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Accelerated Development of Molnupiravir

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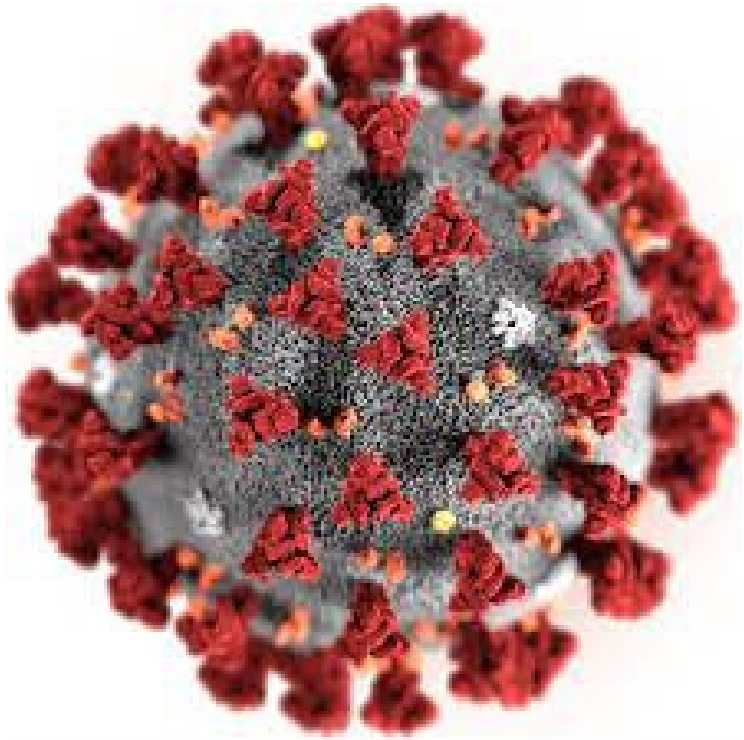
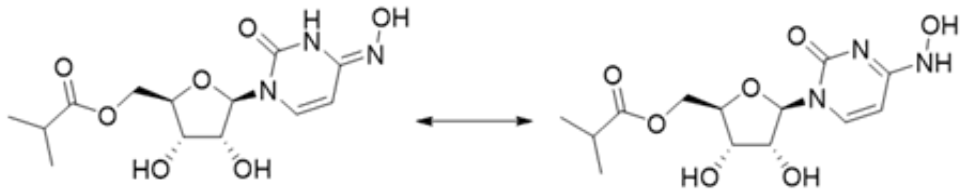


Outline

- Introduction to molnupiravir and a flashback to summer 2020
- Emergency Use Authorization: what exactly is it and what does it mean for CMC?
- Our approach amidst API and timeline constraints
- Our experience with where CMC portions of EUA submissions are on the IND-to-NDA continuum
- Conclusions

Molnupiravir Overview

Mechanism:	Viral error catastrophe
Indication:	COVID-19 treatment
Dose/Duration:	800 mg BID x 5 days
Solubility:	High (41 mg/mL in FaSSIF)
Permeability:	High (rat intestinal perfusion)



- Molnupiravir is an ester-linked prodrug that converts to *n*-hydroxycytidine (NHC)
  - NHC is phosphorylated intracellularly, forming the active moiety (NHC-TP)
- Exerts action through introduction of copying errors during viral RNA replication (viral error catastrophe)
- Drug Product: Granules filled into a size 0 hypromellose capsule
- MOVe-OUT Phase III clinical trial data:

  - Molnupiravir reduced the risk of hospitalization or death by approximately 50%
  - 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated patients (53/377); p=0.0012
  - Through Day 29, no deaths were reported in patients who received molnupiravir, as compared to 8 deaths in patients who received placebo

Remembering Summer 2020: COVID-19 changed the world

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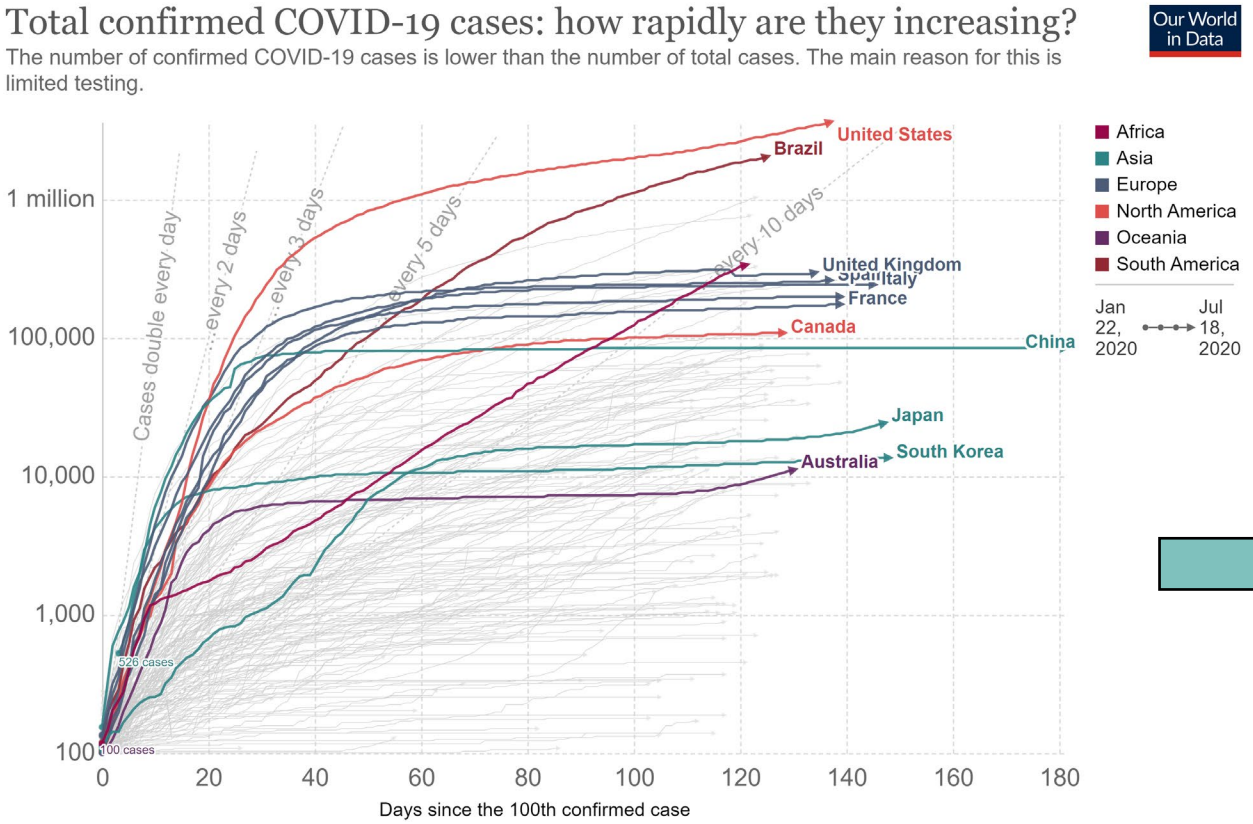
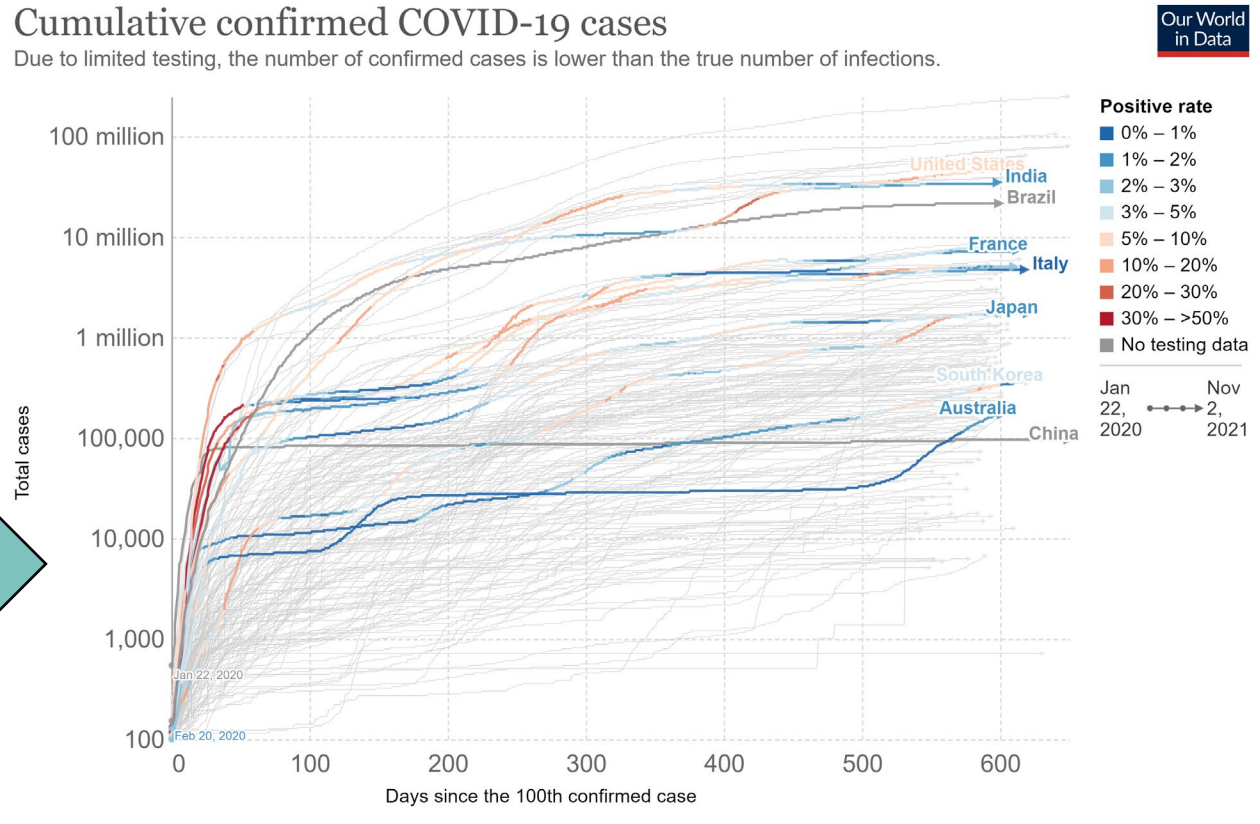
COVID-19 was – and continues to be – proliferating around the world





July 18, 2020
3.83 million confirmed US cases
14.68 million confirmed worldwide cases

November 2, 2021
46.17 million confirmed US cases
247.57 million confirmed worldwide cases

The world is waiting for effective treatments to address this challenge

A Brief History of Molnupiravir

- 23-Oct-2019 → Painter et al (Emory University) report on discovery of EIDD-2801 (now molnupiravir)
- 11-Mar-2020 → WHO declares COVID-19 a pandemic
- 19-Mar-2020 → Emory licenses EIDD-2801 to Ridgeback Biotherapeutics
- 10-Apr-2020 → Ridgeback Biotherapeutics initiates Phase I study of EIDD-2801
- 26-May-2020 → Merck announces collaboration with Ridgeback Biotherapeutics to develop EIDD-2801
- 30-Jun-2020 → Merck announces collaboration deal closure

Team Remit: We are fighting a global pandemic → **<u>speed to launch</u>** is of paramount importance

File emergency use authorization submission based on Ph 2 data in Dec 2020

How are we going do this?

- Emergency Use Authorization (EUA) as a mechanism to bring medicines to patients rapidly
  - "Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the Secretary of HHS declares that an emergency use authorization is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met, including there are no adequate, approved, and available alternatives." (fda.gov)
- FDA Guidance "Emergency Use Authorization of Medical Products and Related Authorities" (Jan 2017) provides the following framework on CMC expectations in order to issue EUA:
  - "Information on chemistry (as applicable), manufacturing, and controls; a list of each site where the product, if authorized, is or would be manufactured, and the current CGMP status of the manufacturing site(s)" is recommended to be part of EUA submission
  - "FDA generally expects that EUA products will be produced, stored, and distributed in compliance with CGMPs; however, limits or waivers may be granted in an EUA on a case-by-case basis, after consideration of the circumstances and of any alternative proposed approach (section 564(e)(3))"
  - "Data from any ongoing testing (e.g., longer term stability data) or other data or information that may change FDA's evaluation of the product's safety or effectiveness and that become available during the period of review or the term of the EUA. Such data should be submitted to FDA when such data become available"

➢ Sounds like FDA may expect **IND-level** of CMC information at time of **EUA submission**… but is that right?

Key Differences in FDA's CMC Expectations between IND and NDA

Attribute	IND Expectations	NDA Expectations
Formulation composition or process unit operation changes	• Stability data from 1 representative (scale agnostic) batch required to justify shelf life • No in vitro or in vivo justification if changes made prior to pivotal clinical trials	• Approaches guided by SUPAC guidance, depending on level of change • Substantial changes likely require stability of 3 representative batches and in vivo bioequivalence study or biowaiver
Justification of process parameters	• No requirement to justify or specify process parameters, so long as product attributes meet specifications (which may be wider than at time of NDA)	• Process parameters must be justified through proven acceptable range or design space supported by representative large scale development data
Stability data to support shelf life	• Data from 1 representative (scale agnostic) batch • Any duration of stability data may be sufficient • Scientific justification may be used to support long-term stability from short-term accelerated conditions	• Data from 3 representative (≥10% commercial scale) batches (one can be smaller than 10% commercial scale) • 12 month duration of stability data at submission • Limited ability to justify long-term stability from short-term accelerated conditions (≤ 2x)

Are we sure FDA will only expect IND level of data at time of EUA submission?

June 2020 Discussion: Formulation Composition & Process Changes

- Phase I DP process was high-shear wet granulation, followed by drying and encapsulation
- Team Proposal: Little-to-no changes to Phase I formulation and process
  - Avoid changes to formulation composition (preserve ability to leverage IND stability data at filing) – including capsule size and color
  - Minimal (SUPAC level 1/2) changes to manufacturing process
  - No more than 2 weeks to assess major manufacturing process liabilities
  - Manufacture Registration Stability Study supplies as quickly as practical thereafter
- Team Expectation: Limited commercial scale data (1-4 batches) available at time of submission to justify control strategy
  - Leverage pilot scale development data to justify product robustness
  - Assume regulatory flexibility (IND level of CMC data)

June 2020 Discussion: Stability to Justify EUA Shelf Life

Team Constraints:

- Only one API lot available by July (same API lot as IND stability)
- Limited API available – batch size will be smaller than typical
- Number of batches may less than typical (driven by near-term API availability and clinical supply needs)
- Dose is not yet determined – must keep multiple strength capsule and capsule count in bottles as potential commercial products
- Clinical resupply likely needed to support Ph 2/3 study and stability batches are best opportunity to supply based on timing

Team's Proposed Approach: 1 batch per strength; one 30 ct bottle per strength

- **Closest to spirit** of ICH batch size guidance (best we can do) → largest possible batch size, even if still <1/10x commercial scale
- Allows for additional FSS time points prior to filing (due to larger batch size) → provides richer data set to regulators with trends
- Allows for diversion of capsules for clinical supply → ensures clinical trial design and execution unlikely to be delayed by drug supply
- 3 new API lots by end Aug → prepare additional registration stability batches (placed on station, 0-1 mo data at filing) → **good faith effort**

	100mg	200mg	Packaging & Time Point Flexibility	Clinical Supply	Max Batch Size
Option 1: 1x per Strength	1x batch	1x batch	2 configurations with ability for additional timepoints (i.e., 1mo)	Yes	67k caps (19.03kg)
Option 2: 3 Batch Matrix	2x batches	1x batch	2 configurations with ability for additional timepoints (i.e., 1mo)	Yes	50k caps (14.29kg)
Option 3: 3x Batch + Single Confirmatory	3x batches	1x batch	2 configurations with LIMITED ability for additional timepoints	Limited	40k caps (11.43kg)
Option 4: Full ICH Q1A Stability	3x batches	3x batches	2 configurations; no additional timepoints	Unlikely	23k caps (6.35kg)

Anticipated Stability Data Available for Dec 2020 Submission

Weight of evidence approach → regulatory flexibility needed to support initial shelf life

- 6 mo IND Stability
  - 1 x 25mg & 1 x 200mg: 30ct in 60cc bottle
- 3 mo Registration Stability (same API lot as IND stability)
  - 1 x 100mg & 1 x 200mg: 30ct in 60cc bottle (more protective, compatible with ex-US markets)
- 3 mo Product Characterization Stability (multiple storage conditions beyond specified in ICH Q1A, to support modeling)
  - 2 x 100mg & 1 x 200mg non-GMP lots + Registration Stability lots
- 0-1 mo Registration Stability (2 alternate API lots)
  - Manufactured and on station by filing; 1 mo data may be available from these batches at time of filing
  - 2 x 100 mg & 2 x 200 mg – or 2 x one strength, if dose is known by September (larger batch size than initial registration stability, >100k capsules)
  - Additional package configurations (i.e., bulk bottle, dose-specific count bottle)
- Consider comparability protocol to continue extending/extrapolating expiry off stability data

Potential Impact to Supply at Launch

- 100 mg and 200 mg strength capsules are only options for launch, despite dose range of 100-800 mg BID
- Process will be “launch fit-for-purpose” and may require higher level of oversight / support and post-approval optimization
- Packaging configurations at launch will be fit-for-purpose, one 30-count bottle and Al/Al blister
- Number of capsules in bottle may not align with number of capsules in a full course of treatment
- Team anticipates that post-approval changes may be needed

Dec 2020 Submission (targeted) → Oct 2021 Submission (actual)

- Submission delayed from original target due to multiple clinical trial factors
- At time of Oct 2021 EUA submission:
  - Formulation composition and process unit operations had been fully defined, inclusive of markings printed on capsule shell
  - Extensive commercial scale process development experience (>100 batches) driven by at-risk investment in stockpiling supply (3.2.P.2.3 section of CTD contains NDA level of control strategy data)
  - Stability batches aligned with ICH Q1A requirements manufactured and placed on station
    - 12 months of clinical IND stability data (1 small scale batch) submitted
    - 9 months of single batch (<100k units) registration stability data submitted ("FSS-1") – ***subsequently updated with 12 month duration***
    - 9 months of two batches (>1/10 commercial scale) registration stability data submitted including non-dose-specific bottles ("FSS-2")
    - 3 months of three batches (>1/10 commercial scale) registration stability data submitted including dose-specific bottles ("FSS-3") – ***subsequently updated 6 mo***
    - Initial characterization of three batches (>1/10 commercial scale) registration stability data submitted including capsules with printed markings ("FSS-4")
- Experience:
  - FDA indicated in pre-EUA discussions that agency expects 3.2.P.2.3 to include control strategy justification (closer to NDA level)
  - FDA exhibited some flexibility during communications in leveraging stability data to justify drug product shelf life
    - Did not appear to leverage clinical IND stability data (1 small scale batch) to support shelf life
    - Willing to leverage the following composite data package to support 24 month shelf life:
      - 12 months of single batch <100k units ("FSS-1")
      - 9 months of three larger batches ("FSS-2") despite some differences between final product and product on stability (capsule markings, count in bottle)
      - 6 months of three larger batches ("FSS-3") in dose-specific bottles

Conclusions

- COVID-19 pandemic required everyone to approach our work differently, always maintaining the rigor of our drug products
  - Industry and regulators collaborated to ensure high quality products moved forward rapidly
- Emergency Use Authorization remains an effective tool to rapidly deliver new therapeutics to patients in times of public health crisis
  - Most EUA submissions (including ours) filed with Ph 3 interim data, when large portion of registrational CMC work has been completed
  - Uncertainty remains about precise CMC expectations at time of EUA submission, particularly for fast-moving clinical programs or EUA submissions based on Ph 2 data
- Our approach was to make a good faith effort to deliver registrational CMC package within context of API and timeline constraints
  - FDA responded with reasonable flexibility

Molnupiravir: It Truly Takes a Village

Merck Ridgeback