COVID-19 Treatment

Kirk Chan-Tack, MD and Sarita Boyd, PharmD
Medical Officers
Division of Antiviral Products
Office of New Drugs

Clinical Investigator Training Course
December 7, 2021

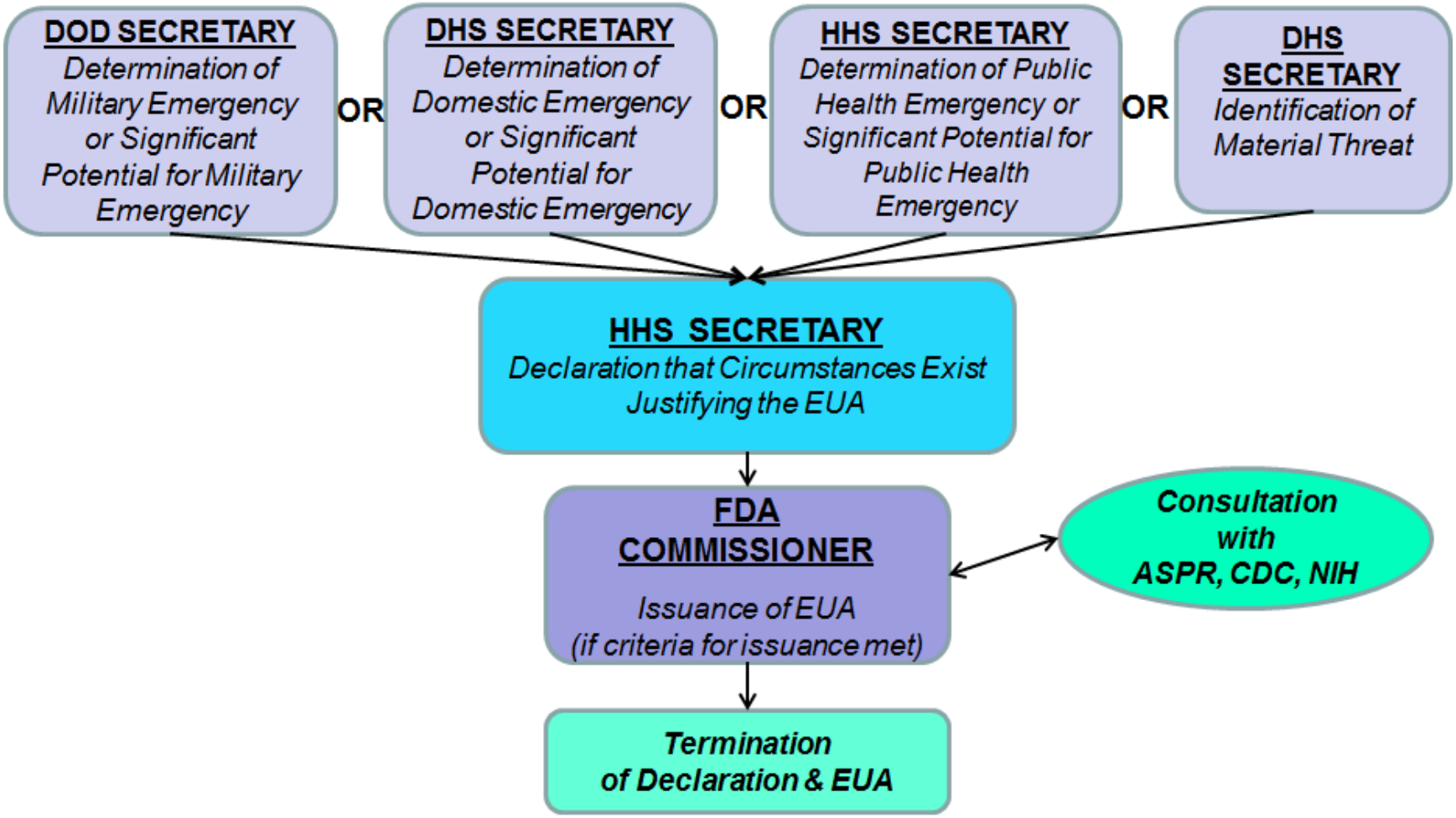
Learning Objectives

- Discuss key differences between an Emergency Use Authorization (EUA) and an FDA approval

- Discuss key considerations in development programs for treatment of COVID-19, using the following as illustrative examples:
  - Remdesivir
  - Sotrovimab

What are key differences between an Emergency Use Authorization (EUA) and an FDA approval?

Process for EUA issuance



EUA vs. FDA Approval

EUA (can be utilized in public health emergency [as declared by HHS secretary]):

- ***May*** be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition
- Known and potential benefits outweigh the known and potential risks for the product
- No adequate, approved, and available alternatives

FDA Approval:

- Safe and effective
- Benefits outweigh risks
- **Substantial** evidence of effectiveness and demonstration of safety for drug's intended use:
  - Higher level of evidence of effectiveness than required for an EUA

Criteria for EUAs and FDA-Approved Prescription Products

Criteria	EUA	FDA-Approved
Access	According to the letter of authorization	By prescription
Use	According to the conditions of authorization	According to labeling and to the practice of medicine
Efficacy requirements	**Reasonable** to believe based on totality of scientific evidence available, including adequate and well-controlled clinical trials	**Substantial** evidence based on adequate and well-controlled clinical trials
Prescriber safety reporting	According to the conditions of authorization	Voluntary MedWatch reporting

EUA vs. FDA Approval

- EUA ≠ FDA approval or licensure
- EUAs do **not** remain in effect indefinitely
- FDA will consider whether a sponsor is working towards seeking FDA approval when evaluating the continued appropriateness of the EUA

Challenge Question #1

Differences between EUAs and FDA-approval include:

A. None, they are the same

B. EUAs do not remain in effect indefinitely

C. FDA approval requires higher level of evidence of effectiveness than EUA

D. B and C

What products (EUAs or FDA-approved) are available for treatment of COVID-19?

What products (EUAs or FDA-approved) are available for treatment of COVID-19?

Outpatient:

- Casirivimab and imdevimab
- Bamlanivimab and etesevimab
- Sotrovimab

Inpatient:

- Remdesivir
- Convalescent plasma
- Baricitinib
- Tocilizumab

What were some key considerations and milestones in the development of remdesivir for treatment of COVID-19?

What was known about remdesivir (RDV) when COVID-19 pandemic began?

- Investigational drug that inhibits viral RNA synthesis
- Activity against SARS-CoV-2 in cell culture and animal models (preliminary data); activity in cell culture and animal models against SARS-CoV and MERS-CoV (closely related viruses)
- Mode of administration: Intravenous (IV)
- Safety data from healthy volunteer studies and clinical studies in Ebola development program
  - Hepatotoxicity (dose-limiting)
- Three COVID-19 Phase 3 clinical trials under US IND
  - Hospitalized patients, moderate to severely ill
  - Multi-national sites; enrolled rapidly

Clinical Trials under IND
Which patients were enrolled?

	ACTT-1 (NIAID)	GS-US-540-5773 (Gilead)	GS-US-540-5774 (Gilead)
Design	Randomized, double-blinded, placebo-controlled	Open-label	Open-label
Population	Hospitalized adults	Hospitalized adults and adolescents with severe COVID-19	Hospitalized adults and adolescents with moderate COVID-19
Key Inclusion Criteria	• ≥18 years • Lab-confirmed SARS-CoV-2 • Illness of any duration, and at least one of the following: • Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), *OR* • SpO2 ≤ 94% on room air, *OR* • Requiring supplemental oxygen, *OR* • Requiring mech ventilation	• ≥12 years • RT-PCR confirmed SARS-CoV-2 • Current hospitalization • Radiographic evidence of pulmonary infiltrates • SpO2 ≤94% on room air *OR* requirement for supplemental oxygen	• ≥12 years • RT-PCR confirmed SARS-CoV-2 • Current hospitalization • Radiographic evidence of pulmonary infiltrates • SpO2 >94% on room air
Key Exclusion Criteria	• ALT/AST >5x upper limit of normal (ULN) • eGFR <30 mL/min • Pregnancy or breastfeeding	• Mech ventilation for ≥5 days • ECMO • Multiorgan failure • ALT/AST >5x ULN • Creatinine clearance <50 mL/min	• Mech ventilation at screening • ALT/AST >5x ULN • Creatinine clearance <50 mL/min

Clinical Trials under IND

	ACTT-1 (NIAID)	GS-US-540-5773 (Gilead)	GS-US-540-5774 (Gilead)
Design	Randomized, double-blinded, placebo (PBO)-controlled	Open-label	Open-label
Population	Hospitalized adults	Hospitalized adults and adolescents with severe COVID-19	Hospitalized adults and adolescents with moderate COVID-19
Study Arms	1. RDV 200 mg IV on Day 1, then 100 mg daily on Days 2-10 2. PBO daily x 10 days	Part A (randomized)* 1. RDV 200 mg IV on Day 1, then 100 mg daily on Days 2-5 2. RDV 200 mg IV on Day 1, then 100 mg daily on Days 2-10 Part B (non-randomized): all subjects receive RDV X 10 days	Part A (randomized)* 1. RDV 200 mg IV on Day 1, then 100 mg daily on Days 2-5 2. RDV 200 mg IV on Day 1, then 100 mg daily on Days 2-10 3. Standard-of-care (SOC) daily x 10 days Part B (non-randomized): all subjects receive RDV X 10 days
Sample Size (primary analysis*)	1062	397	584
Primary Endpoint	Time to recovery through Day 29	Clinical status assessed by a 7-point ordinal scale on Day 14	Clinical status assessed by a 7-point ordinal scale on Day 11
Comments	Topline results became available in late April 2020	Topline results became available in late April 2020	Topline results became available in August 2020
Results	Median time to recovery: faster with RDV (10 days) vs. PBO (15 days), P<0.001	Overall results suggestive of similar treatment effects with 5-day and 10-day regimens	Odds of improvement: - Higher in 5-day RDV group vs. SOC (P = 0.02) - Did not differ significantly between 10-day RDV group vs. SOC

What are RDV's main safety findings?

Hypersensitivity reactions, including infusion-related and anaphylactic reactions:

- Identified through EUA safety reporting
- Manifestations include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering
- Slower infusion rates, with maximum infusion time up to 120 minutes, can be considered as risk-mitigation strategy

Hepatotoxicity (manifested as elevated aminotransferase levels and associated with duration of administration):

- Although rates of Grade 3/4 transaminase elevations were overall lower for RDV compared to PBO in ACTT-1, label includes a warning because transaminase elevations were observed in healthy volunteers who received RDV regimen evaluated in COVID-19 development program and were also reported in patients who received RDV in Phase 3 trials

Higher rate of Grade 3/4 prothrombin time elevation with RDV (9%) vs. PBO (4%) in ACTT-1

Remdesivir (RDV)
EUAs, then FDA-approval

- May 1, 2020: Based on topline results from Phase 3 trials, EUA issued to allow use of RDV for treatment of suspected or laboratory-confirmed COVID-19 in adult and pediatric patients hospitalized with **severe** disease

- August 28, 2020: EUA scope broadened to include treatment of suspected or laboratory-confirmed COVID-19 in **all** hospitalized adult and pediatric patients

- October 22, 2020: FDA approved remdesivir for use in adults and pediatric patients (12 years of age or older and weighing at least 40 kg) for treatment of COVID-19 requiring hospitalization

Remdesivir (RDV)

How did FDA-approval affect existing EUA?

- FDA issued post-marketing requirement for peds clinical trial:
  - Aforementioned pediatric trial is currently ongoing and, once completed, the data may support labeling revision to include use in a broader pediatric patient population

- EUA revised to remove the uses covered under approved NDA

- FDA continues to authorize RDV for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *OR* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg
  - Maintaining pediatric EUA ensures that important information about the recommended use (e.g., dosing recommendations) for pediatric patients not covered under the USPI will continue to be available to providers

Challenge Question #2

Which of the following statements is NOT true?

A. Rates of Grade 3/4 transaminase elevations were higher for RDV compared to placebo (PBO) in ACTT-1.

B. RDV is FDA-approved for use in adults and pediatric patients (12 years of age or older and weighing at least 40 kg) for treatment of COVID-19 requiring hospitalization.

C. Pediatric COVID-19 studies with RDV are ongoing.

D. Rapid initiation of COVID-19 Phase 3 clinical trials was facilitated by data (dose-exploration, safety, etc.) from other RDV development programs.

What were some key considerations and milestones in the development of sotrovimab for treatment of COVID-19?

What were/are the known characteristics of sotrovimab?

Prior to initiation of clinical trials

- Recombinant human IgG neutralizing monoclonal antibody
- Binds to a highly conserved epitope on the spike protein
- LS modification in FC domain
  - Extends half-life (~32 days)
  - Enhanced lung penetration?
  - Does not impair Fc-mediated effector functions

Prior to EUA issued on May 26, 2021

- No overlap between sotrovimab epitope and variants of concern

After initial EUA was issued

- Half-life: ~49 days
- Expected to maintain activity against newly emerging variants

COMET-ICE: Pivotal Outpatient Clinical Trial

Study Design

- Randomized (1:1), double-blind, placebo-controlled trial
- N=1360

Population

- Outpatients with mild-to-moderate confirmed COVID-19
- ≤ 5 days of symptoms
- At high risk of progression to severe COVID-19

Primary Endpoint

- Proportion hospitalized >24 hours for acute management of any illness or death due to any cause through Day 29

COMET-ICE: Pivotal Outpatient Clinical Trial

Planned Interim Analysis #1

- ~41% enrolled through Day 29
- IDMC review of safety, futility, efficacy

Outcome of Interim Analysis #1

- n=583
- Trial met prespecified criteria for stopping enrollment
- IDMC recommended stopping the trial due to efficacy on the primary endpoint
- Trial continued enrollment during interim analysis review

COMET-ICE: What constituted "high risk" for COVID-19 progression?

Sotrovimab and placebo populations were similar.

Risk Factor for COVID-19 Progression[a]	Total (n=583)
Obesity (BMI >30 kg/m^2)	369 (63%)
≥ 55 years	276 (47%)
Diabetes requiring medication	132 (23%)
Moderate to severe asthma	92 (16%)
COPD	24 (4%)
Chronic kidney disease	5 (<1%)
Congestive heart failure	4 (<1%)

a. Inclusion Criteria: (1) Aged 18 years or older and the presence of one or more of the following risk factors: diabetes (requiring medication), obesity (BMI >30 kg/m^2), chronic kidney disease (eGFR <60 mL/min/1.73m^2 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (COPD), or moderate to severe asthma **OR** (2) Aged 55 years or older, irrespective of comorbidities.

Population
- U.S. sites 90%
- Hispanic/Latino 63%

Basis for EUA

- Efficacy results from COMET-ICE Interim Analysis
  - N=583 for efficacy (1:1 sotrovimab vs. placebo)
  - IDMC: study met criteria for stopping enrollment based on high efficacy on the primary endpoint of reduction in rate of hospitalization or death through Day 29

- Retention of activity against current variants of concern
  - Nonclinical data
  - Clinical data forthcoming

- Safety database (sotrovimab recipients)
  - N=430 through Day 15+ from COMET-ICE
  - N=700+ through Day 15+ total across trials

COMET-ICE: Key Efficacy Results

Which results supported the EUA? Interim Analysis Population (n=583)

	Sotrovimab n = 291	Placebo n = 292
Progression of COVID-19 (hospitalization >24 hours or death) (Day 29)		
Proportion (n, %)	3 (1%)	21 (7%)
Adjusted Relative Risk Reduction (97.24% CI)	85% (44%, 96%)	
p-value	0.002	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

Which results are needed for a BLA submission? Full Analysis Population (n=1,057)

	Sotrovimab n = 528	Placebo n = 529
Progression of COVID-19 (hospitalization >24 hours or death) (Day 29)		
Proportion (n, %)	6 (1%)	30 (6%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)

No change in susceptibility (<5-fold) for tested variants with sotrovimab

- Pseudotyped virus-like particle assay
  - Alpha, B.1.1.7, UK
  - Beta, B.1.351, South Africa
  - Delta, B.1.617.2, India
  - Gamma, P.1, Brazil
  - Epsilon, B.1.427/B.1.429, California
  - Iota, B.1.526, New York
  - Kappa, B.1.617, India
  - Delta+, AY.1/AY.2, India
  - Lamba, C.37, Peru
- Authentic variant viruses
  - Alpha, Beta, Gamma

What constituted the safety review for the EUA?

Sotrovimab recipients with follow-up through Day 15: N=700+

Study	Objective	Number of participants (N)
VIR-7831-5001 (COMET-ICE)	Primary evaluation of safety data in support of EUA Request	N=868 (sotrovimab=430)
Supportive safety information from ongoing studies		
216912 (COMET-PEAK [Part A])	Additional blinded safety data in mild-to-moderate COVID-19 outpatients	Planned N~40 (sotrovimab=5)
INSIGHT-014 (ACTIV-3 TICO)	Additional unblinded safety summary from hospitalized patients	N=360 (sotrovimab=182)
J2X-MC-PYAH (BLAZE-4, Arms 7 and 8)	Available unblinded safety data from outpatients (combination only, no sotrovimab monotherapy arm)	N=202 (sotrovimab + bamlanivimab=101)

What were the main safety findings from the sotrovimab EUA review?

- Infusion-related reactions including immediate hypersensitivity reactions
  - Outpatients (COMET-ICE)
    - 1% sotrovimab, 1% placebo
    - Pyrexia, chills, dizziness, pruritus, rash, infusion-related reaction, dyspnea
    - None were severe or serious, all resolved
  - Hospitalized patients (ACTIV-3)
    - Serious/severe events: anaphylaxis, bronchospasm, shortness of breath
- Rash: 2% sotrovimab, <1% placebo
- Diarrhea: 1% sotrovimab, <1% placebo

Benefit/Risk Assessment for EUA

- Based on review of data from COMET-ICE, a randomized, double-blind, placebo-controlled, Phase 1/2/3 trial in outpatient adults with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19:
  - **Sotrovimab monotherapy may be effective** for the proposed indication.
  - The **known and potential benefits of sotrovimab monotherapy outweigh the known and potential risks** of the product for the proposed authorized use.

- Forthcoming data for BLA
  - Final efficacy and safety data from COMET-ICE
  - Up-to-date nonclinical data pertinent to variants

Highlights of Sotrovimab EUA Fact Sheet

- **Indication:** Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (aged 12 years and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at risk for progression to severe COVID-19, including hospitalization or death

- **Limitations of Use:** Not for patients hospitalized for COVID-19 or requiring oxygen/increased oxygen due to COVID-19

- **Dosage and Administration:** 500 mg IV infusion over 30 min

Highlights of Sotrovimab EUA Fact Sheet

- **Criteria for High Risk:**
  - Broader than COMET-ICE high risk population
  - Concise list with link to CDC website
  - Identical for all monoclonal antibody treatments available via EUA

- **Activity against variants**: Non-clinical data

Challenge Question #3

Which one of the following statements is true?

A. Sotrovimab is FDA-approved for the treatment of mild-to-moderate COVID-19 in adults who are at risk for progression to severe COVID-19.

B. Sotrovimab is FDA-authorized for emergency use (EUA) for the treatment of severe COVID-19 in hospitalized adults.

C. Safety data from multiple clinical trials of sotrovimab was considered during the EUA review.

D. Infusion-related reactions including hypersensitivity reactions are no longer a safety concern for sotrovimab when treating mild-to-moderate COVID-19.

Summary

- EUA ≠ FDA approval or licensure

- In public-health emergency, EUAs (based on robust clinical trial data) can facilitate wider access to products that:
  - May be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition
  - Known and potential benefits outweigh the known and potential risks for the product

- FDA approval/licensure remains the ultimate goal of development programs


FDA
U.S. FOOD & DRUG
ADMINISTRATION