

Regulatory Perspectives on the Accelerated Development of Bamlanivimab – a SARS-CoV-2 Neutralizing Antibody



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Outline

- Overview
- High Level Timeline
- Acceleration Elements
- Regulatory Learnings
- Closing Thoughts

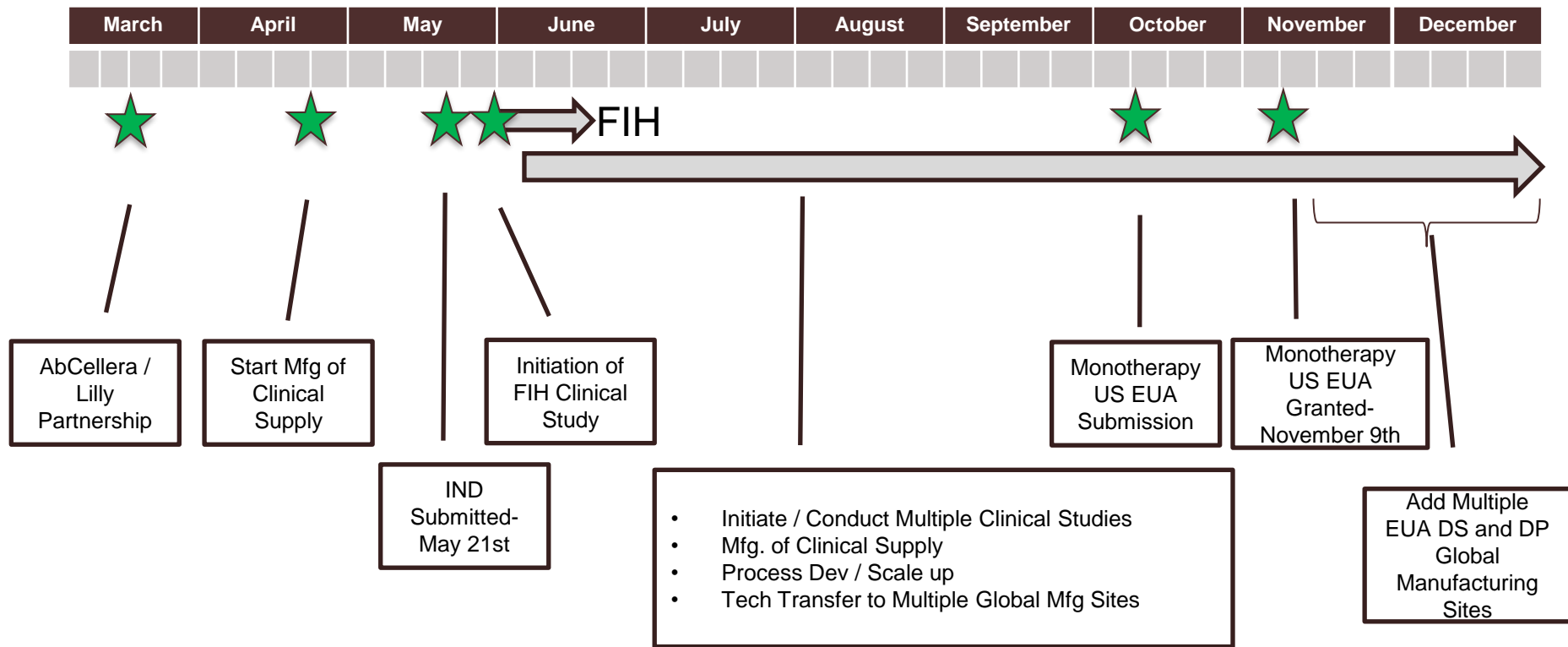
Overview of Bamlanivimab

- Bamlanivimab (LY CoV555, “Bam”): Pronounced = Bam-lan-EEE-vuh-mab
- A recombinant, neutralizing human IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2; designed to block viral attachment and entry into human cells, thus neutralizing the virus to treat COVID-19.
- Bamlanivimab emerged from the collaboration announced on 12 March 2020 between Lilly and AbCellera:
“...select from 500+ unique antibodies isolated from one of the first U.S. patients who recovered from COVID-19 to create antibody therapeutics for treatment and prevention of COVID-19” (Source: AbCellera.com)
- Emergency Use Authorization (EUA) for treatment of recently diagnosed, mild to moderate COVID-19 in high-risk patients (700 mg dose administered intravenously)*

* April 16, 2021- Lilly.com press release: Lilly requests revocation of emergency use authorization for bamlanivimab alone to complete transition to bamlanivimab and etesevimab together for treatment of COVID-19 in the U.S.

Source: www.lilly.com

Key Milestones



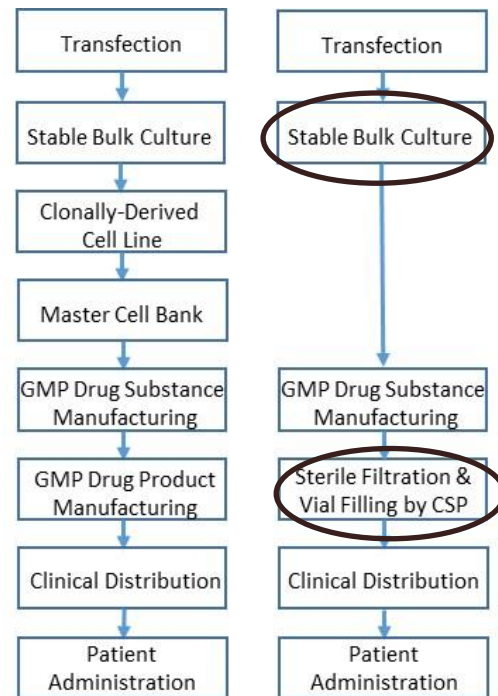
CMC Acceleration to FIH

Key Acceleration Strategies

- Stable bulk culture for drug substance manufacturing
 - ~2 months time reduction
 - Compounded Sterile Preparation (CSP; USP 797) for FIH drug product manufacturing
 - Sterile Mobile Unit
 - DP available for CT use in <1 week
- **Key contributors in reducing time from cell line transfection to first patient dose**
- <2 months as compared to ~17 months for a standard mAb program



Platform Accelerated



CMC Acceleration to FIH

Regulatory strategy aligned prospectively with FDA:

Drug Substance: Stable Bulk Culture

- Address potential for genetic instability, demonstrate batch to batch process consistency
 - Commit to additional “stringent” process and product controls / provide supporting data
- Commit to transition from SBC to clonally derived MCB / WCB as soon as available
- Aligned on comparability strategy to support cell line transition

Drug product: CSP (USP 797)

- Aligned on control strategy / sterility assurance for CSP drug product
- Include instructions in clinical protocol on what to do if sterility failure realized post dosing
- Commit to switch to “traditional” parenteral mfg. facility for all future clinical studies

Moving from Initial IND to EUA

The CMC Challenge:

Lilly anticipates manufacturing up to one million doses of bamlanivimab 700 mg by the end of 2020 – with 100,000 doses ready to ship within days of authorization – for use around the world.

The supply of Lilly's antibody therapy is expected to increase substantially beginning in Q1 2021, as additional manufacturing resources come online throughout the year. Lilly has a robust, global supply chain in place to produce bamlanivimab, with five active pharmaceutical ingredients (API) manufacturing sites worldwide. To ensure rapid access of this treatment to patients around the world, Lilly has invested in large-scale manufacturing of bamlanivimab at risk – even before data demonstrated its potential to become a meaningful therapeutic option for COVID-19.

(source: lilly.com – 28 Oct 2020)

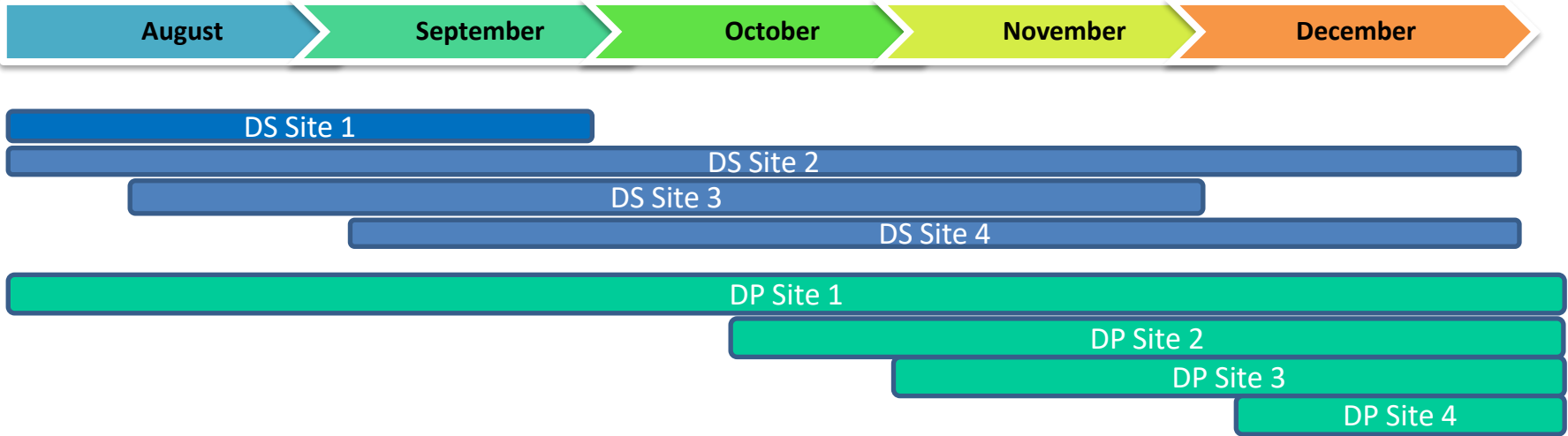
Moving from Initial IND to EUA

- Initial IND (May) to EUA (Nov)
- CMC Activities
 - Process optimization / Scale-up
 - Clonally derived cell line (MCB/WCB)
 - Transition from CSP to “traditional” aseptic manufacturing process and facility
 - Transfer to 3 additional DS and 3 DP global mfg sites
 - Manufacture supply for CTs and potential EUA

Moving from Initial IND to EUA

- Regulatory Activity / Considerations
 - Comparability & Stability strategies
 - IND vs EUA expectations (US)
 - Prepare for global “EUA”-like submissions

Example of Manufacturing Site Addition Plan*



*Timing illustrative only – actual timing may differ

Comparability

Considerations	Approach to Support EUA
Overall Strategy	<ul style="list-style-type: none"> Aligned with concepts outlined in ICH Q5E Leverage extensive mAb platform experience and prior knowledge Alignment with internal Clinical team on impact and timing of changes Prospective protocols for each change / site addition Proactive engagement with FDA – Type C Meeting
Batch Selection	<ul style="list-style-type: none"> Multiple pre-change clinical batches served as the “baseline” for comparison Comparability across DS and DP sites respectively For each Comparability Exercise <ul style="list-style-type: none"> Initial Phase – 1 post-change batch Final Phase – 3 post-change batches
Testing Strategy / Acceptance Criteria / Process Performance	<ul style="list-style-type: none"> Employ extensive biochemical, biological and biophysical testing <ul style="list-style-type: none"> Specification and extended characterization tests Head-to-head and / or co-mixtures for select tests Specification acceptance criteria, comparison to historical ranges, profile comparisons Differences investigated and extensive collaboration with Global Patient Safety and Clinical to assess potential risk to safety and efficacy Process performance assessments to demonstrate process consistency As more post-change data became available also compared across post-change / sites
Stability	<ul style="list-style-type: none"> At least one of each post change batch placed on stability at long term and accelerated conditions. Leverage stress stability as appropriate.

CMC Expectations for EUA Submission?

- Emergency Use Authorization (EUA)
 - No internal experience for a bioproduct
 - Limited EUA-specific guidance
 - *Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders (FDA; January 2017)*
- **Section D.2 Request for an EUA / Information Recommendations:**
 - CMC: 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);
 - *Development and Licensure of Vaccines to Prevent COVID-19 (FDA; June 2020)*
 - *Development of Monoclonal Antibody Products Targeting SARSCoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency (**FDA February; 2021**)
- IND-like? BLA-like?

Content / Level of Detail - Learning

	Initial IND	EUA
Process Controls	<ul style="list-style-type: none">Limited number of controls includedFocus on Safety related controls (e.g., linked to Viral, Sterility etc.)	<ul style="list-style-type: none">BLA like process controls both in the number and typeDifferentiation by criticality not required
Process Validation	<ul style="list-style-type: none">No information provided	<ul style="list-style-type: none">If PV not complete, need to demonstrate process consistency
Specifications	<ul style="list-style-type: none">Control strategy includes a combination of release and characterization testsSelection of tests / criteria based on platform, limited process experience and pre-clinical workInitial criteria are adjusted over course of developmentCell based potency assay typically not required	<ul style="list-style-type: none">Show progression toward BLA- likeElevate select characterization tests to specification testsTighten criteria based on available batch data – limited info available to develop patient centric justificationsExpectation to establish mechanistically relevant potency assay(s)

Content / Level of Detail - Learning

	Initial IND	EUA
Aseptic Process Information	<ul style="list-style-type: none">Limited detail submittedExample: DP process supported by successful media fills rather than providing the detailed supporting data sets	<ul style="list-style-type: none">BLA level of detail expectedDetails of depyrogenation / sterilization of components and equipment, media fills, environmental monitoring, etc.Process Times
Facility Information	<ul style="list-style-type: none">Limited information provided on GMP Facility.	<ul style="list-style-type: none">BLA level of detail expectedInspection history, facility layout, equipment lists, multi-use details, etc.
Transportation / Shipping	<ul style="list-style-type: none">Leverage platform data; describe shipping conditions but data not typically included	<ul style="list-style-type: none">BLA level of detail expectedData to support shipping configuration and modes, seasonal shipments, etc.

Content / Level of Detail - Learning

	Initial IND	EUA
Reporting of Process Changes	<ul style="list-style-type: none">Assess in internal Quality system / change controlRisk based reporting (No reporting, amendment, or annual report)	<p>Condition of Authorization: “Lilly <u>will not implement any changes</u> to the description of the product, manufacturing <u>process, facilities and equipment, and elements of the associated control strategy</u> that assure process performance and quality of the authorized product <u>without notification</u> to and <u>concurrency</u> by the Agency.”</p>
Drug Supply	<ul style="list-style-type: none">Information not typically included	<ul style="list-style-type: none">Provide detailed supply projections by site by month – frequent updates

Key Learnings

- Prospective engagement with regulatory agencies can enable innovation & speed for CMC development
- Alternative, novel approaches are possible when supported by data and sound scientific justification
- Plan for a significant number of Health Authority interactions
Approximate totals for IND / EUA (FDA: April 2020 - March 2021):
 - Briefing Documents: 10
 - Teleconferences: 15
 - Initial Submissions / Amendments: 18
 - Information Requests / Responses: 50

Globalization

- **Goal**
 - Partner with global health authorities to rapidly and safely ensure bamlanivimab is available to patients globally
- **Enabling Strategy**
 - One CMC package / One label / One shelf life / One set of specs / Minimize generation of regional specific docs....

Globalization

- **Challenges**

- Uncertainty in applicable regulatory requirements / pathways during the pandemic
 - CTA or MAA like expectations?
 - Review / approval timelines (initial and amendments)?
 - Process / Method Validation?
 - Control Strategy – criticality assessments / non-critical controls?
 - Stability data to support expiry dating – extrapolation vs. full shelf-life data set?
 - Label content?
- Multiple overlapping submissions, Q/A, amendments
- CMC team focused on manufacturing supply to meet global demand

Globalization

- Approach

- Proactive interactions with Health Authorities to inform on CMC status
 - Inform / align on CMC submission strategy, available data package – what is / is not available, transparency on potential gaps / risks compared to traditional CMC package
- Countries requiring full CMC content received the same dossier
 - Single Module 3 content – no regional customization of DS / DP sections
 - Single global shelf life – leveraged platform knowledge and extrapolation beyond available long-term data
 - Reliance on comparability and process consistency data
 - Methods qualified - suitable for intended purpose
 - Control Strategy – in-process controls (not differentiated by criticality), specs and characterization testing
 - Maintain single global set of release specifications
 - Limit providing regional specific / ancillary documents (e.g. study reports, batch records and etc.)
 - Prospective proposals to communicate CMC changes via notifications (e.g. tell - do) rather than traditional amendments (e.g. tell – wait – do) – notify post concurrence from the US FDA (e.g. site additions)
- Single global label – physical label not differentiated for regional requirements – package insert sends user to website for regional language / specific information
- Response to questions
 - Establish a balance of responding fully vs trying to maintain a single consistent global CMC package
 - Commitment to address requests as development / commercialization proceed

Globalization During a Pandemic

- **Key Learning**

- Prospective, transparent and timely communication is imperative
- Globally acceptable Module 3 / CMC content important to drive speed / efficiency
- Important to have defined / streamlined regulatory pathways and timelines to ensure appropriateness of submission content and timely delivery of supply to patients

Globalization During a Pandemic

- **Future Opportunities**

- How to refine process for holding timely Industry / Health Authorities interactions?
 - Is there an opportunity to do this in a more “centralized” manner rather than country by country?
- How to leverage Reliance¹ / Harmonization concepts to expedite reviews and minimize divergence / regional customization of CMC content?
 - Centralized or joint reviews?
 - Reliance on review by another Health Authority?
 - Globally aligned pathway / timelines?

¹ The path to improved access to medicines through alternative registration pathways (EFPIA 13 Sep 2017) https://www.efpia.eu/media/288557/position-paper-reliance-and-expedited-pathways-in-emerging-markets_final.pdf.pdf

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