Pharma Intelligence
Informa

Q3 Outlook Webinar

Hardik Patel
Therapeutic Area Director, Oncology and Respiratory

Michael Haydock
Senior Director, Infectious Diseases and Cardiovascular and Metabolic

Stephanie Yip
Senior Analyst, CNS and Immunology and Inflammation

Dominique Fontanilla
Therapeutic Area Director, CNS and Immunology and Inflammation

Agenda

Oncology	Entrectinib for solid tumors and non-small cell lung cancer (NSCLC) Fedratinib for myelofibrosis
Cardiovascular/Metabolic	Inclisiran for dyslipidemia Omecamtiv mecarbil for chronic heart failure
Infectious Diseases	Pretomanid for tuberculosis
Immunology and Inflammation	Upadacitinib for rheumatoid arthritis (RA)
CNS	Lumateperone for schizophrenia Arzerra for multiple sclerosis (MS)

entrectinib (RHHBY)

Roche will look to double up on entrectinib, seeking two approvals

Upcoming Q3 catalysts	• Target PDUFA date of August 18th for solid tumors with NTRK fusions and ROS1-positive NSCLC patients	***LOA: 93% in solid tumors (10% above average)***	***LOA: 87% in NSCLC (5% above average)***

Catalyst details – NTRK fusion-positive solid tumors:

- NDA for use in adult and pediatric patients with neurotrophic tropomyosin receptor kinase (NTRK) fusion-positive, locally advanced or metastatic solid tumors who have either progressed following prior therapies or as initial therapy when there are no acceptable standard therapies was submitted in December 2018.
- Filing was based on pooled results of the early-phase STARTRK-1, STARTRK-2, STARTRK-NG, and ALKA-371-001 trials, which showed that patients with NTRK fusion-positive tumors treated with entrectinib had an overall response rate (ORR) of 57.4%, a median progression-free survival (PFS) of 11.2 months, and a median overall survival (OS) of 20.9 months.

Market context – NTRK fusion-positive tumors:

- Eli Lilly's Vitrakvi was already approved for this indication in November 2018.
- Thus far, it appears as though Vitrakvi may be more effective, having demonstrated an ORR of 81% in NTRK fusion-positive patients. However, PFS and OS results have not yet been released for Vitrakvi, and will be a more reliable comparison of efficacy.
- Vitrakvi's specificity also seems to grant it a better tolerability profile. In its integrated dataset, only 9% of patients receiving Vitrakvi required dose reductions due to adverse events versus 27% with entrectinib.

Source: Biomedtracker, July 2019

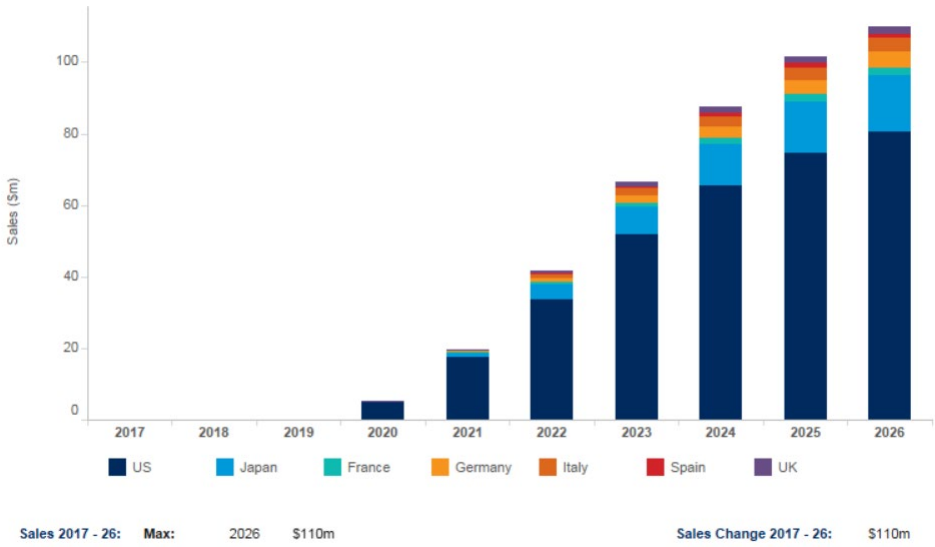
Entrectinib will provide ROS1-positive NSCLC patients with an additional option

Catalyst details – ROS1-positive NSCLC:

- NDA for use in metastatic non-small cell lung cancer (NSCLC) patients with ROS1-positive disease was also submitted in December 2018.
- Filing was based on pooled results of the STARTRK-1, STARTRK-2, STARTRK-NG, and ALKA-371-001 trials, which showed that NSCLC patients with ROS1-positive disease had an ORR of 77.4%, a median duration of response (DOR) of 24.6 months, and a median PFS of 19.0 months.

Market context – ROS1-positive NSCLC:

- About 1-2% of NSCLC patients are ROS1-positive, and although other treatments are recommended by guidelines for off-label use, Xalkori is the only drug currently approved for these patients.
- Efficacy of entrectinib thus far seems to be on par with Xalkori, which showed an ORR of 72%, median DOR of 17.6 months, and a median PFS of 19.2 months in its PROFILE 1001 study.
- Activity in patients with CNS metastases may be a key differentiator for entrectinib since about half of all ROS1-positive patients treated with Xalkori exhibit progression in the CNS.



Source: Biomedtracker, July 2019; Datamonitor Healthcare, July 2019

fedratinib (CELG)

Despite a tumultuous development history, fedratinib will likely help address the unmet need in myelofibrosis

Upcoming Q3 catalysts

- Target PDUFA date of September 3rd in myelofibrosis

LOA: 87%

(5% above average)

Catalyst details:

- Development of fedratinib was halted in 2013 following reports of Wernicke's encephalopathy (WE) occurring in several patients participating in clinical trials.
- Clinical hold was later lifted in 2017 following a retrospective review of the data, which revealed the incidence of WE in fedratinib-treated patients was lower than initially suspected, fedratinib does not directly cause WE, and that WE can be treated/prevented.
- NDA filing in myelofibrosis was submitted in late 2018 and was granted priority review by the FDA. Filing was based on the Phase III JAKARTA and Phase II JAKARTA2 trials, which showed that approximately half of all patients treated with fedratinib experienced a ≥35% reduction in spleen volume at the 24-week mark.

Market context:

- Fellow Janus kinase (JAK) inhibitor Jakafi is currently the only product approved for intermediate- or high-risk myelofibrosis patients, leaving a significant unmet need in relapsed/refractory patients.
- It is unclear if this potential approval will be broad, or if it will specifically be for patients who are resistant or intolerant to Jakafi.
- Initiated in February 2019, the Phase III FREEDOM trial will aim to further validate fedratinib's safety and efficacy in myelofibrosis patients previously treated with Jakafi.

Source: Biomedtracker, July 2019

Inclisiran (MDCO/ALNY)

Attractive dosing schedule and anticipated lower price will allow inclisiran to capture market share from Repatha and Praluent

Upcoming Q3 catalysts

- Top-line data from ORION-10 (US) and ORION-11 (EU) in patients with ASCVD and elevated LDL-C
- Top-line data from ORION-9 in HeFH

LOA: 57%

(10% above average)

Market context:

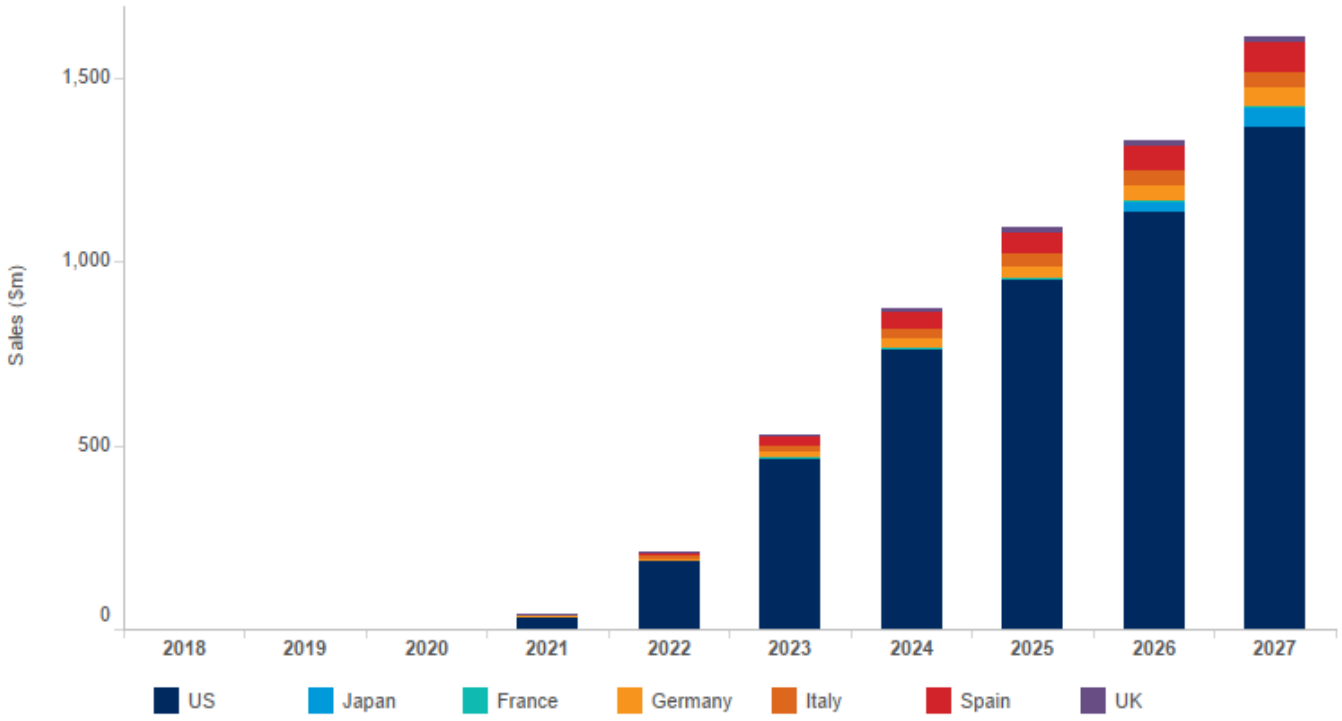
- Repatha (AMGN) and Praluent (SNY/REGN) are established PCSK9 inhibitors which have shown substantial additional LDL-C reductions in patients receiving maximally-tolerated statins
- They have shown MACE reductions (15%) in their cardiovascular outcomes studies, and after substantial discounting in 2018, both are experiencing volume growth
- Inclisiran is set to become the third-to-market PCSK9-targeting agent, but suppresses production (siRNAi) rather than inhibiting extracellular PCSK9 and is dosed every six months.

Catalyst details:

- Topline data from ORION-10/11 need to show comparable reductions in LDL-C to Praluent/Repatha to convince physicians of efficacy. Phase II ORION-3 data showed a mean 51% LDL-C reduction at 22 months, which is comparable to Repatha, but it is not clear if this is a peak or trough value.

Source: Biomedtracker, July 2019

Despite late entry, inclisiran is forecast to achieve 36% PCSK9 market share due to superior dosing



Sales 2018 - 27: **Max:** 2027 $1,615m

Sales Change 2018 - 27: $1,615m

- Uptake will be driven primarily by inclisiran's superior dosing schedule and competitive pricing (assumed ~$4.7k per patient per year)
- Positive ORION-4 CVOT data in high-risk secondary prevention patients are expected to boost sales from 2026

Source: Datamonitor Healthcare, July 2019

Omecamtiv mecarbil (AMGN/CYTK/SAS/ Royalty Pharma)

Omecamtiv mecarbil could address a major unmet need for new therapies capable of increasing cardiac contractility

Upcoming Q3 catalyst

- Topline data from GALACTIC-HF pivotal study in HFrEF

LOA: 49%

(2% above average)

Market context:

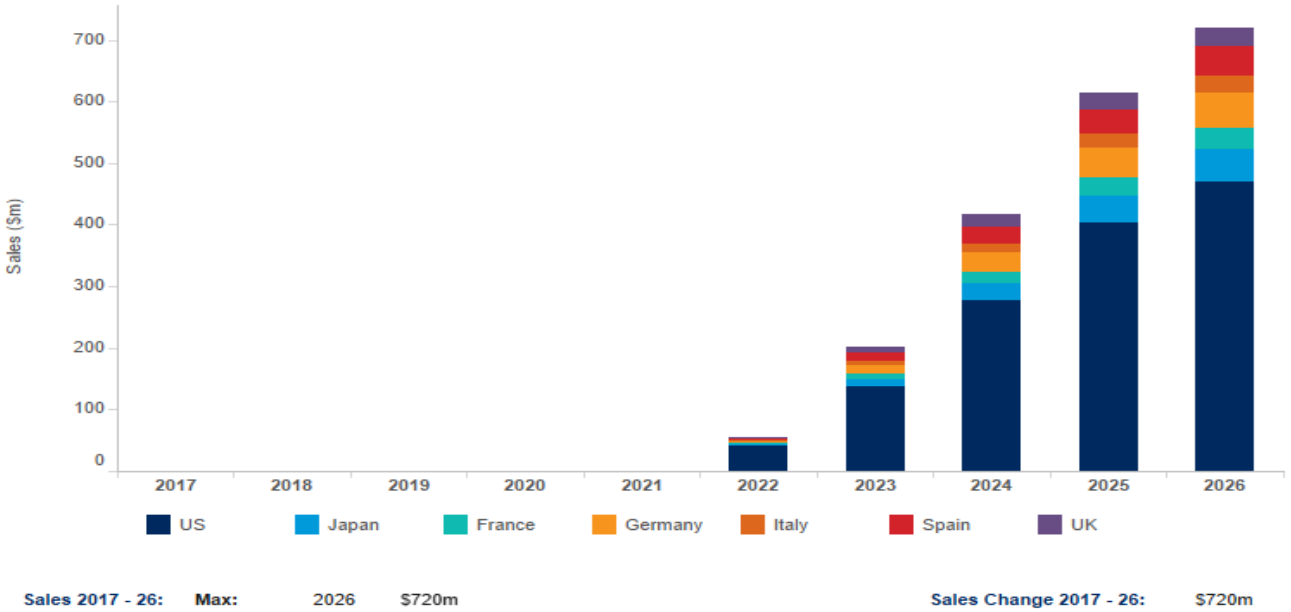
- Current CHF therapies only act by relieving symptoms and reducing the burden on the failing heart, and thus there is great demand for therapies capable of directly increasing cardiac output
- Currently available inotropes have fallen out of favor because they increase intracellular calcium and oxygen demand, and have been linked to increased risk of arrythmia and death
- Omecamtiv mecarbil's unique mode of action (direct myosin ATPase stimulator) could bypass these safety concerns and be used in combination with other SOC agents.

Catalyst details:

- GALACTIC-HF is investigating the addition of omecamtiv mecarbil to SOC, with a primary endpoint of time to CV death or first HF event
- Phase II COSMIC-HF data showed consistent improvements in all cardiac function measures (↑ systolic ejection time and stroke volume, ↓ ventricular volumes, heart rate, and NT-proBNP)
- Small troponin increases are a potential safety concern, although no ischemia was detected.

Source: Biomedtracker, July 2019

If safety data are positive, KOLs were positive about omecamtiv mecarbil's prospects in HFrEF



Sales 2017 - 26: **Max:** 2026 $720m

Sales Change 2017 - 26: $720m

"So long as the clinical data are clear that there is no signal of increased risk, then we would probably be happy to use it because that is what we hope to achieve for our patients, to increase contractility, we just need to do it safely.
– US key opinion leader

"Omecamtiv mecarbil has such a unique and very selective mechanism of action that is completely different than all of those [other inotropes], and it is the first time that we might actually be able to investigate the fundamental defect in heart failure. Multiple studies have demonstrated that the best predictor of improving outcomes in heart failure is reduction in left ventricular volumes, and reduction in NT-proBNP, and omecamtiv mecarbil does both of those things…If the trial is positive, omecamtiv mecarbil has no effect on heart rate, blood pressure, kidney function, potassium, so it could effectively be started at any time without any concerns so all the barriers that were there for ivabradine, and sacubitril/valsartan, and perhaps the SGLT-2 inhibitors are not there for omecamtiv mecarbil." – US key opinion leader

Source: Datamonitor Healthcare, July 2019

Pretomanid (TB Alliance/Mylan)

B-L-Pa regimen addresses unmet needs for greater efficacy and shorter treatment durations in MDR/XDR-TB patients

Upcoming Q3 catalyst

- FDA approval decision expected in Aug/Sep

LOA: 94%

(6% above average)

Market context:

- TB resistance is a growing issue, with an estimated 460,000 MDR-TB cases in 2017. Roughly 8.5% of MDR cases are classified as XDR-TB by the World Health Organization
- Prolonged treatment durations and poor tolerability profiles of current MDR/XDR-TB regimens leads to poor compliance. Globally, only 55% of MDR-TB cases are successfully treated.

Catalyst details:

- The NDA is based on preliminary data (n=45) from the single-arm NIX-TB study. MDR/XDR-TB patients were treated with the B-L-Pa regimen for 6–9 months, with 88% achieving durable cure.
- FDA Adcom panel voted 14-4 to recommend pretomanid's approval as part of the B-L-Pa regimen, but noted an inability to discern pretomanid's contribution to the regimen due to lack of control arm
- Outstanding safety issues (hepatotoxicity/fertility toxicity) are not expected to prevent approval, but uptake will be limited until ongoing liver/renal PK and semen analyses are complete.
- Cost will also restrict access given bedaquiline is already more expensive than other anti-TB agents

Source: Biomedtracker, July 2019

Upadacitinib (ABBV)

Upadacitinib to become the 3rd Janus Kinase (JAK) inhibitor approved for rheumatoid arthritis (RA)

Upcoming Q3 catalysts

- Target PDUFA date of 20 August 2019 for RA

LOA: 98%

(11% above average)

Catalyst details:

- Approval will be supported by AbbVie's pivotal SELECT program, which met all primary and secondary endpoints across five Phase III studies.
- The SELECT program consists of a broad clinical data package spanning various patient cohorts including: inadequate responders to methotrexate (MTX), biologic disease-modifying anti-rheumatic drugs (DMARDs), and MTX-naïve RA patients.

"I suspect it will be approved; they have received fast track status from the US Food and Drug Administration (FDA) and we are not seeing anything that makes us believe that that will be derailed, certainly we have not seen any announcements regarding an FDA advisory committee meeting, or ad-comm. It is already July, that usually implies that things are moving along quite well… I suspect in general it will be one of the most effective drugs we have in rheumatoid arthritis and it'll be oral."

- US key opinion leader

Market context:

- Upadacitinib will join Pfizer's Xeljanz (tofacitinib) and Eli Lilly's Olumiant (baricitinib) as part of the expanding oral JAK inhibitor class.
- AbbVie's Humira will face its US patent cliff in 2022 and already lost EU exclusivity in October 2018.

Source: Biomedtracker, July 2019

Lumateperone (ITCI/BMY)

Lumateperone's chances in schizophrenia are uncertain given mixed trial results

Upcoming Q3 catalysts

- Target PDUFA date of September 27, 2019 for schizophrenia
- FDA Advisory Panel Meeting planned for July 31, 2019

LOA: 81%

(4% below average)

Catalyst details:

- The drug has produced inconsistent results, with a failed pivotal Phase III trial (Trial 302) and successes in two controlled studies (Phase II and Phase III).
- Long-term safety issues in non-human toxicology studies surfaced in May 2017, but the FDA determined the animal toxicity would not be an issue in humans.
- Lumateperone is a novel drug with a unique and complicated mechanism of action and has shown modest efficacy with a favorable side effect profile.

"Efficacy-wise, I think it is marginal. If anything, I think maybe the safety profile of the drug could be better than the efficacy. […] There will always be that patient that has failed other treatments and may respond to the drug."

- US key opinion leader

Market context:

- The schizophrenia market is crowded, however unmet needs remain.
- Key unmet needs include treatments targeting negative symptoms, improved tolerability, and improved options for patients with refractory positive symptoms.
- Lumateperone is also in Phase III development for bipolar depression with top-line results released this week.

Source: Biomedtracker, July 2019

Arzerra (NVS)

ASCLEPIOS I and II trial results will determine if Novartis can expand their MS franchise

Upcoming Q3 catalysts

- Top-line results are expected from two Phase III Trials (ASCLEPIOS I and II)

LOA: 54%

(2% above average)

Catalyst details:

- Results from these two pivotal studies will potentially support Arzerra's filing for relapsing MS expected in Q4 2019.
- Both trials are head-to-head with Sanofi's Aubagio and the primary endpoint of both studies is annualized relapse rate.
- Phase II MIRROR trial results were promising with Arzerra treatment (SC) resulting in a 65% reduction in new T1 lesions after 12 weeks, with a >90% reduction at higher doses.

Market context:

- Arzerra is initially targeting the relapsing MS segment, which is becoming increasingly saturated. Instead, there is a pressing need for treatment options for progressive forms of MS.
- If successful, Novartis can add another asset to it's successful MS franchise which includes Gilenya and Mayzent. An additional approval would also potentially boost CNS revenues for Novartis as Gilenya faces generic competition in Europe.
- Although ASCLEPIOS I and II are head-to-head against Aubagio, future potential market competition will likely come from Roche's Ocrevus, another CD-20 directed monoclonal antibody.
- Arzerra (IV) was approved for the treatment of chronic lymphocytic leukemia in 2009, but has only experienced modest uptake in Oncology.

Source: Biomedtracker, July 2019

Pharma Intelligence
Informa

Thank you for listening

Questions:

pharma@informa.com