Celgene (CELG) / Bristol-Myers Squibb (BMY)

Update

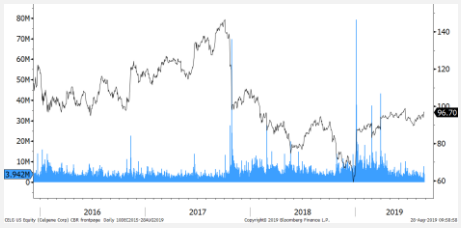
Based on the regulatory progress and the potential upside from the CVR we would consider setting up the deal spread.

Deal Terms

1 CELG = $50 + 1 BMY + 1 CVR ($9/share)

Target: Celgene	
Country	US
Bloomberg	CELG
Sector	Biotech
Share price (USD)	96.70
Market cap (USDm)	68,535.3
Free float (%)	100
Acquirer: Bristol-Myers Squibb	
Country	US
Bloomberg	BMY
Sector	Pharma
Share price (USD)	47.93
Market cap (USDm)	78,402.3
Free float	100

CELG Price Chart (Last 12 months)



Status

Otezla divestiture to Amgen announced Aug 26.

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Update

- On August 26, Amgen announced the acquisition of Otezla from Celgene subject to approval by the FTC.
- The acquisition and the CELG/BMY deal is now expected to close by end-2019

CBR View

- Amgen already has marketed drugs and pipeline products in Otezla`s therapeutic field:
  - Enbrel is Amgen`s main marketed product for moderate/severee plaque psoriasis and psoriatic arthritis (Otezla is also approved for both).
- We note that **CELGENE is mentioned by Amgen as a key competitor in the US/Canada for Enbrel.**
  - Other competing products mentioned include AbbVie`s Humira, JNJ`s Stelara and Remicade.
- **We expect the Otezla acquisition to be approved by the FTC based on the following:**
  - Route of administration and working mechanism is different.
  - We note that both BMY`s pipeline psoriasis product and Otezla are small molecule oral treatments. This overlap prompted the FTC to require divestiture in the CELG/BMY deal.
  - By contrast, **Amgen`s main approved psoriasis treatment Enbrel is a biologic (TNF-Alpha blocker) that comes in the form of an injection. Otezla is a PDE-4 inhibitor tablet.**
  - We note that biologics and small molecule treatments have several distinctive features (method of administration, side effects, cost of treatment).
  - We also believe that the affected parties might have consulted with the FTC prior to striking the deal to divest Otezla to Amgen.
- Amgen`s ABP 798 (biosimilar rituximab) - a biologic intravenous treatment - is being evaluated for the treatment of moderate-to-severe **rheumatoid arthritis.**

CVR:

- As per the latest CELG presentation, CVR related pipeline products are progressing well.
  - Ozanimod
    - U.S. NDA for RMS accepted (Mar. 25, 2020 PDUFA date)
    - Approval deadline Dec 31, 2020
  - Liso-cel
    - Data from pivotal TRANSCEND™ trial in R/R DLBCL expected in Q4:19 U.S. BLA submission expected in H2:19; approval expected in mid-2020
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- Based on the regulatory progress and the potential upside from the CVR we would consider setting up the deal spread.

Otezla divestiture

- On August 26, Amgen announced the acquisition of Otezla from Celgene subject to approval by the FTC.
- The acquisition and the CELG/BMY deal is now expected to close by end-2019
- Announcement highlights:
  - ENBREL is most frequently prescribed to treat moderate-to-severe rheumatoid arthritis, while Otezla is positioned as a therapy of first-choice in patients with moderate-to-severe psoriasis who are not satisfied with topical therapies given its differentiated mechanism of action and established efficacy and safety profile.
  - In PsA, Otezla is positioned for use in patients early in their disease and/or with moderate joint involvement. Additionally, studies are currently underway exploring potential new indications for Otezla, including mild-to-moderate psoriasis.
  - The closing of the acquisition is contingent on Bristol-Myers Squibb entering into a consent decree with the Federal Trade Commission in connection with the pending Celgene merger, the closing of the pending merger with Celgene and the satisfaction of other customary closing conditions. The transaction is expected to close by the end of 2019.
  - Otezla is currently approved for three indications in the U.S.—the treatment of patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy; adult patients with active psoriatic arthritis; and adult patients with oral ulcers associated with Behçet's Disease.

CBR View

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  - Enbrel is Amgen`s main marketed product for moderate/severee plaque psoriasis and psoriatic arthritis (Otezla is also approved for both).
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Product	Territory	Competitor-marketed product	Competitors
ENBREL	U.S. & Canada	REMICADE®*	Janssen Biotech, Inc. (Janssen)(1)
	U.S. & Canada	HUMIRA®	AbbVie Inc.
	U.S. & Canada	STELARA®(2)	Janssen(1)
	U.S. & Canada	Otezla®(2)	Celgene Corporation (Celgene)

Source: Amgen annual report

- **We expect the Otezla acquisition to be approved by the FTC based on the following:**
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  - By contrast, **Amgen`s main approved psoriasis treatment Enbrel is a biologic (TNF-Alpha blocker) that comes in the form of an injection. Otezla is a PDE-4 inhibitor tablet.**
  - We note that biologics and small molecule treatments have several distinctive features (method of administration, side effects, cost of treatment).
  - We also believe that the affected parties might have consulted with the FTC prior to striking the deal to divest Otezla to Amgen.
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Enbrel

- Amgen markets ENBREL primarily in the United States.
- It was launched in 1998 and is used primarily in indications for the treatment of adult patients with the following conditions:
  - moderately to severely active **rheumatoid arthritis**;
  - chronic **moderate-to-severe plaque psoriasis patients** who are candidates for systemic therapy or phototherapy; and
  - active **psoriatic arthritis.**
- Etanercept (Enbrel), a TNF-alpha blocker, plaque ps, pa, injection,

  - Enbrel (etanercept) is a tumor necrosis factor (TNF) blocker. It works by decreasing TNF, a protein produced by the immune system to helps the body fight infections. In people with autoimmune disorders, the immune system produces too much TNF and mistakenly attacks healthy cells.
  - Enbrel is used to treat rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, and to prevent joint damage caused by these conditions.
  - Enbrel is also used to treat plaque psoriasis in adults and children who are at least 4 years old.
- In the United States, companies now have approved biosimilar versions of ENBREL.
- Enbrel is a biologic treatment that comes in the form of an injection

ABP 798

- ABP 798 (biosimilar rituximab)
- In January 2019, Amgen and Allergan announced positive top-line results from a phase 1/phase 3 study evaluating the pharmacokinetics, efficacy and safety of ABP 798, a biosimilar candidate to RITUXAN® (rituximab), compared to rituximab in patients with moderate-to-severe **rheumatoid arthritis.**
- The results demonstrate that the study met its primary endpoint of pharmacokinetic similarity. Additionally, equivalent efficacy was established and a similar safety profile was demonstrated
- Biologic, administered IV

Otezla

- **Apremilast (Otezla)**
  - Apremilast is a drug you take by mouth that's approved to treat **psoriatic arthritis and plaque psoriasis** in adults. It curbs phosphodiesterase-4 (PDE-4), an enzyme that controls inflammation.
  - Phosphodiesterase-4 (PDE4), mainly present in immune cells, epithelial cells, and brain cells, manifests as an intracellular non-receptor enzyme that modulates inflammation and epithelial integrity. Inhibition of PDE4 is predicted to have diverse effects via the elevation of the level of cyclic adenosine monophosphate (cAMP) and the subsequent regulation of a wide array of genes and proteins.
  - Over the past decades, numerous PDE4 inhibitors have been designed and synthesized, among which roflumilast, apremilast, and crisaborole were approved for the treatment of inflammatory airway diseases, psoriatic arthritis, and atopic dermatitis, respectively.
  - Otezla is a small molecule treatment that is delivered orally

Biologics vs small molecules

- There are several disadvantages associated with biological therapies since they must be administered either subcutaneously or intravenously, making it somewhat difficult for the patient.
- In addition, several of these biologicals, which are immunosuppressant agents, have important safety concerns such as increased risk of opportunistic infections, and the need for ongoing laboratory monitoring. Significant costs are also associated with these types of products and must be factored in as part of the decision in selecting therapy.
- In general, biologics work on psoriasis because they:
  - Curb T cells (a form of white blood cell)
  - Block a substance called tumor necrosis factor-alpha (TNF-alpha), one of the main messenger chemicals in the immune system
  - Stop a family of your immune system's chemical messengers called interleukins
  - Bind to proteins that cause inflammation
- Another relatively new approach to the management of these conditions has been through the targeted inhibition of phosphodiesterase 4, causing increases in intracellular cyclic AMP (cAMP) which leads to multiple favorable therapeutic effects including a decrease in the production of several of the pro-inflammatory mediators.

Table 1: Salient differences between small molecules and biological agents

Parameter	Small molecules	Biologics
Molecular weight	Small <1000 Da	Large >1000 Da
Chemical composition	Organic small molecule	Protein
Target specificity	Intracellular-less specific	Extracellular-more specific
Mechanism of action	Enzyme inhibition	Blocking/depletion
Half-life	Usually short	Longer
Stability	Usually stable	Heat and protease sensitive
Distribution	Potential for extensive distribution	More limited distribution
Administration	Oral/topical	Parenteral
Immunogenicity	Generally not a concern	Common concern
Manufacturing cost	Low/variable	High

Source:

Other psoriasis treatments include:

- **Biologics:**
  - Adalimumab (Humira), a TNF-alpha-blocking antibody for the treatment of plaque psoriasis (PP) and psoriatic arthritis (PA), injection
  - Adalimumab-adbm (Cyltezo), a biosimilar to Humira
  - Brodalumab (Siliq) a human antibody against interleukins – PP, injections
  - Certolizumab pegol (Cimzia), a TNF-alpha blocker, psoriasis and PA, injection
  - Etanercept-szzs (Erelzi), a biosimilar like Enbrel, TNF blocker
  - Guselkumab (Tremfya), an antibody against interleukins, PP, inj
  - Infliximab (Remicade), a TNF-alpha blocker, IV
  - Ixekizumab (Taltz) – PP and PA, inj. an antibody that binds to inflammation-causing proteins/interleukins
  - Skyrizi – IL-23 inhibitor, PP, inj, an antibody against interleukins
  - Secukinumab (Cosentyx) PP and PA, inj, a human antibody against interleukins
  - Ustekinumab (Stelara) – PP and PA, inj, a human antibody against interleukins
  - Abatacept (Orencia) – PA – injection - Celgene
  - Golimumab (Simponi) - Psoriatic arthritis, injection

- **Small molecules**
  - Crisaborole (AN2728 by Pfizer), a boron-containing drug for the topical treatment of psoriasis and atopic dermatitis. It was approved by the FDA on December 14, 2016 under the brand name Eucrisa for the treatment of mild-to-moderate atopic dermatitis (eczema) in patients 2 years of age and older.
    - PDE-4 inhibitor
  - BMS-986165
    - "We have 17 new IO compounds in clinical development and studies across more than 35 different tumor types. In addition, we advanced certain other non-IO R&D programs in our pipeline, including FGF21 for the treatment of NASH and TYK-2 inhibitor for the treatment of immune diseases such as psoriasis." - oral
      - First oral Tyk2 inhibitor
      - BMS small molecule, oral
    - BMS-986165 is a novel, oral, selective TYK2 inhibitor with a unique mechanism of action distinct from other kinase inhibitors, and is being studied in a wide spectrum of immune-mediated diseases.
    - Tyk2 is part of the interleukin (IL)-23 pathway, a key pathway in the pathogenesis of psoriasis, Dr. Wu said. "But Tyk2 is not part of other pathways that may reduce blood counts or worsen cholesterol levels."
    - TYK2, an intracellular signaling kinase, mediates cytokine-driven immune and pro-inflammatory signaling pathways that are critical in the cycle of chronic inflammation central to immune-mediated diseases. TYK2 mediates signaling of IL-23, IL-12, and Type I IFN-driven responses but not cytokine responses mediated by other kinases, such as IL-6, hematopoietic growth factors and the IL-2 family. TYK2 signaling is implicated in the pathophysiology of various immune-mediated diseases including psoriasis, lupus and inflammatory bowel disease.

- Tyrosine kinase 2 (Tyk2) is a non-receptor tyrosine-protein kinase, an enzyme that in humans is encoded by the TYK2 gene. Tyk2, together with three other family subtypes, namely, Jak1, Jak2, and Jak3, belong to the JAK family.

CVR update

- As per the latest CELG presentation, CVR related pipeline products are progressing well.
- Latest update on CVR related pipeline products:
  - Ozanimod:
    - U.S. NDA for RMS accepted (Mar. 25, 2020 PDUFA date)
    - Approval deadline Dec 31, 2020
  - Liso-cel
    - Data from pivotal TRANSCEND™ trial in R/R DLBCL expected in Q4:19
    - U.S. BLA submission expected in H2:19; approval expected in mid-2020
    - Approval deadline Dec 31, 2020
  - Bb2121
    - U.S. BLA submission expected in H1:20; approval expected in R/R MM in H2:20
    - Approval deadline March 31, 2021

- **CVR conditions:**
- Pursuant to the Merger Agreement, at or immediately prior to the closing of the Merger, BMS and a trustee will enter into a Contingent Value Rights Agreement (the "CVR Agreement") governing the terms of the CVRs. Each CVR will entitle its holder to receive $9.00 in cash if the U.S. Food and Drug Administration approves, by the dates noted below, Celgene, BMS or their respective affiliates to commercially manufacture, market and sell in United States all of the following three products for the indications noted below:
  - by December 31, 2020, the product known as "JCAR017" for the treatment of relapsed-refractory diffuse large B cell lymphoma in humans
  - by December 31, 2020, the product known as "Ozanimod" for the treatment of relapsing multiple sclerosis in humans; and
  - by March 31, 2021, the product known as "BB2121" for the treatment of relapsed/refractory multiple myeloma in humans

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