

News from the EMA

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Regulatory harmonisation of clinical trials in the EU: New Clinical Trials Information System launched

January 25, 2022

On January 31, 2022, the Clinical Trials Regulation (CTR) will come into application harmonising the submission, assessment, and supervision processes for clinical trials in the European Union (EU). The backbone of the changes brought about by the CTR is the new Clinical Trials Information System (CTIS). CTIS is a single entry point for sponsors and regulators of clinical trials for the submission and assessment of clinical trial data which includes a public searchable database for healthcare professionals, patients and the general public.

In the past, sponsors had to submit clinical trial applications separately to national competent authorities (NCAs) and ethics committees in each country to gain regulatory approval to run a clinical trial, and registration and posting of results were also separate processes. With CTIS, sponsors can now apply for authorisations in up to 30 EU/EEA countries at the same time and with the same documentation. Publication of the trial information is built in the system.

The application of the CTR and the go live of CTIS – in the EU and the European Economic Area (EEA) countries (Iceland, Liechtenstein

and Norway) – will strengthen Europe's position as an attractive location for clinical research. The new regulation streamlines the application and supervision of clinical trials, and their public registration: all clinical trial sponsors will use the same system (CTIS) and follow the same process to apply for the authorisation of a clinical trial, no matter where they are located and with which NCA or ethics committee they are dealing. The new system has a dedicated secure workspace for trial sponsors where they can apply for and manage their clinical trial applications. There is a similar secure workspace for the authorising authorities, who can easily interact with the sponsor and quickly collaborate and exchange information with other authorities.

Because transparency is a major feature of the CTR, CTIS also includes a searchable public website, that will prospectively contain detailed information on, and outcomes of, all clinical trials authorised through the system.

The CTR foresees a 3 year transition period. Member States will work in CTIS immediately after the system has gone live. For 1 year, until January 31, 2023, clinical trial sponsors can still

choose whether to submit an initial clinical trial application in line with the current system (Clinical Trials Directive) or via CTIS. From January 31, 2023, submission of initial clinical trial applications via CTIS becomes mandatory, and by January 31, 2025, all ongoing trials approved under the current Clinical Trials Directive will be governed by the new Regulation and have to be transitioned to CTIS.

The authorisation and oversight of clinical trials is the responsibility of EU/EEA Member States while the European Medicines Agency (EMA) is responsible for maintaining CTIS. The European Commission (EC) oversees the implementation of the Clinical Trials Regulation.

Accelerating Clinical Trials in the EU (ACT EU) for better clinical trials that address patients' needs

Building on the application of CTR and CTIS, the EC, the Heads of Medicines Agencies (HMA) and EMA also launched the Accelerating Clinical Trials in the EU (ACT EU) initiative that seeks to transform how clinical trials are initiated, designed, and run. The aim is to further develop the EU as a focal point for clinical research, promote the development of high-quality, safe and effective medicines, and to better integrate clinical research in the European health system.

ACT EU will strengthen the European environment for clinical trials, whilst maintaining the high level of protection of trial participants, data robustness and transparency that EU citizens expect. The ACT EU strategy paper published on January 13, 2022 lists the ten priority actions for 2022/2023, including enabling innovative trial methods, establishing a multi-stakeholder platform, and supporting the modernisation of good clinical practice. Together, they will contribute to achieving the ambitious goals for innovation in clinical trials set out in the European medicines agencies network strategy (EMANS) to 2025 and the European Commission's Pharmaceutical Strategy.



New EU rules for safe and high-quality medicines for animals become effective

January 28, 2022



Today, the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6) becomes applicable. It contains new measures for stimulating innovation and increasing the availability and access to safe and high-quality veterinary medicines for veterinarians, farmers and pet owners to treat and prevent animal diseases and also supports the EU action against antimicrobial resistance (AMR). The tools and systems introduced by the new Regulation will ensure wider access to information on medicines for animals to all stakeholders and will also provide for an enhanced monitoring of suspected side effects.

The new rules put in place a range of measures to limit the development of AMR, while ensuring that necessary treatments remain available for animals and people, a true “One Health” approach. The new provisions foresee that preventive antimicrobial use is permitted only in exceptional circumstances and introduce the possibility to restrict or prohibit the use of important antimicrobials in animals, reserving the most important of them for treatment of certain conditions in humans.

The new Regulation contains measures that will simplify regulatory processes, striving to reduce administrative burden for current marketing authorisation holders and developers of new

and innovative veterinary medicines to further encourage medicine innovation and development.

For the first time, information about all veterinary medicines authorised in the EU and EEA countries will be available on a central website.

Another key novelty is that from now on veterinary prescriptions will be valid throughout the EU. Furthermore, a common logo was established to facilitate identification of online retailers, which are authorised to sell veterinary medicines that require prescription. Online retailers will have to display the common logo on their website and link it to the relevant EU/EEA national authority website. These authorities will list all registered online medicine retailers in their country on their websites.

During the lead-up to the entering into application of the Regulation, EMA has revised its procedures and regulatory and scientific guidance documents. The Agency has also led, in collaboration with the Member States and stakeholders, the development and implementation of the IT systems required by the Regulation:

1. Union Product Database
2. Union Pharmacovigilance Database
3. Manufacturing and Wholesale Distribution Database

The Union Product Database gathers information on all veterinary medicines authorised in EU/EEA countries and will enable some post-authorisation procedures. The system has been set up and will be maintained by EMA in collaboration with the Member States and the EC. While EMA and the regulatory network are finalising the upload of product data, activities to improve the data quality have also been initiated.

The Veterinary Medicines information website will provide public access to the data held in the Union Product Database. It is the first website that provides details on all veterinary medicines authorised in the EU and EEA. The website will enable veterinary healthcare professionals and all interested users to find out in which EU Member States and EEA countries a specific veterinary medicine is available, or to find information that could help identify potential treatment alternatives. At the same time, by providing a single source of up-to-date information on the availability of veterinary medicines in the EU it will support a better functioning of the single market.

The Union Pharmacovigilance Database was launched as an enhanced and upgraded EudraVigilance Veterinary (EVVet3) system for the exchange and processing of suspected adverse reaction reports related to veterinary medicines authorised in the EEA. EVVet3 is supplemented by an upgraded analytics tool and new functionality to support pharmacovigilance monitoring activities. Integrating all these components, the Union Pharmacovigilance Database is the key tool for the continuous monitoring of the safety of veterinary medicines after they are authorised.

The Manufacturing and Wholesale Distribution Database includes information on the granting, suspension or revocation by competent authorities of any manufacturing authorisation, wholesale distribution authorisation, certificates of good manufacturing practice and registration of manufacturers, importers and distributors of active substances for both veterinary and human domains. The system launched today is an enhanced and upgraded version of EudraGMDP, the EU database of manufacturing authorisations and certificates of good manufacturing practice, with changes affecting both the veterinary and the human domains.

More information on these databases can be found on the Veterinary Medicinal Products Regulation page.



European medicines regulatory network adopts EU common standard for electronic product information

February 22, 2022

Today, The European Medicines Regulatory Network has adopted a Common Standard for the electronic product information (ePI) on medicines in the EU. This will pave the way for wider dissemination of the unbiased, up-to-date information on all medicines available to patients in the EU through an ever-expanding range of electronic channels.

The product information (PI) of a medicine includes the package leaflet for patients and the summary of product characteristics (SmPC) for healthcare professionals. These documents accompany every single medicine authorised in the EU and explain how it should be used and prescribed.

The EU ePI Common Standard will support the provision of harmonised electronic information on medicines within the EU and is a step

towards improved delivery of information for patients, consumers and healthcare professionals to aid their informed decision-making.

The ePI can be updated immediately, as soon as new information becomes available. The structured nature of ePI will also offer new opportunities to personalise the product information to individual needs and to make it more easily accessible to users with diverse abilities. Future developments of the ePI could include functionalities such as automatic update notifications, access to supportive videos or audio content and online adverse-reaction reporting tools.

The Common Standard was one of the key deliverables of an ePI project run by the EMA, national competent authorities (NCAs) and the EC in 2021. A follow-on pilot project supported

by the EU's funding programme EU4Health will now focus on developing tools and guidance to pilot the use of ePI prior to implementation. EMA will publish regular progress updates and will share the results with patients, healthcare professionals, academia, and the pharmaceutical industry.

The adoption of the Common Standard is in line with the ePI key principles which were established following stakeholder consultations and guide the development of the ePI in the EU. The EU ePI Common Standard is based on Fast Healthcare Interoperability Resources (FHIR), an international technical standard describing data formats and elements and an application programming interface for exchanging electronic health records. FHIR also supports the exchange of information about medicinal products, substances, and related referential data in the European medicines regulatory network.

New medicine for rare type of eye cancer

February 25, 2022

EMA has recommended granting a marketing authorisation in the EU for Kimmtrak (tebentafusp; applicant, Immunocore Ireland Limited), a monotherapy for the treatment of adult patients with uveal melanoma, a rare type of eye cancer.

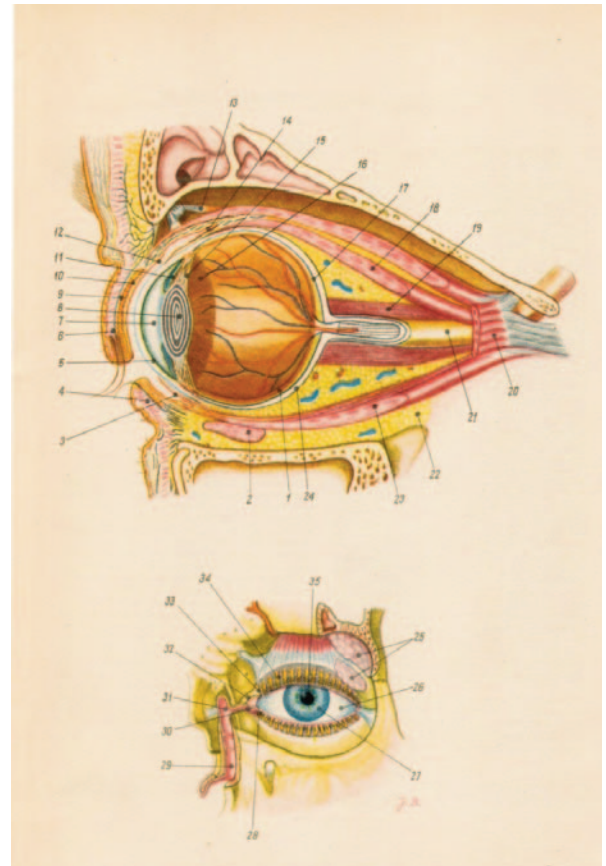
Uveal melanoma is a rare and aggressive disease in which cancer cells form in the tissues of the eye. Signs of uveal melanoma include blurred vision or a dark spot on the iris. Patients with uveal, or ocular, melanoma often have a poor prognosis as the disease can resist treatments and spreads quickly through the body with the liver being the most frequent site of metastasis (cancer spreading to other parts of the body). Once the disease has spread, many patients survive less than a year.

Currently, the most widely used first-line treatment options for non-metastatic disease for this cancer are surgery, radiation therapy, and enucleation (procedure by which the entire eye is removed). The condition is found primarily in the population with light skin pigmentation and light-coloured eyes. It is estimated that uveal melanoma affects between five and eleven patients per million.

Tebentafusp, the active substance of Kimmtrak, is a type of treatment called a bispecific fusion protein. It works by helping immune cells to get close enough to the cancer cells to attack them. The treatment can be used in adult patients who are human leukocyte antigen (HLA)-A*02:01-positive and have unresectable (cannot be removed surgically) or metastatic uveal melanoma.

EMA's human medicines committee (CHMP) reviewed the application for marketing authorisation under an accelerated timetable to enable faster patient access to this medicine in view of the high unmet medical need. Kimmtrak had been designated as an orphan medicinal product on February 19, 2021.

The CHMP based its recommendation on data from a randomised Phase 3 pivotal study and a supportive study. The pivotal study included 378 previously untreated patients with advanced uveal melanoma, of whom 252 patients were randomly selected to receive tebentafusp and 126 patients were in the control group and received one of three already established therapies for the condition (dacarbazine, ipilimumab or pembrolizumab). Tebentafusp was administered to patients via intravenous infusion. The main measure of effectiveness was overall survival (how long the patients lived). The study showed that Kimmtrak prolonged patients' lives: the median overall survival was 21.7 months for patients receiving tebentafusp and 16 months for patients in the control group. The most common side effects observed in clinical trials were skin rashes, fever, and itching.



The opinion adopted by the CHMP is an intermediary step on Kimmtrak's path to patient access. The opinion will now be sent to the EC for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

EMA establishes Cancer Medicines Forum with academia to optimise cancer treatments in clinical practice

March 31, 2022

EMA, in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), has launched the Cancer Medicines Forum (CMF). Bringing together representatives from academic organisations and the European medicines regulatory network, the forum aims at advancing research into optimising cancer treatments and will contribute to foster high standards in cancer care in the EU.

Since its establishment in 1995, EMA has

reviewed and recommended for approval over 170 cancer medicines that have gone on to play an important role in the treatment and management of various types of cancers. The field of oncology has seen the emergence of major innovations in recent years, including the arrival of personalised medicines, immunotherapies, and advanced therapy medicinal products. Such innovations have helped cancer patients across Europe by offering them new tools in their fight against the disease. However, at the time new

medicines enter the market, there is an opportunity to improve many aspects with respect to their optimal use and integration into the existing array of treatments. Addressing these opportunities for treatment optimisation may require the conduct of studies to collect robust data to further guide clinical practice.

The CMF met today for the first time to discuss challenges around the research into optimisation of treatments, such as dose-optimisation and similar approaches tailored to the characteristics of the patient and the disease. Meetings will be organised quarterly, including

New gene therapy to treat adult patients with multiple myeloma

March 25, 2022

EMA has recommended a conditional marketing authorisation in the EU for Carvykti (ciltacabtagene autoleucl; applicant, Janssen-Cilag International NV) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment.

Multiple myeloma is a rare cancer of the plasma cells, a type of white blood cell that produces antibodies and is found in the bone marrow. In multiple myeloma, the proliferation of plasma cells is out of control, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. When plasma cells become cancerous, they no longer protect the body from infections and produce abnormal proteins that can cause problems affecting the kidneys, bones, or blood.

Despite the development and approval of a range of new medicines for the treatment of multiple myeloma over the past few years, there are limited therapeutic options for patients who have already received three major classes of drugs (immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies) and whose disease has come back or no longer responds to these medicines. Therefore, new medicines are needed for these patients.

Ciltacabtagene autoleucl, the active substance of Carvykti, is a chimeric antigen receptor (CAR)-T cell medicine. It is an advanced therapy for cancer that is based on collecting and modifying patient's own immune T-cells to

create a patient personalised treatment that is infused back.

Carvykti had been designated as an orphan medicinal product and was supported through EMA's PRiority MEdicines (PRIME) scheme, which provides early and enhanced scientific and regulatory support to medicines that have a particular potential to address patients' unmet medical needs.

The main study on which the recommendation for a conditional marketing authorisation is based, is a single arm, open-label, multicentre



clinical trial. The study investigated the efficacy and safety of ciltacabtagene-autoleucl in 113 adult patients with relapsed and refractory multiple myeloma who had received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and who didn't respond to the last treatment regimen. About 84% of patients enrolled in the study responded to the treatment

with a durable response (a period without disease signs or symptoms after treatment). Around 69% showed a complete response, meaning the signs of cancer disappeared.

The most common side effects are cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, infections and encephalopathy, i.e. a brain disorder. The consequences of CRS can be life-threatening and, in some cases, even fatal. Furthermore, other important safety aspects are neurologic toxicity, prolonged cytopenia and serious infections. Monitoring and mitigation strategies for these side effects are described in the product information and in the risk management plan that is an integral part of the authorisation.

Additional risk minimisation measures required from the marketing authorisation holder will ensure that centres that dispense the therapy are qualified to recognise and manage CRS and neurotoxicity associated with the treatment of Carvykti.

Additional efficacy and safety data are being collected through the submission of follow-up data from the main clinical trial and through an ongoing study that will compare the efficacy and safety of the medicine with standard triplet regimens in patients with relapsed and lenalidomide-refractory multiple myeloma.

Because Carvykti is an advanced-therapy medicinal product (ATMP), it was assessed by the Committee for Advanced Therapies (CAT), EMA's expert committee for cell- and gene-based medicines, and EMA's CHMP, which recommended approval based on the CAT assessment.

representatives of key academic organisations from EMA's Healthcare Professionals Working Party. The results of these discussions will support the prioritisation of actions to fight cancer included in the Regulatory Science Strategy to 2025 and the Academia Collaboration Matrix Action Plan. Following a 1-year pilot phase, the composition and working procedures of the forum will be re-evaluated.

Further information about the Cancer Medicines Forum will be published on EMA's academia webpage.

