GAZYVA®/ GAZYVARO™ -
The Success Story of a Glycoengineered Antibody

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# The Molecule

| **Tradename** | GAZYVA® (US, other countries)  
|               | GAZYVARO™ (EU, Switzerland) |
| **INN, other names** | Obinutuzumab, GA101 |
| **Molecule Type** | Recombinant, humanized, monoclonal Type II glycoengineered anti-CD20 antibody (IgG1) |
| **Indications** | • chronic lymphocytic leukemia (CLL)  
|               | • indolent non-Hodgkin’s lymphoma (iNHL)  
|               | • diffuse large B-cell lymphoma (DLBCL) |
| **Start of clinical trials** | Sept 2007 |
| **First market approvals (CLL)** | 01 Nov 2013 (US)  
|               | Approved in EU, Switzerland, Canada, Australia, South Korea, others |
Obinutuzumab Molecule

Obinutuzumab is a Glycoengineered Type II Antibody with a Unique Mode of Action

Glycoengineering (GlycoMAb™ Technology)

• Co-transfection of genes encoding for the antibody with genes encoding for glycosylation-modifying enzymes

• Glycosylation-modifying enzymes:
  – GnTIII (N-acetylglcosaminyltransferase III)
  – ManII (α-Mannosidase II)

• Co-expression of the antibody with glycosylation-modifying enzymes during cell culture

→ Modified glycosylation pattern with reduced levels of core-fucosylation

→ Increase in antibody-dependent cell-mediated cytotoxicity (ADCC)
Biosynthesis of Glycosylation - Pathway

Endoplasmic Reticulum
- Oligosaccharyl transferase
- α-glucosidase I
- α-glucosidase II
- ER α-MAN

Golgi
- α-MAN I
- GnT I
- UDP
- α-MAN II
- GnT II
- UDP
- Fucosyltransferase
- GDP

△ Glc
○ Man
★ GlcAc
▲ Fuc
■ NANA
♦ NGNA
◊ Gal

NANA:NGNA ratio can vary:
Glycostructures – “Normal antibody”

G0

G1*

G2

G0-GlcNac

G0-Fuc

G1-Fuc

Man5

Gal2-NANA

G1, α-1-3 linked antenna (* isobaric structures)

G1, α-1-6 linked antenna
Glycostructures – “Glycoengineered Antibody”

Isobaric structures:

- **Hyb_bMan4G1-Fuc**
- **G2-Fuc**
Obinutuzumab Exhibits up to 100-fold Higher ADCC Potency than Rituximab and Ofatumumab

Herter et al., MCT, 2013
Obinutuzumab Mediates Increased Direct Cell Death Induction on a Panel of NHL Cell Lines

Mössner et al., Blood, 2010; Herter et al. Mol Canc Ther, 2013
Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

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Abstract

The monoclonal anti-CD20 antibody rituximab, combined with chemotherapeutic agents, has been shown to prolong overall survival in physically fit patients with previously untreated chronic lymphocytic leukemia (CLL) but not in those with coexisting conditions. We investigated the benefit of the ty2,2 glycoengineered antibody obinutuzumab (also known as GA101) as compared with rituximab, each combined with chlorambucil, in patients with previously untreated CLL and coexisting conditions.

Methods

We randomly assigned 781 patients with previously untreated CLL and a score higher than 6 on the Comorbidity Index Risk Score (CRS) (range, 0 to 56; with higher scores indicating worse health status) or an estimated creatinine clearance of 30 to 69 ml per minute to receive chlorambucil, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. The primary end point was investigator-assessed progression-free survival.

Results

The patients had a median age of 73 years, a creatinine clearance of 62 ml per minute, and a CRS score of 8 at baseline. Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil, as compared with chlorambucil monotherapy, increased response rates and prolonged progression-free survival (median progression-free survival, 267 months with obinutuzumab–chlorambucil vs. 111 months with chlorambucil alone; hazard ratio, 0.85; 95% CI, 0.74 to 0.98; P = 0.011). Treatment with obinutuzumab–chlorambucil, as compared with chlorambucil alone, prolonged overall survival (hazard ratio for death, 0.81; 95% CI, 0.63 to 0.93; P = 0.013). Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in prolongation of progression-free survival (hazard ratio, 0.79; 95% CI, 0.63 to 0.99; P = 0.031) and higher rates of complete response (20.7% vs. 7.9%) and molecular response. Infusion-related reactions and neutropenia were more common with obinutuzumab–chlorambucil than with rituximab–chlorambucil, but the risk of infection was not increased.

Conclusions

Combining an anti-CD20 antibody with chemotherapy improved outcomes in patients with CLL and coexisting conditions. In this patient population, obinutuzumab was superior to rituximab when each was combined with chlorambucil. (Funded by Roche.)

This article was published on January 8, 2014, at NEJM.org.
Obinutuzumab Versus Rituximab in CLL: Progression-free Survival

Obinutuzumab for first-line treatment of CLL in combination with chlorambucil approved by the FDA as GAZYVA® on 1 November 2013 based on stage 1a data: G-Clb vs Clb and by Swissmedic and EMA 2014 as GAZYVARO™ based on stage 2 data: G-Clb vs R-Clb

Regulatory Status for CLL Indication

- Orphan drug status has been granted in several countries (e.g., USA, EU, Switzerland, South Korea)
- Breakthrough Designation was granted in US (May 2013)
- Approval of Marketing Authorization:
  - 2013: US
  - 2014: EU, Switzerland, Canada, Australia, Mexico, South Korea, others
- Review of Marketing Authorization currently ongoing in many other countries
Technical Development of GAZYVA
Full Quality by Design (QbD) Approach

• A full Quality by Design (QbD) approach was used for technical development of GAZYVA for both, Drug Substance and Drug Product.

• Roche/ Genentech QbD tools were already used for development of other monoclonal antibodies

• GAZYVA has received approval for a process-wide Design Space (from FDA, EMA, Swissmedic, others)
What is Quality by Design (QbD) ?

ICH Q8: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

• Leverages knowledge of structure-function relationship to define product attributes that are important

• Uses science-based and risk-based approaches to define the commercial manufacturing process and the management of the post-approval lifecycle

• Aims at developing deeper product & process understanding throughout the lifecycle of a product
  - Control system tailored to product requirements
  - Process robustness enhanced
  - Deviation and change assessments facilitated
Quality by Design Tools and their Purpose

Systematic approach to Control System and Design Space

CQA Identification (RRF Tool)

Which attributes are critical?

CQA Acceptance Criteria Determination

Which levels are critical?

Attribute Testing Strategy (RRF Tool)

What should be tested?

Attribute Testing Strategy Robustness

Do we have the right tests?

Risk Assessments for Process Parameters

Which parameters should be studied?

Multivariate & Univariate PC/PV Studies

How does the process impact the CQAs?

Linkage Studies of Worst-Case Conditions

How robust is the overall process?

CPP Identification and Design Space Definition

Which parameters need to be controlled?

RRF: Risk ranking and filtering; PC/PV: process characterization/process validation
The Roche Quality by Design Workflow

- **Critical Quality Attribute (CQA) Identification (RRF Tool)**
  - What should be measured?

- **CQA Acceptance Criteria Determination**
  - What levels?

- **Attribute Testing Strategy (RRF Tool)**
  - What should be tested?
  - What is critical?

- **Attribute Testing Strategy Robustness**
  - Do we have the right tests?

- **Process Characterization (PC/PV Study Design RRF)**
  - What parameters should be studied?

- **Design of Experiments & Univariate Studies**
  - How does the process impact the CQAs?

- **Linkage Studies of Worst-Case Conditions**
  - How robust is the overall process?

- **CPPs Identification & Design Space Definition**
  - What is critical?

*QbD provides a systematic approach to answer these questions*
What are Potential Critical Quality Attributes for a Monoclonal Antibody?

ICH Q8 R1: **Critical Quality Attributes - Link Directly to Patient Safety & Efficacy**

A physical, chemical, biological or microbiological property or characteristic that should be within an **appropriate** limit, range, or distribution **to ensure the desired product quality**.
# Critical Quality Attributes (CQAs)

## Categorization

<table>
<thead>
<tr>
<th>Category of Attribute</th>
<th>Assessment</th>
<th>Rationale for Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Variants</td>
<td><strong>Risk Ranking and Filtering</strong></td>
<td>Impact to patient safety and product efficacy is specific to variant in question, mechanisms of action, route of administration, etc.</td>
</tr>
<tr>
<td>Process-related impurities</td>
<td><strong>Risk Ranking and Filtering</strong></td>
<td>Clinical data from similar products can be used to assess safety</td>
</tr>
<tr>
<td>Composition and Strength</td>
<td>Obligate CQA</td>
<td>Potentially high impact to safety and efficacy</td>
</tr>
<tr>
<td>Adventitious Agents</td>
<td>Obligate CQA</td>
<td>Potentially high impact to safety</td>
</tr>
<tr>
<td>Raw Materials</td>
<td><strong>Compare Estimated Daily Intake and Acceptable Daily Exposure</strong></td>
<td>Extensive data available from safety and toxicity studies</td>
</tr>
</tbody>
</table>
The Roche Quality by Design Workflow

Critical Quality Attribute (CQA) Identification (RRF Tool)
- What should be measured?

CQA Acceptance Criteria Determination
- What levels?

Attribute Testing Strategy (RRF Tool)
- What should be tested?
- Do we have the right tests?
- Does the process control this? Is it stable?

Attribute Testing Strategy Robustness

Process Characterization (PC/PV Study Design RRF)
- What parameters should be studied?

Design of Experiments & Univariate Studies
- How does the process impact the CQAs?

Linkage Studies of Worst-Case Conditions
- How robust is the overall process?

CPPs Identification & Design Space Definition
- What is critical?
Attribute Testing Strategy (ATS) – A Major Component of the Overall Control Strategy

CQAs are defined
Acceptable levels determined
Evaluation of residual risk of process and stability to stay in AC defines testing strategy

ATS RRF
Control System
Monitoring
No Testing
Robustness assessment

CQA RRF
CQA-AC definition

Residual risk to be outside CQA-AC
Low risk to be outside CQA-AC
Lowest risk to be outside CQA-AC

Process impact/stability impact
The Roche Quality by Design Workflow

Critical Quality Attribute (CQA) Identification (RRF Tool)
- What should be measured?

CQA Acceptance Criteria Determination
- What levels?

Attribute Testing Strategy (RRF Tool)
- What should be tested?

Attribute Testing Strategy Robustness
- Do we have the right tests?

Control System

Process Characterization (PC/PV Study Design RRF)
- What parameters should be studied?

Design of Experiments & Univariate Studies
- How does the process impact the CQAs?

Linkage Studies of Worst-Case Conditions
- How robust is the overall process?

CPPs Identification & Design Space Definition
- What is critical?
Control System for GAZYVA® Drug Substance

<table>
<thead>
<tr>
<th>Testing of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Potency by Bioassay</td>
</tr>
<tr>
<td>Clarity/Opalescence</td>
<td>Identity</td>
</tr>
<tr>
<td>pH</td>
<td>Purity by SE-HPLC, CE-SDS, IE-HPLC</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Glycosylation (e.g., Afucosylation)</td>
</tr>
<tr>
<td>Content of Excipients</td>
<td>Bioburden</td>
</tr>
<tr>
<td>Content of Protein</td>
<td>Bacterial Endotoxins</td>
</tr>
</tbody>
</table>

- Obligatory testing is implemented
- Testing is based on the residual risk of attributes to stay within acceptance criteria:
  - In case of residual risk: attribute is tested and specified
  - Testing may differ between release and stability
## Testing of

<table>
<thead>
<tr>
<th>Physical State</th>
<th>Identity</th>
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</thead>
<tbody>
<tr>
<td>Color</td>
<td>Purity by SE-HPLC, IE-HPLC</td>
</tr>
<tr>
<td>Clarity/Opalescence</td>
<td>Potency by Bioassay</td>
</tr>
<tr>
<td>Extractable Volume</td>
<td>Content of Protein</td>
</tr>
<tr>
<td>Particles (visible, subvisible)</td>
<td>Sterility</td>
</tr>
<tr>
<td>pH</td>
<td>Bacterial Endotoxins</td>
</tr>
<tr>
<td>Osmolality</td>
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Overall Commercial Control Strategy

The overall commercial control strategy covers different aspects:

• allowed ranges for CQAs and process parameters
• control of materials
• GMP controls
The PALM Plan describes how process parameters and CQAs are monitored during product lifecycle.

The PALM Plan describes how changes are managed in the Quality Management System.
Benefits of Quality by Design

• QbD can be a highly effective global driver of change in the industry providing:
  – Enhanced level of product quality and process robustness
  – The foundation for continued improvement

• The work done to enable Design Space claims has clearly enhanced overall process robustness and product quality
  – More extensive evaluation of process impacts on CQAs
  – Driven DoE approaches to become “state of the art”
  – More systematic and inclusive identification of CPPs and non-CPPs
  – More rigor in developing the overall control strategies
  – More assurance that process is robust upon approval
  – More assurance of supply
  – Facilitates change - and deviation management
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…many others
Doing now what patients need next