Faster than fast - Technology transfer to meet demand for a repurposed biologic

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Outline

Evaluation of existing medicines for COVID-19 treatment

Dynamic adaptation of the tocilizumab (Actemra) supply chain

Challenges and successes of an accelerated drug product technical transfer

Interactions with Health Authorities

Learnings and future outlook

Genentech/Roche COVID-19 response: By the numbers

5

sponsored clinical trials of our medicines in COVID-19

20+

investigator-initiated, company-supported studies for 6 of our FDA-approved medicines*

$42M

funding for emergency response and longer-term community recovery efforts

1000+

patient support service calls per day

5

Roche diagnostic tools

* These medicines are being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, such as pneumonia. None of these medicines are FDA-approved to treat COVID-19 or associated symptoms.

Roche's investigational medicines for COVID-19

5 Genentech and Roche sponsored trials

Actemra® (tocilizumab)

COVACTA, MARIPOSA, EMPACTA:
Phase II/III trials to evaluate the medicine in hospitalized patients

REMDACTA;
Phase III combination study with remdesivir

Anti-ST2 & IL-22Fc

COVASTIL
Phase II trial in patients hospitalized with severe COVID-19 pneumonia

20+ Investigator-initiated, company-supported studies for 6 of our FDA-approved medicines*

ACTIVASE® ALTEPLASE
A RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

ACTEMRA® tocilizumab

TNKase® Tenecteplase
SINGLE-BOLUS

AVASTIN® bevacizumab
100 MG/4 ML INJECTION FOR IV USE

Esbriet® (pirfenidone) tablets 267 mg 801 mg

Pulmozyme® dornase alfa INHALATION SOLUTION

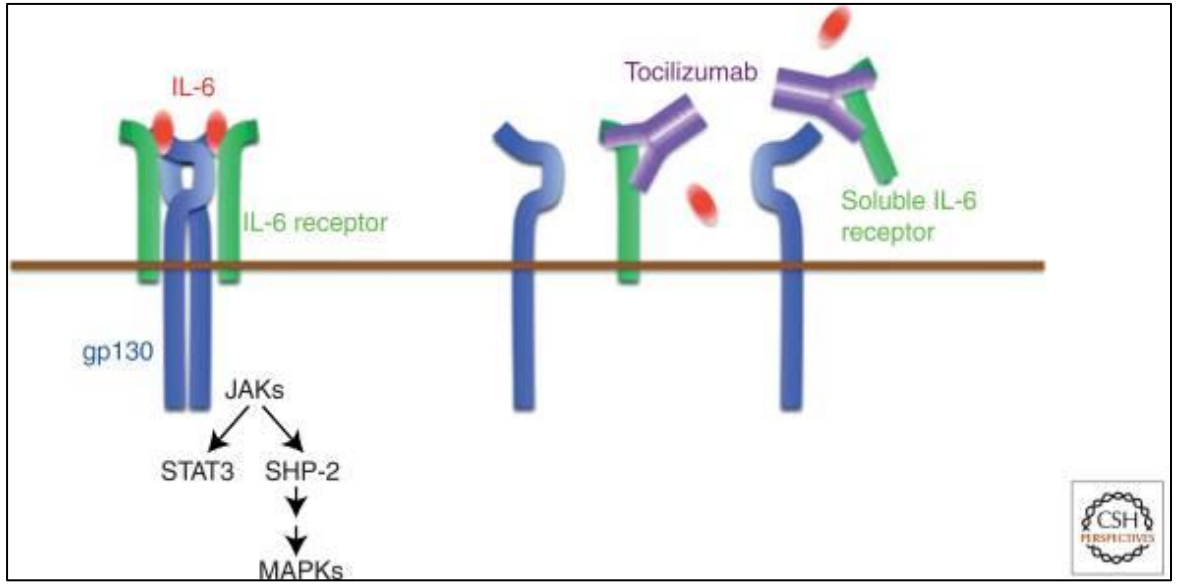
* These medicines are being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, such as pneumonia. None of these medicines are FDA-approved to treat COVID-19 or associated symptoms.

Mechanism of Action

ACTEMRA® tocilizumab

Roche

- ACTEMRA (tociliziumab) is an anti interleukin-6 (IL-6) therapy
  - IL-6 is a common protein found in all joints in the body and is a natural substance that can raise inflammation.
  - During the so-called “cytokine storm,” a potentially fatal immune reaction induced by hyperactivation of T cells, a major boost in IL-6 production is observed.[1]



IL-6 binds to soluble and transmembrane IL-6R and the complex, then induces homodimerization of gp130, leading to activation of the signaling system.
Tocilizumab, blocks IL-6-mediated signaling pathway by its inhibition of IL-6 binding to both receptors.

[1]*IL-6 in Inflammation, Immunity, and Disease*; Tanaka T, Narazaki M, Kishimoto T, Cold Spring Harb Perspect Biol. 2014 Oct; 6(10): a016295. doi: 10.1101/cshperspect.a016295

EMPACTA study

*Evaluating Minority COVID-19 Patients with Actemra**

Groundbreaking in advancing inclusive research!

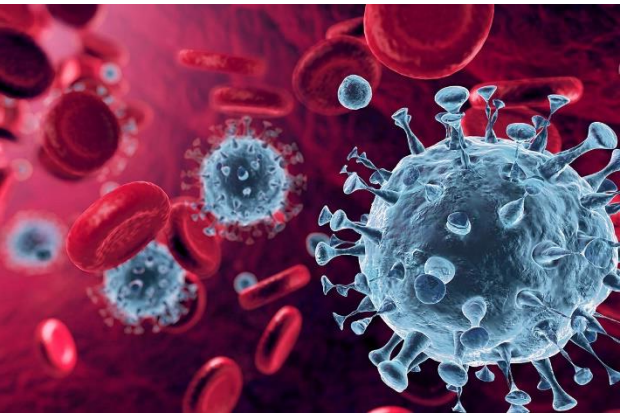
Study enrolled patients who have been disproportionately affected by the COVID-19 pandemic: approximately **85%** of the 389 patients were **from minority racial and ethnic groups.**

In the EMPACTA study, patients with COVID-19 associate pneumonia who received **tocilizumab plus SoC** were **less likely to progress to mechanical ventilation** compared to patients who received placebo plus SoC.

Note: tocilizumab has not been shown to reduce mortality in the EMPACTA study.

* While Actemra is being evaluated for the potential treatment of patients with severe COVID-19 associated symptoms, it is currently not approved for this use.

Problem statement – What happened in March 2020



- Covid-19 pandemic surged in early March.
- Anecdotal evidence for use of Actemra in Italy and France.
- Actemra demand forecasts were projected to be >500% above 2019 baseline.
- Actemra stock-outs were projected to occur within a month.

Dynamically adapting the Actemra i.v. supply chain to increase supply

Status beginning of March 2020

- **Drug substance** was transferred to **Vacaville, CA** from Utsunomiya, Japan in combination with a process upgrade (improved yield).
- Vacaville submissions were under review at FDA and EMA.
- **Drug product** vials were manufactured in **Japan.**

Activities started with the onset of the pandemic (mid-March 2020):

- Expedited transfer of **drug product** manufacturing to **Hillsboro, OR**.
- **Accelerate** the submission of Vacaville **drug substance** site globally.

Challenges during technical transfer

1 Drug product primary container components sourced from Japan	Use components of an approved product at Hillsboro, with caps of a **different color**; leachables and extractables studies.
2 Compounding step to formulate for filling	Use compounding procedure for another approved product at Hillsboro.
3 Labeling and packaging configuration different based upon equipment at Hillsboro	Use Hillsboro site packaging configuration and DHCP letter to inform users of change.
4 No data to support approved shelf-life	Set shelf-life to 6 months in accordance with ICH guidelines.

Health Authority interactions – Approach

Proactive dialogue facilitated pathways

FDA

- Engaged with Drug Shortage Staff

  → *Demand signals, supply outlook, and timing of potential shortage*

- Proposed a DP technical transfer and batch specific release for interim supply

  → *Protocol for CMC information and concurrent data generation for submission*

- Meetings with CDER OBP reviewers and OC staff on specific approaches and data expectations

EMA

- Engaged with Quality Defects and Rapporteur
- EMA issued guidance for COVID-19 transfers called “Exceptional Change Management Process (ECMP)” in April 2020
- Discussion with EMA on use of the ECMP guideline:
  - Technical transfer to Hillsboro is covered
  - Container-closure system (CCS) change had to be submitted separately as a Type 2 Variation

Health Authority interactions - Approach

Protocol approach enabled expedited batch release

- FDA protocol scope to
  - support a **risk-based approach** leveraging historical data.
  - support **expedited batch** release (incl. 7 day sterility testing).
  - support use of a **different vial and stopper** with **a different cap and seal color** and a **different secondary packaging** configuration.
  - provide approved **internal protocols** for generation of batch release, process verification, and stability data concurrent with manufacture, as well as a batch release checklist.
- Included descriptions of the manufacturing and testing sites, manufacturing process, in-process controls, release and stability testing requirements, and acceptance criteria.
- Proposed to submit **batch specific BLA amendments** for release that included in-process and release testing data and batch-specific environmental monitoring data.

Health Authority interactions – Outcome

Proactive dialogue facilitated pathways

FDA

- **accepted** proposals and provided regulatory discretion for release of 3 batches on a batch by batch basis.
- strongly recommended filing a **supplement** to the BLA for DP transfer as long-term supply strategy.

  → *Filed **Comparability Protocol**/PAS (June 2020) and subsequent **CBE-30** (Nov 2020) following data availability.*

EMA

- Review and approval of the CCS variation was expedited and achieved in **14 days**.
- **Local importation licensure** to Mannheim, Germany was authorized to allow for secondary packaging.
- Within **6 months** from first batch distributed, the Type II Variation was submitted to EMA (October 2020).

Rest of the World Supply Strategy

Prioritized based upon demand signals

The **Top 50** Actemra i.v. markets were actively approached:

- **Common label** make-up (in lieu of country specific) was readily accepted.
- Acceptability of drug product from Hillsboro for rest of the world was primarily based on
  - **Reliance pathways** from US and EU acceptability of Hillsboro filled material
  - **Temporary or special licenses** on a lot by lot basis or for a pre-defined emergency use duration.
- Only a **few** countries requested a **full review** of the Hillsboro DP site prior to accepting material.

Key Take-Aways

Tech Transfer

- Small, empowered, focused cross-functional teams from donor and recipient sites.
  Identified decision makers and limited governance of the work.
- Reliance on prior knowledge, risk management and understanding gaps and differences to support product quality assessments.

Health Authorities Engagement

- Active engagement with HAs to provide consultation and input into the strategy.
- Granting regulatory discretion for release is not sustainable.

Future Outlook – Topics of discussion

- General acceptability of visually different primary packaging materials in one market (e.g. different dimensions and cap colors)?
- Enablers for reliance pathways in ROW: Approval letters and/or assessment reports. What is possible without this information?
- EU/ROW: Use of common make-up (labelling) for emergency use in hospital setting possibly in combination with e-leaflet?

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Doing now what patients need next