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Ministry of Food and Drug Safety		담 당 과	첨단제품허가담당관 바이오생약국 바이오의약품정책과 식품의약품안전평가원 신속심사과 유전자재조합의약품과
		과 장	정현철 (☎043-719-5351) 신준수 (☎043-719-3302) 김희성 (☎043-719-5061) 정지원 (☎043-719-3501)
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MFDS begins review of Celltrion's COVID-19 monoclonal antibody therapy

MFDS aims to assess the safety and efficacy of the treatment thoroughly and swiftly within 40 days

☐ Following Celltrion Inc.'s submission of marketing authorization application for its COVID-19 treatment, Regkirona Inj. 960 mg (regdanvimab, code name: CT-P59), the Ministry of Food and Drug Safety (MFDS, Minister Kim Ganglip) revealed the upcoming approval process as follows.

[Product Overview]

☐ Regkirona Inj. is a recombinant neutralizing antibody drug which Celltrion Inc. is currently developing as a new drug.

○ The active pharmaceutical ingredient of Regkirona Inj. is a COVID-19 neutralizing antibody** recognized as Regdanvimab under the International Non-proprietary Name.*

- It is a biological product produced after selecting a neutralizing antibody gene expressed in a COVID-19 convalescent patient's blood and inserting the selected gene into a host cell.

* International Non-proprietary Name (INN): generic name of a pharmaceutical substance determined by WHO. Being given an INN is critical since medical professionals in most countries (e.g. Europe and the U.S.) use INN to write prescriptions.

** COVID-19 neutralizing antibodies: antibodies that can neutralize or disable a

COVID-19 virus.

- Therefore, the neutralizing antibodies can be produced in large-scale using the genetic recombination technology without the need to continuously collect antibodies from the blood samples of a COVID-19 convalescent patient.

○ Veklury Inj. (remdesivir), which was approved earlier as a COVID-19 treament, suppresses the replication of COVID-19 virus in an infected cell. Regkirona Inj. (regdanvimab) antibody drug, however, binds to the RBD(Receptor-binding domain) of the spike protein of the virus to inhibit its interaction with its cellular receptor, angiotensin converting enzyme 2 (ACE2) and blocks the entrance of the virus.

○ Regkirona Inj. is expected to be given to patients with mild-to-moderate COVID-19 symptoms, and the planned route of administration and dosage form would be intravenous infusion over 90 minutes. The proposed indication is to treat mild-to-moderate COVID-19-infected patients.

[Development process]

○ MFDS significantly reduced the time frame for Phase II clinical trial to 10 months by having close consultation with the manufacturer since February 2020 from the early stages of the development to the submission of the application.

○ To help design a Phase II clinical trial in which the exploratory significance and therapeutic effect can be confirmed, the Ministry also provided other supports including the recommendation of expanding the target patients and the provision of expert consultation.

○ Celltrion has submitted MA dossier following the completion Multinational Phase II clinical trial. Multinational Phase III clinical trial will be conducted on schedule irrespective of the recent application.

- Phase II clinical trial was aimed at confirming the reduction of recovery

period from 7 different COVID-19 symptoms* including fever in 327 mild to moderate COVID-19 infected patients and the timespan from positive to negative SARS-CoV-2 RNA detection.

* fever, cough, difficulty breathing or shortness of breath, sore throat, muscle or body aches, fatigue, headache

- Phase III is planned to be conducted in 720 mild-to-moderate COVID-19 infected patients and set to confirm the reduction of proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection.

[Approval and Review Process]

□ As with regular pharmaceutical review and approval process, MFDS initiated the approval and review of the treatment when Celltrion submitted the application and relevant dossier through the Ministry's drug safety website (e-government service platform, nedrug.mfds.go.kr).

○ The "Director for Novel Products Approval" first conducts a preliminary review of the submitted dossier. Then, the "COVID-19 Vaccine·Treatment Review Task Force" comprised of experts in their respective fields will review the non-clinical, clinical, quality data and other dossier required for the approval.

○ In the next step, MFDS will determine the rationality of an approval considering the wholistic comments of the reviewers and grant final approval after consulting with Central Pharmaceutical Advisory Committee (CPAC) comprised of external experts.

[Dossier for review/approval]

□ Main components of Celltrion's dossier submitted for the marketing approval include data on non-clinical and clinical trials, quality, risk management plan (RMP), manufacturing and quality management.

○ Non-clinical data demonstrates toxicity and pharmacological activity verified under laboratory conditions before a drug is administered to a person. Clinical data shows the safety and efficacy of the drug evaluated through human trials.

○ Quality data involves the drug's manufacturing process management, and "Standards and test methods" for quality management. Risk management plan includes data regarding comprehensive safety management plan including risk mitigation steps such as patient information sheet and elements to assures safe use.

* Risk Management Plan (RMP) : Comprehensive plan on safety management activities intended to ensure the collection of safety and efficacy data, investigation, testing, risk minimization throughout the life-cycle of drugs from pre-approval to post-marketing stage.

○ Data on Good Manufacturing Practice (GMP)* compliance evaluation is comprised of 10 types of documents on facility/environment management, quality assurance system and other aspects related to the candidate product.

* Good Manufacturing Practice (GMP): Standards that a drug manufacturer must comply with respect to the whole manufacturing process, facility, and equipment in order to manufacture quality-assured pharmaceuticals.

[Approval·review plan]

□ MFDS will thoroughly evaluate the safety and efficacy of COVID-19 treatments through the operation of "COVID-19 Vaccine·Treatment Review Task Force" to ensure the distribution of safe and effective COVID-19 treatments.

○ (Review of submitted dossier) Focus on ensuring the safety and quality and confirming the therapeutic effects through indicators such as the alleviation of symptoms such as fever and cough, and the reduction in the positive-to-negative conversion period

○ (Investigation of Clinical Clinical Practice compliance) Check with the institution conducting clinical trial on its compliance with the Good Clinical Practice with respect to the elements of the overall clinical trial such as the safety of test subjects, the reliability of test results

* Good Clinical Practice (GCP) for pharmaceuticals

○ (Investigation of manufacturing facility) Conduct investigation on the manufacturing site and take into account the results of the preliminary review of the GMP evaluation data completed before the actual submission of the application

○ (Expert consultation) seek consultation from external expert to ensure the scientific expertise and objectivity of the review results.

- Hold consultations with external experts such as the "COVID-19 treatment expert panels" comprised of toxicologists, infectologists and other medical specialists to discuss the validity of the submitted data and the its applicability in the clinical settings; and seek final advice from the Central Pharmaceutical Advisory Committee.

○ (Decision on conditional marketing authorization) Grant conditional approval if the review of the application dossier the expert consultation proves that the product is safe and effective, provided that the company submits the results of the Phase III clinical trial later when they become available.

□ MFDS aims to cut the regular processing period (180 days or longer) down to 40 days to step up the review and approval of Celltrion's product and other COVID-19 vaccines and treatments.

○ MFDS has conducted the rolling review of some non-clinical, quality and GMP data according to the request of the manufacturer since Nov. 20. The Ministry completed the review on non-clinical data and requested the company to submit supplementary quality and GMP data.

[Domestic and global landscapes on COVID-19 treatment development]

□ Domestic and global landscapes on COVID-19 treatment development is as follows.

○ Globally, Lilly and Regeneron are conducting a Phase III clinical trial of their antibody drug. The drug received an Emergency Use Authorization in the U.S.

- In addition, Baricitinib (arthritis medication) and other existing pharmaceuticals are put under clinical trials to be granted additional approval regarding the efficacy and effectiveness in the treatment of COVID-19.

○ In Korea, clinical trials are being conducted to test 15 different products (13 drug substances). The products include ‘Regkirona Inj.’ and other antibody therapies developed for the treatment of COVID-19.

□ Celltrion is currently conducting Phase II/III clinical trial with Regkirona Inj. after it was granted approval for the trial from the U.S., Europe and other countries. The company is currently consulting the possibility of receiving the Emergency Use Authorization (U.S.) and the conditional marketing authorization (Europe) to plan its entrance into the global market in 2021.

○ This product is the third COVID-19 antibody drug in the world to be reviewed by a regulatory authority following the products from Lilly and Regeneron.

□ MFDS will do its utmost to expedite the approval process of COVID-19 therapeutics and vaccine candidates while closely evaluating their safety and efficacy.