

Favipiravir, a drug candidate against COVID-19 – a FIZ Karlsruhe case study exploring the patent situation

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Several strategies are currently being pursued to combat the corona pandemic: (a) non-pharmaceutical measures, such as contact restrictions; (b) the development of vaccines (c) the development of new medicines, e.g. antibodies for passive immunization and existing early-stage projects for antiviral medicines, and (d) the repurposing of existing drugs by identifying and testing known active pharmaceutical ingredients already developed and approved for another disease.

New vaccines against the corona virus are expected to be available in 2021. The development and approval of new pharmaceutical compounds takes in general more than 10 years. Therefore the focus is to repurpose existing drugs developed against other viral infections caused by corona viruses such as influenza or SARS and MERS^{1,2}. The main goal is to provide rapid and reliable help for patients and to alleviate the course of the disease. A number of existing drugs are currently being tested for their suitability against the corona disease Covid-19, most of them being evaluated within international clinical trials. Among these drug candidates is favipiravir, which we use as an example to show how the IP situation of a drug can be explored by using the STN Online Service.

Challenges for the global distribution of a medicine – an IP focused view on favipiravir

As soon as the approval process for a drug candidate is successful further important steps are required for the rapid introduction into patient care. Since it will have to be produced in large quantities, even for existing drugs the production process with its production capacity limits will be challenging as well as the worldwide distribution under existing IP rights. The experience and resources of companies that have been developing and selling medicines for many years will be essential. We are in particular interested in who developed the drug and who holds IP-rights. What is the current patent situation, how long does patent protection last and in which countries? This allows, for example, to deduce whether cost-effective generics can be produced when there is a high level of demand. It is also interesting to find out, if newer patent applications exist, from which companies and in which countries. To answer these questions, we performed a thorough patent search and analysis in renowned databases on STN®.

Favipiravir (brand name Avigan®) is a broad-spectrum antiviral drug currently considered in several clinical trials to assess the safety and efficacy in patients with COVID-19.



Avigan (generic name Favipiravir) KAZUHIRO NOGI/AFP

Fig. 1 - Avigan tablets (KAZUHIRO NOGI/AFP).

Favipiravir was discovered through screening chemical library for anti-viral activity against the influenza virus by Toyama Chemical Co., Ltd. (now FUJIFILM Toyama Chemical Co., Ltd.)³. The drug was launched in Japan in 2014 exclusively for emergency use in severe infectious diseases like avian flu or Ebola for which there are no viable options⁴. In the context of the coronavirus pandemic the Japanese government intends to stockpile two million treatment courses of Avigan® and FUJIFILM Toyama Chemical revealed it will engage with other countries after consultation with the Japanese government⁵. As this drug is considered a promising potential therapeutic approach against SARS-

CoV-2 the German Ministry of Health (Bundesministerium für Gesundheit) recently initiated central purchasing of Avigan® for COVID-19-patients in Germany.

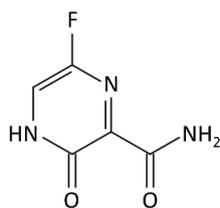


Fig. 2 - Chemical structure of favipiravir, CAS Registry Number 259793-96-9.

From a chemical and pharmacological point of view favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a small-molecule prodrug which is metabolized in vivo by an intracellular enzyme to its active form, favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP). Favipiravir-RTP acts as a substrate for viral RNA-dependent RNA polymerase (RdRp) thereby preventing replication by inhibiting the viral RNA-dependent polymerase activity of RNA viruses⁶. Since the catalytic domain of RdRp is conserved among various types of RNA viruses, this mechanism of action underpins a broader spectrum of anti-viral activities of favipiravir. Favipiravir is effective against a wide range of types and subtypes of influenza viruses, including strains resistant to existing anti-influenza drugs.

Patent Protection of Favipiravir

Patent Search in Value-added Patent Databases

Searching for specific drugs in the patent literature is a challenging task, as it requires expert knowledge of how the drug is represented in the different types of patents. While patents in the early development of the drug (e.g. chemical synthesis patents) use chemical structures to describe the drug, later patents (e.g. formulation patents) often use development codes, generic drug names or trade names. For favipiravir, either the prodrug itself or the metabolized active drug could be part of the patent application.

In this case study we searched the renowned databases of Chemical Abstracts Service and Derwent on STN® to access the worldwide patent literature for favipiravir. This includes the Derwent World Patents Index™ with the associated structure databases Derwent Chemistry Resource and Derwent Markush Resource, and also CPlus® together with CAS REGISTRY® and MARPAT®.

An exhaustive structure search based on the powerful STN® retrieval capabilities was complemented with a keyword search, considering the different terminologies used for the drug favipiravir. The structure search covered all patents with favipiravir (prodrug and active drug) represented as a specific or generic (Markush) structure.

This drug search does not claim to be exhaustive, but will give a good overview of the key patents of favipiravir.

Another major challenge was to reliably determine the legal status of the respective patents. For this task we consulted the database INPADOC on STN® and the national registers of the patent offices.

Analysis of Key Patents covering Favipiravir

A total of 148 inventions⁷ were identified with favipiravir either playing a central role in the invention (orange bars) or being an optional component of a formulation (blue bars) and thus less relevant for our case study (Fig. 3). While patenting activities started more than twenty years ago on a low level, they have seen a major increase over the last decade. Only 40% of the overall inventions mentioning favipiravir have been ranked as highly relevant.

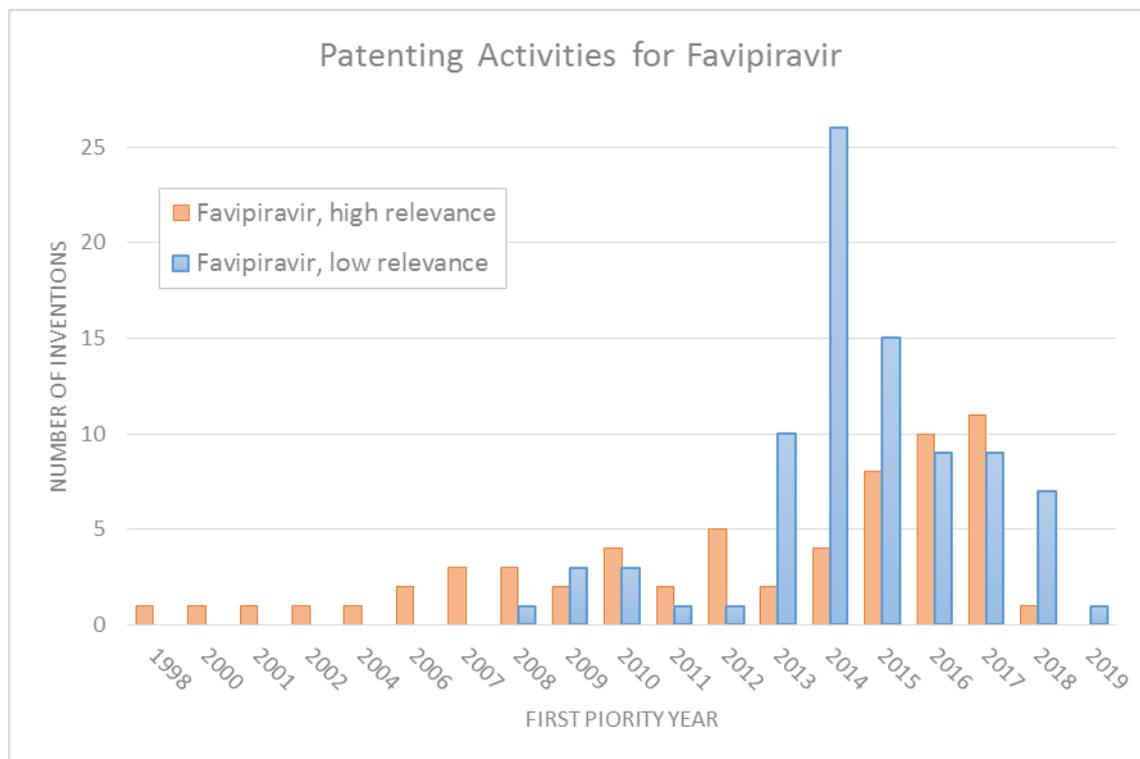


Fig. 3 - Patenting activities for favipiravir (number of inventions vs priority year, first)

The following patent analysis concentrates on those 60 inventions in which favipiravir plays a major role. When looking at the inventions that were filed over time, five major categories could be identified (Fig. 4).

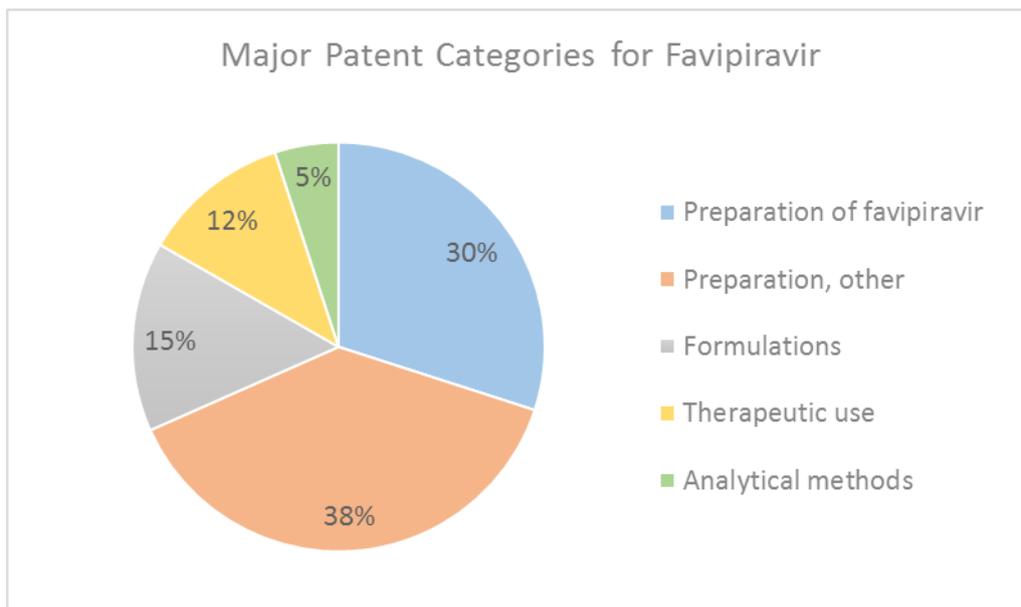


Fig. 4 - Major patent categories for favipiravir (number of relevant inventions per category)

About two thirds of the inventions relate to the synthesis of favipiravir (Fig. 4, Preparation of favipiravir) or its nucleotide variants or reaction intermediates (Fig. 4, Preparation, other), only 27 % relate to new formulations or new therapeutic indications. For most approved drugs the percentage of inventions regarding new formulations and therapeutic indication is much higher. This supports the fact that favipiravir is a drug which has its potential as an emergency drug and companies do not expect favipiravir to be approved for use in standard antiviral medicine.

Innovation around favipiravir concentrates on improved methods for the synthesis of the drug and its derivatives, making the large-scale manufacture of the drug more cost-effective and more environmentally friendly. Formulation patents mainly cover tablets with enhanced drug release, but there is also an invention combining favipiravir with a traditional Chinese medicine (Radix Isatidis) which should have antiviral activity⁸. While the original patent of favipiravir claimed the treatment against influenza, later patents protect new indications like Ebola infections.

In 1998 the original patent was filed by FUJIFILM Toyama Chemical, claiming the preparation and antiviral use of a substance class covering favipiravir. In the following years until 2014 the chemical synthesis of favipiravir, its intermediates and derivatives dominated the filing activities. As part of the life-cycle management relevant formulation patents and new therapeutic use patents have been filed in the years that followed (Fig. 5).

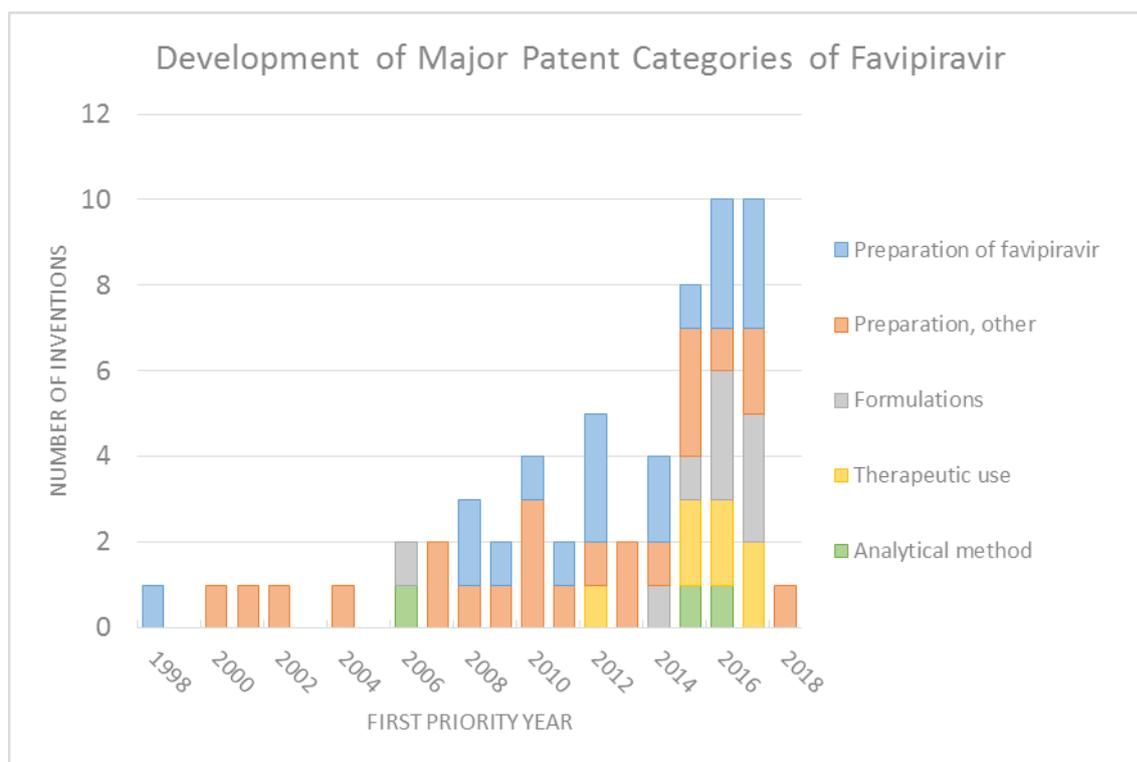


Fig. 5 - Major patent categories for favipiravir developing over time (no of inventions vs priority year first)

The original Patent of Favipiravir

The original patent of FUJIFILM Toyama Chemical protects the compound, the preparation and the use of favipiravir as an antiviral drug especially against influenza infections. The drug itself is claimed as part of a generic chemical structure (Markush) covering a broad range of similar structures (Fig. 6.)

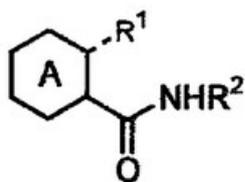


Fig. 6 - Generic structure of favipiravir claimed in WO2000/10569 A1

FUJIFILM Toyama Chemical filed an international PCT application (WO2000/10569 A1) at the Japanese Patent Office on August 18, 1999. This first filing was the basis for the worldwide patent protection in Asia, Europe, Australia, America and South Africa, including 27 patent authorities in total. 20 years later in August 2019 the original patent lost its patent protection in China, Europe and many other countries⁹. Due to a 5-year patent term extension, the patent will still be valid in Japan until August 2024¹⁰. Our research also revealed a patent term extension in Brazil until November 2023.

The patent situation in the U.S.A. regarding US6787544 B2 (US43748 E) is unclear. According to the patent register of the USPTO the patent is still valid, even though all facts suggest that the US patent expired¹¹.

In 2016 FUJIFILM Toyama Chemical concluded a license agreement concerning favipiravir with the Chinese company Zhejiang Hisun Pharmaceutical¹². This agreement was cancelled in 2019. Due to the

corona pandemic and the loss of patent protection in China, Chinese companies may be preparing to bring favipiravir on the generics market. In February 2020 the Chinese company Zhejiang Hisun Pharmaceutical obtained official approval to produce a generic version of favipiravir¹³.

Favipiravir Patents of FUJIFILM Toyama Chemical

The original patent holder FUJIFILM Toyama Chemical stands out with 17 inventions which have been applied over the last twenty years. The timeline below sums up the patent development in more detail (Fig. 7).

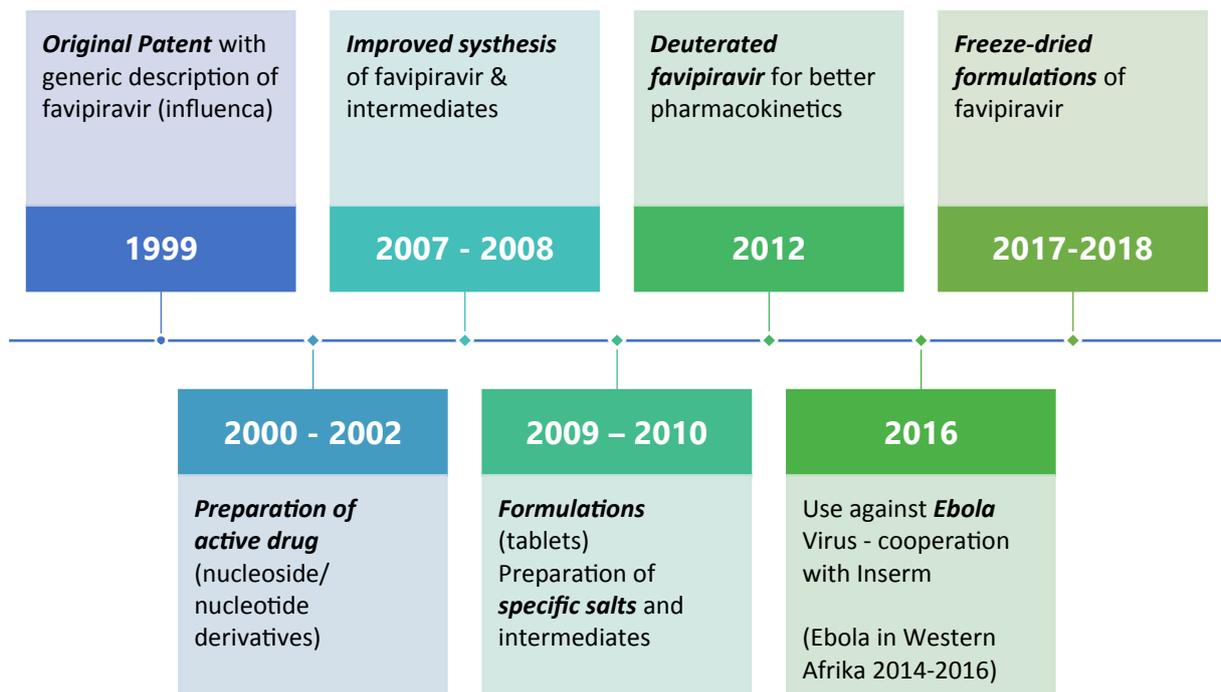


Fig. 7 - Development of favipiravir patents of Fujifilm Toyama Chemical according to application year

In the 10 years following the original patent, several patents concerning preparations of nucleoside/nucleotide derivatives, intermediates and also improved synthesis of favipiravir were filed.

In March 2011, FUJIFILM Toyama Chemical submitted favipiravir for approval of treating influenza (type A and B) in Japan¹⁴. Shortly before that time, Toyama had started to file pharmaceutical formulation patents, in particular tablets (WO2010/104170 A1, patent expiry in 2030).

When Western Africa was hit by the Ebola epidemic between 2014 and 2016, FUJIFILM Toyama Chemical signed a partnership agreement with Inserm (French national institute of health and medical research) to investigate the antiviral efficacy of favipiravir against the Ebola virus¹⁵. The cooperation resulted in joint patenting of WO2016/120301 A1 in 2016. The patent was granted in the United States (US10098879 B2) with Inserm being the current patent owner.

The most recent inventions of FUJIFILM Toyama Chemical were filed in 2017/2018, covering new methods to produce freeze-dried formulations of favipiravir (WO2018/3946 A1, WO2019/131223 A1) which show enhanced drug stability and solubility.

FUJIFILM Toyama Chemical holds 15 active patent families around favipiravir, most of them filed with relevant patent offices worldwide. So far, patent protection has been extended to 2036 for new preparations (WO2016/199824 A1) and to 2031 for another three inventions related to new salts/new preparations of favipiravir (WO2012/63931, WO2012/43700, WO2012/43696).

Favipiravir Patents of other Companies and Institutions

Taking a look at other patent applicants, it is striking that most inventions are from Chinese companies and institutions, which apply for patent protection in China only. The majority of these patents is related to the preparation of favipiravir and new formulations, while Chinese universities also protect the new therapeutic use of favipiravir (canine distemper virus, enterovirus EV-D68). These filing activities in China started in 2012 and are still ongoing.

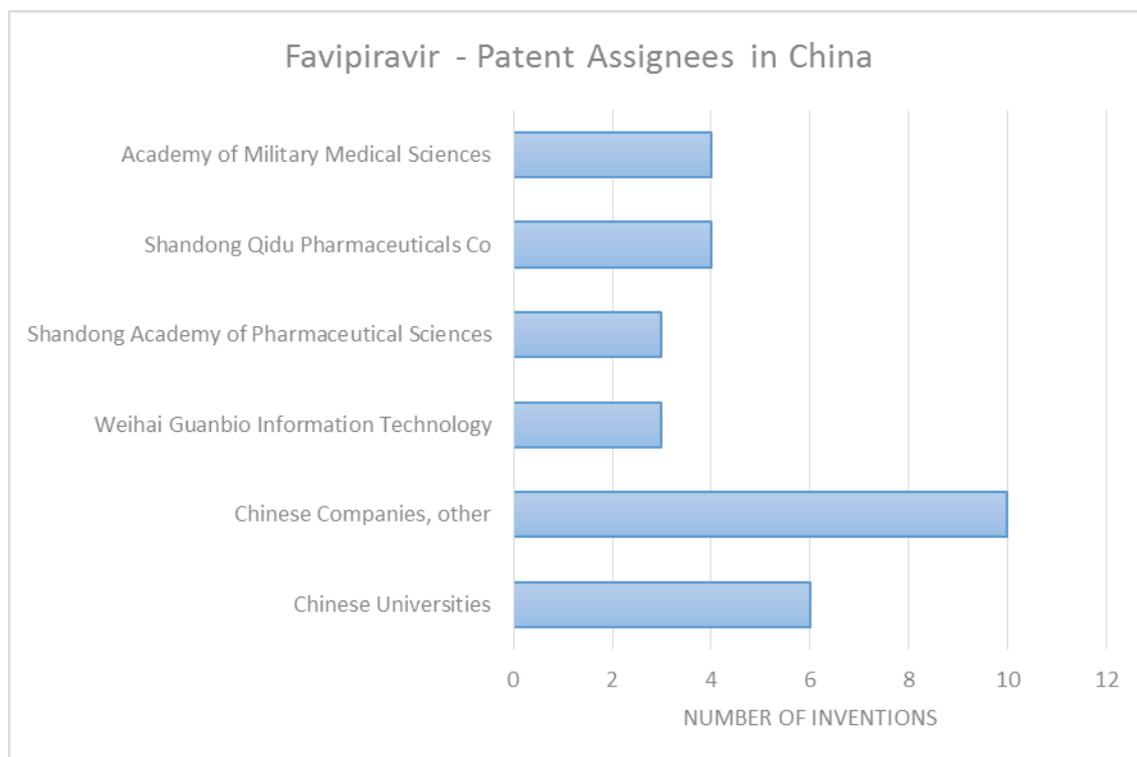


Fig. 8 - Patent assignees in China and the no of inventions related to favipiravir

There are only 11 favipiravir inventions from patent assignees outside Japan and China, 7 of which are from US assignees (and one with a French cooperation), with 4 of them being universities. The other four assignees are from Singapore, Sweden, France and Austria. Most of the non-Japanese or non-Chinese inventions concern preparations of nucleotides/nucleosides derivatives or the therapeutic use against the Ebola virus or Leishmania.

Current clinical Trials

Several clinical trials for **COVID-2019 infections** are ongoing **in the US, China, the Middle East and Japan**¹⁶:

- Phase III, Japan, COVID-2019 infections
- Phase II, United States, COVID-2019 infections

- Clinical (Phase Unknown), China, COVID-2019 infections
- Clinical (Phase Unknown), Middle East, COVID-2019 infections

Detailed development:

- **April 2020:**
 - FUJIFILM Corporation initiated a phase II proof-of-concept trial to evaluate the safety and efficacy of favipiravir with standard of care (SoC) or SoC alone in patients with COVID-2019 infections¹⁷.
 - Clinical development for treatment of COVID-2019 infections was underway in the Middle East. Results from clinical studies in COVID-2019 infections in China were generally positive¹⁸.
- **March 2020:**
 - FUJIFILM Toyama Chemical initiated a phase III trial in Japan, to assess the safety and efficacy of favipiravir, for patients afflicted with COVID-2019 infections¹⁹.
 - Zhejiang Hisun Pharmaceutical conducted a clinical trial in collaboration with Zhongnan Hospital in 120 patients with COVID-2019 infections and another trial in collaboration with Third People's Hospital of Shenzhen in 80 patients with COVID-2019 infections. For both trials results were released²⁰.
- **February 2020:** Sihuan Pharmaceutical Holdings Group initiated **clinical trials for favipiravir tablet for COVID-2019 infections**. A total of 60 cases of regular COVID-19 patients are planned to be recruited for a treatment period of 10 days²¹.

Summary

- In-depth patent searching for favipiravir requires the value-added patent databases of Chemical Abstract Service and Derwent on STN to achieve reliable and fast access to relevant inventions.
- Many of the key inventions of favipiravir could not be retrieved with a simple keyword search in patent fulltext databases, in particular patents claiming new methods for the synthesis of the drug.
- Favipiravir is an antiviral drug which has only been approved for emergency use in Japan. This special situation accounts for the rather unusual patent development of favipiravir which has a strong focus on enhanced manufacturing solutions.
- Although the original favipiravir patent lost its patent protection in many countries, FUJIFILM Toyama Chemicals can still commercially exploit their original invention worldwide with a series of valid chemical process and formulation patents.
- On the one hand the corona pandemic may have revived interest in producing generic versions of the drug. On the other hand, however, favipiravir may not be attractive for traditional generic companies due to its restricted approval, its unclear effectiveness and its potentially severe side effects.
- The Japanese government continuously expands its stockpile of Avigan® so that there is enough to treat 2 million patients²².

- ¹ <https://www.nature.com/articles/d41587-020-00003-1>.
- ² *ACS Cent. Sci.* 2020, 6, 3, 315–331 Publication Date: March 12, 2020, <https://doi.org/10.1021/acscentsci.0c00272>
- ³ Abgerufen am 26.5.2020: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5713175/pdf/pjab-93-449.pdf>
- ⁴ <https://www.deutsche-apotheker-zeitung.de/news/artikel/2020/04/06/laeuft-ein-nischenprodukt-zu-voller-form-auf>.
- ⁵ <https://www.europeanpharmaceuticalreview.com/news/116981/production-of-avigan-tablet-favipiravir-accelerated-for-use-against-covid-19/>.
- ⁶ *Pharmacology & Therapeutics* 209 (2020) 107512, <https://www.ncbi.nlm.nih.gov/pubmed/32097670>.
- ⁷ Search performed in April 2020; no of inventions equals no of INPADOC patent families on STN®.
- ⁸ Zhou W, Zhang XY. Research progress of Chinese herbal medicine Radix isatidis (banlangen). *Am J Chin Med.* 2013;41(4):743-764. doi:10.1142/S0192415X1350050X.
- ⁹ According to INPADOC Legal Status and national patent registers, patent protection ceased in AT, AU, CA, CN, CZ, DE, DK, EP, ES, HU, IN, KR, NO, NZ, PT, ZA.
- ¹⁰ According to the Patent register of the Japanese Patent Office, <https://www.j-platpat.inpit.go.jp>.
- ¹¹ US patent register (USPAIR): <https://portal.uspto.gov/pair/PublicPair>, 12/05/2020.
- ¹² Licensing agreement: <https://www.fujifilm.com/news/n160622.html>, 12/05/2020.
- ¹³ <https://asia.nikkei.com/Business/Pharmaceuticals/China-says-Japan-developed-drug-Avigan-works-against-coronavirus2>.
- ¹⁴ Source: IMSRESEARCH on STN®.
- ¹⁵ Signature of Franco-Japanese Research Agreement: <https://presse.inserm.fr/en/signature-of-a-franco-japanese-research-agreement/20881/>.
- ¹⁶ Search for favipiravir in: ADISINSIGHT COPYRIGHT (C) 2020 Springer International Publishing AG.
- ¹⁷ FUJIFILM Corporation. Fujifilm announces the start of a phase II clinical trial of its influenza antiviral drug Avigan(R) Tablet for COVID-19 patients in the U.S. Media Release. : 9 Apr 2020. Available from: URL: <http://www.fujifilm.com> (English).
- ¹⁸ ChemRar Hi-Tech Center. Russia to try antiviral drug Favipiravir as coronavirus treatment after 'excellent results' in China. Media Release. : 7 Apr 2020. Available from: URL: <http://www.en.chemrar.ru> (English).
- ¹⁹ FUJIFILM Toyama Chemical. Fujifilm announces the start of a phase III clinical trial of influenza antiviral drug ##8220##Avigan Tablet##8221## on COVID-19 and commits to increasing production. Media Release. : 31 Mar 2020. Available from: URL: <http://www.fujifilm.com> (English).
- ²⁰ Zhejiang Hisun Pharmaceutical. Zhejiang Hisun Pharmaceutical Co. Ltd.:Favipiravir Works - Preliminary Clinical Studies Suggest Positive Effects on COVID-19 Patients. Media Release. : 19 Mar 2020. Available from: URL: <http://www.hisunpharm.com> (English).
- ²¹ Sihuan Pharmaceutical Holdings Group. Sihuan Pharmaceutical Announces Clinical Research of Favipiravir, A Drug for Coronavirus Disease 2019, Co-Developed with the Academy of Military Medical Sciences of the People's Liberation Army, Has Commenced. Media Release.: 2 Mar 2020.
- ²² <https://asia.nikkei.com/Business/Companies/Fujifilm-pictures-new-pharma-heavy-identity-with-Avigan>, 25/05/2020.