PRODUCTS | DRUG DELIVERY | CONTRACT DEVELOPMENT

OctoPlus

Enhancing biosimilars through drug delivery

The upside of drug development without the burn

OctoPlus N.V.
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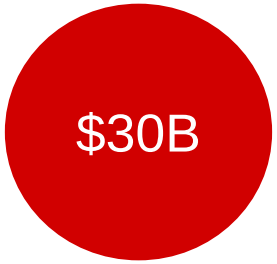
Background OctoPlus N.V.

- Established 1995
- Located in Leiden, the Netherlands
- Business units:
  - Drug Delivery
  - Contract Development
  - Manufacturing
- Publicly traded on NYSE Euronext Amsterdam (OCTO) since 2006

The growing interest in biosimilars makes it a very attractive market

- By 2011, 12% of the total pharmaceutical market will consist of protein-based products with an increasing market share for biosimilars*



- Biosimilars will need to differentiate, because unlike small molecules biosimilars will not automatically substitute current biologicals
- Many companies make substantial investments in biosimilars, e.g. Novartis, MSD, AstraZeneca, Lonza, Teva, etc.
- In addition pharma seeks creative ways to fill their empty pipelines and out-sources more R&D, preferably through partnerships with one-stop shops
  - Opportunity to create a “Lonza model” in drug delivery:
  - Development + manufacturing activities within one company

Global discussions regarding market exclusivity for innovator products

- Politicians and regulators seek to reduce healthcare spending
- Market exclusivity for innovator biotech products
  - Gathering data on biological, thereby sufficient references
- Global discussions on reducing market exclusivity
- FDA discusses abbreviated application process for biosimilars
  - Current proposal is to show “no *clinically* meaningful differences”
- EMEA discusses similar process
  - Current proposal is to show “no meaningful differences”
- If biosimilars market opens earlier, large, highly competitive companies will jump on it: competition will be fierce
- Develop modified product with additional market exclusivity (new IP?)

Modification options for biologics

- Modifications that positively affect half-life:
  - PEGylation of the protein (PEG-Intron)
  - Fusion protein with human albumin (Albuferon)
  - Lipidisation, phosphorylcholine

  - Consequences chemical modifications
    - Potential reduction in bio-activity
    - Increase dose needed
    - Still a high peak – trough ratio: adverse events
    - Process yield drops due to downstream processing
    - Product heterogeneity
    - Regulatory speaking it's a New Molecular Entity
    - Increased risk of immunogenicity (fusion proteins)

- Controlled release of unmodified proteins

Controlled release technologies provide a competitive advantage for biosimilars

Improve duration of action

+ Many novel biotech drugs need controlled release
+ Multiple injections of proteins affect continued patient-usage of the drug

Avoid or reduce side effects

+ Nasty symptoms associated with biotech drugs substantially reduced
+ Controlled release can reduce the quantity of drug required to achieve efficacy

Improve efficacy

+ Higher doses may be given
+ Continued patient-usage can be improved

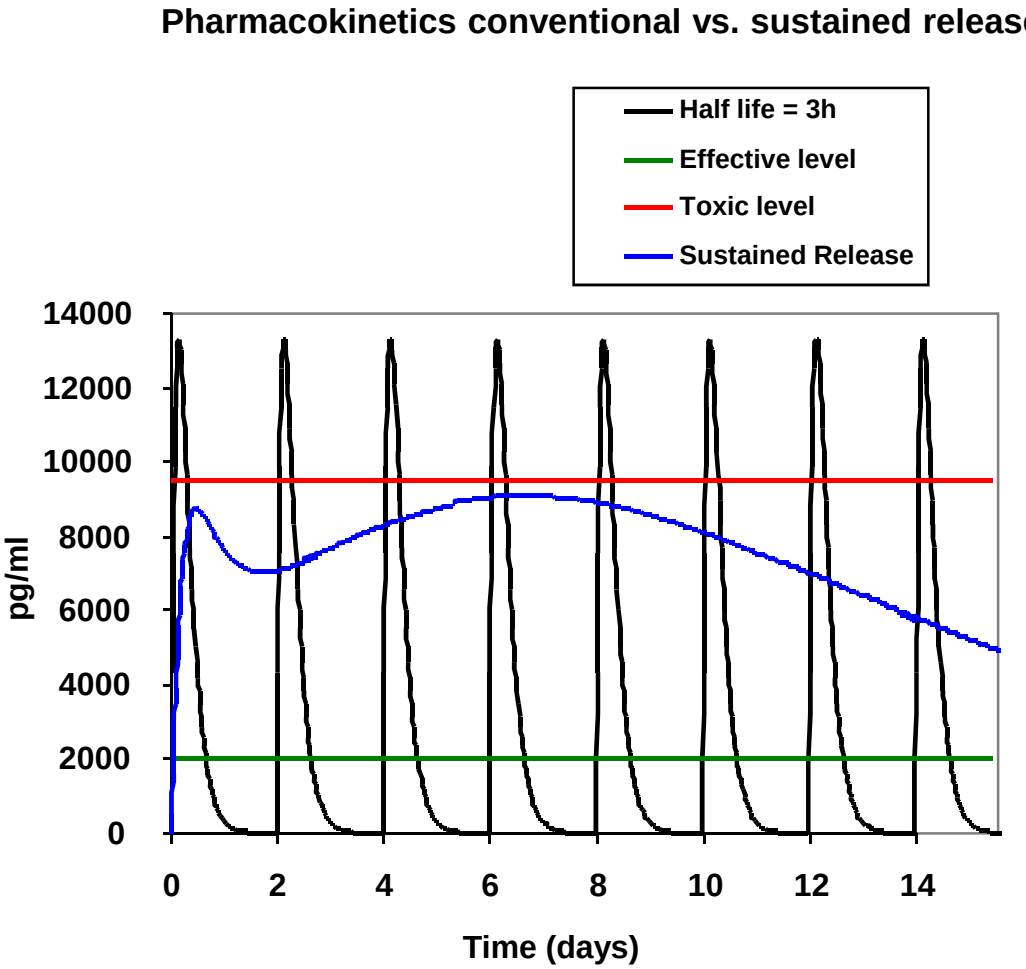
Regulatory challenges for controlled release biosimilars

- Every new combination is regulated as a biological device combination product
- In US, review by both CDER (drug) and CDRH (device)
- EMEA has published several guidelines related to biosimilars and new biological products
- If original biological is approved, abbreviated clinical development program can suffice

Why controlled release delivery?

- Overcome limitations of conventional therapeutic protein products
  - Less frequent injections: patient comfort and improved compliance with the therapy
  - Prevent serum level excursions above toxic and below effective
  - Choose maximum or minimum exposure level
  - Save API (AUC)

Avoiding peak levels using controlled release formulations



Case study: Locteron®

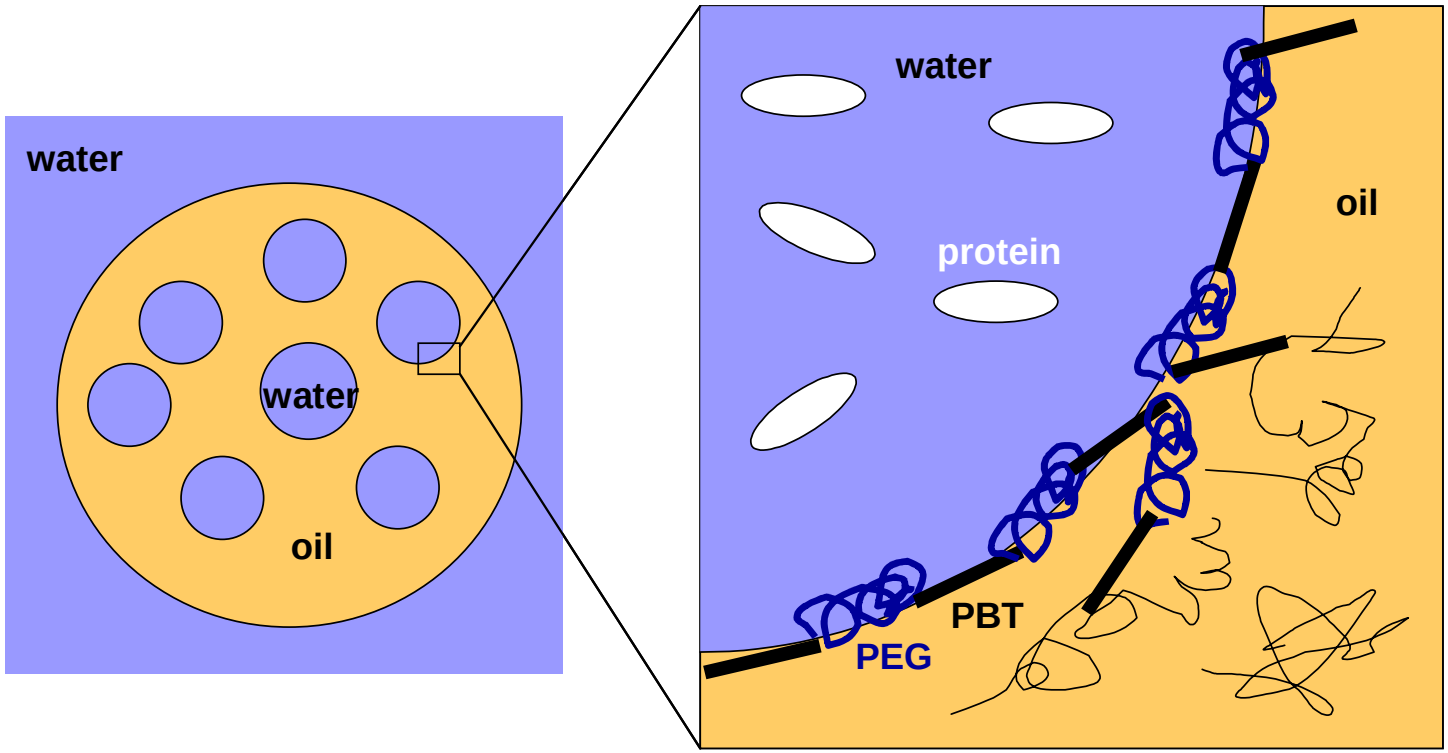
IFNa2b in PolyActive microspheres

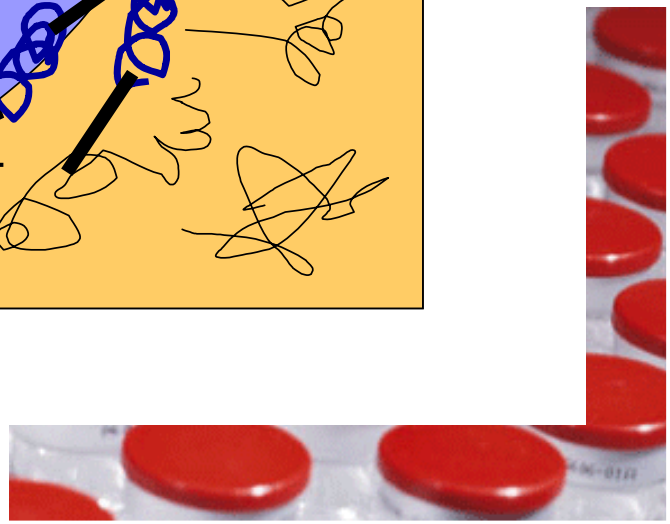
PolyActive™ technology

- Delivery system for controlled release of therapeutic proteins, peptides and lipophilic small molecules.
- Based on hydrogel microspheres, films, rods, gels.
- Prolonged efficacy of single injection, up to several months release of drugs
- Steady-state drug levels

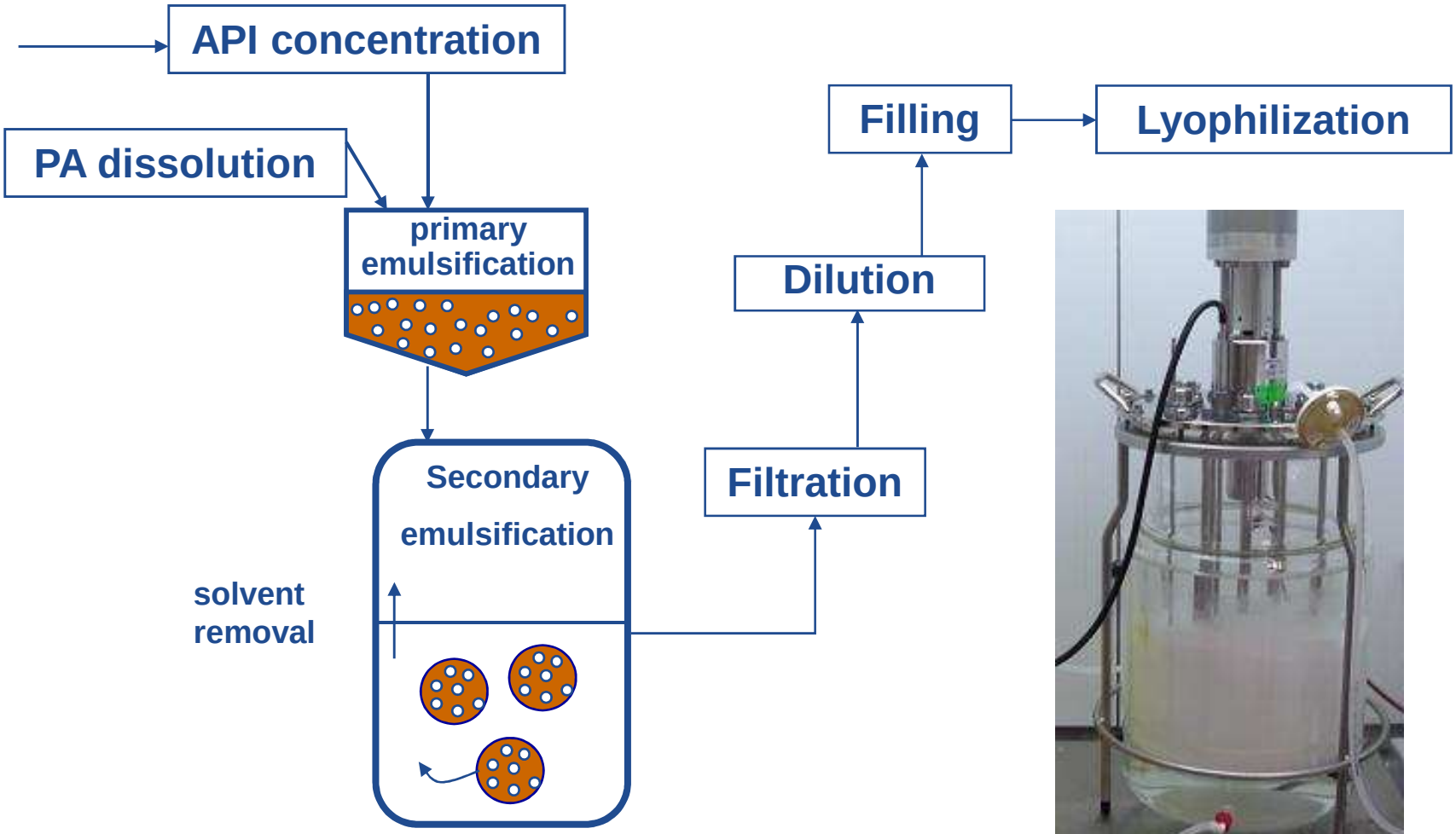
Water-in-oil-in-water emulsion

Protection of labile proteins by the amphiphilic nature of the multiblock copolymers



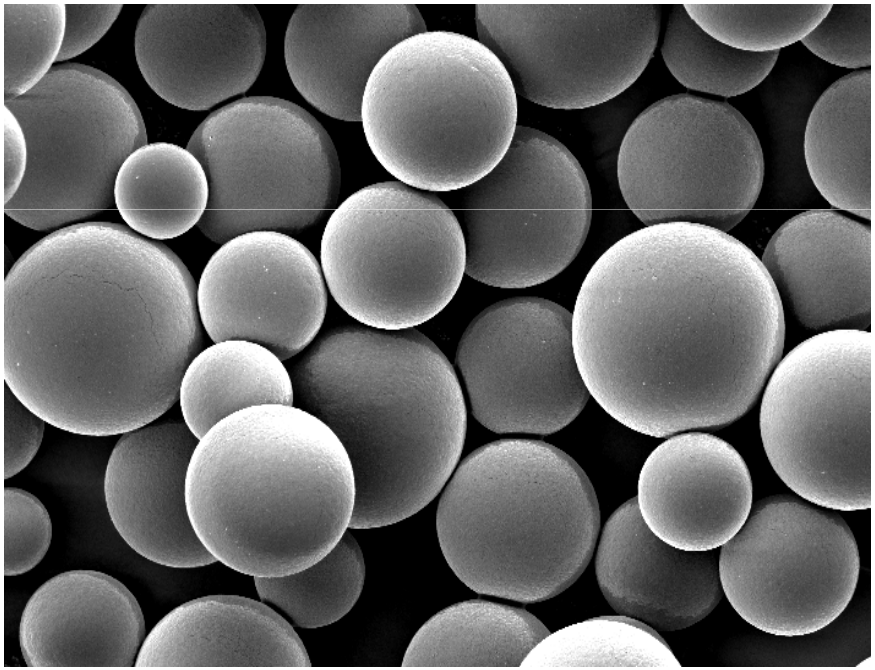


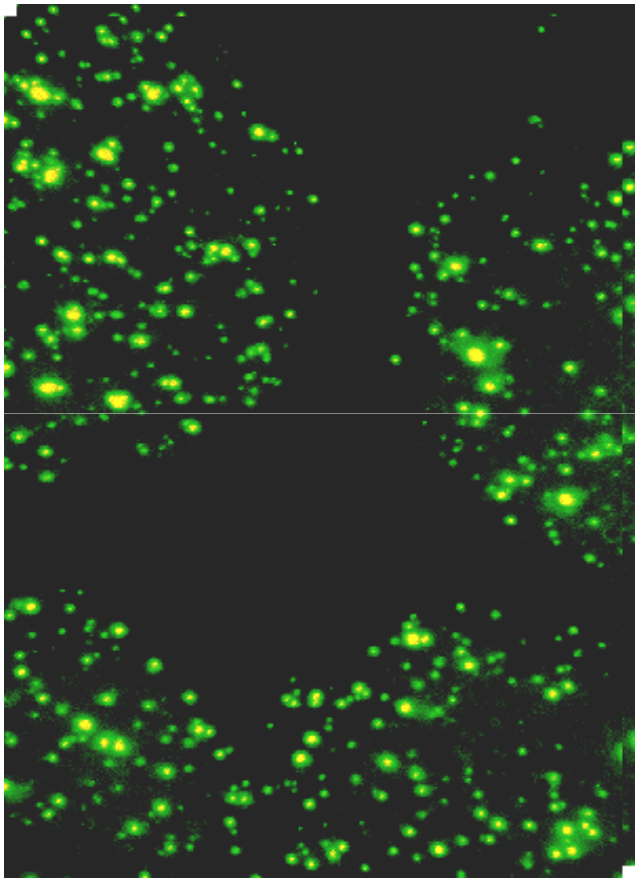
Microsphere double emulsion process

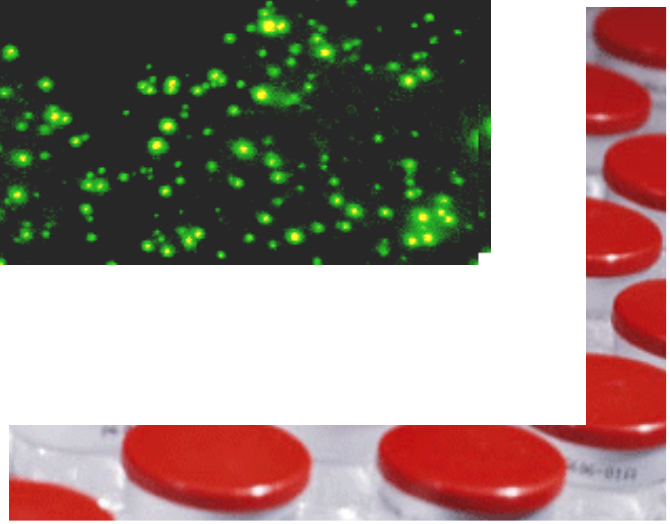


PolyActive™ microspheres morphology

Distribution of FITC labeled lysozyme

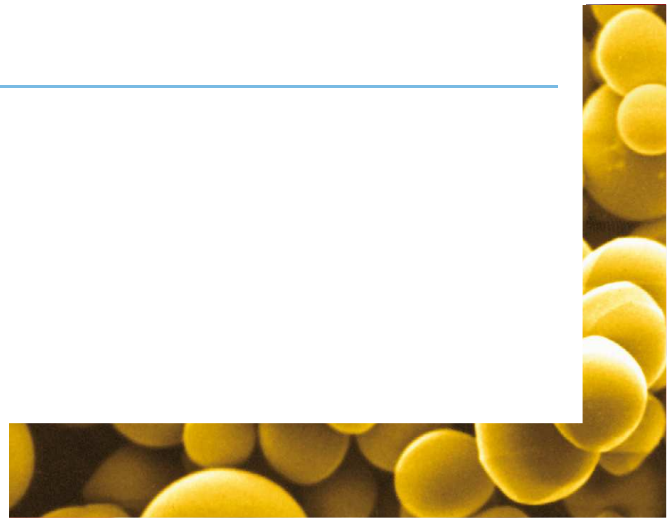




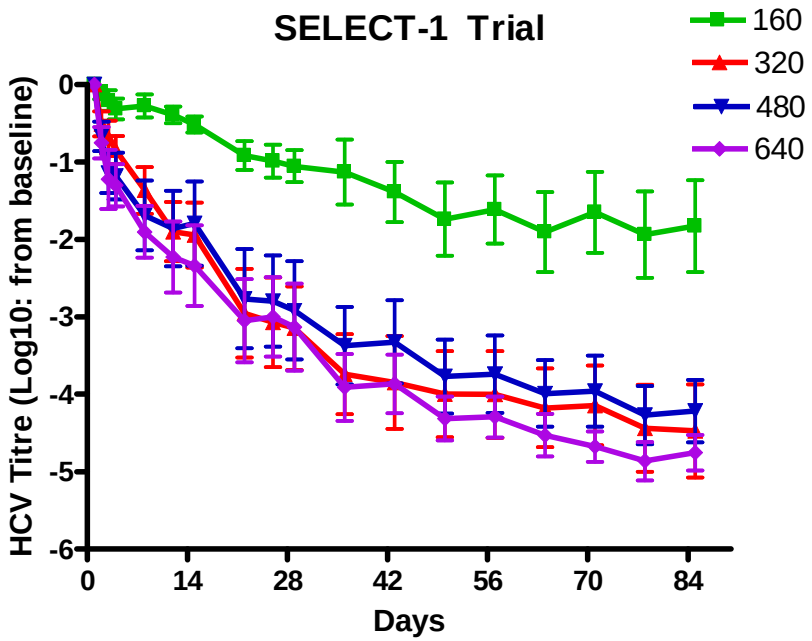


Locteron SELECT-1 phase IIa clinical study

Design	+ 32 patients, chronic HCV infection, genotype-1, treatment naive + Four doses of Locteron (160, 320, 480 and 640 µg) administered once every two weeks for 12 weeks + Weight-based ribavirin administered twice daily at standard doses for HCV
Objective	+ Assess safety of Locteron at four doses, including two doses higher than those studied in Phase I + Assess impact of Locteron on HCV RNA levels
Status	+ Study completed



Efficacy and safety of controlled release biosimilar IFNa2b



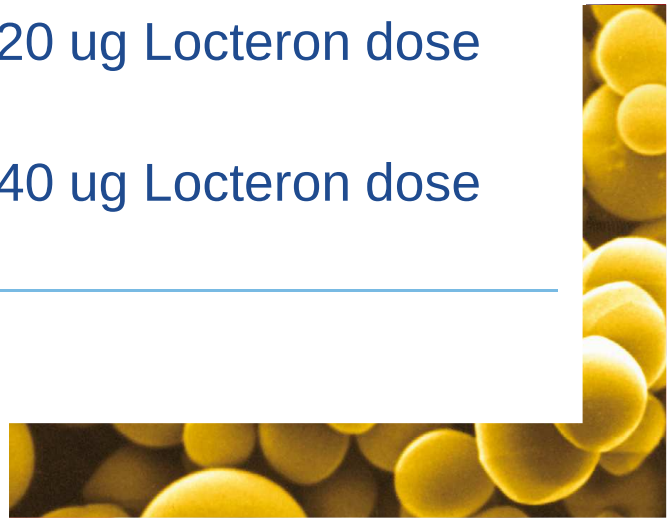
+ Preliminary data showed good tolerability
+ ~ 90% of adverse events were rated as mild

+ Early Virological Response rates of up to 100%

- RVR: Rapid Viral Response: HCV RNA negative at 4 weeks
- EVR: Early Viral Response: HCV RNA drop by at least 2 logs from baseline
- 12-Wk Neg: HCV RNA negative after 12 weeks of treatment
- Negative HCV RNA: level below 28 IU/mL

Locteron demonstrated improved safety profile in clinical studies

Phase I	+ Locteron is safe and well tolerated at all doses tested + Gradual release and sustained plasma levels of active interferon for 14 days after single injection + Flu-like symptoms fewer, less severe and of shorter duration compared with PEG-Intron
Phase II	+ Very low incidence of fever and severe adverse events observed in two clinical studies + Over 90% of Locteron side effects were rated mild
Comparison to CSOC	+ 80% less flu-like side effects for 320 ug Locteron dose compared to PEG-Intron + 30% less flu-like side effects for 640 ug Locteron dose compared to PEG-Intron



Summary

- Fierce competition in biosimilar field
- Need for modified products that provide competitive advantage
- Controlled release formulations can be a solution
- Additional market exclusivity can be obtained for new products
- Clinical studies will most likely be needed for biosimilars and are surely needed for controlled release formulations of biosimilars

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Thank you for your attention!

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