**ΕΒΕΑ 13/09/2021**
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Συνημμένα αποστέλλεται πληροφοριακό έντυπο για τα σχετικά σκευάσματα.

Παρακαλούμε για τις σχετικές σας ενέργειες ΠΡΟς την εταιρεία σε περίπτωση ενδιαφέροντος.

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# qifenda™ 400


AiPharma

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# qifenda™ 400

**Qifenda** is a broad-spectrum antiviral in oral tablet form. It is a selective inhibitor of viral RNA-dependent RNA polymerase (RdRP) with potent antiviral activity against single-stranded RNA viruses, including coronaviruses.

Developed by FujiFilm Toyama Chemical Co and originally approved in Japan (2014) as a treatment for pandemic influenza, this drug is one of the few oral antiviral candidates in Phase 3 clinical development to treat newly diagnosed COVID-19 patients.

## THE JOURNEY OF THE ORIGINAL BROAD-SPECTRUM ANTIVIRAL BRAND

### 2011

- PMDA* application
- Seasonal influenza A or B virus infection

### 2014

- Approved in Japan for outbreak of novel or re-emerging influenza virus

### 2020

- Repurposed for COVID-19 treatment
- Received approval and emergency use authorization in many markets
- AiPharma portfolio company, Global Response Aid and Dr Reddy's Laboratories are the exclusive worldwide license holders of Avigan 200mg (excluding Russia, China and Japan)
- AiPharma signed an exclusive license agreement for the development and distribution of Avigan 200mg in Russia and China

### 2021

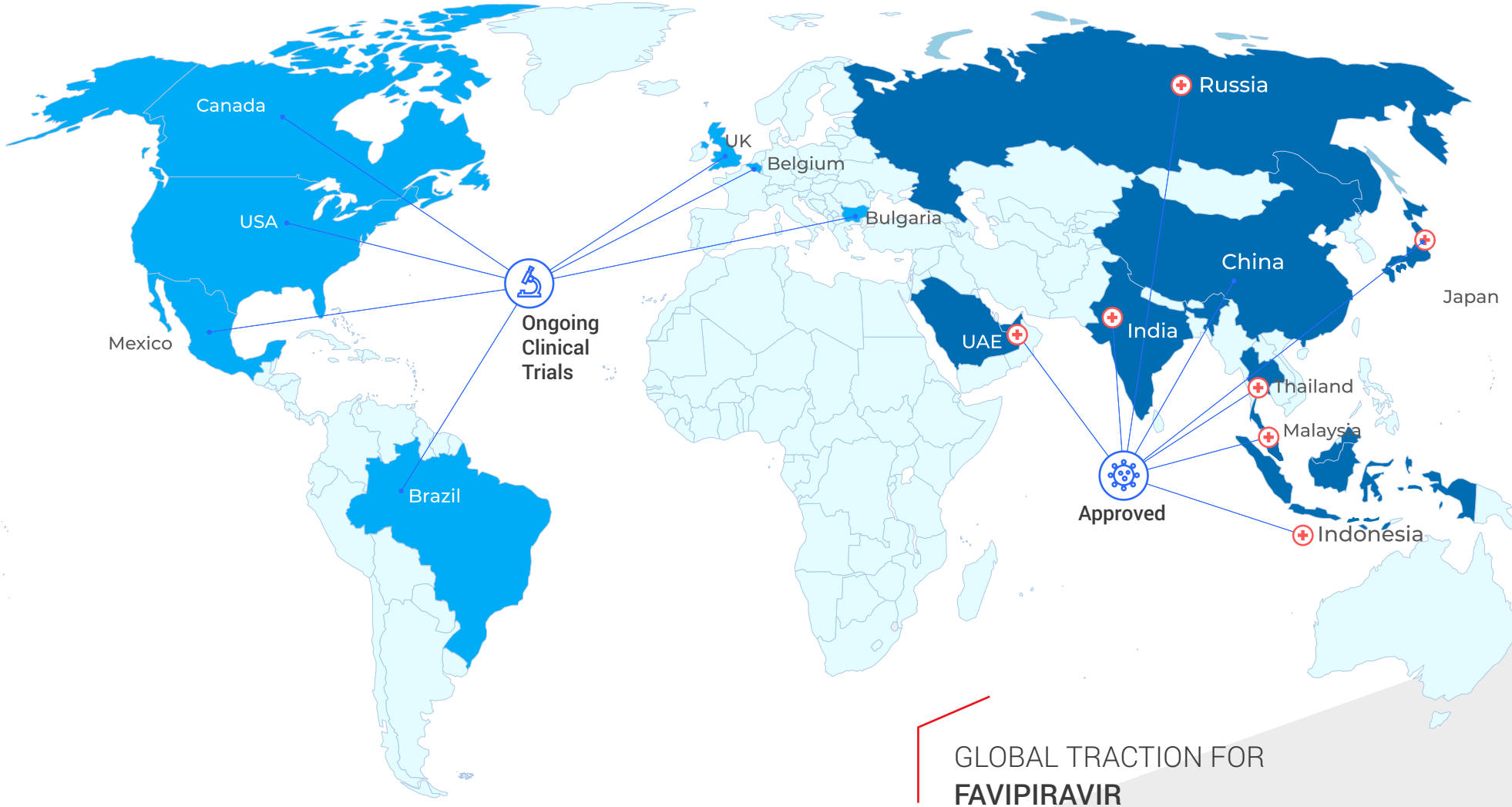
- Favipiravir is approved in more than 20 countries & growing
- More than 4,000,000 patients treated with Favirpiravir medications for mild-moderate symptoms of COVID-19
- Nearing completion of Phase 3 US clinical trial, with positive interim read out in May 2021
- Increased manufacturing capabilities to produce Qifenda at scale
- AiPharma signed global exclusive license with FujiFilm for the development and commericalisation of qifenda 400mg and 800mg
- AiPharma submit multiple dossiers for marketing authorisations of qifenda 400mg in a number of countries

**Qifenda is a highly effective oral antiviral that is administered at home, early in the course of infection, preventing transmission of the virus and hospitalization, ultimately saving lives. Qifenda is uniquely positioned to address the current COVID-19 pandemic and future viral outbreaks now and into the future.**

* Pharmaceuticals and Medical Devices Agency

# **QIFENDA** | SAFE AND EFFECTIVE

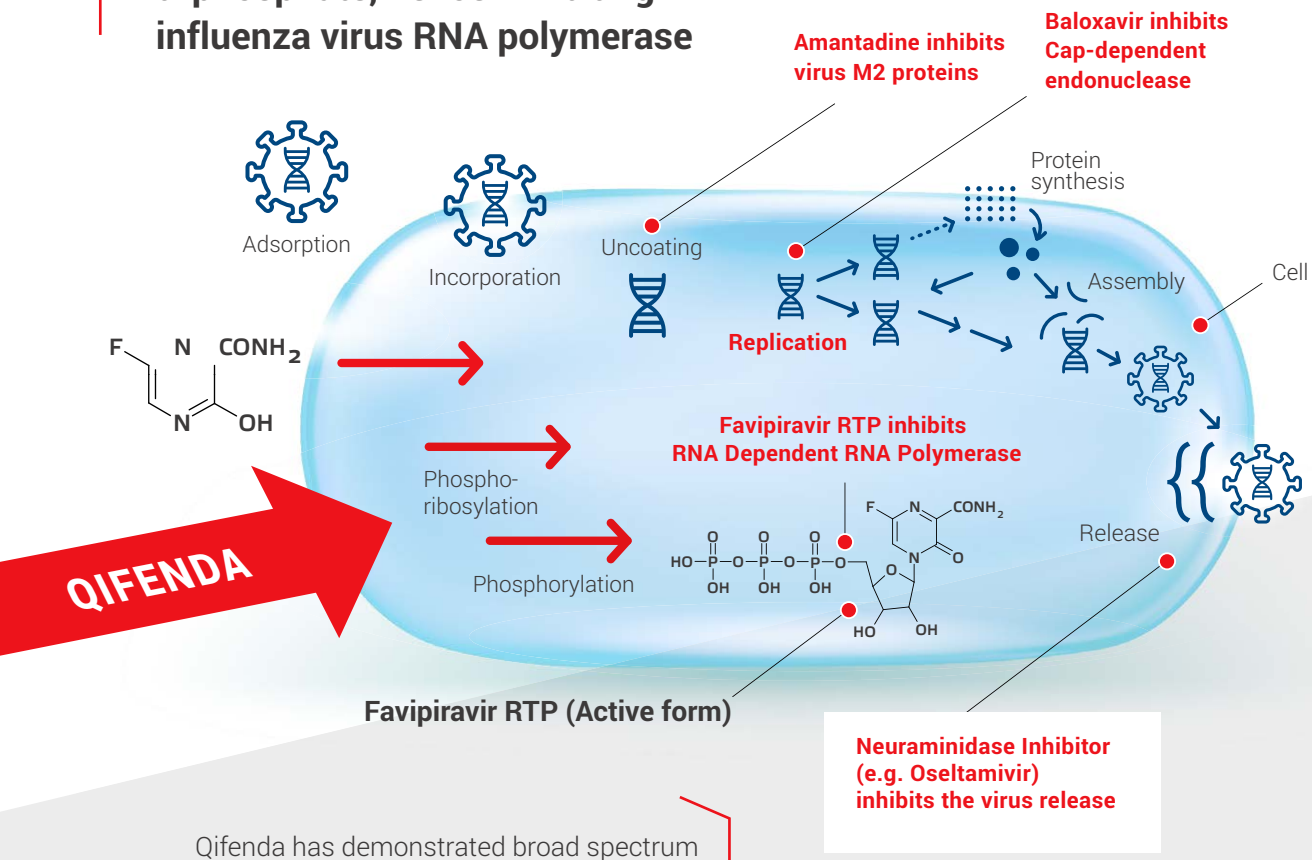
qifenda™ 400




GLOBAL TRACTION FOR
**FAVIPIRAVIR**

qifenda™ 400

**Qifenda is converted into ribosyl triphosphate, hence inhibiting influenza virus RNA polymerase**




Qifenda has demonstrated broad spectrum activity against RNA viruses in twelve viral families in *in vitro* studies

qifenda™ 400

- **Novel antiviral drug**
- **Small molecule**
- **Available for storage at room temperature**
- **Well absorbed after oral administration**

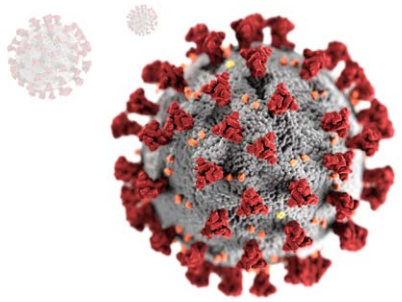
## WHAT IS THE MECHANISM OF ACTION WITH QIFENDA?

**Qifenda 400mg** (Favipiravir) is a selective inhibitor of viral RNA-dependent RNA polymerase (RdRP) with potent antiviral activity against single-stranded RNA viruses including coronaviruses. This is the protein responsible for "building" the viral proteins.
Qifenda is able to target the protein necessary for the coronavirus to replicate, creating mutations that make it impossible for the virus to copy itself.

# qifenda™ 400

**Broad Spectrum Antiviral by Selective Inhibition of viral RNA-polymerase**

| | |
|---|---|
| **API (Active Principle)** | Favipiravir 400 mg |
| **First approval** | Japan 2014 |
| **Original Approval** | Influenza Virus |
| **Safety** | Qifenda has a well understood safety profile. Since 2014, it has been extensively studied in more than 4,000 patients and evaluated in 40 clinical studies prior to the start of the COVID-19 pandemic. The data clearly indicates Qifenda is very safe |
| **Human Toxicity** | Low, does not interfere with normal cell DNA/RNA processess |
| **Cost** | Cost effective |
| **Key Material** | Diethyl aminomalonate hydrochloride [CAS 13433-00-6] |
| **Key Material** | 6-Bromo-3-hydroxypyrazine-2-carboxamide [CAS 259793-88-9] |



## COVID-19
**CORONA**VIRUS

**Effective against the new SARS-CoV-2 by stopping viral replicating in the cell**

## ADVANTAGES

- Readily available, fast to produce drug
- Long history of clinical trials
- Very large safety database
- 2 Year zone IVb shelf life
- Available to use on every patient, with no significent limitation due to previous or concurrent health problems
- 400mg scored tablet for easiness of dosage
- **Effective against 12 classes of viruses** *(Filoviridae, Bunyaviridae, Orthomyxoviridae, Togaviridae, Coronoviridae, Paramyxoviridae, Arenaviridae, Flaviviridae, Picornaviridae, Caliciviridae, Rhabdoviridae, Astroviridae)* including Ebola.

# USE FOR COVID-19 FOCUSES ON MILD & MODERATE CASES OF INFECTION

qifenda™ 400

## TREATMENT AT HOME

With **Qifenda**, patients can administer the drug at home for mild to moderate symptoms.

**QIFENDA reduses the risk** that the infection envolves towards moderate/ severe conditions and hospitalization

## HOSPITALIZATION

Hospital treatment can be applied from moderate to severe Covid infections

**QIFENDA does not apply** to patients in a severe condition (e.i. in case of intubation and ventilation)

### QIFENDA SCOPE OF MEDICAL APPLICATION

| ASYMPTOMATIC, MILD | MODERATE | SEVERE |
|---|---|---|
| • Cough<br>• Chills<br>• Temperature | • Shortness of breath<br>• High temperature<br>• Severe influenza | • Severe breath issues<br>• Risk of death |

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**Today no active principles other than Favipiravir medications such as the molecule originator, qifenda 400mg, are approved for treatment of mild/moderate cases of COVID-19**

# 4 MAJOR SEGMENTS

| | | |
|---|---|---|
| **Covid-19** | • **Current COVID-19 pandemic wave**<br>• **Variants and future endemic Covid** | • Ideal first line of defense to offload hospital burden<br>• Oral, antiviral with no hospital admissions and cost effective |
| **Severe Influenza** | • **Yearly influenza severe cases** (10%-12% of the total Influenza cases) | • Initially developed for pandemic influenza in Japan |
| **Other Epidemic** | **Effective against 12 classes of viruses** *(Filoviridae, Bunyaviridae, Orthomyxoviridae, Togaviridae, Coronoviridae, Paramyxoviridae, Arenaviridae, Flaviviridae, Picornaviridae, Caliciviridae, Rhabdoviridae, Astroviridae)* including Ebola. | • Stockpile<br>• Oral, effective, safe original antiviral & cost effective |
| **Strategic Stockpile** | • **Governments will augment the strategic stockpile to be prepared for potential future pandemic** | • Long shelf-life, and ample action.<br>• Government can stockpile one drug for multiple viruses saving cost and logistics |

# QIFENDA | MPROVED COMPLIANCE PILL BURDEN ARGUMENT

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- The term "pill burden" is a reference to the number of pills a patient is required to take each day.
- While the concept is commonly overshadowed by more pronouncedly enduring issues such as safety and efficacy, the pill burden is a crucial element in achieving successful treatment as it substantially affects adherence to therapeutic protocols.
- The current recommended dosage for Favipiravir is 3,600mg (1,800mg BID*1) (Day 1) + 1,600mg (800mg BID) (Days 2-10).
- This translates to 18 tablets on Day 1 followed by 8 tablets on each subsequent day of treatment.

The question posed by AiPharma is "how can we reduce the pill burden and enhance therapeutic adherence?"
In order to ensure optimum survivability for COVID-19 patients, AiPharma embarked upon the mission of dissecting the issue at the fine-scale level.

**AIPHARMA HAS SINCE DEVELOPED A 400MG TABLET TO REDUCE THE PILL BURDEN BY HALF WITHOUT SACRIFICING THE UNIQUELY DELICATE QUALITY OF THE DRUG.**

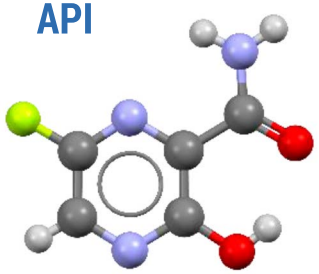
History is our greatest mentor and the above concept of reducing the pill burden has not only achieved greater treatment success rates in other infectious diseases but has also culminated in lower pharmacy costs, fewer hospital admissions and lower hospital costs (see reference below).

**Reference:**

Cohen CJ, Meyers JL, Davis KLAssociation between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIVBMJ Open 2013;3:e003028. doi: 10.1136/bmjopen-2013-003028 (data retrieved 2020-08-25).

## **QIFENDA:** THE ORIGINAL BRAND DIFFERENTIAL QUALITIES

### API



Production process for the removal of a genotoxic impurity (3-hydroxy-2-pyrazinecarboxamide) in the preparation of the Favipiravir Molecule

FujiFilm has a patent granted on the process EU 16.807.530.7

- Molecule presents less impurities
- Improved bio-availability of the main compound
- Reduced toxicity of the molecule
- In some markets like in US, FDA has specifically pointed out the genotoxic compound as a problem

### FORMULATION


Patent JP2009061837 related to the preparation of the pill for stability and the subsequent release of the Favipiravir (bioavailability)

Patent JP2007-251191 and JP2010-253414 for the improvement of the formulation stability

- Improved bio-availability of the main compound
- Better tablet stability

qifenda™ 400

**A better drug, with improved bioavailability, longer shelf life and reduced toxity**

## PHASE 3

**Placebo-controlled, double-blind, randomized trial** enrolling adult outpatients in US, enriching for elderly and high-risk patients

## COUNTRY

USA

## SPONSOR

APPILI

## TARGET

**Outpatients Mild to Moderate**

## >900 subjects

**Total enrollment target of 920 patients** (Aug 2021) Include a sub-study to evaluate viral shedding in cohort of 136 patients

## PRIMARY endpoint

Time to sustained clinical recovery.

**Second endpoints** include time to viral clearance, hospitalization rates, safety

## CURRENT status

First Patient in Nov 2020. Interim **Outlook positive. Results in Sept 2021**

https://clinicaltrials.gov

**The US based Phase 3 PRESECO** (Preventing Severe COVID-19 Disease) study is a double blinded, placebo-controlled multi-center trial investigating the safety and efficacy of favipiravir in the early treatment outpatient setting for adults infected with COVID-19 and showing mild to moderate symptoms. 826 eligible participants who were recently diagnosed as COVID-19 positive with mild to moderate symptoms have been recruited to the trial. Investigators have enrolled patients at multiple clinical trial sites in the U.S., with expansions into Mexico in June 2021. Participants are outpatients who do not require hospitalization and who have had a recent positive COVID-19 test. Participants self-administer the drug regimen in their homes, with clinical investigators monitoring them remotely.

**Interim Top-Line Readout:** Completed Q2 2021 (positive and advised to continue with the trial)
**Complete Top-Line Readout:** Expected Q3 2021

# QIFENDA | THE CLINICAL EVIDENCE

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| STUDY | STUDY TYPE | DATA REMARKS |
|---|---|---|
| **Japan Study** | Observation study, multicenter (407 hospitals), 2158 patients evaluated and stratified in mild vs moderate vs severe category | • After 7 days, 73.8% improved in mild category, 66.6% improved in moderate category<br>• Overall 88% patients recovered by day 14 |
| **China Study** \| March | **Favipiravir vs Lopinavir/Ritonavir.** Multicenter, Open label, N=80 | • Median recovery 4 days for favipiravir vs.11 days for lopinavir/ritonavir (p<0.001)<br>• At day 14.91.4% patients improved on favipiravir vs 62.2% on lopinavir/ritonavir (p=0.004) |
| **China Study** \| March | **Favipiravir vs Arbidol.** Multicenter, randomized, open label, N=240 | • 7 day clinical recovery rate for Arbidol was 55.86% and 71.43% with Favipiravir treatment (p=0.0199) for non-severe patients (mild to moderate) |
| **Russia Study** \| June | **Coronavir (favipiravir) vs Standard of Care (SOC).** Multicenter, open label, randomized study in mild to moderate COVID patients, N=168 | • Rate of clinical improvement was 55% at 7 days and 77% at 14 days as compared to 20% and 40% in SOC arm<br>• Rate of viral clearance on Day 5 was 77.5% as compared to 55% in SOC arm |
| **Russia Study** \| May | **Avifavir (favipiravir) vs Standard of Care**. N=60 | • Median elimination of the virus took 4 days compared to 9 days with standard therapy<br>• Body temperature of 68% of patients taking Avifavir returned to normal earlier (on the 3rd day) than in the control group (on the 6th day) |
| **India Study** \| July | **Glenmark Favipiravir vs SOC.** Open label randomized Phase 3 clinical Trial, N=150 | • 3 day clinical cure with Favipiravir vs 5 days in the control arm (p=0.029)<br>• 64.8% clinical cure at day 4 vs 44% in the control arm (p=0.019)<br>• **Longer median time before first use of oxygen, 5 days vs 2 days in the control arm** |
| **Bangladesh Study** \| July | **Favipiravir vs Standard of Care.** Double blind, placebo controlled randomized clinical trial, N=50 | • **48% of patients clear by Day 4 vs 26% of the placebo group**<br>•The patient group on Favipiravir showed lung function improvement 3x times higher than placebo group<br>•The Favipiravir group had 44% more viral clearance than those on placebo |
| **Japan Fujita University** \| July | **Qifenda vs Standard of Care.** Open label randomized, N=89 | • Underpowered and not-statistically significant but 2.1 days for fever reduction vs 3.1 days in control group and 94.4% of patients had viral load reduction at Day 6 vs 78.8% in the control group |
| **Thailand Study** \| July | **Favipiravir vs Standard of Care.** Observational Study, N=247 | • 66.7% improvement rate at Day 7<br>• Lowering the favipiravir dose was a poor prognostic factor |
| **Turkey Study** \| August | **Favipiravir vs Standard of Care.** Open label-controlled study to be published shortly by Lancet | • **50% reduction in ICU Admission rate**<br>• **ICU Admission rate for patients below 60 years old 6% vs 20% of the control arm** |
| **Japan Study** \| September | Single blind, randomized clinical Study **Qifenda vs SOC,** N=156 | • The median (95% CI) time to improvement in body temperature. Sp02. and findings from chest imaging and recovery to SARS-CoV-2 negative from the start of administration of the study drug were 11.9 days (10.0 to 13.1) in the Qifenda group and 14.7 days (10.5 to 17.9) in the control group, with a median difference of 2.8 days (p= 0.01361. |
| **Kuwait Study** \| January | Phase 3 double blind randomized placebo controlled multicentre study on Hospitalized moderate to severe patients | • Primary endpoint non conclusive<br>• **Subgroup of 181 patients with low NEWS score at admission (Early treatment) with positive results on 3 days reduction for Time To Discharge (p=0.0063)**<br>• Analysis still undergoing |

**7**
**YEARS**
of influenza treatment around the world

**3K**
**PATIENTS**
involved in clinical trials

**40**
**CLINICAL STUDIES**
prior to the start of the COVID-19 pandemic

**4M+**
**PATIENTS**
prescribed drug since start of pandemic

**Qifenda** is uniquely positioned to address the current COVID-19 pandemic and future viral outbreaks now, not in the future, because there is an enormous amount of safety data on the drug. Qifenda has been extensively studied in over 3,000 patients and evaluated in 40 clinical studies prior to the start of the COVID-19 pandemic. The data clearly indicates Qifenda is very safe. Favipiravir medications have been administered to more than 4,000,000 patients since the COVID-19 outbreak.


## IN VITRO STUDY SHOWED INHIBITION OF SARS-COV-2 BY QIFENDA

## DATA FROM CLINICAL STUDIES SUGGEST:

- Faster viral clearance
- Faster fever resolution
- Faster resolution of Chest CT changes
- Faster clinical recovery
- Reduction in case progression
- Long shelf life
- The original brand with very low level of impurities – lower than generic alternatives

**High rate of viral replication can be controlled with early use of Qifenda**

## CONTACT YOUR REGIONAL OFFICE TO DISCUSS FURTHER

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