Q4 2018 Outlook Webinar

Key Catalysts and Their Impact on Pharma Markets

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Agenda

CNS	• Zulresso for PPD • SAGE-217 for MDD and PPD
I&I	• Filgotinib for UC/RA/axSpA
Infectious Disease	• Inarigivir for hepatitis B • ARO-HBV for hepatitis B • Tivicay/Epivir for HIV
Oncology	• Isatuximab for multiple myeloma • Tivozanib for renal cell cancer • Larotrectinib for NTRK gene fusions

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Zulresso
SAGE-217
(SAGE)

Zulresso would be SAGE Therapeutics' first pharmaceutical and the first medication indicated for the treatment of PPD

Upcoming Q4 catalysts

- Target PDUFA date of December 19, 2018 for PPD
- FDA Advisory Panel Meeting – November 2, 2018

LOA: 99%

(14% above average)

- Two pivotal Phase III trials (Hummingbird 202 B and 202C) were conducted in severe and moderate PPD. Zulresso achieved the primary endpoint in both trials, a mean reduction from baseline in the HAM-D total score over placebo at 60 hours (Study 202B: 3.7 [p=0.0242] for 90 µg/kg/h dose and 5.9 [p=0.0011] for 60 µg/kg/h dose; Study 202C: 2.2 [p=0.0160] for 90 µg/kg/h dose).
- The drug has been generally well tolerated in studies with similar adverse event rates across all treatment arms. The most common adverse events were headache, somnolence, and dizziness.
- As an IV treatment, will be limited to hospital administration unlike SAGE-217.
- *"In patients with extremely severe depression I could see the IV [Zulresso] being used, and then a switch to the oral [SAGE-217]. For the majority of patients, I think the oral formulation is going to be preferred. Ease of use, ability to use in different situations, the IV has a very, very rapid onset, which is what is important, but the oral, the onset is good too, and that study is ongoing, and there is a geriatrics study as far as I remember, and to me we are looking at a whole new type of medication for depression, and it is looking good*." – US KOL
- *"…A very exciting breakthrough. Since you approved Prozac, I think this is probably one of the greatest approvals we've ever seen…"* – Dr. Narenda, FDA AdCom Meeting

Source: Biomedtracker, November 2018

Positive pivotal trial results could advance SAGE-217 as the first short-course oral treatment for MDD and PPD.

Upcoming Q4 catalysts

- Top-line data from a pivotal Phase II trial in severe PPD
- Placebo-controlled Phase III trial in MDD to initiate in Q4 2018

LOA: 20%

(8% above average)

- SAGE-217's efficacy profile in MDD met the primary endpoint of an initial Phase II trial, showing rapid, clinically meaningful reduction from baseline in HAM-D of 17.6 points at Day 15 (-10.7 points over placebo). Improvements were observed on Day 2 and were present on Day 28.
- Currently no data for SAGE-217 in PPD.
- Positioned as a novel 2-week short course of treatment.
- Future pivotal trials include two placebo-controlled Phase III trials in MDD and in Severe PPD.
- *"I am just looking at the rate of remission, the data here. The profile is interesting, it has that rapid onset of action, I do not see much long-term data here, so that would be my question as far as – I mean it is obviously useful if you have a post-partum patient that is imminently dangerous or not functioning, it could be a valuable tool, I am just not sure about long-term durability."* – US KOL

Source: Biomedtracker, November 2018

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Filgotinib (GILD)

Filgotinib has considerable potential and could become a market leader in inflammatory indications

Upcoming Q4 catalysts

- Top-line Phase III pivotal results are expected in moderate to severe Ulcerative Colitis
- Updated results from filgotinib's Phase III FINCH 2 trial in RA and the Phase II TORTUGA trial in axSpA were released in Q4

LOA

UC: 59% (same as avg)

RA: 69% (10% above avg)

axSpA: 23% (3% above avg)

- In the Phase III (FINCH 2) data in RA filgotinib (100mg/200mg) achieved its primary endpoint in the proportion of patients achieving ACR20 response at Week 12 (57.5%/66.0% vs placebo [31.1%]).
- Two additional pivotal Phase III trials (FINCH 1 and FINCH 3) are enrolling for moderate-to-severe RA who have inadequate response to methotrexate, and moderate-to-severe RA patients who are naïve to methotrexate therapy.
- Filgotinib met its primary endpoint, the mean change from baseline in ASDAS at week 12, in patients with moderate-to-severe ankylosing spondylitis. The mean change from baseline in the filgotinib arm was -1.5 versus -0.6 ($p<0.0001$) in the placebo arm. Further, the placebo-adjusted ASAS20 responder rate was 36%.
- 47% of patients treated with filgotinib 200 mg achieved clinical remission at week 10 versus 23% of patients treated with placebo ([95% CI 9–39], p=0.0077) in filgotinib's Phase II FITZROY trial in Crohn's Disease.

Source: Biomedtracker, November 2018

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ARO-HBV (JNJ/ARWR)

Impressive HBsAg reductions could position ARO-HBV as the backbone of future HBV regimens

Upcoming Q4 catalysts

- Updated data from higher dose cohorts of the Phase I/II ARO-HBV1001 study

LOA: 29%

(2% above average)

- Topline data from 100mg and 200mg monthly cohorts have been highly promising after three months of treatment, with HBsAg declines of 93-99%. Longer treatment durations and/or combination therapy could achieve functional cure
- Abstract with data from higher dose cohorts has been released, but interestingly there is no clear dose response.
- ARWR partnership with JNJ facilitates combinations with in-house CpAMs, a therapeutic vaccine, and/or TLR-7 agonist
- ARB-1467 is the most advanced siRNA threat to ARO-HBV but it has an unattractive IV formulation and showed lesser declines in 2mg/kg and 4mg/kg cohorts
- ARB-1467 expected to be replaced by second-generation siRNA (AB-729) with new GalNAc subcutaneous delivery system

Source: Biomedtracker, November 2018

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Inarigivir (SBPH)

Positioning as a tolerable ‘oral immunomodulator’ paves way for sequential and/or combination treatment strategies

Upcoming Q4 catalysts

- Updated data from the 200mg cohort of the Phase II ACHIEVE study
- Topline data from Phase II 12-week combination treatment with inarigivir (50mg or 200mg) with Vemlidy (25mg)

LOA: 29%

(2% above average)

- 25mg/50mg/100mg data have shown only a moderate impact on HBV DNA and RNA in HBeAg-positive patients, but greater efficacy in HBeAg-negative patients.
- 13/47 (28%) of inarigivir-treated patients showed a predefined HBsAg decline of 0.5log10, suggesting combination therapy is required to achieve high ‘functional cure’ rates
- **Combination treatment with an siRNA agent is a promising route forward** - inarigivir has a greater impact on HBV DNA and RNA in patients with lower HBsAg levels.
- Studies in 2019 will investigate use as part of a triple combination with Vemlidy + an siRNA agent or alternative MOA
- Additional studies will investigate inarigivir + nucleotide analog (likely Vemlidy) in add-on and sequential strategies in virologically-suppressed patients

Source: Biomedtracker, November 2018

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Tivicay/Epivir (ViiV)

Pooled analysis of GEMINI-1/2:

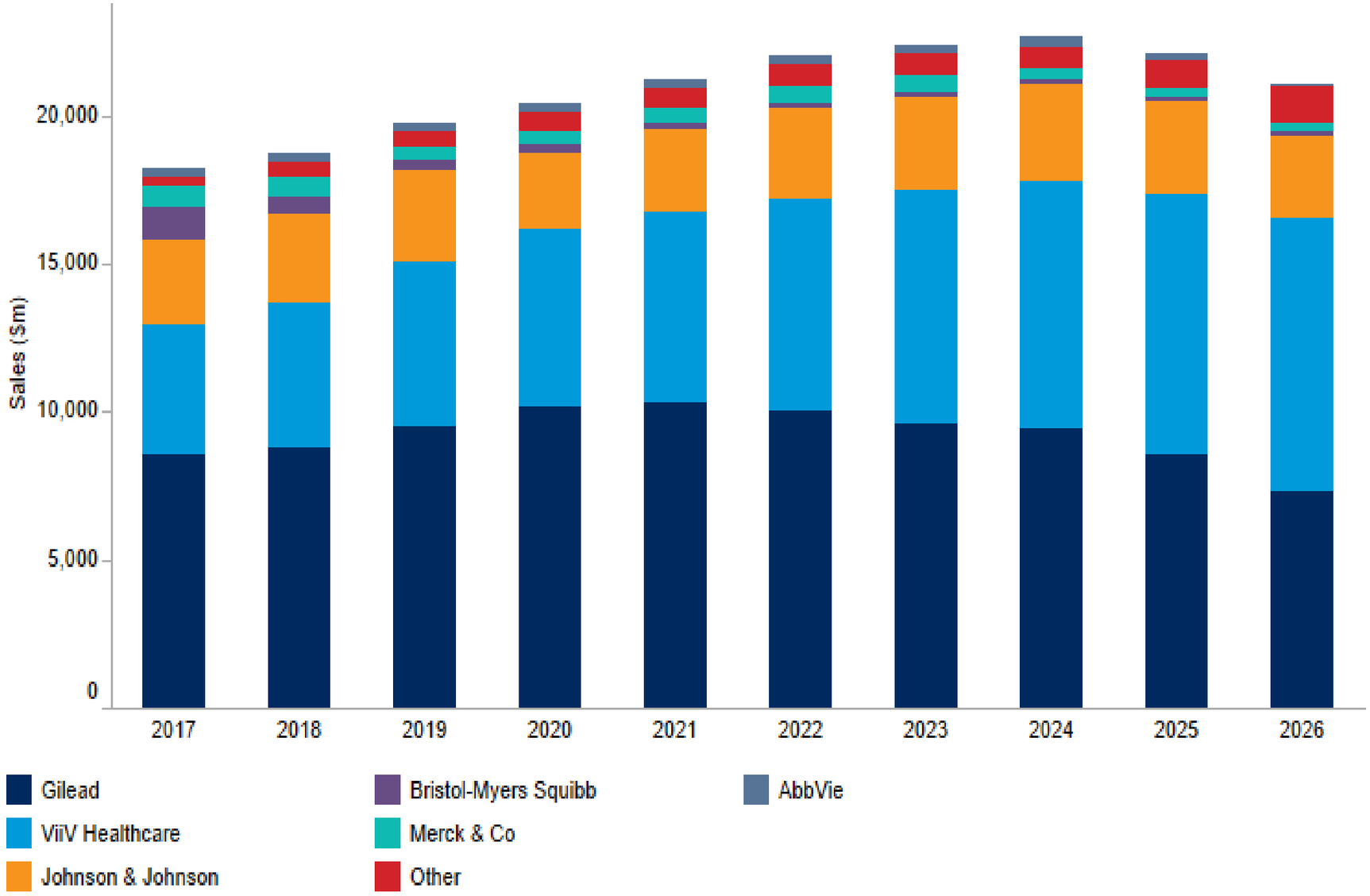
LOA: 96%

(8% above average)

	Tivicay/Epivir	Truvada + Tivicay
Overall plasma HIV-1 RNA <50 copies/ml at Week 48	91%	93%
Plasma HIV-1 RNA <50 copies/ml at Week 48 in patients with baseline <100,000 copies/ml	91%	94%
Plasma HIV-1 RNA <50 copies/ml at Week 48 in patients with baseline >100,000 copies/ml	92%	90%
Rate of virologic failure	<1%	<1%
Drug-related adverse events	18%	24%
Source: Biomedtracker		

- Importantly, efficacy and rates of virologic failure were comparable across treatment arms in patients with high and low baseline viral loads
- No NRTI or INSTI resistance observed in virologic failures in either study arm
- Ongoing TANGO study is investigating use as a switching regimen

Tivicay/Epivir and other two-drug regimens will drive growth for ViiV Healthcare



- ViiV Healthcare's market share will grow from 24% in 2017 to 44% in 2026
- Lower cost is expected to be primary driver of Tivicay/Epivir's uptake until long-term resistance data are available
- Other two-drug regimens include Juluca and cabotegravir + rilpivirine long-acting injectable

Source: Datamonitor Healthcare, November 2018

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Forecast Report

Datapack Patient-Based Market Forecast

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Forecast: HIV

by Ines Mihel 22 December, 2017

Description

Datamonitor Healthcare uses a patient-based approach to size the commercial potential of the HIV market across the US and five major EU markets (France, Germany, Italy, Spain, and the UK). This analysis contains an assessment of key HIV therapies on the market and in the late-phase pipeline, a discussion of HIV market dynamics, and a 10-year patient-based sales forecast.

FORECAST DATA DASHBOARD

View HIV Interactive Forecast Dashboard

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Isatuximab (SNY/IMGN)

Uptake of second-to-market CD38-targeted MAb is dependent on upcoming results

Upcoming Q4 catalysts

- Top-line results from the pivotal Phase III ICARIA trial
- US BLA filing in combination with Pomalyst and dexamethasone for relapsed/refractory multiple myeloma patients who have received at least two prior lines of therapy

LOA: 35%
(same as average)

- In combination with Pomalyst and dexamethasone, isatuximab demonstrated an ORR of 56% in patients with a median of four prior lines of treatment during a Phase Ib study.
- Two other pivotal Phase III trials also on-going in multiple myeloma:
  - Phase III IKEMA trial – in combination with Kyprolis and dexamethasone for relapsed/refractory patients who have received one to three prior therapies
  - Phase III IMROZ trial – in combination with Velcade, Revlimid, and dexamethasone for newly diagnosed patients who are ineligible for SCT
- Projected to generate over $625m in annual revenue across the seven major markets by 2026 despite stiff competition from fellow CD38-targeted monoclonal antibody, Darzalex, in all settings.

Source: Biomedtracker, November 2018

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Tivozanib (AVEO)

Tivozanib's tumultuous development history continues

Upcoming Q4 catalysts

- Top-line results from the pivotal Phase III TIVO-3 trial were reported earlier this week
- US approval for renal cell cancer (RCC) now in question following mixed results from both the TIVO-1 and TIVO-3 trials

LOA: 30%
(5% below average)

- NDA based on TIVO-1 was first submitted in September 2012, but was met with a complete response letter in June 2013 due to discordant survival results.
- MAA was submitted in Europe in March 2016, and tivozanib was approved in August 2017 (marketed as Fotivda).
- Phase III TIVO-3 trial testing tivozanib in third- or fourth-line patients was initiated in May 2016 in order to support US approval, and a potential label expansion in the EU.
- Data reported for TIVO-3 earlier this week showed an improvement in PFS (5.6 months vs 3.9 months); however, initial OS trend does not look promising (HR=1.06, p=0.69).
- Final survival data is expected in August 2019, and AVEO hopes to submit an NDA based on TIVO-1 and TIVO-3 in approximately six months.
- Further testing in combination with immunotherapies may provide tivozanib with alternate path forward.

Source: Biomedtracker, November 2018

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Larotrectinib (LOXO/BAYRY)

Approvals for tumor agnostic indications will likely continue with larotrectinib

Upcoming Q4 catalysts

- FDA target action date of November 26th set for larotrectinib's NDA seeking approval in patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion

LOA: 96%
(14% above average)

- Pooled data from three early-phase trials were recently presented at ESMO, and showed larotrectinib's impressive clinical profile:
  - ORR of 81% and CR of 17% in patients with NTRK gene fusions
  - Median DOR not reached after a median follow-up of 17.6 months
  - Responses observed regardless of patient tumor type or age
  - Of 122 patients, only one patient discontinued treatment due to adverse events
- Will likely see significant usage across a wide variety of cancers as the first therapy available for patients with NTRK gene fusions, but uptake may initially be throttled by mutational testing practices.
- Roche's TRK inhibitor, entrectinib, will likely follow close behind and become larotrectinib's primary competitor.

Source: Biomedtracker, November 2018

Thank you for listening

Questions:

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