EP701

BATCH-TO-BATCH CONSISTENCY OF A HIGHLY O-GLYCOSYLATED LONG-ACTING hGH (MOD-4023)

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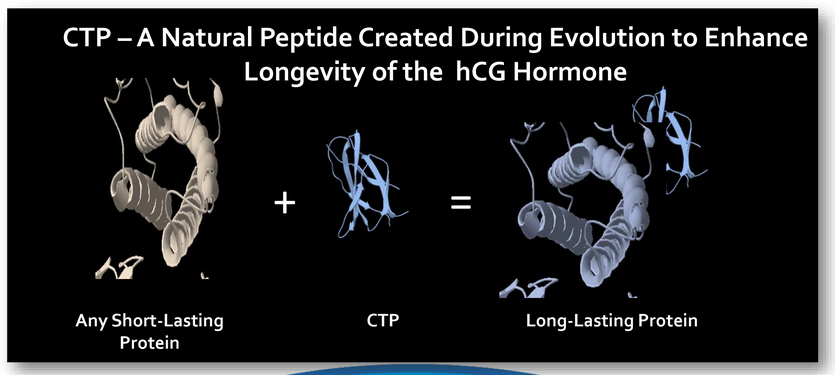
Introduction

- OPKO Biologics is a clinical stage company developing biobetter long acting versions of existing therapeutic proteins utilizing a technology called CTP.
- Almost all available recombinant human growth hormones (hGH), being a non-glycosylated protein, are manufactured in E-coli. In order to develop a long acting CTP-hGH (MOD-4023) with proper
- O-glycosylation of the CTP portion, the objective was to develop a highly-producing upstream manufacturing process of MOD-4023 by recombinant DNA technology using CHO cells in a chemically defined medium, followed by robust and scalable downstream process purifying the highly glycosylated protein.



Objectives

The objective of the study was to develop a highly O-glycosylated drug product with respect to protein quality attributes, process reproducibility, and batch-to-batch consistency.

Methods

The consistency of MOD-4023 glycosylation was tested by applying various analytical methods:

- O-glycan and sialic acid analysis by HPLC
- Capillary Zone Electrophoresis (CZE)
- Isoelectric Focusing (IEF)

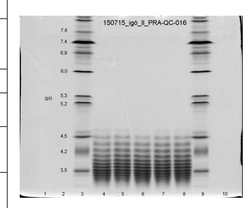
MOD-4023 potency was assessed in vitro by a cell-based assay (CBA), utilizing cells that stably express the human growth hormone receptor (GHR).

Results

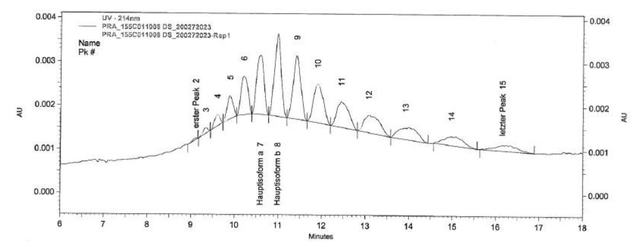
- Similar O-glycan and Sialic Acid contents were obtained in various MOD-4023 batches, supporting the consistency of the drug substance glycosylation profile in each batch.
- Several batches of MOD-4023 had shown similar levels of binding and activation of the human GHR as assessed by the CBA

	GMP-1	GMP-2	GMP-3	GMP-4	GMP-5	GMP-6	GMP-7	GMP-8
Sialic Acid (mol/mol)	14.0	15.1	14.4	13.1	15.1	14.4	14.4	13.6
%CV	1.9	-5.5	-0.95	8.9	-5.5	-0.9	-0.9	4.9
O-Glycan (mol/mol)	13.2	13.0	12.1	12.1	12.6	12.6	13.3	12.8
%CV	-3.7	-2.2	5.0	5.0	0.9	0.9	-4.4	-0.7
CBA (% relative potency)	0.8	0.9	1.1	1.1	0.9	1.2	1.4	1.1

A representative IEF gel containing two different batches and stability samples

	Sample	[µg/ Sample]	Colloidal Blue
1	DDW	-	
2	DDW	-	
3	Serva IEF Marker pH 3-10	N/A	
4	MOD-4023 Reference Standard	10	
5	DP (GMP-8)	10	
6	DS GMP-2_-70 °C 36 Months	10	
7	DS GMP-8_-70 °C 3 Months	10	
8	DS GMP-8_5 °C 3 Months	10	
9	Serva IEF Marker pH 3-10	N/A	
10	DDW	-	

A representative CZE chromatogram of a single batch conforms to Reference Standard



- Comparable results for across various batches were also obtained using both CZE and IEF analysis

Conclusions

- A robust manufacturing process was developed for the production of MOD-4023.
- Critical quality attributes show a high batch-to-batch consistency.
- The process target the manufacturing and purification of a highly O-glycosylated product supporting the extended half-life of MOD-4023

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