indicated that they expect up to submit regulatory submissions to both the US and EU authorities by the end of 2021 which could lead to a US mosunetuzumab approval by the end of 2022. A Phase III trial is expected to initiate in H1 2021 and will compare mosunetuzumab + Revlimid to rituximab + Revlimid for second-line or later FL.

Tags: First Approval, New Mechanism

Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL) and Marginal Zone Lymphoma (MZL)

Incyte’s parsaclisib is a PI3K delta inhibitor designed to avoid the hepatotoxicity associated with first-generation inhibitors. CITADEL-203, -204 and -205 are pivotal Phase II trials evaluating parsaclisib for third-line or later FL and second-line or later (with or without a prior BTK inhibitor) MZL or MCL, respectively. The CITADEL trials are using step-down dosing to minimize toxicity with parsaclisib administered at 20 mg once daily for eight weeks followed by either 20 mg once weekly or 2.5 mg daily. The 2.5 mg step down dose has generally shown better interim results with an ORR of 75% and CR of 13.5% for FL, an ORR of 66%, CR of 11% and PFS of 11 months for MCL and an ORR of 58% and PFS of 11.5 months for MZL. There are four approved PI3K delta inhibitors for FL (Zydelig, Copiktra, Aliqopa and Ukoniq), one for MCL (Ukoniq), and none for MZL. Following updated results from the CITADEL trials, Incyte expects to submit an NDA for relapsed/refractory (R/R) NHL by the end of 2021. A Phase III trial, CITADEL-302, will test parsaclisib plus an anti-CD20 for R/R FL and MZL while CITADEL-310 will test parsaclisib plus bendamustine and rituximab for newly diagnosed MZL.

Tags: First Approval
Oncology

**NAVITOCLAX** | **ABBV** | **LOA: ABOVE AVERAGE**

### Myelofibrosis (MF)

AbbVie and Roche’s navitoclax is an analog of Venclexta. While Venclexta is specific for BCL-2, navitoclax inhibits a wider range of anti-apoptotic proteins, namely BCL-2, BCL-XL and BCL-W. A pivotal Phase II trial is evaluating navitoclax combined with Jakafi in MF patients that had prior Jakafi. Interim results from the trial indicate that 29% of patients achieved a spleen volume reduction (SV35) of ≥35% from baseline while six patients (25%) had bone marrow fibrosis improvement. In MF, the abnormal cell population releases several cytokines and growth factors that lead to marrow fibrosis and stroma changes. The reduction in bone marrow fibrosis could be interpreted as evidence that navitoclax has disease-modifying properties, something not seen with Jakafi. AbbVie anticipates further data from the Phase II trial in 2021 which are expected to lead to a regulatory submission in 2022 and a possible accelerated approval in late 2022. Two Phase III trials with expected readouts in early 2022 are ongoing. TRANSFORM-2 will compare navitoclax + Jakafi to best available therapy in patients with relapsed/refractory MF while TRANSFORM-1 will compare navitoclax + Jakafi to Jakafi in Jakafi naïve patients.

**Tags: First Approval, Practice Changing**

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**MAGROLIMAB** | **GILD** | **LOA: ABOVE AVERAGE**

### Myelodysplastic Syndrome (MDS)

Gilead’s magrolimab, a potentially first-in-class anti-CD47 antibody, is designed to interfere with recognition of CD47 on cancerous cells by the SIRPα receptor on macrophages, thus blocking the “don't eat me” signal and rendering cancer cells susceptible to macrophages. In September 2020, the FDA granted magrolimab Breakthrough Therapy designation for the treatment of newly diagnosed MDS.

Gilead is expecting data from a potentially pivotal cohort of a single arm Phase Ib trial in H2 2021. The pivotal cohort is evaluating magrolimab combined with azacitidine in previously untreated higher risk MDS. If the results are positive, Gilead expects to submit a BLA by the end of 2021 with approval expected in late 2022. Magrolimab + azacitidine is being compared to azacitidine in the same setting in ENHANCE, a Phase III trial with an estimated primary completion date of August 2022. Class competitors for magrolimab include ALX Oncology’s ALX418 which is being evaluated in combination with azacitidine in ASPEN-02, a Phase Ib/II trial for previously untreated higher risk MDS. Results from the Phase I portion of ASPEN-02 are expected in Q4 2021.

**Tags: First Approval, New Mechanism, Practice Changing**
Novartis’ sabatolimab (MBG453) is a potentially first-in-class antibody specific for TIM-3. TIM-3 is expressed on (i) T-cells where it inhibits T-cell activation and (ii) leukemic stem cells (LSC). Hypomethylating agents have been shown to upregulate TIM-3 on LSC.

Hypomethylating agents such as azacitidine and decitabine have been used for over a decade for MDS and lead to a modest survival benefit. Response rates average about 40% but are mostly transient. STIMULUS-MDS1 is a randomized Phase II trial comparing sabatolimab + azacitidine to azacitidine + placebo in previously untreated higher risk MDS. Novartis expects data for the primary endpoint of complete response rate in H2 2021. If the results are positive, a BLA will be submitted by the end of the year leading to possible approval in late 2022. A Phase III trial, STIMULUS-MDS2 is similar to STIMULUS-MDS1 but is enrolling more patients (500 versus 127), has overall survival as the primary endpoint, and has an estimated primary completion date of May 2027. There are no class competitors for sabatolimab being developed for MDS.

Tags: First Approval, New Mechanism, Practice changing

Takeda’s pevonedistat targets the NEDD8-activating enzyme in the ubiquitin-proteasome pathway, and in July 2020, was granted Breakthrough Therapy designation for the treatment of higher risk MDS. PANTHER is a Phase III trial comparing pevonedistat + azacitidine (aza) to aza alone in patients with higher risk MDS as well as patients with low-blast acute myeloid leukemia (AML). The primary endpoint is event-free survival (EFS) and Takeda has indicated that they are expecting data in Q2/Q3 2021. As such, they are expecting approval of pevonedistat for MDS and AML in FY 2022 (prior to March 31, 2023) and FY 2025, respectively. The delay for AML may be due to the FDA requiring overall survival data for that indication. In an underpowered 120 patient randomized Phase II trial, pevonedistat missed the primary overall survival endpoint for the combined MDS and AML ITT population. However, there was a significant improvement in EFS for pevonedistat combined with aza compared to aza alone in a subpopulation of patients with higher risk MDS (20.2 vs 14.8 months; HR 0.54, p=0.045). The MDS subpopulation also showed improvements in both ORR (74% vs 57%) and CR (52% vs 27%) with the pevonedistat combination.

Tags: First Approval, New Mechanism, Practice changing
Oncology

**COPIKTRA | SECURA BIO | LOA: ABOVE AVERAGE | 🔗**

### Peripheral T-Cell Lymphoma (PTCL)

Copiktra is a dual inhibitor of the delta and gamma isoforms of the lipid kinase PI3K. While the delta isoform is expressed in malignant cells, the gamma isoform is expressed in the micro-environment. Copiktra, like a number of other PI3K-delta inhibitors (Zydelig, Aliqopa and Ukoniq), is approved for B-cell lymphoma but Copiktra is positioned to be the first PI3K inhibitor approved for a T cell lymphoma. Copiktra's pivotal Phase II trial, PRIMO, is enrolling patients with relapsed/refractory (R/R) PTCL. Results from the dose selection part of the trial showed encouraging overall response rates of 40% and 62% for the 25mg (n=20) and 75mg (n=13) dose cohorts, respectively. In comparison, most approved therapies for R/R PTCL have response rates of less than 30%. The expansion phase of the PRIMO trial will investigate duvelisib starting at 75 mg BID for 2 cycles to rapid tumor response, followed by 25 mg BID to maintain long-term disease control and mitigate the potential for later onset toxicity (Copiktra is currently approved at 25 mg with a black box warning for fatal and serious toxicities). Results are expected in late 2021 which could lead to a regulatory submission and possible approval by late 2021.

*Tags: Label Expansion (New Indication)*

**TABLECLEUCEL | ATRA | LOA: ABOVE AVERAGE | 🔗**

### Post-Transplant Lymphoproliferative Disease (PTLD)

Atara biotherapeutics' tabelecleucel (tab-cel) consists of T cells collected from an HLA-matched donor that have been selected and amplified for recognition of EBV antigens. Tab-cel, an off-the-shelf product, is being developed for EBV-associated PTLD, an ultra-rare, aggressive cancer that occurs in immunosuppressed patients after transplant. Patients that relapse or are refractory to rituximab ± chemotherapy have high mortality, with OS of 1.7 and 3.3 months for hematopoietic cell transplant (HCT) and solid organ transplant (SOT) patients, respectively. Tabelecleucel has Breakthrough Therapy designation from the FDA. ALLELE is a Phase III trial evaluating tabelecleucel in HCT and SOT patients who have EBV-associated PTLD and who have failed rituximab ± chemotherapy. ALLELE does not have a comparator arm and has an estimated enrollment of 66 patients. An interim analysis of all patients with 6 month follow up reported a 50% ORR across HCT and SOT cohorts which exceeds the 37% threshold set for this primary endpoint. Atara expects to complete a rolling BLA in Q3 2021 which could lead to the first approval of an allogeneic T-cell immunotherapy in H1 2022. Atara estimates that there are several hundred target patients in the US.

*Tags: First Approval, New Mechanism, Practice changing*
Ophthalmology
**FARICIMAB | RHHBY | LOA: ABOVE AVERAGE**

**Wet Age-Related Macular Degeneration (Wet AMD)**

Competition in this market may soon be heating up with faricimab, Roche’s bispecific antibody targeting both VEGF-A and angiopoietin (Ang)2. The drug has a novel mechanism of action among current brands and has so far demonstrated a benign safety profile similar to Lucentis. Furthermore, Phase II data indicate that faricimab provides vision gains that are maintained with a 16-week dosing schedule and are slightly better than results from a monthly dose of Lucentis.

Faricimab is currently being evaluated head-to-head in two Phase III trials (LUCERNE and TENAYA) against Eylea and will likely be its direct competitor once it successfully reaches the market in 2022. The anticipated uptake of this bispecific antibody will contribute directly to the forecasted growth of the wet AMD market, and faricimab is expected to generate annual revenues of $1.5bn in the US, Japan, and five major European markets by 2030.

*Tags: First Approval, New Drug Class, Potential Blockbuster*

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**PDS-1.0 | RHHBY | LOA: ABOVE AVERAGE**

**Wet Age-Related Macular Degeneration (Wet AMD)**

Lucentis’ label has the potential to expand to include the ranibizumab Port Delivery System (PDS-1.0), a novel refillable intraocular implant. Top-line Phase II results from the LADDER trial indicate the implant can be refilled every 9–15 months and can theoretically provide patients with a continuous non-injectable solution of a well-known efficacious drug. Preliminary efficacy outcomes in both the LADDER trial and the Phase III Archway study where patients received 100mg/ml refills every six months have shown that visual acuity gains were non-inferior to monthly ranibizumab 0.5mg injections.

The rates of potential infection with an implantable device are a concern with PDS-1.0, and Roche will have to overcome this barrier given the high bar for safety that Eylea and intravitreal Lucentis have set. As such, Roche has initiated the long-term extension Phase III Portal study to assess the safety of PDS-1.0 for up to three years.

*Tags: Label Expansion (Existing Indication)*
Psychiatry

CAPLYTA | ICTI | LOA: ABOVE AVERAGE | 🌟

Bipolar Disorder

Caplyta (lumateperone) is expected to become the market leader for bipolar disorder as a uniquely differentiated prospect with a competitive clinical profile. Impressively, it is the first treatment to demonstrate efficacy for bipolar depression both as a monotherapy and as an adjunct to mood stabilizers in underserved bipolar I and II depression patients. Not only does Caplyta fulfill unmet need for bipolar depression, but it also boasts an attractive tolerability profile. The once-daily oral product is currently under review by the US Food and Drug Administration (FDA), following the acceptance of Intra-Cellular Therapies’ supplemental New Drug Application in May 2021. We anticipate a smooth road to approval in December 2021 with Caplyta's likelihood of approval (LOA) at 5% above average. Datamonitor Healthcare forecasts a $2.2bn peak revenue opportunity for Caplyta in the bipolar disorder market across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) by 2029.

Bipolar depression is a key target indication as it is associated with great unmet need. Vraylar (cariprazine), Latuda (lurasidone), the fixed-dose combination Symbyax ([olanzapine + fluoxetine]), and Seroquel/Seroquel XR (quetiapine) are the only drugs approved for bipolar depression. Of these products, only Seroquel/Seroquel XR is FDA-approved for the treatment of bipolar type II depression. Given the limited options, Caplyta's broad relevance across both types of the bipolar depression niche is highly attractive. Furthermore, established drugs for bipolar depression are commonly associated with burdensome adverse effects such as sedation, weight gain, or akathisia, which often lead to treatment discontinuation. In contrast, one of Caplyta's principal strengths is its placebo-like safety and tolerability profile, which has prevailed consistently throughout its clinical trial programs for bipolar disorder and schizophrenia. Critically, Caplyta is associated with low rates of extrapyramidal/motor adverse events and lacks metabolic/weight gain issues.

Tags: Label Expansion (New Indication), Potential Blockbuster
LYBALVI | ALKS | LOA: ABOVE AVERAGE

Schizophrenia/Bipolar Disorder

Alkermes’ ALKS 3831/Lybalvi, a distinct formulation of olanzapine and the novel opioid receptor antagonist samidorphan, is an antipsychotic drug candidate designed to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain, which is a firmly established side effect of most antipsychotics. In trials, the drug has demonstrated similar efficacy to olanzapine and less weight gain, and a recent advisory committee panel largely agreed with the metabolic benefits of the drug, though deemed preventive measures necessary to circumvent the risk associated with the opioid antagonist action of samidorphan to opioid users. Despite the positive advisory committee outcomes, Alkermes received a complete response letter from the FDA for its original Lybalvi filing. The FDA stated that no further clinical or non-clinical data were required, and that the decision was in relation to the tablet coating of certain batches of the drug. Alkermes states it has since resolved this issue and resubmitted the NDA, with a second PDUFA date now set for 1 June 2021 for both the treatment of Schizophrenia and Bipolar disorder.

Key Opinion Leaders indicate they are excited by Lybalvi because the drug makes the use of olanzapine safer by avoiding the weight gain and metabolic side effects seen with olanzapine treatment alone, which is arguably one of the best antipsychotics currently on the market.

Tags: First Approval
SAGE-217 (zuranolone) is forecast by Datamonitor Healthcare to become a market-leading drug with a $2.1bn revenue opportunity in major depressive disorder (MDD) and post-partum depression (PPD) across the seven major markets (US, Japan, France, Germany, Italy, Spain, and the UK) by 2030. SAGE-217 boasts prominent novelty and targets unmet need in numerous respects: its mechanism of action as a positive allosteric modulator of y-aminobutyric acid A (GABA_A) receptors; its efficacy in PPD; its rapid-acting effects; and its episodic, short-course oral dosing schedule. Results from the SHORELINE trial (ClinicalTrials.gov identifier: NCT03864614) highlighted that responders to the initial 14-day course of 30mg SAGE-217 only used an average of 2.2 treatments in the 12-month study. SAGE-217's anticipated success is also attributed to its positioning for several facets of the depression patient population, including PPD and MDD patients. Within MDD, the drug is being trialed at Phase III as an episodic therapy, to treat patients with co-morbid insomnia, and as an acute rapid response therapy (RRT) in patients with MDD when co-initiated with new standard antidepressant therapy, which importantly positions the drug for early use in the treatment algorithm.

Conversely, SAGE-217 still needs to prove itself through its pivotal Phase III clinical trials, which should yield data during 2021. SAGE-217's likelihood of approval (LOA) currently sits at 3% below average, which reflects its spotty performance so far in its clinical trial program for depression. In the Phase III MOUNTAIN MDD trial (ClinicalTrials.gov identifier: NCT03672175), SAGE-217 failed to achieve statistical significance on the primary endpoint and was associated with the serious adverse event of syncope. This disappointing outcome was accounted for by non-compliance to the study drug and patients’ depression severity being skewed towards the mild end of the spectrum compared to previous trials. It is more challenging to generate a strong effect size with milder patients, and there is greater heterogeneity among these patients. Nevertheless, Sage Therapeutics has already secured robust data for PPD and MDD from two positive pivotal Phase II trials, and SAGE-217 will be in a healthy position if these results are consolidated in pending Phase III trials. Further strengthening the product's potential, Sage Therapeutics has entered into a strategic partnership with Biogen for the development and commercialization of SAGE-217, with shared responsibilities in the US and Biogen taking the lead with development outside of the US (excluding Japan, Taiwan, and South Korea).

Tags: First Approval, Potential Blockbuster, Practice Changing
Renal
Alport Syndrome

After a tortured history, where safety findings derailed the drug in diabetic nephropathy, development of bardoxolone targeted orphan conditions where the safety issues could be better managed/avoided. As a result, it is now looking to be the first drug approved in the US for chronic kidney disease (CKD) caused by Alport syndrome. The FDA PDUFA is scheduled for February 25, 2022. An MAA filing for the EMA is expected Q4 2021.

Bardoxolone has showed relative stability of eGFR versus placebo after 100 weeks, and while that is only a marker of disease activity, it maintained a statistically significant, albeit somewhat diminished, effect after four weeks off drug. It also has shown a trend for a reduction in a kidney failure event composite, though some of the components of the endpoint were also based on eGFR, as well as a numerically lower proportion of non-kidney adverse events associated with Alport syndrome. One issue that has caused some concerns, is that the drug increases albuminuria, which normally may be a sign of damage, though for bardoxolone there is no other evidence for an adverse effect and preclinical evidence suggests other reversible causes. Nevertheless, an FDA advisory committee will first discuss the application.

Tags: First Approval, New Drug Class, Practice Changing, Potential Blockbuster
Renal

**SPARSENTAN | TVTX | LOA: ABOVE AVERAGE (FSGS) and SAME AS AVERAGE (IgAN) | [link]**

**Focal Segmental Glomerulosclerosis (FSGS)/Immunoglobulin A (IgA) Nephropathy**

Sparsentan was designed to improve on approved angiotensin II receptor blockers (ARBs), by adding inhibition of the endothelin receptor type A (ETA). In a pivotal Phase III study in primary FSGS, an orphan condition, sparsentan demonstrated greater partial remission of proteinuria than the ARB irbesartan, though the difference was moderate. Since there were no specific thresholds that regulators set, more details are needed on the difference in mean or median proteinuria and whether there were positive initial trends on eGFR, to gain confidence. The partial remission of proteinuria endpoint is being used for conditional approval, with final eGFR data for full approval. More details are also needed on safety, since there are potential issues for endothelin antagonists, though the class is approved in pulmonary arterial hypertension, and there is a need for further options in FSGS. An NDA filing is expected in the second half of 2021. If successful, sparsentan would be the first drug with a specific approval for FSGS, though current treatment for primary FSGS consists of ACE inhibitors/ARBs, corticosteroids, and other immunosuppressive therapies.

Sparsentan does not yet have good data in IgAN, another orphan condition, but a Phase III trial was initiated based on mechanistic considerations, the correlation of proteinuria with outcomes from other studies, and success in FSGS. If interim proteinuria data is positive, it could likewise lead to conditional approval in 2022. There currently are no drugs approved specifically for IgAN, but Nefecon, which targets delivery of a concentrated dose of the corticosteroid budesonide to the Peyer’s patches in the ileum, has a PDUFA in September 2021. Other current therapy options are similar to FSGS.

*Tags: First Approval, New Drug Class, Practice Changing*
Respiratory
Tezepelumab is a first-in-class human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine. Positive topline results were reported from the Phase III NAVIGATOR study, meeting the primary endpoint of exacerbation reduction in patients with low levels of eosinophils as well as the eosinophilic patient subset. Importantly, tezepelumab was associated with reductions in asthma exacerbations irrespective of baseline blood eosinophil counts, including in patients with eosinophil counts fewer than 150 cells/μL. Dupixent was unable to differentiate from placebo in patients with low baseline eosinophils in the LIBERTY ASTHMA QUEST study. These results should provide tezepelumab with broader access to treat severe asthmatics, while other biologics remain restricted by subtype.

Tags: First Approval, New Drug Class, Potential Blockbuster

Results from three Phase III studies evaluating PT027 in asthma are expected to read out in the second half of 2021. The inhaled budesonide/albuterol combination is unique in its delivery of both an inhaled corticosteroid (ICS) and short acting beta-2 agonist (SABA) through a single inhaler. Recent changes to the guidelines for asthma favor this combination over the traditionally used SABA inhaler. The ICS component, formoterol, is specifically called out as the ICS of choice in guidelines for reliever use as this corticosteroid is particularly quick-acting.

Tags: First Approval, Practice Changing
## Appendix

### Drugs covered (listed alphabetically):

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>ABALOPARATIDE-TD</td>
<td>RDUS</td>
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<td>AMT-061</td>
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<td>KRYS</td>
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**Key Potential Drug Launches in 2022 (As of April 2021)**
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