# The Rhineland Biopatent Gazette

brought to you by Michalski Huettermann & Partner Patent Attorneys - Issue 8/2017

**Duesseldorf/Munich**, **13 October 2017** The times they are a'changing – particularly in the Biopatent discipline. Biopatent professionals live in a quickly developing world, which is sometimes hard to keep pace with. Michalski • Huettermann & Partner Patent Attorneys have decided to produce relief to this situation, and are proud to present a new information service related to Patent issues in Biotechnology. This newsletter issues on an irregular basis in order to provide information with respect to actual events, as well as in-depth-analyses of long-term developments. Patent Attorneys from our firm explain the meaning of recent developments and decisions affecting the Biopatent community, and provide expert insight into what's going on behind the scenes. In this issue, we focus on an agreement that has been reached between AbbVie and competitor Amgen, about the latter's Humira biosimilar, and about Novartis' Car-T cell product Kymriah, which has obtained FDA approval in August, while the respective patent was also recently granted by the EPO.

## Double win for Kymriah CAR-T

First Car T cell product approved, and also patented

On August 30, 2017, the US Food and Drug Administration (FDA) approved Novartis new CAR-T cell therapy Kymriah™ (tisagenlecleucel), formerly called CTL019. Kymriah is the first approved chimeric antigen receptor T cell (CAR-T) therapy, and is approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) which are refractory or in second or later relapse.

Kymriah is a one-time treatment consisting of T-cells taken from the patient, engineered to comprise a Chimeric Antigen Receptor (CAR), and re-administered to the patient.

The CAR essentially consists of an anti CD19 scFv (commonly known as FMC63) a transmembrane domain, 4-1BB as costimulatory domain and a CD3ζ signaling domain.

The thus programmed T-cells do then effectively attack and eradicate lymphoblastic cells that featured CD19 on their surfaces, with so far unprecedented efficacy.

The success came quite surprising after one of Novartis' competitors, Juno Therapeutics, discontinued its lead CAR-T cell candidate JCAR015, probably because five people died in a trial.

JCAR015 has a similar structure as Kymriah, yet a different anti CD19 scFv (known as SJ25C1), and CD28 instead of 4-1BB as a costimulatory domain

Novartis reports in a press release that that an 83% (52/63) overall remission rate was obtained in a patient chohort comprising children and young adults with B-cell ALL that is refractory or has relapsed at least twice.

## AbbVie and Amgen agree to put Amjevita into the waiting room

Humira one step closer to exclusivity until 2022

AbbVie's Humira patent strategy is a model case about how to fend off a blockbuster from generic competition,

We have previously reported about the Humira patent estate. Find our article "Of patents and patent disputes: The TNFα patent files" here, or ask for a reprint.

In the past, AbbVie's CEO, Richard Gonzalez, made several full-bodied announcement that due to the extensive patent strategy, Humira would be protected from biosimilar competition until 2022, and, based on this strategy, AbbVie's sales would climb to 18 bn USD by 2020.

Now it seems that, due to a recent agreement with Amgen, Mr Gonzalez is one step closer to keeping this promise.

Despite an ongoing patent litigation between the two parties, the FDA has on September 23, 2016 approved Amgen's adalimumab biosimilar Amjevita™ ("adalimumab-atto"). Approval in Europe (where the product is called Amgevita) followed March 23, 2017.

The biosimilar comes in a 40 mg/0.8 ml or 20 mg/0.4 ml prefilled syringe or prefilled autoinjection pen. The formulation of Amjevita differs markedly from that of Humira, in particular in that it comprises an acetate buffer instead of the citrate/phosphate buffer, and sucrose instead of mannitol – a difference which obviously did not

**+ from our firm +**

### MHP opens satellite office in Frankfurt

We can report that we have now opened a satellite office in Frankfurt, to improve our presence and availability in the Rhein/Main and Rhein/Neckar area.

Important Biotech hubs, like the Mainz/Ingelheim region, the Langen region, the Bad Homburg region and the Mannheim/ Heidelberg region, are now within easy reach for Biotech attorneys from our firm.

Further, being situated close to FRA airport, we can easily accommodate meetings in the FRA airport conference centers for visitors on transit.

We trust that this new satellite helps to improve our services to our clients in these regions.

If you want to make an appointment, please send us an email.

Said new therapy comes with a price tag. $475,000 is what Novartis demands for a treatment. Admittedly, Kymriah seems to be very efficacious. Patients usually need it only once, and the R&D costs until approval must have been horrendous.

Hence, Kymriah seems to be an asset that actually justifies sound patent protection.

And, Novartis and its licensor, University of Pennsylvania (UPenn) have done their homework. On July 19, 2017, European Patent was granted to UPenn, with, inter alia, the following claim 1:

> 1. A T cell genetically modified to express a CAR wherein the CAR comprises
>
> (a) an antigen binding domain that is an anti-CD19 scFv comprising the amino acid sequence of SEQ ID NO:20,
> (b) a costimulatory 4-1BB signaling region, and
> (c) a CD3ζ signaling domain comprising the amino acid sequence of SEQ ID NO: 24,
>
> for use in a method for treating cancer in a human, wherein a remission of the cancer is obtained, and wherein the human is resistant to at least one chemotherapeutic agent.

Now it appears that the scope of this patent is so broad that it also encompasses two other of Juno's candidates, JCAR014 and JCAR017, which both have FMC63 as anti CD 19 scFV), 4-1BB as costimulatory domain and a CD3ζ signaling domain.

Although the sequences that Juno uses in these two candidates are not disclosed, it appears at least likely that the two candidates fall under the scope of UPenn's patent.

And, Juno is not the only competitor. Servier's UCART19 also targets CD19 (although unclear which antibody is used) and uses 4-1BB as a costimulatory domain

What is also interesting is that UPenn's patent was granted despite the fact that a CAR T cell comprising a CD19/4-1BB/CD3ζ receptor construct has already been disclosed in prepublished US patent 7,446,190 (assigned to Sloan Kettering and licensed by Juno Therapeutcs).

The EP examiner was aware of this prior art reference, yet, obviously, a later added restriction according to which a remission of the cancer is obtained, and the patient is resistant to at least one chemotherapeutic agent was deemed sufficient to render the claims non obvious.

Another prior art document is US patent 8,399,645 (assigned to St Jude's hospital, and likewise assigned to Juno), which also discloses a CAR T cell with the said three elements.

The opposition term of the patent ends April 19, 2018. With similar price tags for competing products in mind, it appears that competitors developing CAR-T cells with a CD19/4-1BB/CD3ζ receptor construct will have enough motivation to file oppositions. We will keep you tuned.

affect its biosimilar status. Amjevita is approved for the commercially most important indications of Humira. Yet, Amjevita still did not make it to the US market so far, and now we know why.

On Sept. 28, 2017, Amgen surprisingly announced that they have reached a settlement with AbbVie.

Under this settlement, the parties have agreed that Amgen will wait until Jan. 31, 2023, to launch Amjevita, in the U.S, while in Europe market entry is expected sooner, namely Oct. 16, 2018.

Reportedly, the settlement includes a patent license awarded to Amgen and royalties Amgen has to pay.

Yet the agreement seems to be a setback for Amgen, because in 2016, Amgen indicated that due to the ongoing litigation with AbbVie, it would be unlikely that Amjevita would see US market launch before 2018 – while, initially, 2017 was the year they had in the focus. So the delay of market entry now adds up to about 5 years.

Still, in their press release regarding the settlement, Amgen announced that the agreement would allow them to secure a strong foothold in the $4 billion European adalimumab market.

With the caveat that Amgen is not alone there.

Due to a weaker patent position in Europe (see several issues of this Gazette), quite a few players have already staked their claims on European ground.

On August 24, 2017, the European Commission granted marketing authorization for Samsung Bioepis' Imraldi.

Boehringer Ingelheim's BI 695501 (now called Cyltezo) was accepted for regulatory review by the European Medicines Agency in January 2017, and received a positive opinion in September 2017, making an approval likely in the fourth quarter of 2017.

And, on May 18, 2017, the EMA has accepted Fuji Kirin's FKB327 for review.

Hence, the adalimumab biosimilar market in Europe is going to be quite competitive.

**Feedback please !**

What do you think about this newsletter? Let us have your comments here.

**Archive**

To obtain a neat overview of the quickly changing world of Biopatents, find prior issues of the Rhineland Biopatent Gazette here.

## EURIPTA® EEIG is getting personal... Today: David Terrell, PhD, LL.B – IP Lodge

After 25 years R&D experience in a wide variety of chemical areas with different companies in different roles in the Netherlands, Germany and Belgium (Philips Nat Lab, Philips Forschungslaboratorium, Agfa-Gevaert), David joined the IP department of the international imaging group Agfa-Gevaert, where he became responsible for managing the patent portfolio of one of the three entities within the group.

Before joining IPLodge in 2014, David had already worked as a European patent attorney in private practice at Bird Goën & Co., where he managed the non-pharmaceutical chemistry IP team.

David has extensive expertise in invention harvesting, in the drafting and prosecution of patent applications, in oppositions before the EPO and in conducting patent litigation cases. His technical areas of interest include polymers, imaging, and organic electronics.

David is qualified as a European patent attorney. As a qualified British jurist, he is also entitled to represent clients before the future Unified Patent Court. David's native language is English, and his working languages include Dutch and German.

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