

Insulin Detemir, Certolizumab PEGOL & Others

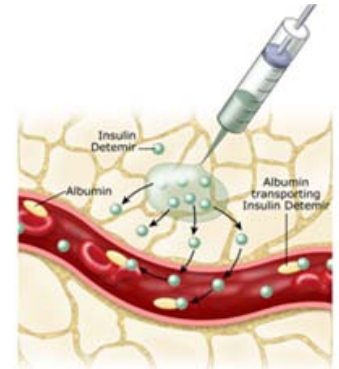
Technology from the group of Natasa Skoko
at **International Centre for Genetic Engineering and
Biotechnology, Trieste, Italy**



About Insulin Detemir

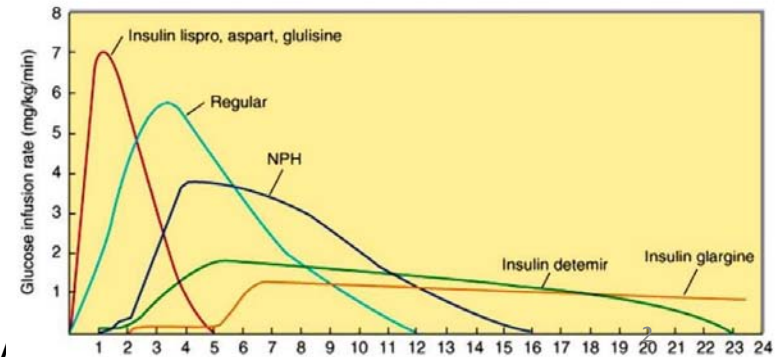
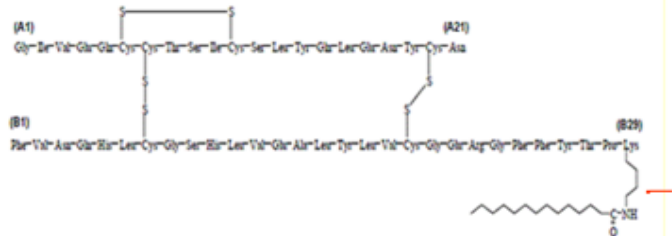
Insulin detemir is a **long-acting** (up to 24-hour duration of action) recombinant **human insulin analog**.

- **Originator / reference product:** Long lasting insulin analogues Detemir (Novo Nordisk's Levemir[®], the **patent expired in 2019 in US**. (Source: [Novo Nordisk Annual Report](#))
- **Indications:** Treatment of **Type 1 and 2 Diabetes Mellitus**



Detemir
[LysB29-tetradecanoyl, des(B30)]human insulin
once-daily administration

Detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted and a C14 fatty acid chain has been attached to the side chain of amino acid B29Lys.



Market and Industry Overview

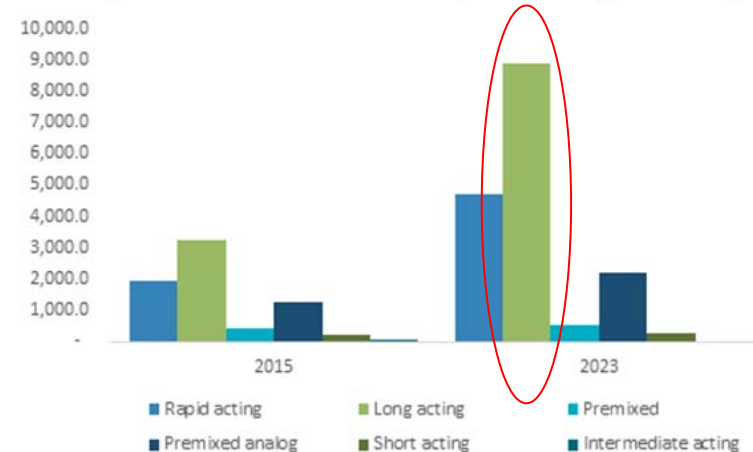
Market:

The global basal insulin market (Detemir, Glargine and Degludec) is expected to register **a CAGR of 8.2% during the forecast period of 2019–2024**, the market is estimated to reach **\$11.4 billion by 2019**. (Source: [Research and Markets](#))

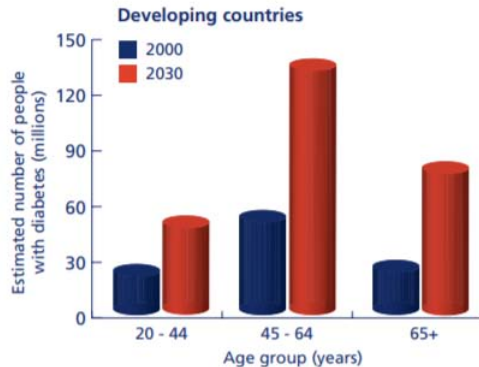
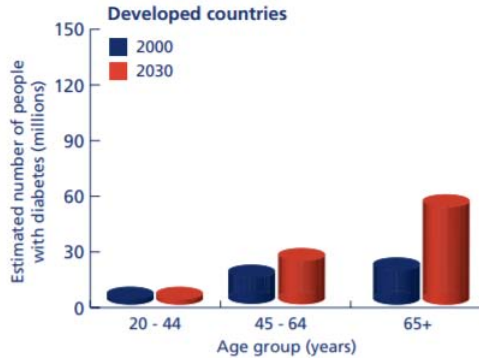
Industry players:

- **Global:** Novo Nordisk, MNKD, Bristol-Meyer Squibbs, Emisphere
- **India :** Biocon

Europe insulin antidiabetics market size, 2015 & 2023, (USD Million)



The Opportunity: Why you should be interested?



Estimated number of adults with diabetes.

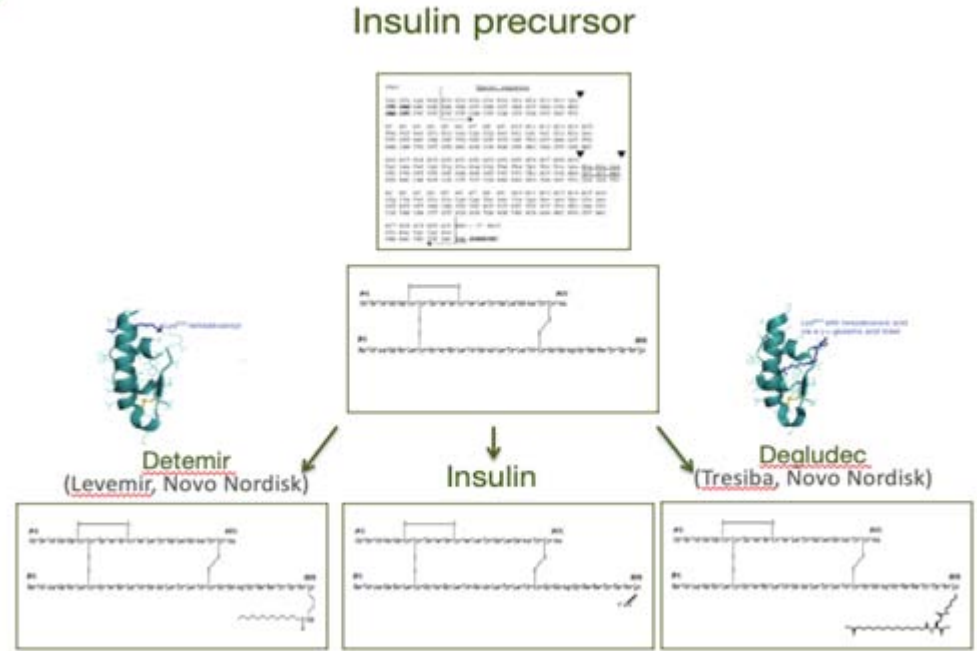
- **Market interesting: A rising global burden:** According to World Health Organization (WHO), the number of people with diabetes will more than double over the next 25 years, to reach a **total of 366 million by 2030**. Most of this increase will occur as a result of a **150% rise in developing countries**. (Source: [WHO](#))
- **Cost still high:** Levemir (Insulin Detemir) treatment (taken once a day) costs around **\$500/month** and annual cost of treatment is around **\$6,000 (very high, if it is to be taken for a lifetime)**. Insulin Detemir is to be taken for a lifetime.
- **Industry not yet crowded: Few players** manufacturing long acting insulins

The Technology Offering

Insulin precursor

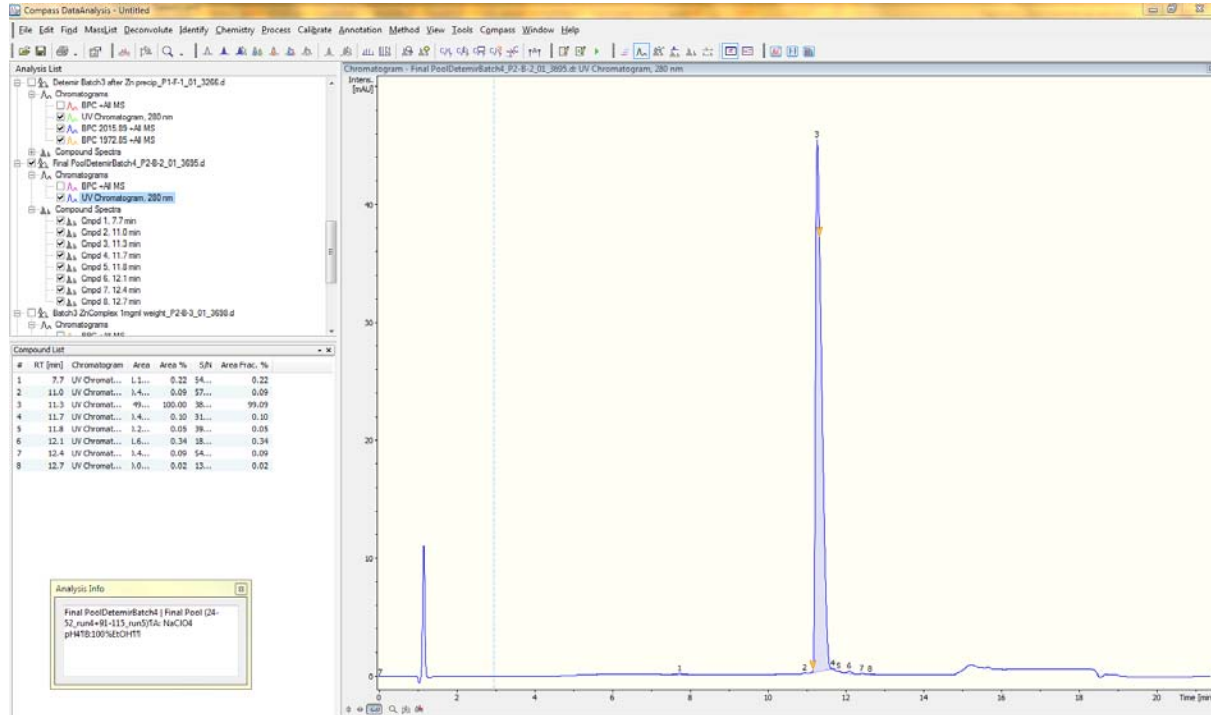


- Insulin precursor is produced in the yeast *Pichia pastoris*.
- From the insulin precursor we developed three technologies: **short lasting insulin and two long-lasting insulins (detemir and degludec)**.
- **Yield** of Insulin precursor: **3-4 g/L**



Selected Data: Biosimilarity- Physicochemical characterization

RP-HPLC analysis: The purity of purified Detemir pool is **> 98%**

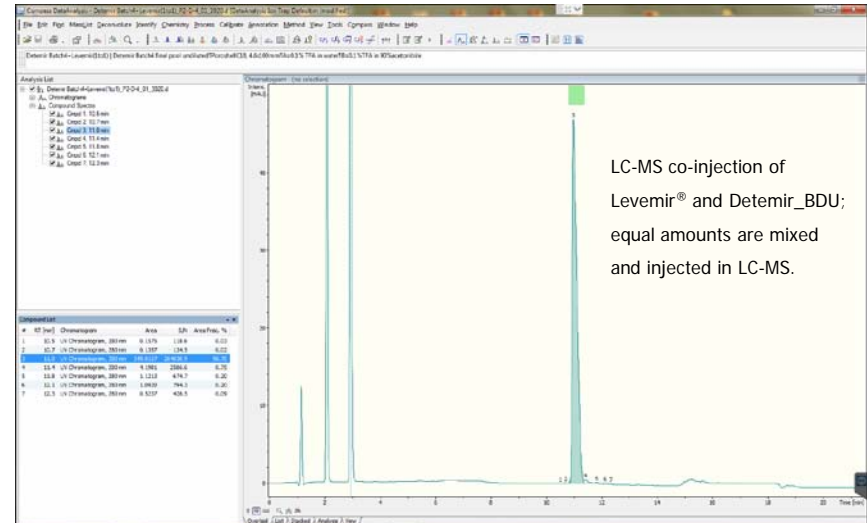
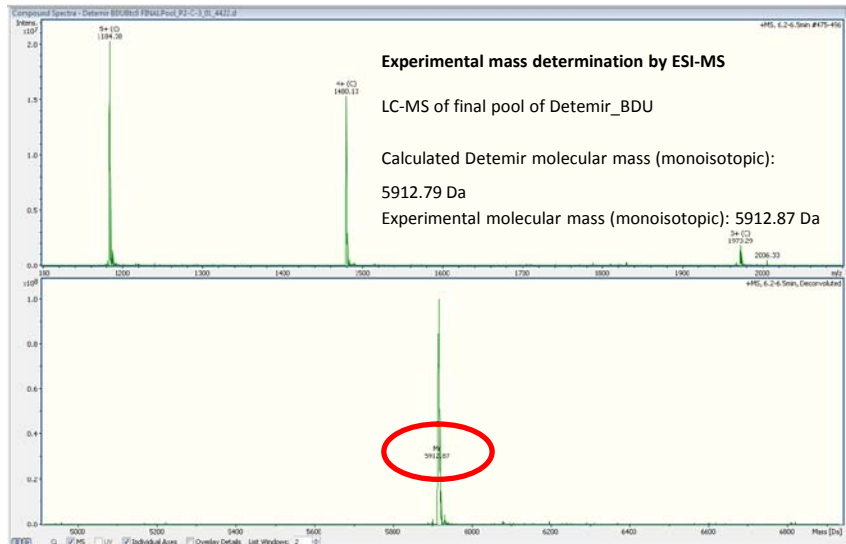


Selected Data: Biosimilarity - Intact mass analysis

Biosimilarity - Intact mass analysis and co-injection with originator

LC-MS with full protein MS: Electrospray Mass Spectrometry **confirms the correct molecular mass of Detemir.**

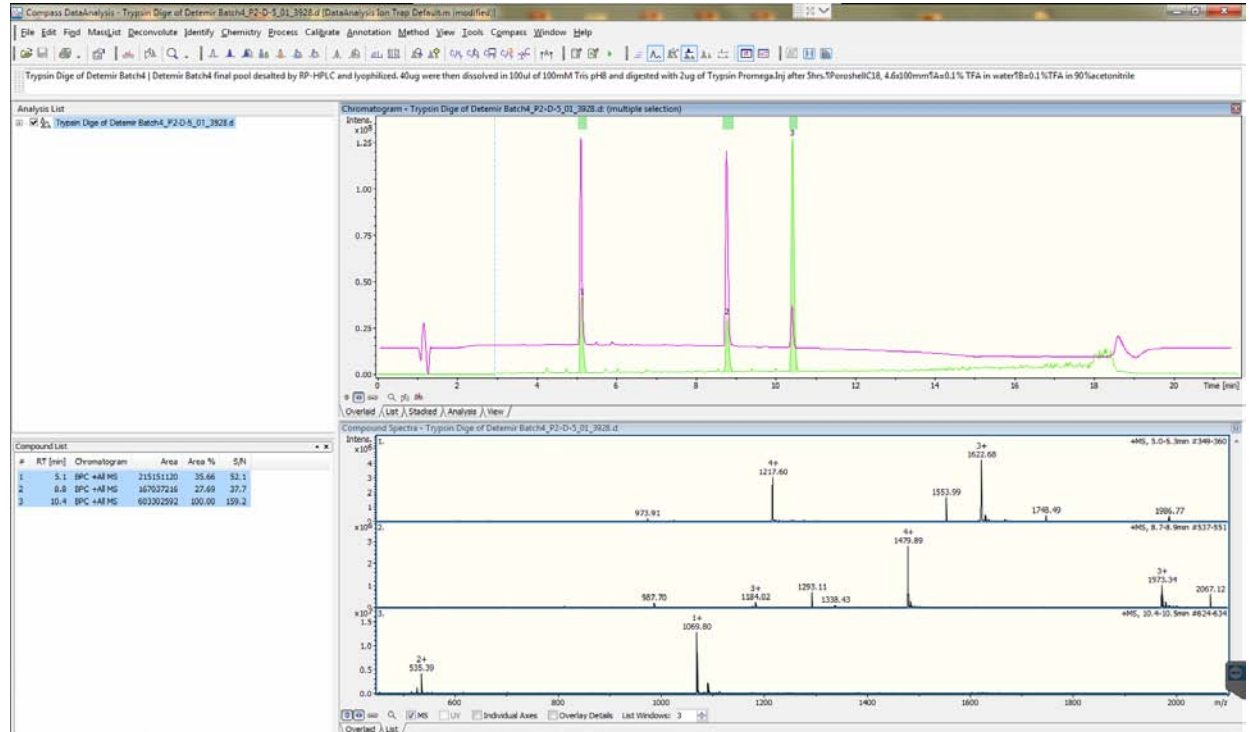
LC-MS co-injection of Levemir[®] and Insulin Detemir_BDU confirms **that Detemir BDU has the same Retention Time as commercial Levemir[®]**



Selected Data: Biosimilarity- Peptide mapping

Biosimilarity - Peptide mapping

Determination of site of fatty acid attachment: experimental peptide mapping (trypsin digestion) corresponds to the theoretical one and demonstrates the site of fatty acid attachment in B29 Lys.



Selected Data-Insulin Precursor production and Detemir preparation

Production: 10L fermentation (5 day methanol induction) **yields around 30-40 g of Insulin precursor.**

Purification:

- **Preparation of desb30:** DesB30 by protease digestion of **recombinant Human Insulin Precursor** is performed at 2.3 grams scale with the yield of at least 50%
- **Preparation of linker:** Preparation of Tetradecanoic acid 2,5-dioxo-pyrrolidin-1-yl active ester linker (Myr-OSu) is performed at 10 grams scale with the yield of at least 60%
- **Synthesis and detemir purification:** Attachment of Myr-OSu linker to DesB30 **Human Insulin (1.5 gram scale) is performed to obtain Insulin Detemir.** Preparative RPHPLC separation/purification of **Detemir yields at least 20% in respect to recombinant Human Insulin Precursor.**

Current Status of Technology and Path Ahead

Stage of Development

- Protein expressed in 10L bioreactor.
- Achieved yield of **30-40 g (Insulin precursor) in 10L bioreactor.**



Development of Hypotheses and Experimental Designs

Non-clinical *in-vitro* studies: Physicochemical characterization for Biosimilarity

Non-clinical *in-vitro* studies: Functional characterization for Biosimilarity

Non-clinical animal studies: toxicity, PK/PD, immunogenicity

Generation of three consistent batches. Formulation development. Approvals for preclinical candidate compound from the relevant body.

Clinical studies: PK, PD, Immunogenicity

Regulated Production, Regulatory Submission

Scale-up, Completion of GMP Process Validation and Consistency Lot Manufacturing and Regulatory Approvals.

Clinical Trials Phase 3 and Approval or Licensure

What are we seeking?

Technology ready to transfer on non-exclusive basis. Transferred to different entities from China, South Africa, Bangladesh and Iran so far.

We offer TT package and training in-house or video-based training.

PHASE1

- Scientists from the Company spend **4-6 weeks** in the ICGEB Laboratories gaining hands-on experience in the production of selected technologies OR **video-based training** and online technical assistance.

- Supply of **Protocols** describing process for the development of cell lines and complete down and upstream procedures and QC

PHASE 2

- Post training **assistance** to the industrial partner in establishing the process at its own facility

Dr Natasa Skoko's Group: Biotechnology Development Unit



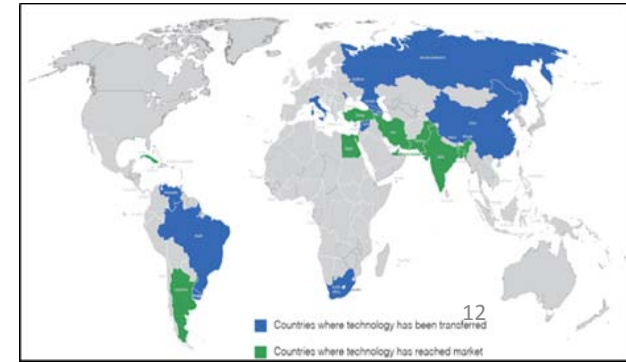
Lead Scientist: Dr Natasa Skoko

Group Leader, Biotechnology
Development Unit, ICGEB, Italy

Member and reviewer, Women in
Science in the Developing World

Expertise: Production of biologics in
bacteria, yeast and mammalian cells,
bioprocessing operations such as
upstream, downstream and quality
control analysis following European
Pharmacopoeia monographs

- ◆ **Key assets and strengths of Dr Skoko's Lab:**
 - ◆ **Authored more than 20 publications** in her areas of expertise
 - ◆ Team strength: 8
 - ◆ Well equipped labs and analytical facilities
 - ◆ Microbial and mammalian cell line facility
 - ◆ Downstream processing, chemical lab and **QC lab**
 - ◆ **Clean rooms in Class C and D**
 - ◆ Industry Project /Tech transfer
 - ◆ More that 25 years of experience in the field of biologics/biosimilars, **more than 70 technology transfer agreements with companies**
 - ◆ Companies from 22 countries, more than 100 scientists trained in our lab



For more information contact:

Case Manager:

Pradnya Aradhya
pradnya@venturecenter.co.in
+91-88050-09010

Lead Scientist:

Dr. Natasa Skoko
skoko@icgeb.org
www.icgeb-bdu.org

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