# ABP 215 – Bevacizumab Biosimilar Candidate

## FDA Advisory Committee

13 July 2017

# Introduction

**Richard Markus, MD, PhD**

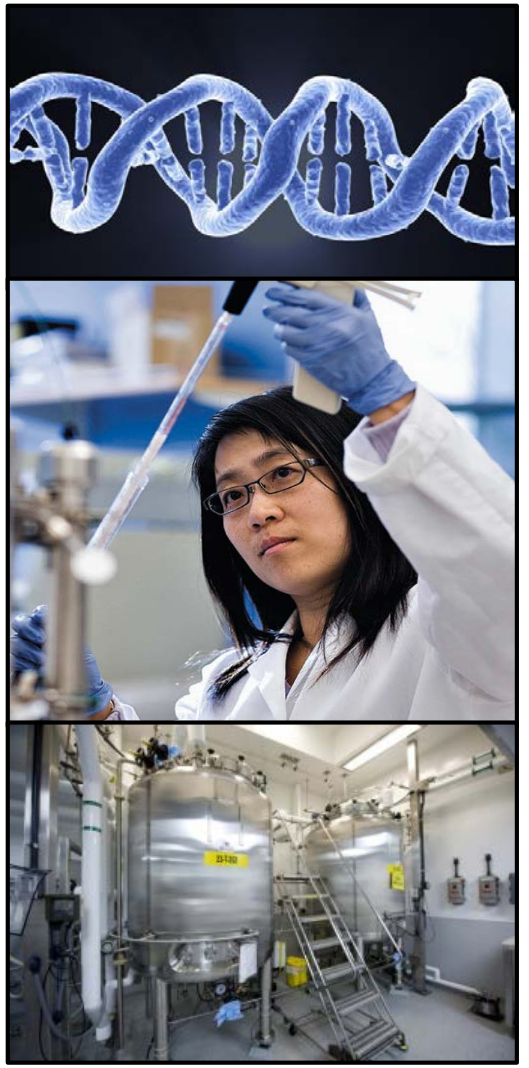
*VP Global Development, Amgen*

# Agenda

| | |
|---|---|
| **Introduction** | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| **Analytical Similarity** | **Simon Hotchin**<br>*Regulatory Affairs, Amgen* |
| **Non-Clinical and Clinical Similarity and Extrapolation to All Indications** | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| **Conclusion** | **Lisa Bollinger, MD**<br>*Regulatory Affairs and Safety, Amgen* |

# Amgen:  A Biotechnology Pioneer

- More than 35 years as innovative leader
- Capability to discover, develop, and manufacture complex biologics
- Broad pipeline of innovative medicines, and also biosimilars
- Same scientists and laboratories to develop our biosimilars
- Same manufacturing network and quality systems to produce our biosimilars

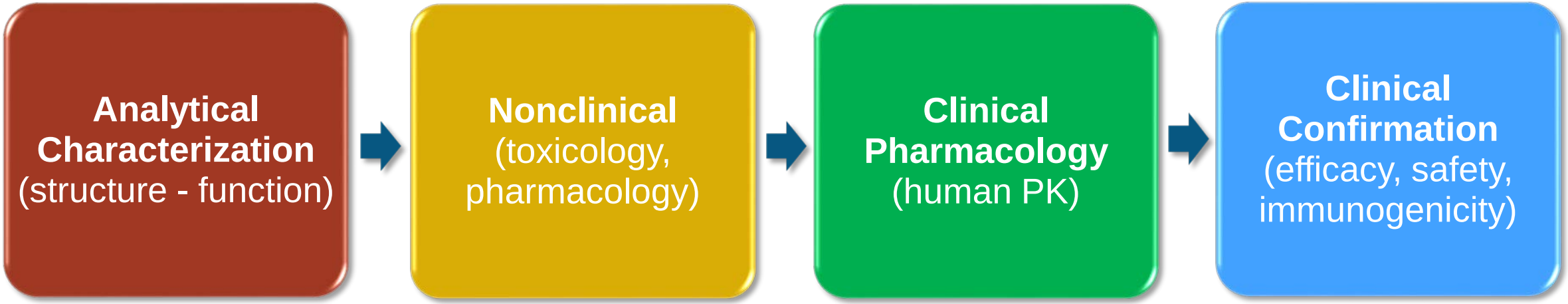


# Bevacizumab and ABP 215 Mechanism of Action

- VEGF is secreted by tumors
- Products bind and neutralize VEGF

# ABP 215 | A proposed biosimilar of bevacizumab

# Biosimilar Development and Approval Is Based on the Totality of Evidence



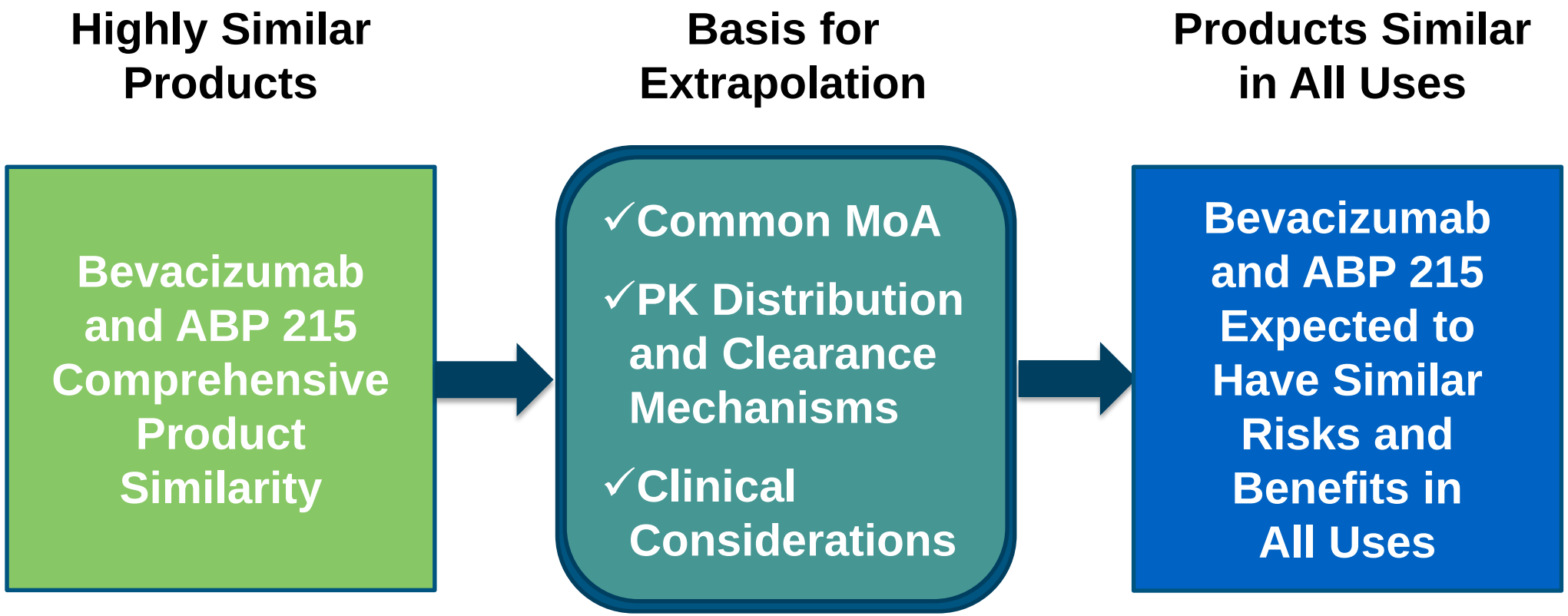

- **Same amino acid sequence and strength**
- **Equivalent potency**
- **Highly similar structure and function**

- **Similar toxicology**
- **Similar dose-response effect on tumors and vasculature**

- **Equivalent Pharmacokinetics (PK)**

- **Equivalent Efficacy**
- **Similar Safety**
- **Similar Immunogenicity**

# Biosimilar Extrapolation of Indications



# ABP 215 Proposed Indications of Use

- Nonsquamous Non-small Cell Lung Cancer
- Metastatic Colorectal Cancer
- Metastatic Renal Cell Carcinoma
- Glioblastoma
- Cervical Cancer

# Agenda

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# Analytical Similarity to Bevacizumab

**Simon Hotchin**

*Executive Director, Regulatory Affairs, Amgen*

# Overview

- **ABP 215 development**
- **Design of the analytical similarity assessment**
- **Analytical similarity results and conclusions**
  - Structural and purity attributes
  - Functional activities

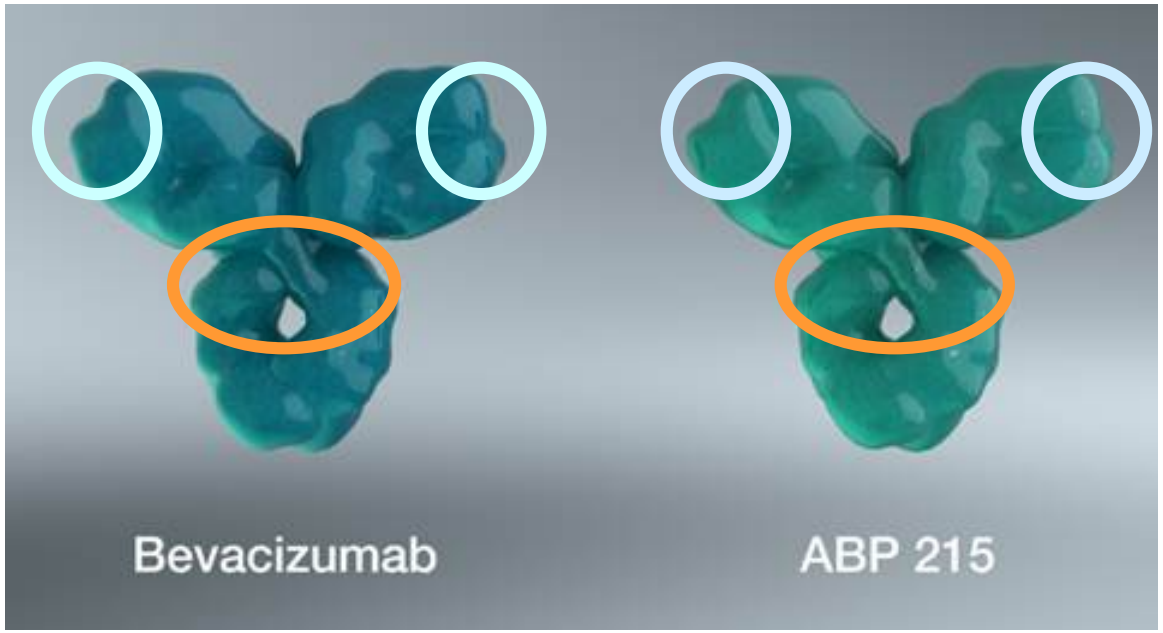
# ABP 215 Development

# ABP 215 Product and Process Design

- **Cell Line Development**
  - Amgen carefully designed the ABP 215 cell line, screening a large number of clones
  - Matched amino acid sequence and critical attributes of the reference product
- **Manufacturing Process and Formulation**
  - Process developed with multiple controls to ensure similarity
  - Commercial manufacturing process established at the outset of development
  - Drug product presentations and formulation match the reference product

# Design of the Analytical Similarity Assessment

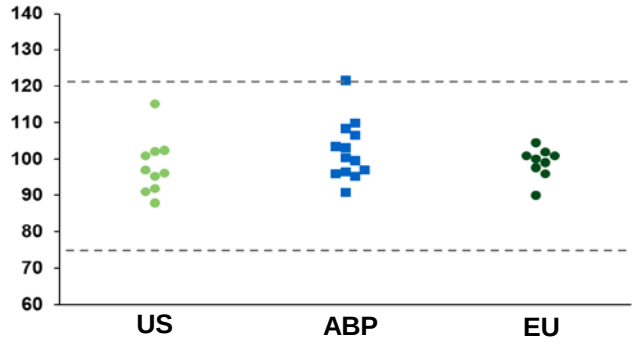
# Design Considerations: Fab and Fc Domain Characterization



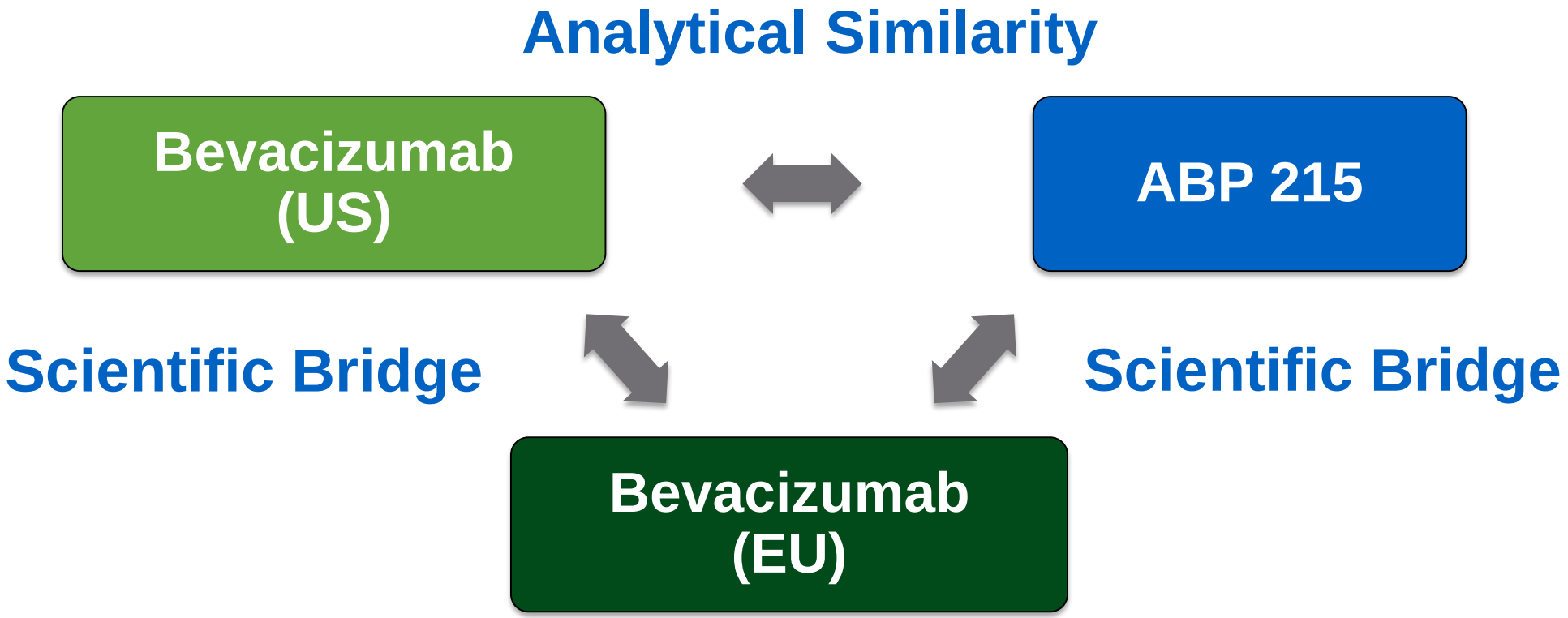

- The mechanism of action for ABP 215 and bevacizumab in all indications is to bind and neutralize VEGF
- The Fab domain binds all isoforms of VEGF

- The Fc domain binds Fc receptors, as well as complement component C1q in-vitro
- Fc-mediated effector functions do not occur for these products
- Tested for confirmation of structural similarity

# Design Considerations: Analytical Similarity Assessment Criteria

| Considerations and Criteria | Results |
|---|---|
| **Attributes with the highest risk to clinical outcomes and includes assay(s) that evaluate clinically relevant primary mechanism(s) of action**<br><br>**Similarity if 90% CI around difference in means is within ± 1.5 x SD of US reference product** |  <br>**EAC = equivalence acceptance criteria** |
| **Attributes with relatively lower risk to clinical outcomes**<br><br>**Similarity if at least 90% of the ABP 215 lots are within mean ± 3 x SD of the US reference product** |  |
| **Attributes with the lowest risk to clinical outcomes**<br><br>**Qualitative comparisons** | |

# Design Considerations: Establishing the Scientific Bridge




**Analytical and PK Similarity Data Established the Required Scientific Bridge**

# Analytical Similarity of ABP 215 to Bevacizumab Was Demonstrated for ~ 100 Attributes/Assays

| | Analytical Testing/Attributes |
|---|---|
| Biological Activity | Inhibition of proliferation in HUVEC |
| | Binding to VEGF by ELISA |
| | On and off rates (VEGF) |
| | Binding to VEGF isoforms |
| | Inhibition of VEGFR-2 RTK autophosphorylation |
| | Specificity for VEGF by VEGFR-2 RTK autophosphorylation |
| | FcRn binding |
| | FcγRIa binding |
| | FcγRIIa (131H) binding |
| | FcγRIIb binding |
| | FcγRIIIa (158V) binding |
| | FcγRIIIa (158F) binding |
| | FcγRIIIb binding |
| | C1q binding |
| | Lack of ADCC |
| | Lack of CDC |
| Primary Structures | Intact molecular mass |
| | Intact molecular mass; profiles |
| | Reduced and deglycosylated molecular masses of HC and LC |
| | Reduced and deglycosylated molecular masses of HC and LC; profiles |
| | Reduced peptide map |
| | Reduced peptide map; profiles |
| | Non-reduced peptide map |
| | Non-reduced peptide map; profiles |
| | Glycan Map; % high mannose |
| | Glycan Map; % galactosylation |
| | Glycan Map; % afucosylation |
| | Glycan Map; % sialylation |
| | Glycan Map; profiles |
| | Capillary isoelectric focusing: Isoelectric point |
| | Capillary isoelectric focusing: Profile |
| | Amino acid analysis/UV spectroscopy |
| | Identity by ELISA |

| | Analytical Testing/Attributes |
|---|---|
| Higher Order Structure | FTIR: Spectral similarity |
| | FTIR: Profile |
| | Near UV CD: Spectral similarity |
| | Near UV CD: Profile |
| | DSC: $T_m1$ |
| | DSC: $T_m2$ |
| | DSC: Profile |
| Particles and Aggregates | HIAC: ≥ 2 μm particles |
| | HIAC: ≥ 5 μm particles |
| | HIAC: ≥ 10 μm particles |
| | HIAC: ≥ 25 μm particles |
| | MFI: ≥ 5 μm particles |
| | MFI: ≥ 5 μm non-spherical particles |
| | FFF: Submicron particles |
| | DLS (Hydrodynamic Radius) |
| | AUC-SV: % Monomer |
| | AUC-SV: Profile |
| | SLS: Molar mass |
| Product-related Substance and Impurities | SE-HPLC: HMW |
| | SE-HPLC: Profile |
| | rCE-SDS: HC+LC |
| | rCE-SDS: NGHC |
| | rCE-SDS: LMW + MMW |
| | rCE-SDS: Profile |
| | nrCE-SDS: Main peak |
| | nrCE-SDS: Pre-peaks |
| | nrCE-SDS: Profile |
| | CEX-HPLC: Acidic peaks |
| | CEX-HPLC: Main peak |
| | CEX-HPLC: Basic peaks |
| | CEX-HPLC: Profile |

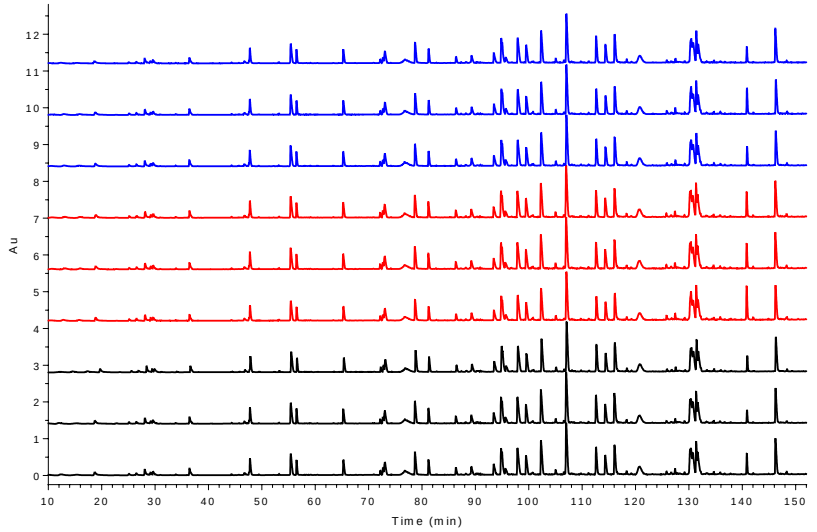
| | Analytical Testing/Attributes |
|---|---|
| Thermal Degradation @ 50°C | SE-HPLC: HMW |
| | rCE-SDS: HC + LC |
| | rCE-SDS: LMW + MMW |
| | CEX-HPLC: Main peak |
| | CEX-HPLC: Acidic peaks |
| | CEX-HPLC: Basic peaks |
| | Proliferation inhibition bioassay |
| Thermal Stability @ 40°C | SE-HPLC: HMW |
| | rCE-SDS: HC + LC |
| | rCE-SDS: LMW + MMW |
| | CEX-HPLC: Main peak |
| | CEX-HPLC: Acidic peaks |
| | CEX-HPLC: Basic peaks |
| | Proliferation inhibition bioassay |
| Thermal Stability @ 25°C | SE-HPLC: HMW |
| | rCE-SDS: HC + LC |
| | rCE-SDS: LMW + MMW |
| | CEX-HPLC: Main peak |
| | CEX-HPLC: Acidic peaks |
| | CEX-HPLC: Basic peaks |
| | Proliferation inhibition bioassay |
| General Properties | Protein Concentration |
| | Volume |
| | Osmolality |
| | pH |
| | Appearance |
| | Color |
| | Clarity |
| Process-related Impurities | HCP ELISA |
| | HCP LC-MS |
| | HCP 2D-DIGE |
| | Residual Protein A ELISA |
| | Residual DNA qPCR |

# Evaluation of Structural and Purity Attributes

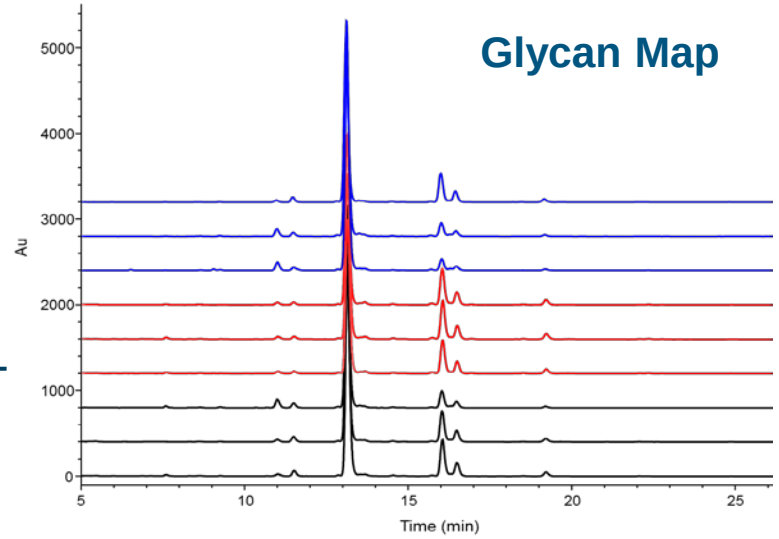
# Primary Structure Similarity Results

| Primary Structure | Similarity Outcome |
|---|---|
| Intact whole mass | ✓ |
| Reduced deglycosylated molecular mass | ✓ |
| Reduced peptide map | ✓ |
| Nonreduced peptide map | ✓ |
| Glycan map | Minor quantitative differences |
| cIEF | ✓ |
| Extinction coefficient | ✓ |
| Identity by ELISA | ✓ |

## Reduced Peptide Map




## Glycan Map



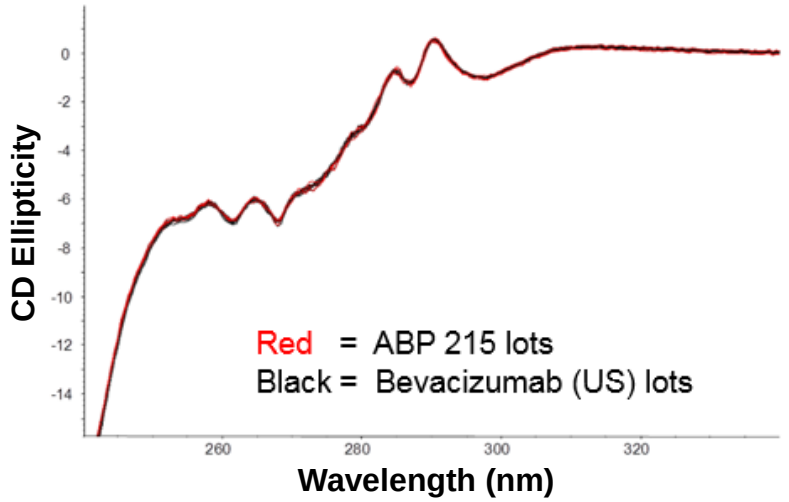

Blue = Bevacizumab (EU) lots
Red = ABP 215 lots
Black = Bevacizumab (US) lots

# Higher Order Structure and Particles and Aggregates Similarity Results

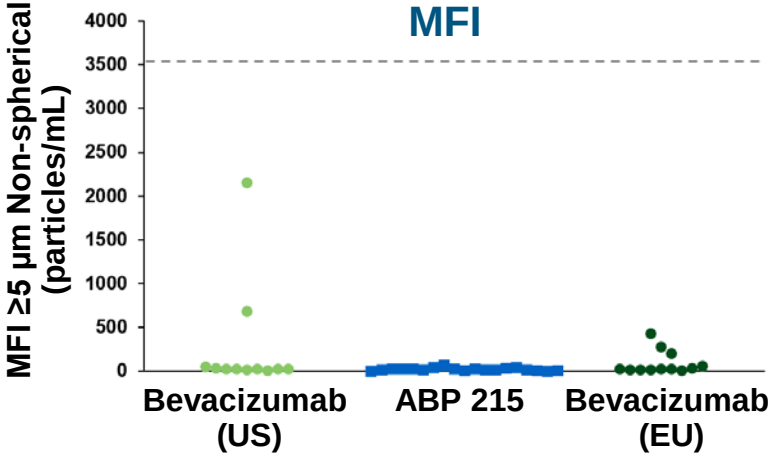
| Higher Order Structure | Similarity Outcome |
|---|---|
| FTIR | ✓ |
| Near UV circular dichroism | ✓ |
| DSC | ✓ |

| Particles and Aggregates | |
|---|---|
| Microflow imaging (MFI) | ✓ |
| Subvisible particle counts by HIAC | ✓ |
| Field flow fractionation | ✓ |
| Dynamic light scattering | ✓ |
| AUC sedimentation velocity | ✓ |
| SE-HPLC with light-scattering | ✓ |

## Near UV Circular Dichroism




## Subvisible Particles by MFI

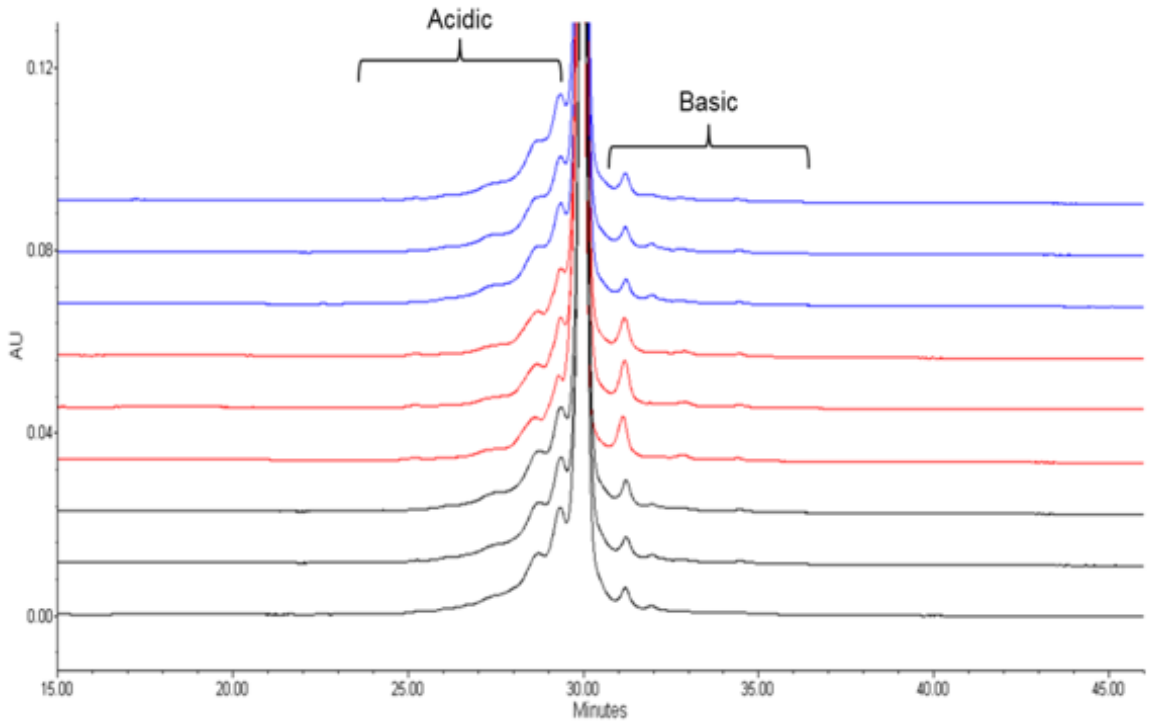


# Product-related Substances and Impurities Similarity Results

| Product-related Substances and Impurities | Similarity Outcome |
|---|---|
| Size Variants<br>SE-HPLC<br>rCE-SDS<br>nrCE-SDS | Minor quantitative differences, all less than 2% |
| Charge Variants<br>CEX-HPLC | Quantitative differences |

- **No new species observed**
- **No impact on functional activities**

**CEX-HPLC**

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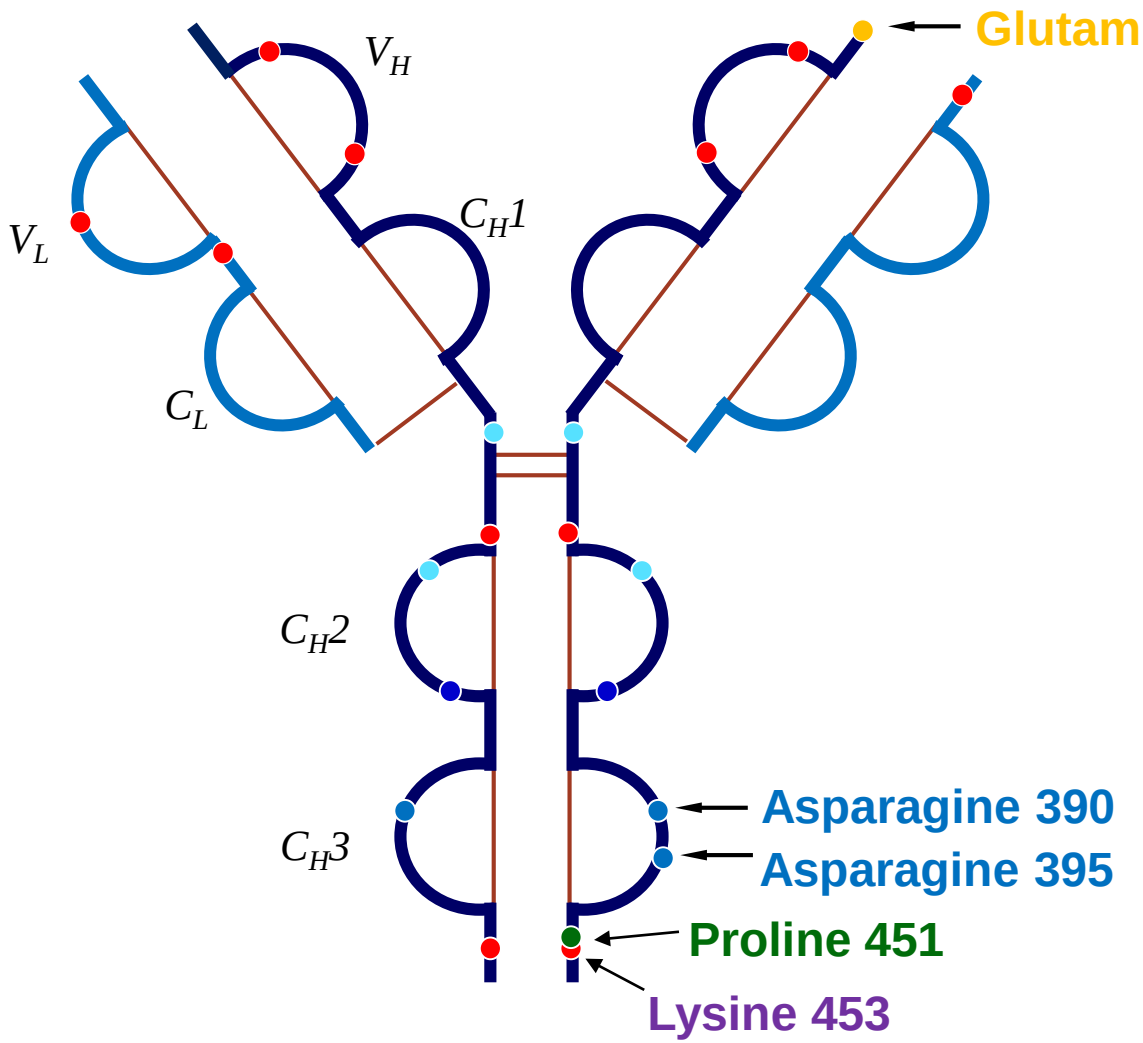
Red = ABP 215 lots
Black = Bevacizumab (US) lots

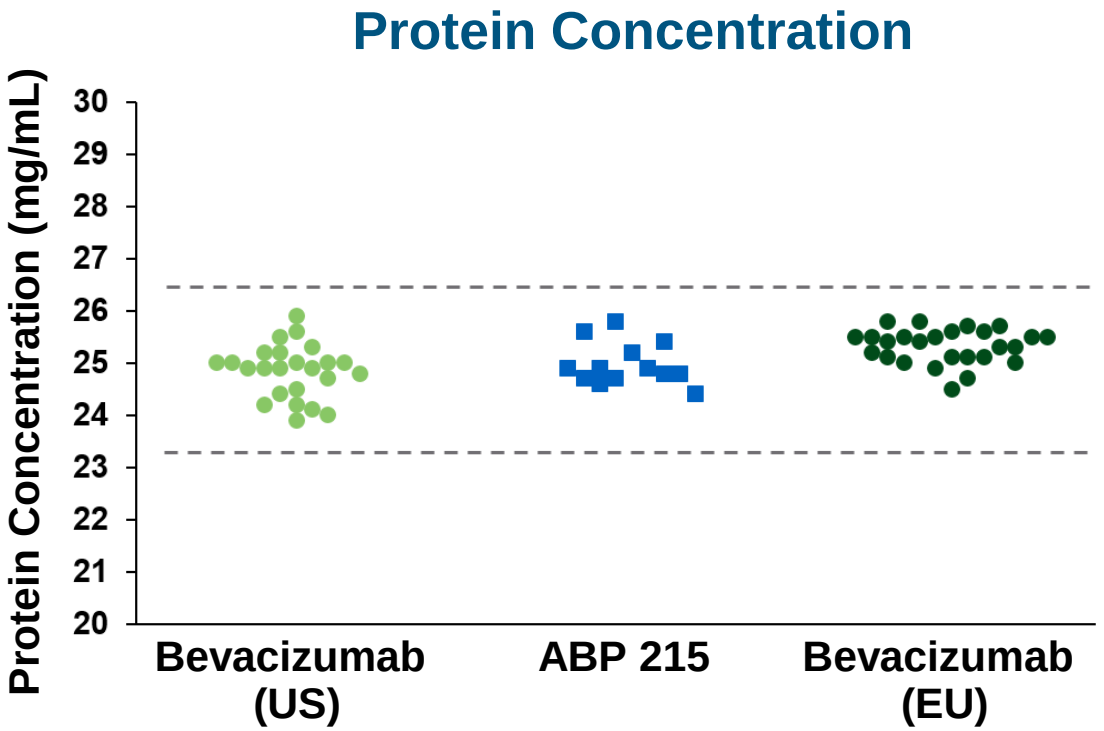
# Assessment of Charge Profile Differences




- Same charge variants present in the reference product
- Charge variants are not within the Fab or Fc binding domains
- No observed impact to PK, efficacy, safety, or immunogenicity

# General Properties Similarity Results

| General Properties | Similarity Outcome |
|---|---|
| Appearance | ✓ |
| Color | ✓ |
| Clarity | ✓ |
| pH | ✓ |
| Osmolality | ✓ |
| Volume | ✓ |
| Protein concentration | ✓ |



# Evaluation of Functional Activities

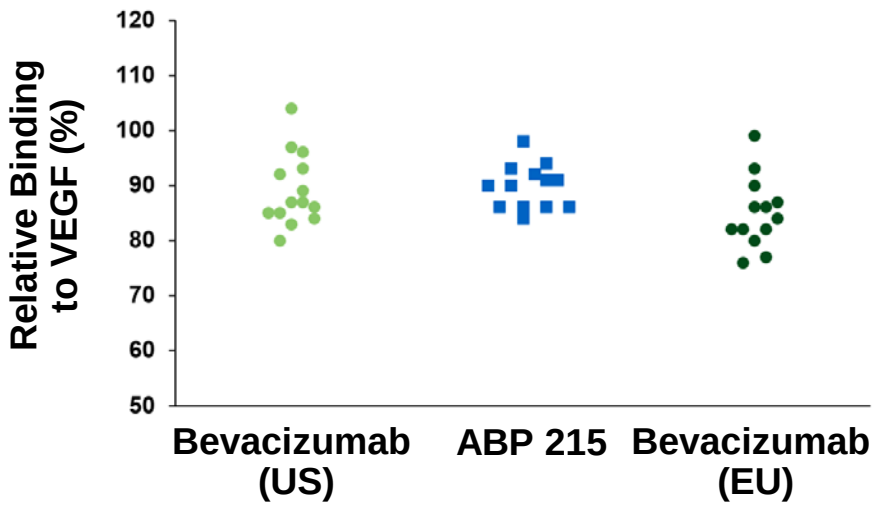
# Similarity was Demonstrated in Functional Activities Evaluated

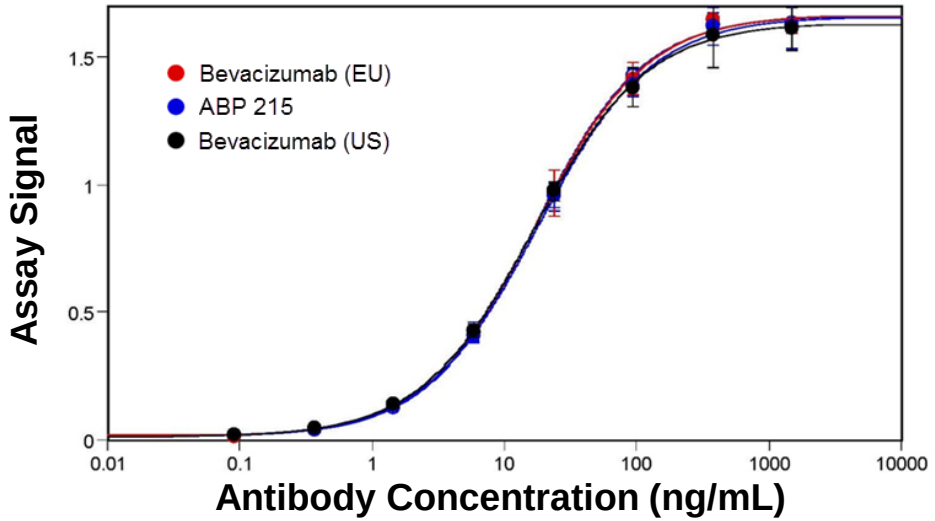
| Fab-mediated Activities | |
|---|---|
| Binding to VEGF | ✓ |
| Inhibition of proliferation in HUVEC (potency) | ✓ |
| On and off rates (VEGF) | ✓ |
| Binding to VEGF isoforms | ✓ |
| Inhibition of VEGFR-2 RTK autophosphorylation | ✓ |
| Specificity for VEGF by VEGFR-2 RTK autophosphorylation | ✓ |

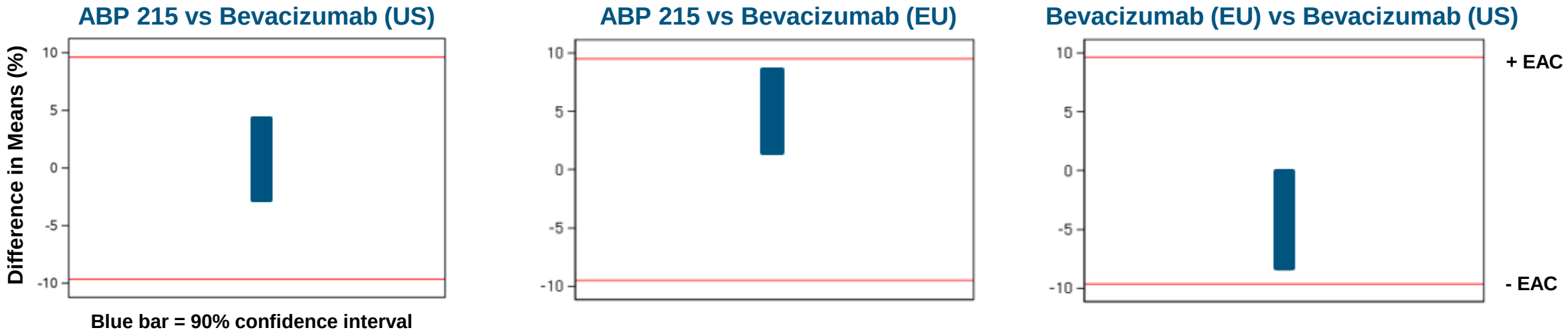
| Fc-mediated Characterization | |
|---|---|
| FcRn binding | ✓ |
| FcγRIa binding | ✓ |
| FcγRIIa (131H) binding | ✓ |
| FcγRIIb binding | ✓ |
| FcγRIIIa (158V) binding | Minor difference unrelated to MoA |
| FcγRIIIa (158F) binding | ✓ |
| FcγRIIIb binding | ✓ |
| C1q binding | ✓ |

| Fab- and Fc-mediated Characterization | |
|---|---|
| Lack of ADCC | ✓ |
| Lack of CDC | ✓ |

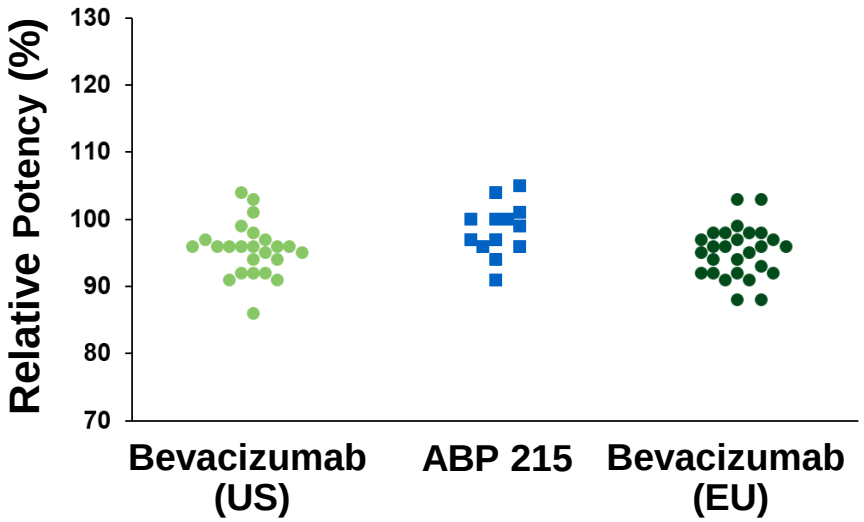
# Binding to VEGF Meets Assessment Criteria

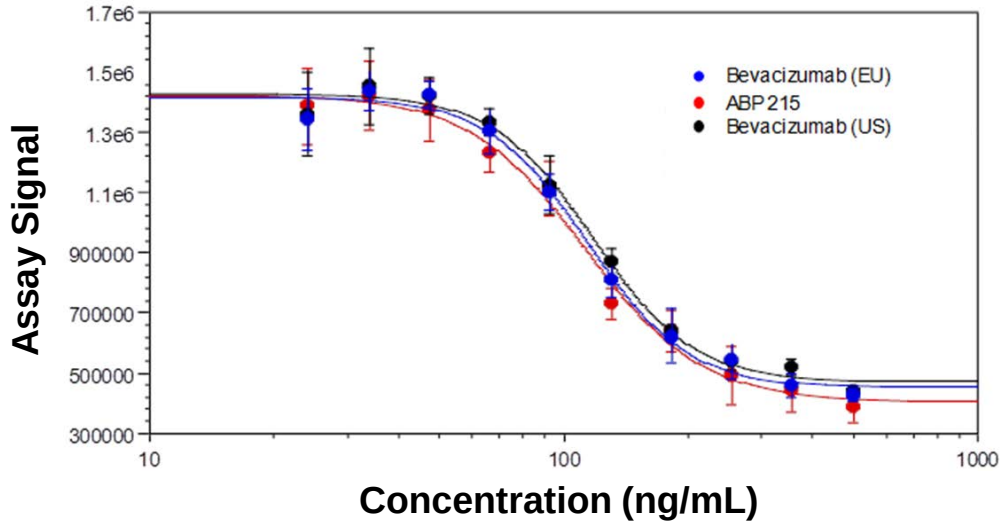


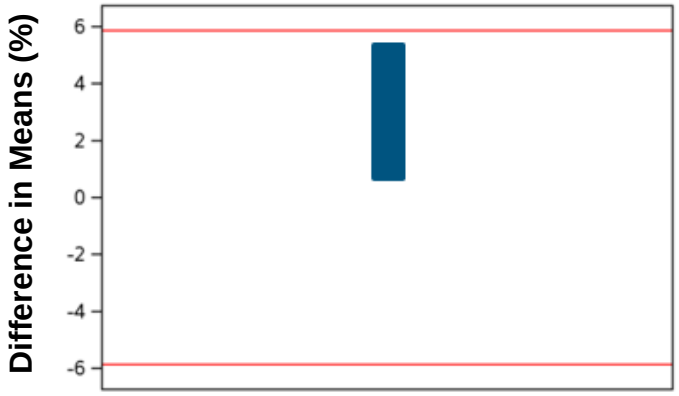



# Potency via Inhibition of Proliferation Meets Assessment Criteria



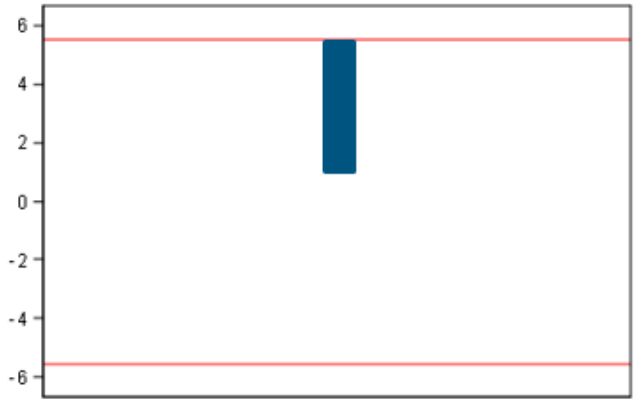




## ABP 215 vs Bevacizumab (US)

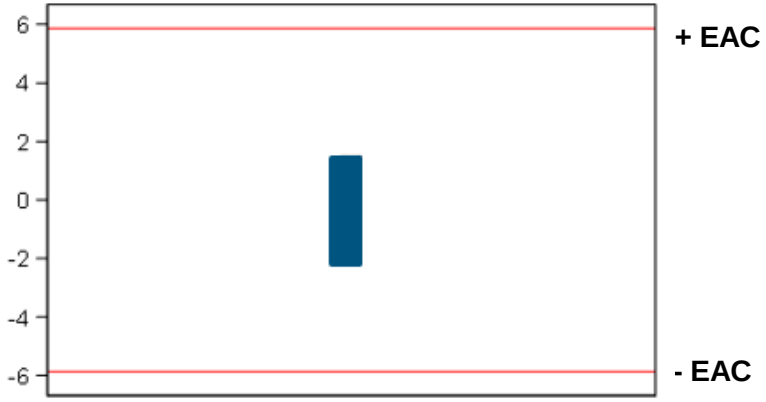



Blue bar = 90% confidence interval

## ABP 215 vs Bevacizumab (EU)




## Bevacizumab (EU) vs Bevacizumab (US)



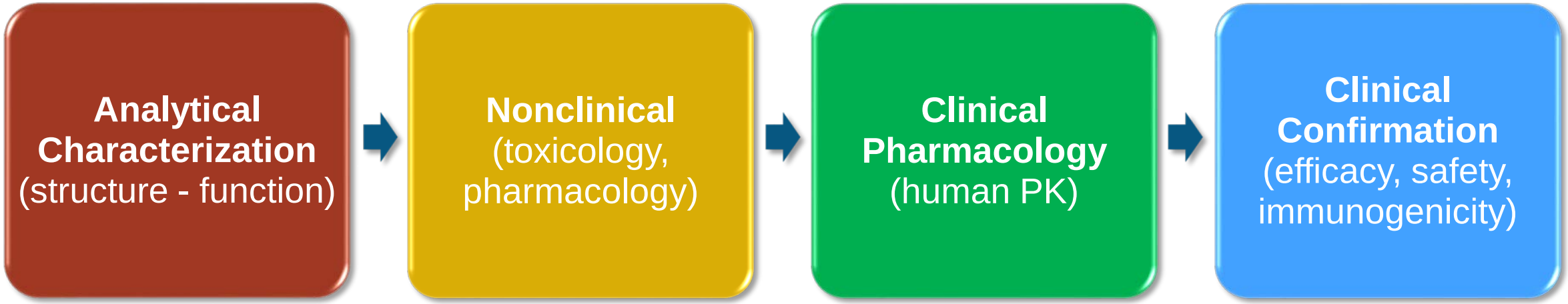
# Analytical Similarity of ABP 215 to Bevacizumab Was Demonstrated for ~ 100 Attributes/Assays

| | Analytical Testing/Attributes | Results |
|---|---|---|
| Biological Activity | **Inhibition of proliferation in HUVEC** | **Similar** |
| | **Binding to VEGF by ELISA** | **Similar** |
| | On and off rates (VEGF) | Similar |
| | Binding to VEGF isoforms | Similar |
| | Inhibition of VEGFR-2 RTK autophosphorylation | Similar |
| | Specificity for VEGF by VEGFR-2 RTK autophosphorylation | Similar |
| | FcRn binding | Similar |
| | FcγRIa binding | Similar |
| | FcγRIIa (131H) binding | Similar |
| | FcγRIIb binding | Similar |
| | FcγRIIIa (158V) binding | Minor Diff |
| | FcγRIIIa (158F) binding | Similar |
| | FcγRIIIb binding | Similar |
| | C1q binding | Similar |
| | Lack of ADCC | Similar |
| | Lack of CDC | Similar |
| Primary Structures | Intact molecular mass | Similar |
| | Intact molecular mass; profiles | Similar |
| | Reduced and deglycosylated molecular masses of HC and LC | Similar |
| | Reduced and deglycosylated molecular masses of HC and LC; profiles | Similar |
| | Reduced peptide map | Similar |
| | Reduced peptide map; profiles | Similar |
| | Non-reduced peptide map | Similar |
| | Non-reduced peptide map; profiles | Similar |
| | Glycan Map; % high mannose | Minor Diff |
| | Glycan Map; % galactosylation | |
| | Glycan Map; % afucosylation | Similar |
| | Glycan Map; % sialylation | Similar |
| | Glycan Map; profiles | Similar |
| | Capillary isoelectric focusing: Isoelectric point | Similar |
| | Capillary isoelectric focusing: Profile | Similar |
| | Amino acid analysis/UV spectroscopy | Similar |
| | Identity by ELISA | Similar |

| | Analytical Testing/Attributes | Results |
|---|---|---|
| Higher Order Structure | FTIR: Spectral similarity | Similar |
| | FTIR: Profile | Similar |
| | Near UV CD: Spectral similarity | Similar |
| | Near UV CD: Profile | Similar |
| | DSC: $T_m1$ | Similar |
| | DSC: $T_m2$ | Similar |
| | DSC: Profile | Similar |
| Particles and Aggregates | HIAC: ≥ 2 μm particles | Similar |
| | HIAC: ≥ 5 μm particles | Similar |
| | HIAC: ≥ 10 μm particles | Similar |
| | HIAC: ≥ 25 μm particles | Similar |
| | MFI: ≥ 5 μm particles | Similar |
| | MFI: ≥ 5 μm non-spherical particles | Similar |
| | FFF: Submicron particles | Similar |
| | DLS (Hydrodynamic Radius) | Similar |
| | AUC-SV: % Monomer | Similar |
| | AUC-SV: Profile | Similar |
| | SLS: Molar mass | Similar |
| Product-related Substance and Impurities | SE-HPLC: HMW | Minor Diff |
| | SE-HPLC: Profile | Similar |
| | rCE-SDS: HC+LC | Minor Diff |
| | rCE-SDS: NGHC | |
| | rCE-SDS: LMW + MMW | |
| | rCE-SDS: Profile | Similar |
| | nrCE-SDS: Main peak | Minor Diff |
| | nrCE-SDS: Pre-peaks | |
| | nrCE-SDS: Profile | Similar |
| | CEX-HPLC: Acidic peaks | Minor Diff |
| | CEX-HPLC: Main peak | |
| | CEX-HPLC: Basic peaks | |
| | CEX-HPLC: Profile | Similar |

| | Analytical Testing/Attributes | Results |
|---|---|---|
| Thermal Degradation @ 50°C | SE-HPLC: HMW | Similar |
| | rCE-SDS: HC + LC | Similar |
| | rCE-SDS: LMW + MMW | Similar |
| | CEX-HPLC: Main peak | Similar |
| | CEX-HPLC: Acidic peaks | Similar |
| | CEX-HPLC: Basic peaks | Similar |
| | Proliferation inhibition bioassay | Similar |
| Thermal Stability @ 40°C | SE-HPLC: HMW | Similar |
| | rCE-SDS: HC + LC | Similar |
| | rCE-SDS: LMW + MMW | Similar |
| | CEX-HPLC: Main peak | Similar |
| | CEX-HPLC: Acidic peaks | Similar |
| | CEX-HPLC: Basic peaks | Similar |
| | Proliferation inhibition bioassay | Similar |
| Thermal Stability @ 25°C | SE-HPLC: HMW | Similar |
| | rCE-SDS: HC + LC | Similar |
| | rCE-SDS: LMW + MMW | Similar |
| | CEX-HPLC: Main peak | Similar |
| | CEX-HPLC: Acidic peaks | Similar |
| | CEX-HPLC: Basic peaks | Similar |
| | Proliferation inhibition bioassay | Similar |
| General Properties | Protein Concentration | Similar |
| | Volume | Similar |
| | Osmolality | Similar |
| | pH | Similar |
| | Appearance | Similar |
| | Color | Similar |
| | Clarity | Similar |
| Process-related Impurities | HCP ELISA | Similar |
| | HCP LC-MS | Similar |
| | HCP 2D-DIGE | Similar |
| | Residual Protein A ELISA | Similar |
| | Residual DNA qPCR | Similar |

# Analytical Characterization Supports Biosimilarity




- **Comprehensive analytical characterization was conducted**
- **Results demonstrate that ABP 215 is highly analytically similar to bevacizumab**
- **Analytical similarity results form the foundation of the scientific justification for extrapolation**

# Agenda

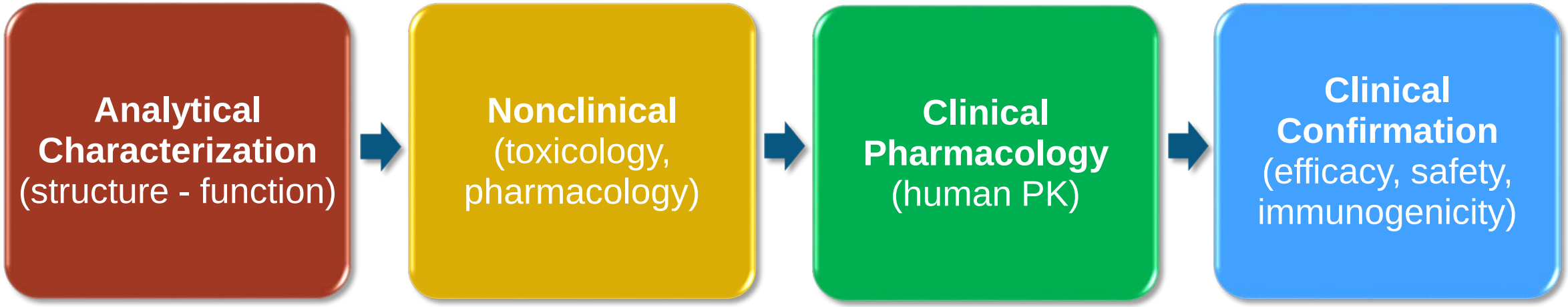
| | |
|---|---|
| Introduction | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| Analytical Similarity | **Simon Hotchin**<br>*Regulatory Affairs, Amgen* |
| **Non-Clinical and Clinical Similarity and Extrapolation to All Indications** | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| Conclusion | **Lisa Bollinger, MD**<br>*Regulatory Affairs and Safety, Amgen* |

# Non-Clinical and Clinical Similarity and Extrapolation to All Indications

**Richard Markus, MD, PhD**

*VP Global Development, Amgen*

# Nonclinical Assessment is Next in Stepwise Development




- **Same amino acid sequence and strength**
- **Equivalent potency**
- **Highly similar structure and function**

# Nonclinical: Toxicology

## Study Design:

- ABP 215 vs bevacizumab
- Four weeks: 50 mg/kg IV twice a week
- 3 male and 3 female cynomolgus monkeys/group

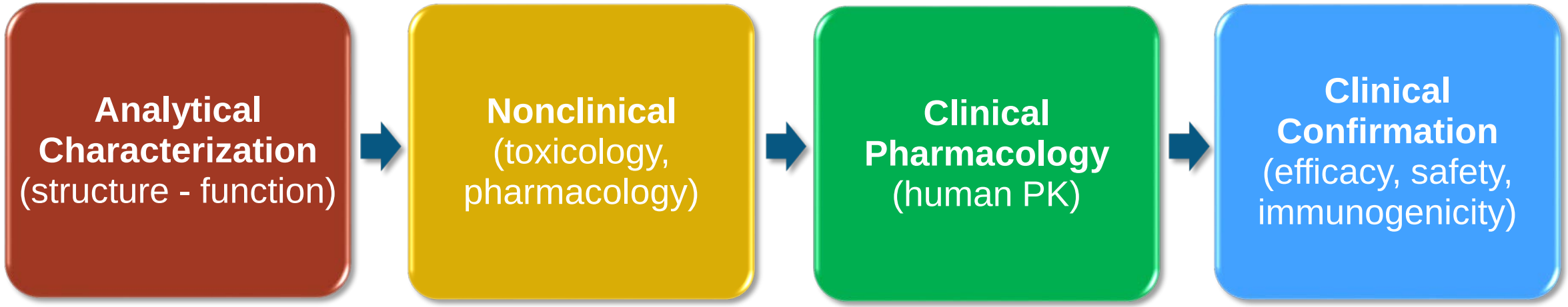
## Findings:

- Anticipated finding of physeal dysplasia of the femur similar in incidence and severity in both groups
- No unexpected toxicities

# Nonclinical Pharmacology Studies

| Evaluation | Treatment Arms | Results |
|---|---|---|
| **A431 Xenograft (Epidermoid Cancer Model)** | Bevacizumab & ABP 215 10 and 100 µg; IgG1 control 100 µg | ABP 215 inhibited tumor growth and vasculature similar to bevacizumab |
| **Colo205 Xenograft (Colon Cancer Model)** | Bevacizumab & ABP 215 10 and 100 µg; IgG1 control 100 µg | ABP 215 inhibited tumor growth and vasculature similar to bevacizumab |
| **Vascular Permeability induced by huVEGF expressing cells** | Bevacizumab & ABP 215 3, 10, 30, and 100 µg; IgG1 control 100 µg | ABP 215 inhibited vascular permeability similar to bevacizumab |

# Clinical Pharmacology is Next in Stepwise Development

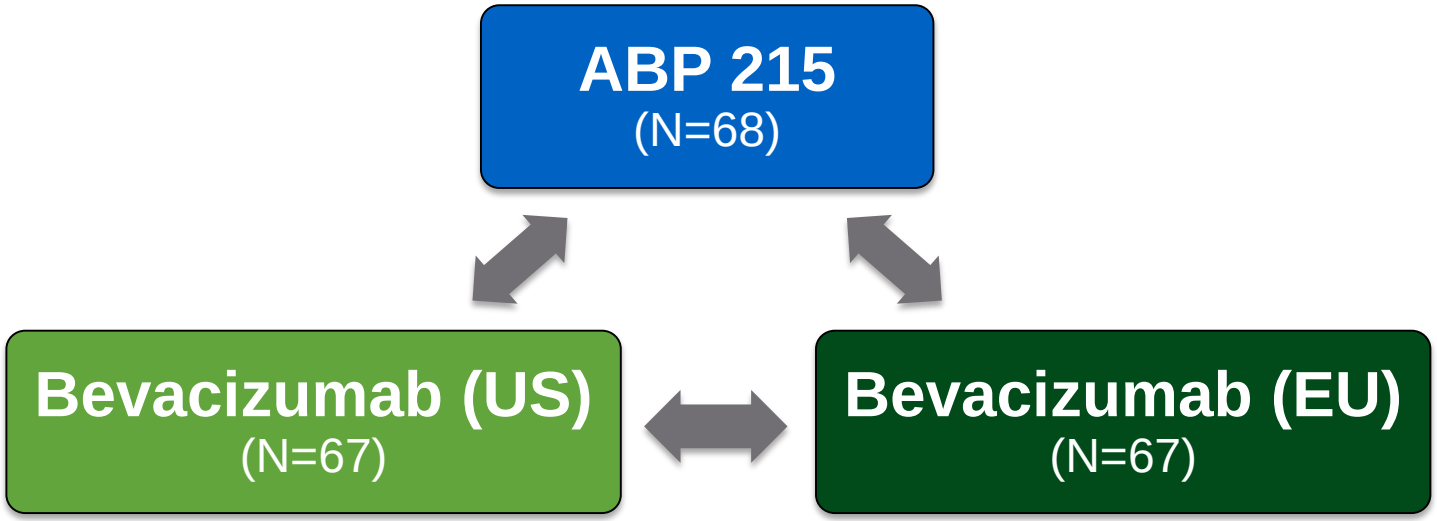



- **Same amino acid sequence and strength**
- **Equivalent potency**
- **Highly similar structure and function**

- **Similar toxicology**
- **Similar dose-response effect on tumors and vasculature**

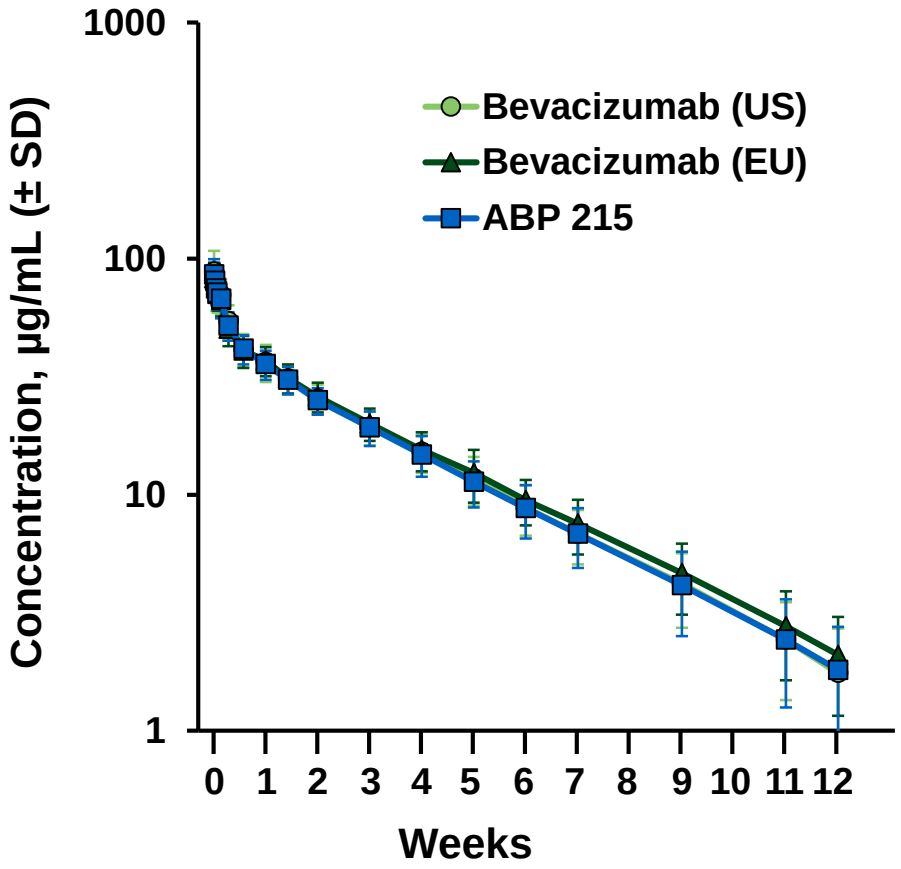
# Clinical Pharmacology – PK Similarity

- **Design:**
  - Healthy male volunteers
  - Single 3 mg/kg IV dose
  - 85 days follow-up
- **Endpoints:**
  - $C_{max}$, $AUC_{inf}$, $AUC_{last}$ (Margin 80-125%)
  - Safety
  - Immunogenicity

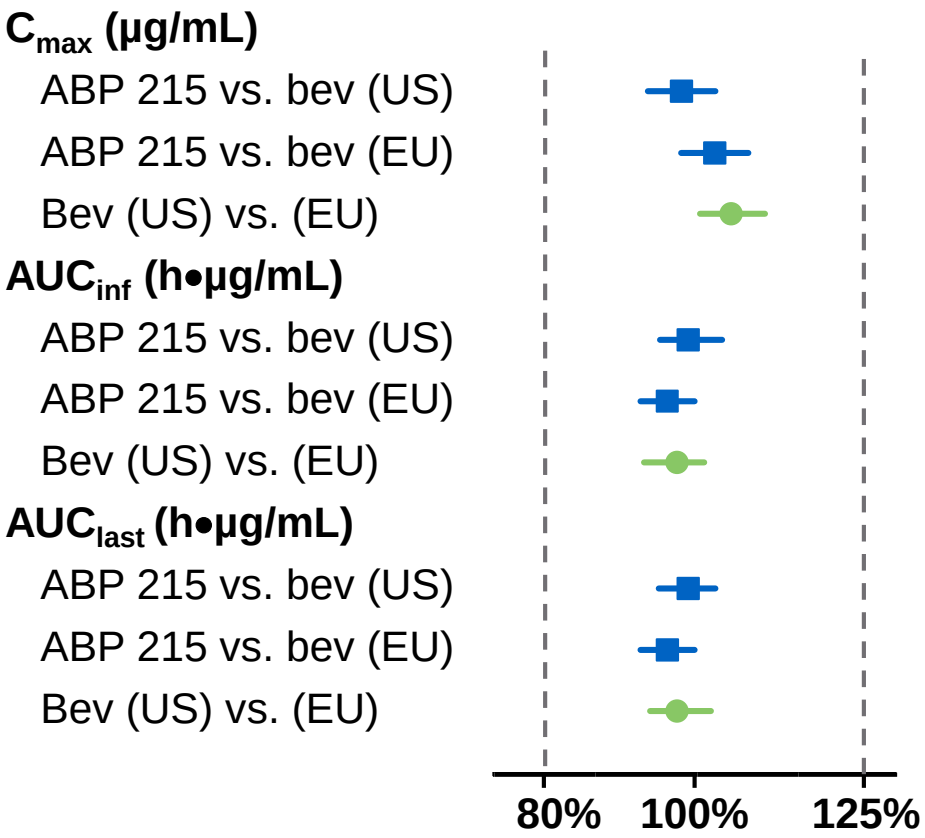


# PK Similarity Results

## Mean (±SD) Serum Concentration-Time Profiles

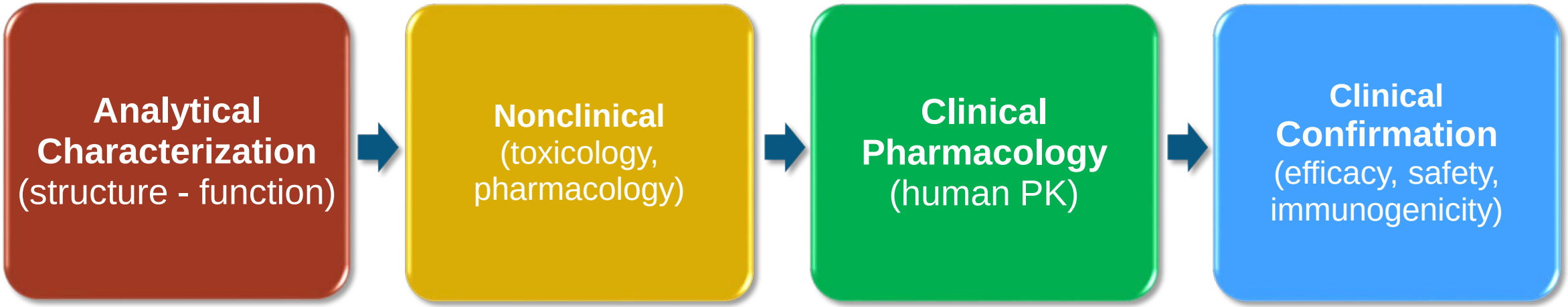



## Ratio of Adjusted LS Geometric Means with 90% CI




LS = least squares.

# Clinical Confirmation is Next in Stepwise Development




- **Same amino acid sequence and strength**
- **Equivalent potency**
- **Highly similar structure and function**

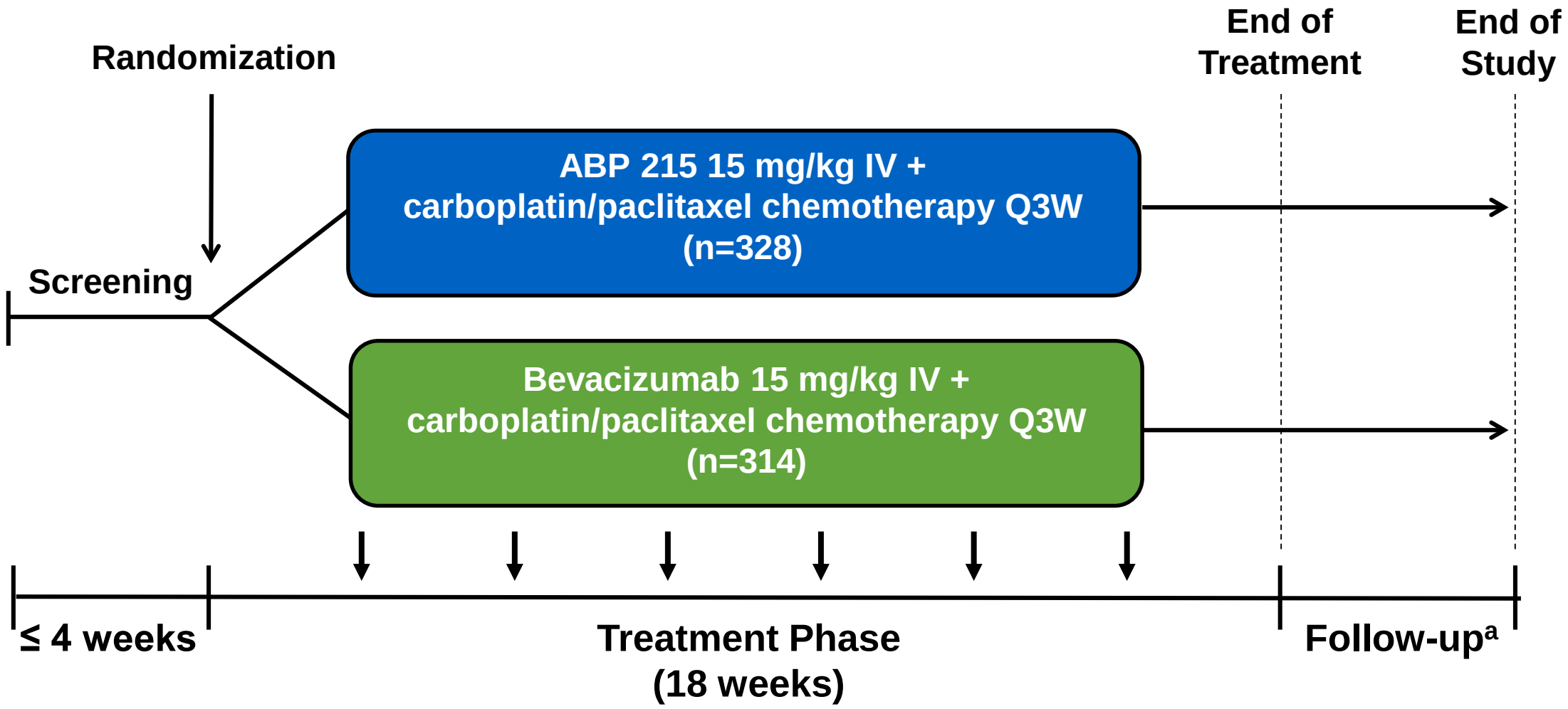
- **Similar toxicology**
- **Similar dose-response effect on tumors and vasculature**

- **Equivalent Pharmacokinetics (PK)**

# Clinical Study Considerations

- **Objective: Head-to-head comparison of anti-tumor efficacy, safety, and immunogenicity**
  - Confirm similarity with no clinically meaningful differences
- **Advanced NSCLC with tumor response primary endpoint**
  - Objective response rate (ORR) is a measurement of anti-tumor activity due to treatment
  - ORR of Bevacizumab in NSCLC has relatively large magnitude of response

# Study Schema – Advanced NSCLC




a. Maintenance monotherapy not included.

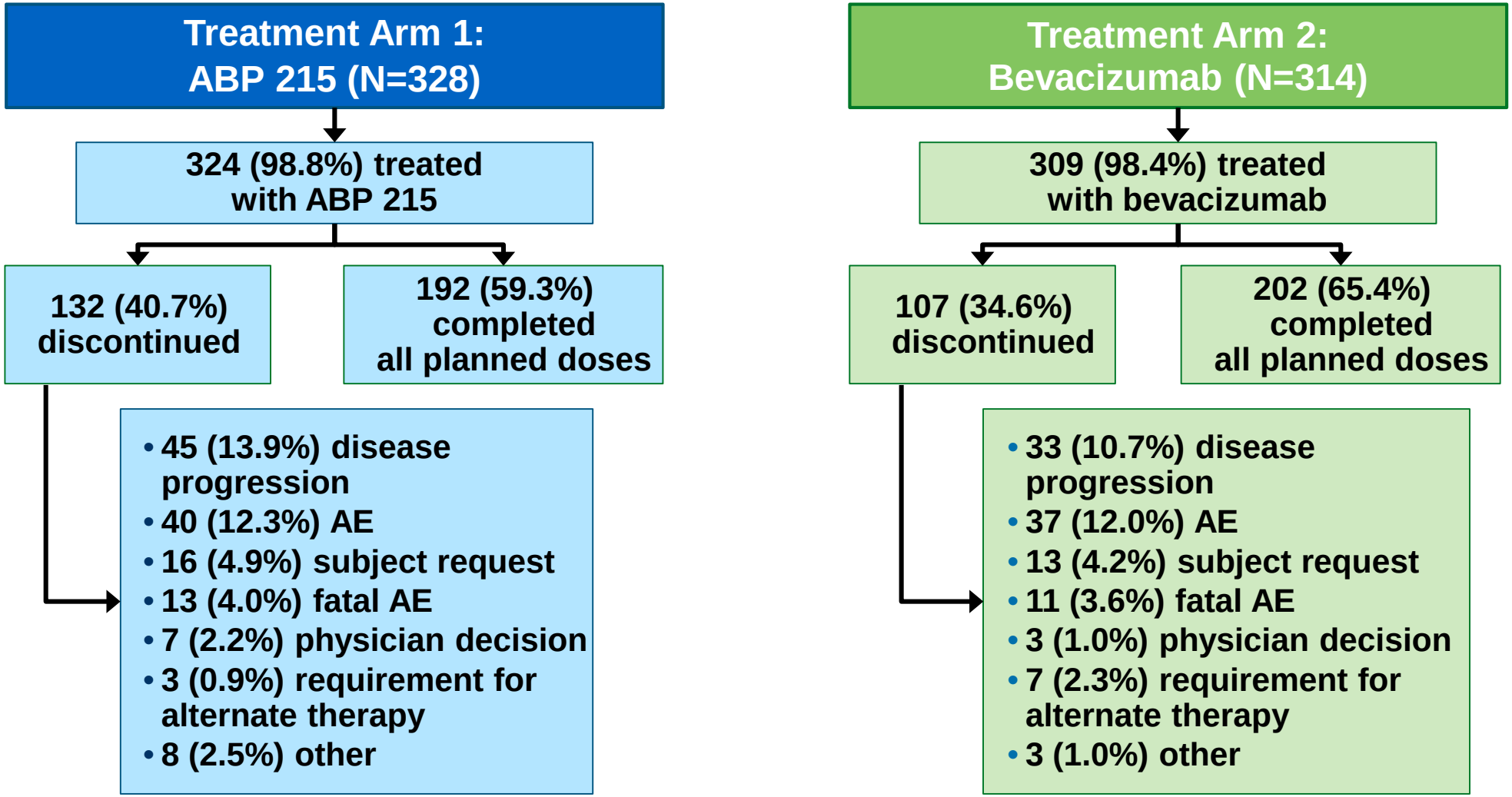
# Endpoints

- **Primary endpoint**
  - Risk Ratio (RR) of objective response rate (ORR)
- **Secondary endpoints**
  - Risk difference of ORR
  - Progression-free survival
  - Duration of response
- **Safety endpoints**
  - AE’s and SAE’s
  - Overall survival
  - Development of anti-drug antibodies

# Primary Analysis

- **Objective Response Rate (ORR): Best overall response rate (complete response or partial response)**
  - ORR based on independent central radiology evaluation
- **Pre-specified similarity margin for RR = (0.67, 1.50)**
  - FDA revised margin RR = (0.73, 1.36)
- **90% confidence interval for RR must be entirely within the pre-specified similarity margin**
  - Equates to ORR risk difference within 6%

# Subject Disposition



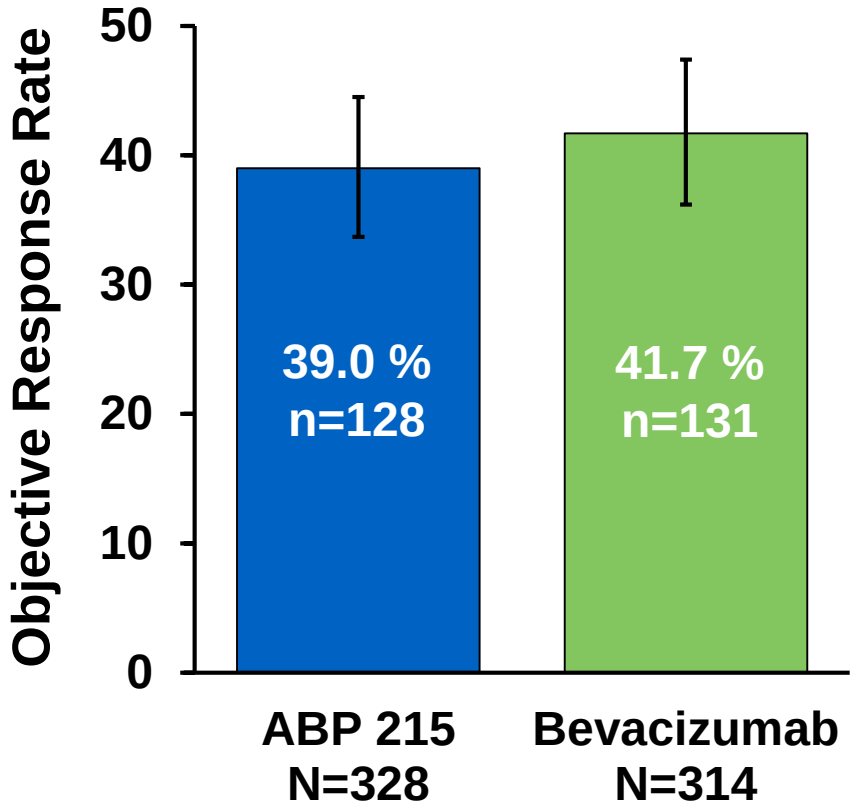
# Baseline Demographics

| Characteristic | ABP 215 N=328 | Bevacizumab N=314 |
|---|---|---|
| **Age, years, mean (SD)** | 61.6 (9.1) | 61.6 (8.9) |
| **< 65 years, n (%)** | 199 (60.7) | 191 (60.8) |
| **≥ 65 years, n (%)** | 129 (39.3) | 123 (39.2) |
| **Weight, kg, mean (SD)** | 71.2 (14.7) | 73.5 (15.3) |
| **White, n (%)** | 315 (96.0) | 300 (95.5) |
| **Male, n (%)** | 196 (59.8) | 188 (59.9) |
| **Smoking status, n (%)** | | |
| **Never** | 65 (19.8) | 76 (24.2) |
| **Former** | 163 (49.7) | 158 (50.3) |
| **Current** | 100 (30.5) | 80 (25.5) |

# Baseline Disease Characteristics

| Characteristic, n (%) | ABP 215 N=328 | Bevacizumab N=314 |
|---|---|---|
| **Staging of original diagnosis** | | |
| **≤ Stage IIIA** | 23 (7.0) | 25 (8.0) |
| **Stage IIIB** | 2 (0.6) | 7 (2.2) |
| **Stage IV** | 303 (92.4) | 281 (89.5) |
| **Stage IV/recurrent disease at baseline** | | |
| **Stage IV** | 309 (94.2) | 290 (92.4) |
| **Recurrent disease** | 19 (5.8) | 24 (7.6) |
| **Weight loss in last 6 months** | | |
| **0%–5%** | 289 (88.1) | 276 (87.9) |
| **> 5%–10%** | 39 (11.9) | 37 (11.8) |
| **ECOG PS** | | |
| **Grade 0** | 127 (38.7) | 117 (37.3) |
| **Grade 1** | 201 (61.3) | 197 (62.7) |

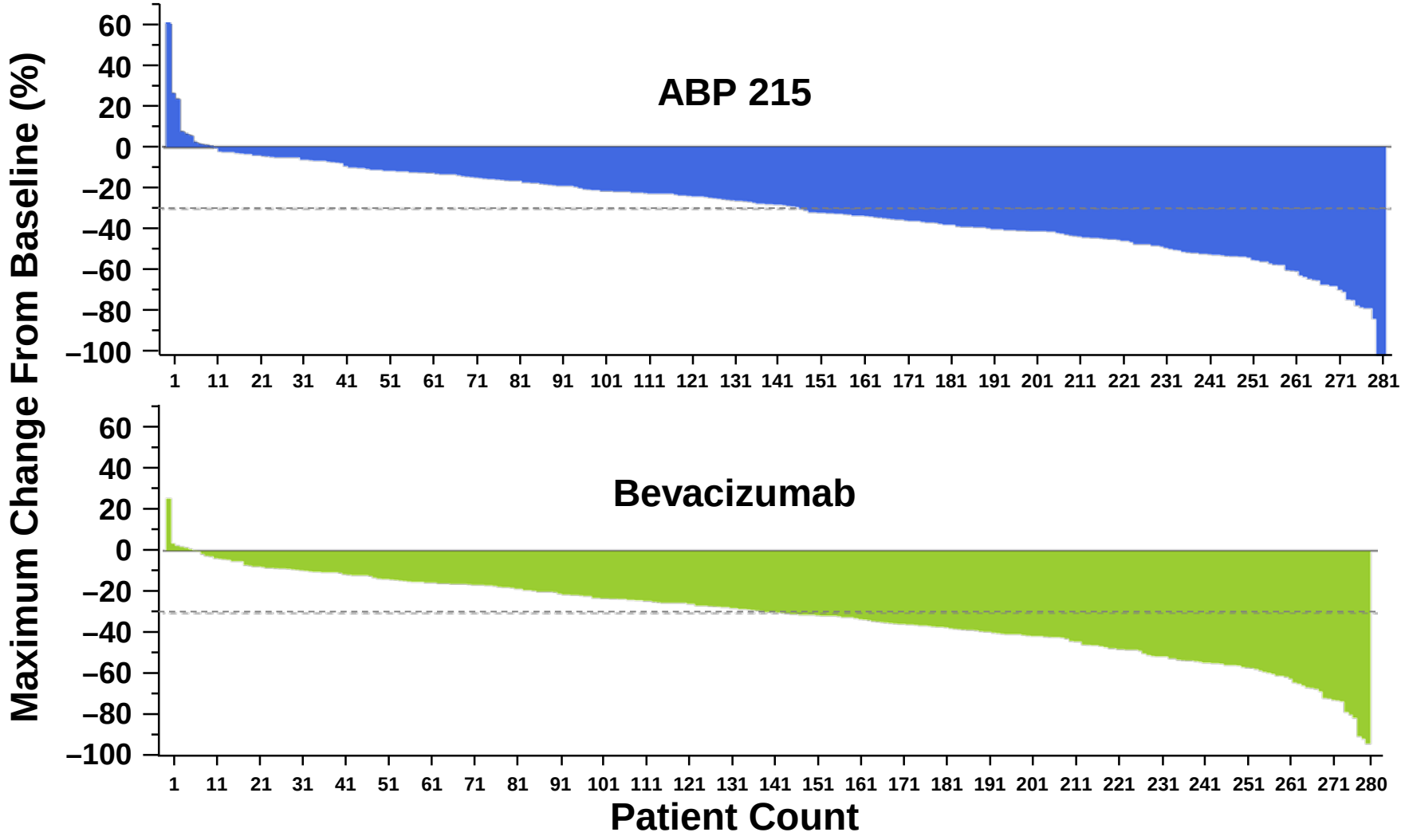
# Primary Endpoint Results




| Primary Analysis | ABP 215 vs Bevacizumab |
|---|---|
| RR (90% CI) | 0.93 (0.80, 1.09) |
| Pre-specified equivalence margin | (0.67, 1.50) |
| FDA revised margin | (0.73, 1.36) |

Primary analysis of ORR using RECIST 1.1 by central radiology review of ITT population.
Generalized linear model adjusted for randomization stratification factors; geographic region, ECOG PS, and sex.
Whiskers in the bar chart represent 95% CI of ORR.

# Similar Magnitude of Tumor Response



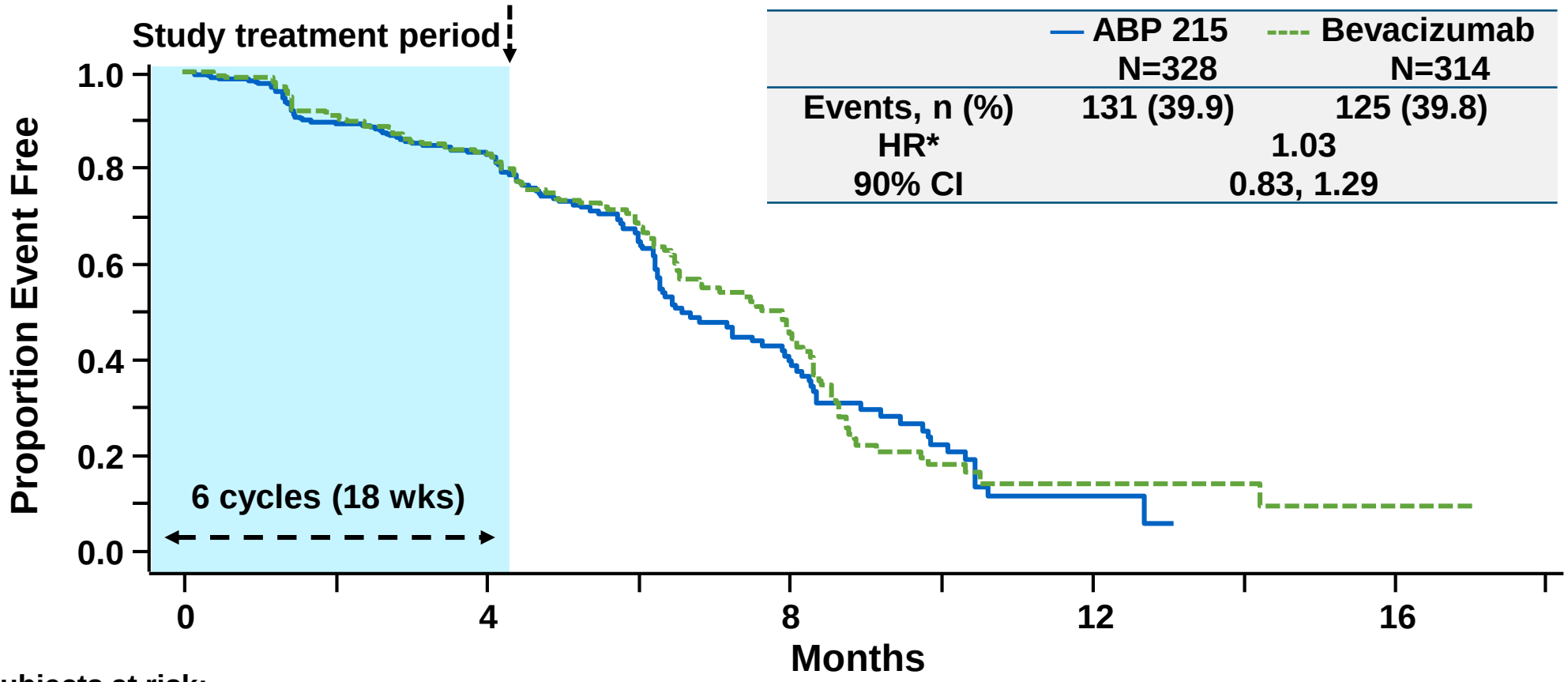

Based on independent central tumor review using RECIST v1.1.
Figures exclude patients with a missing maximum change from baseline.

# Secondary Efficacy Endpoints

| Endpoint | ABP 215 N=328 | Bevacizumab N=314 |
|---|---|---|
| **Objective Response Rate (ORR)** | | |
| **Responders, n** | 128 | 131 |
| **ORR % (95% CI)** | 39.0 (33.7, 44.5) | 41.7 (36.2, 47.4) |
| **Risk Difference % (90% CI)[a]** | -2.90 (-9.26, 3.45) | |
| **Progression Free Survival (PFS)** | | |
| **Progression or death, n (%)** | 131 (39.9) | 125 (39.8) |
| **HR (90% CI)[b]** | 1.03 (0.83, 1.29) | |
| **Duration of Response (DOR)** | | |
| **Responders, n (%)** | 128 (39.0) | 131 (41.7) |
| **Progression among responders** | 43 (33.6) | 45 (34.4) |
| **Median Time, months (95% CI)** | 5.8 (4.9, 7.7) | 5.6 (5.1, 6.3) |

[a] Based on generalized linear model adjusted for randomization stratification factors: geographic region, ECOG PS, and sex.
[b] Based on a Cox proportional hazards model stratified by geographic region, ECOG PS, and sex.

# NSCLC: Progression Free Survival




| | ABP 215 N=328 | Bevacizumab N=314 |
|---|---|---|
| Events, n (%) | 131 (39.9) | 125 (39.8) |
| HR* | 1.03 | |
| 90% CI | 0.83, 1.29 | |

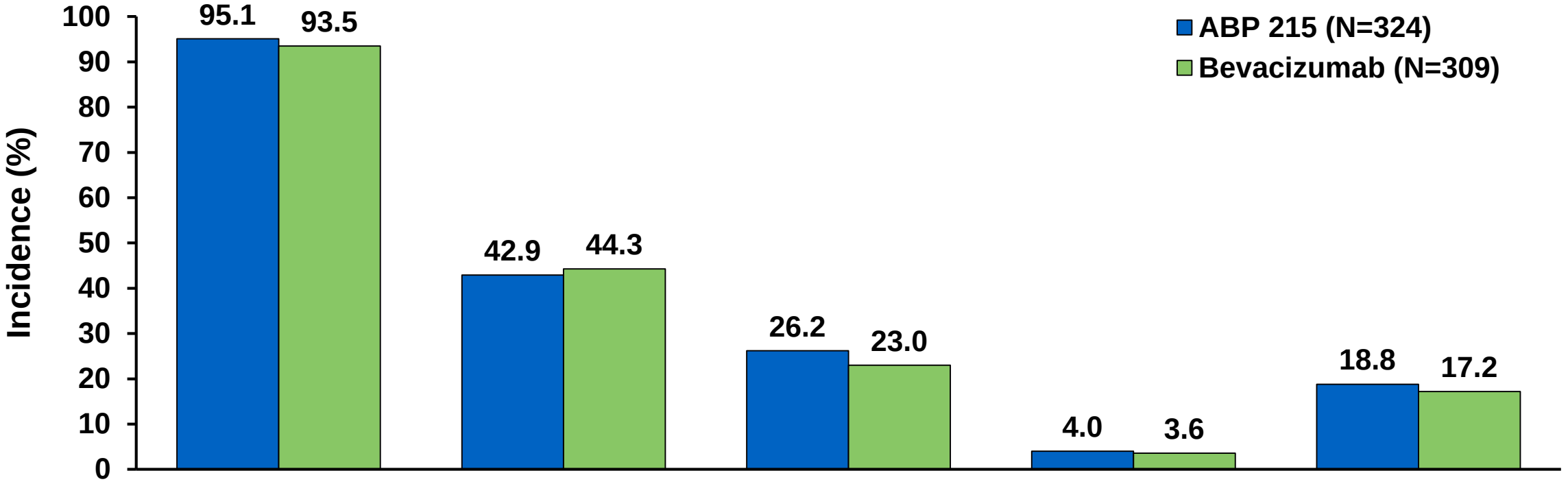
**Subjects at risk:**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ABP 215, n= 328 | 254 | 202 | 98 | 39 | 15 | 4 | 0 | 0 | 0 |
| Bev, n= 314 | 253 | 201 | 92 | 49 | 12 | 5 | 3 | 1 | 0 |

ITT population. Independent central radiology review.
*Hazard ratio (HR) for ABP 215 relative to bevacizumab, based on a Cox proportional hazards model stratified by randomization factors.

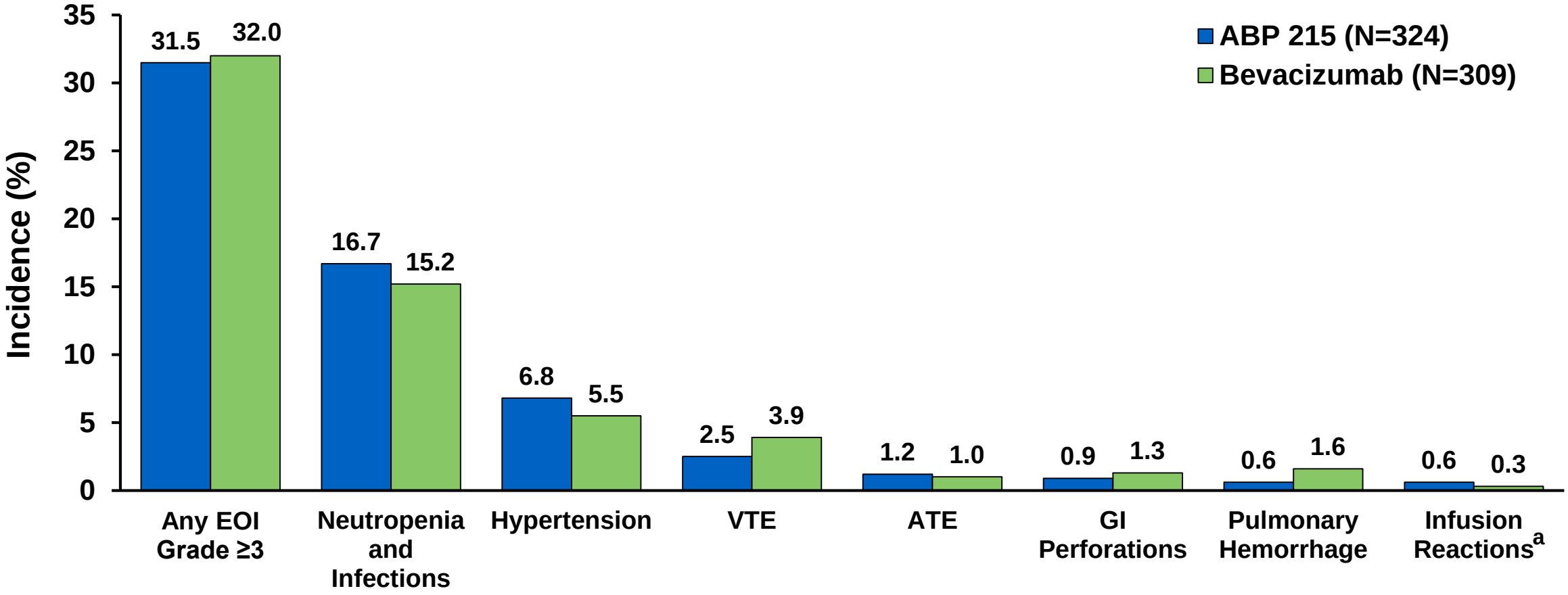
# Clinical Safety and Immunogenicity

# Summary of Adverse Events




| | AE | AE Grade ≥3 | SAE | Fatal AE | AE Leading to Discontinuation of IP |
|---|---|---|---|---|---|
| ABP 215, n= | 308 | 139 | 85 | 13 | 61 |
| Bev, n= | 289 | 137 | 71 | 11 | 53 |

# Key Events of Interest Grade ≥3




| | Any EOI Grade ≥3 | Neutropenia and Infections | Hypertension | VTE | ATE | GI Perforations | Pulmonary Hemorrhage | Infusion Reactions[a] |
|---|---|---|---|---|---|---|---|---|
| ABP 215, n= | 102 | 54 | 22 | 8 | 4 | 3 | 2 | 2 |
| Bev, n= | 99 | 47 | 17 | 12 | 3 | 4 | 5 | 1 |

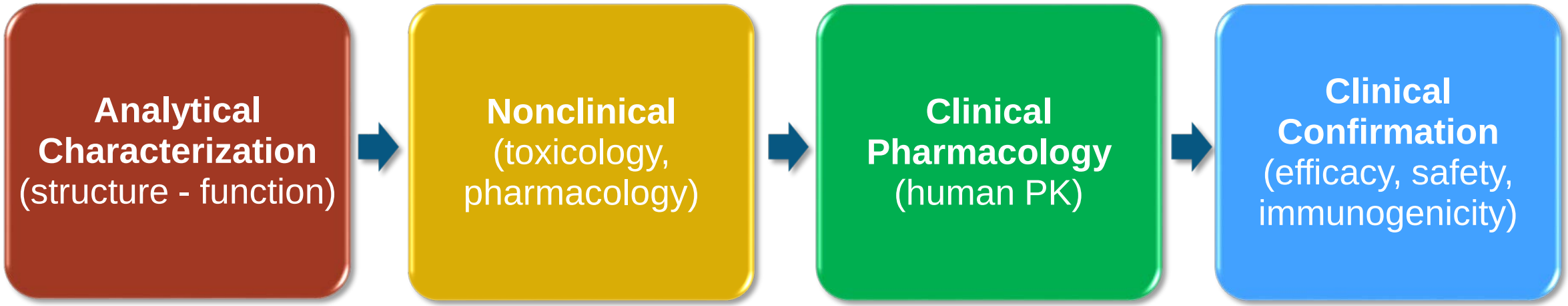
a. Infusion reactions = events within 2 days of first dose; VTE = Venous Thromboembolic Events; ATE = Arterial Thromboembolic Events; GI=Gastrointestinal.

# Immunogenicity: Anti-drug Antibodies

| Number of Subjects | ABP 215 N=324 | Bevacizumab N=309 |
|---|---|---|
| **Baseline** | 315 | 303 |
| **Pre-existing binding antibody incidence, n (%)** | 0 | 3 (1.0) |
| **Post-baseline** | 294 | 284 |
| **Binding antibody positive post-baseline with a negative or no result at baseline, n (%)** | 4 (1.4) | 7 (2.5) |

- **No neutralizing antibodies in either group**

# Totality of Evidence Supports Biosimilarity




- **Same amino acid sequence and strength**
- **Equivalent potency**
- **Highly similar structure and function**

- **Similar toxicology**
- **Similar dose-response effect on tumors and vasculature**

- **Equivalent Pharmacokinetics (PK)**

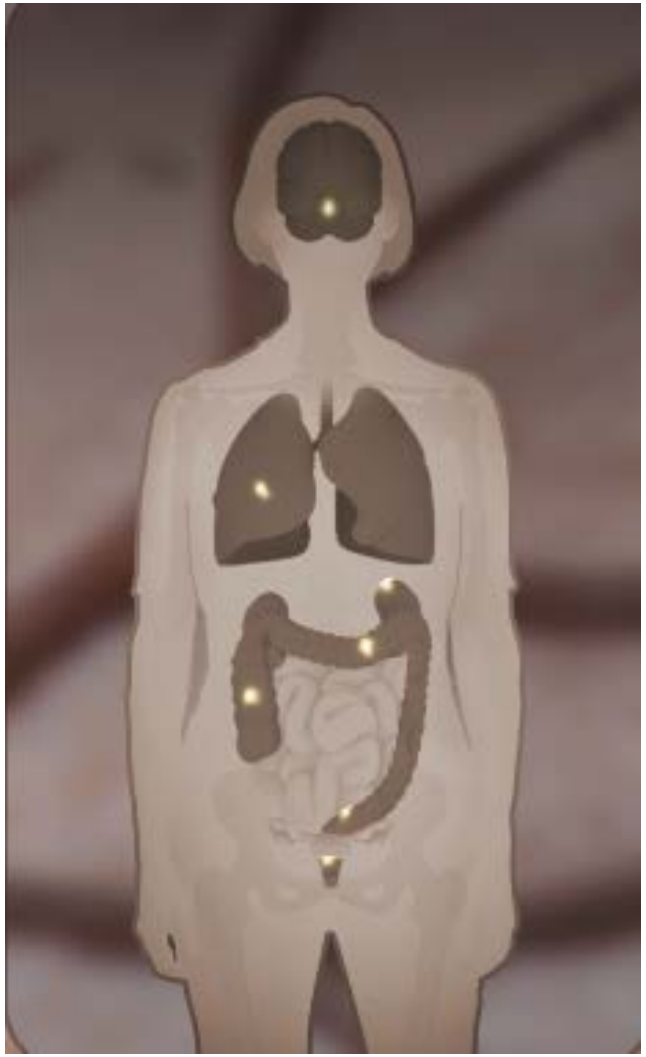
- **Equivalent efficacy**
- **Similar safety**
- **Similar immunogenicity**

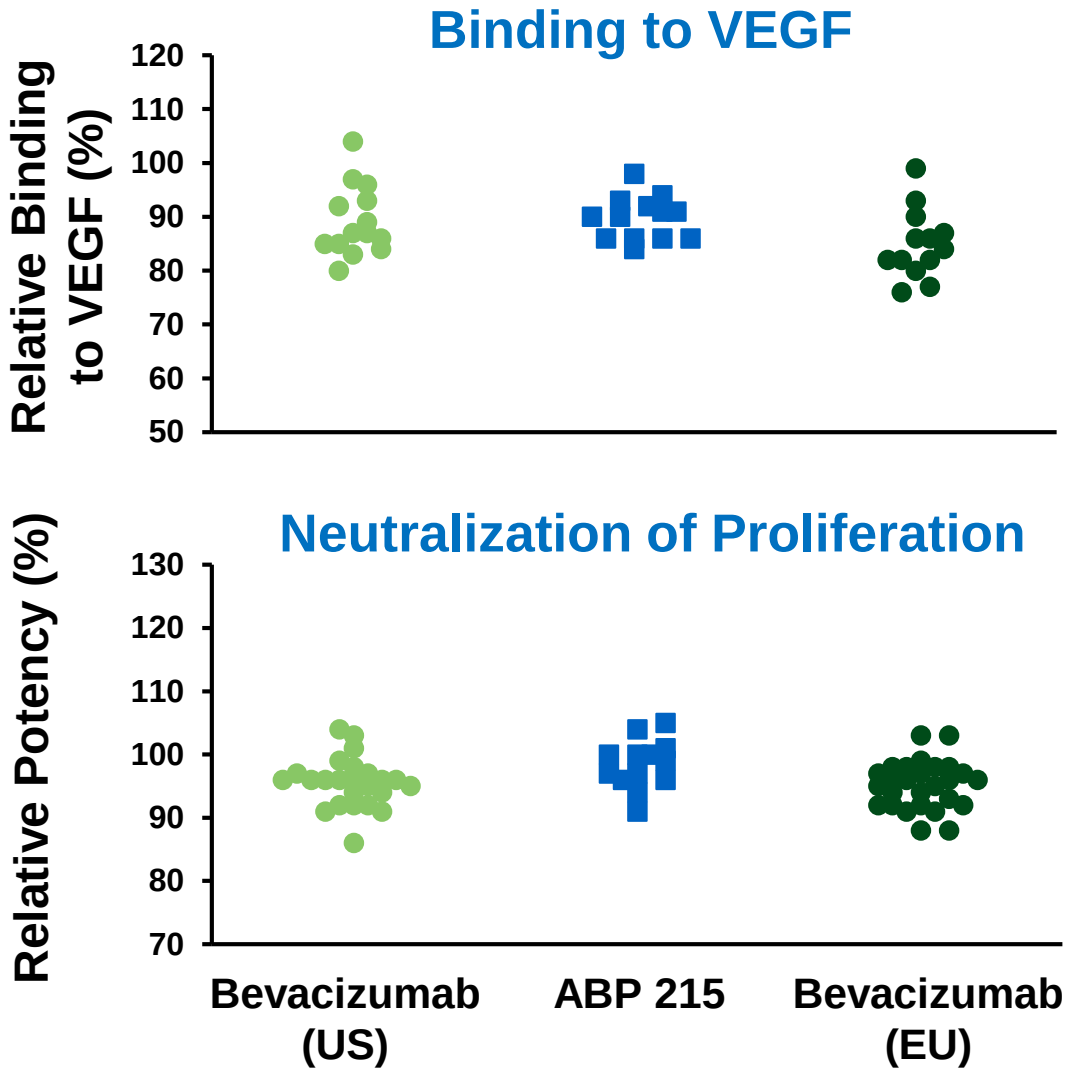
# Extrapolation Considerations

- **Product similarity (ABP 215 and bevacizumab)**
  - Analytical similarity
  - Nonclinical
  - Clinical pharmacology
  - Safety, efficacy, and immunogenicity
- **Considerations across indications (bevacizumab)**
  - Mechanism of action
  - PK distribution and clearance
  - Clinical considerations

**Extrapolation is applying the knowledge of efficacy and safety of the reference product to the highly similar biosimilar**

# Mechanism of Action in All Uses





# Similar Mechanism of Action

## Key Molecular Mechanisms

- Binding to all splice isoforms of VEGF-A
- Neutralization of all downstream VEGF-A signaling outcomes through VEGFR1 and VEGFR2—irrespective of cell type

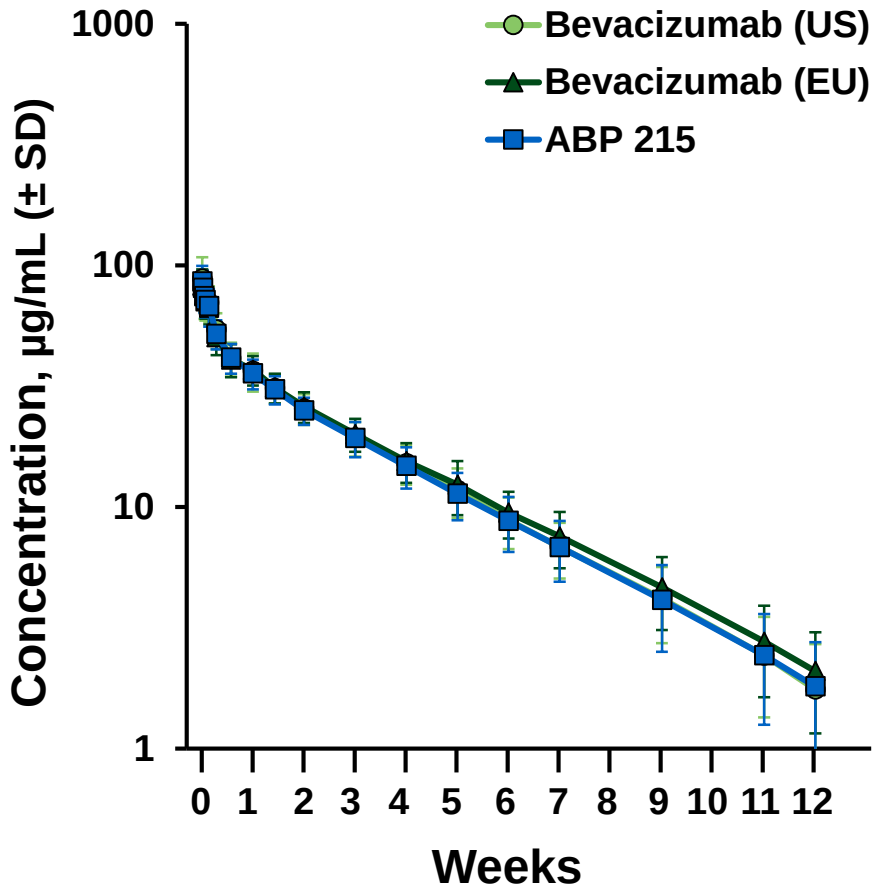
✓Common MOA

## Proposed Indications

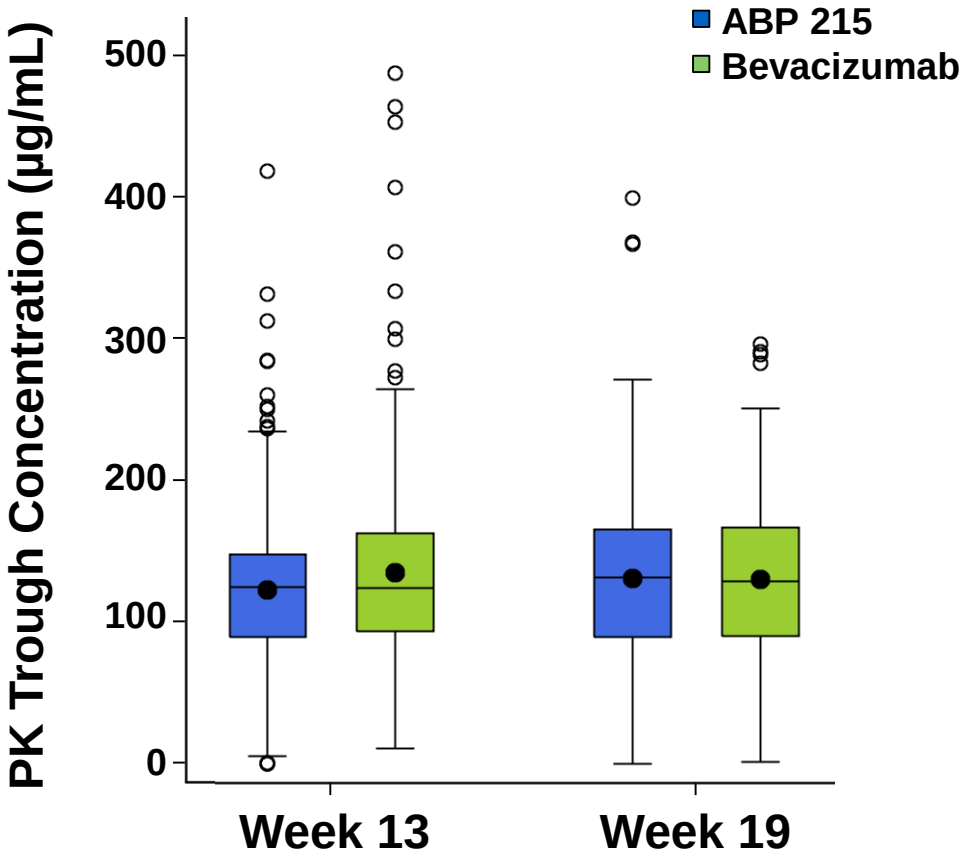
- Nonsquamous Non-small Cell Lung Cancer
- Metastatic Colorectal Cancer
- Metastatic Renal Cell Carcinoma
- Glioblastoma
- Cervical Cancer

# ABP 215 and Bevacizumab Pharmacokinetics

## Healthy Volunteers (3 mg/kg)

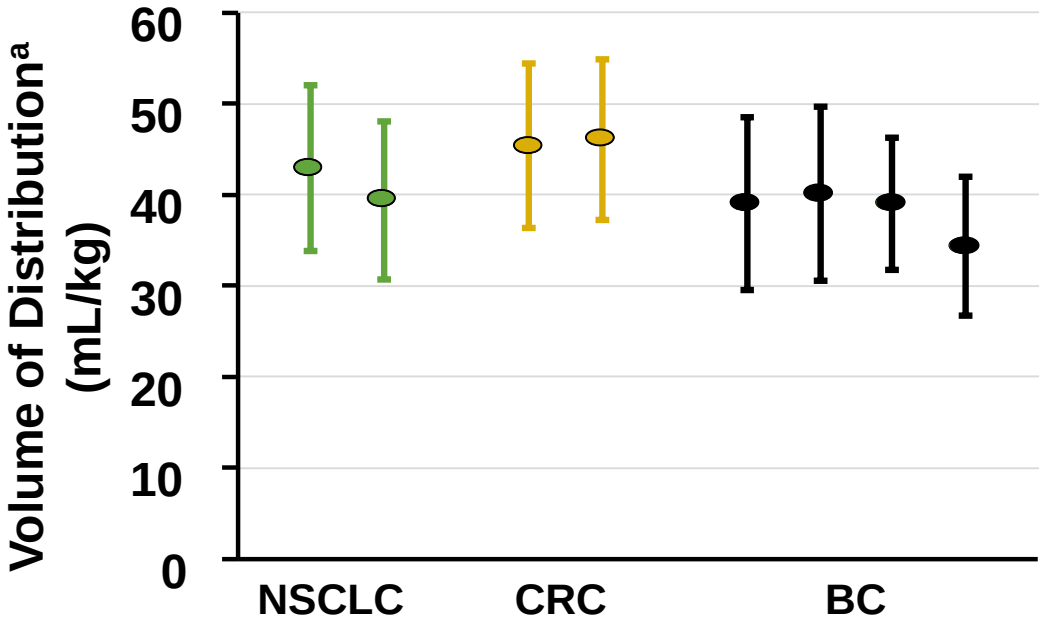


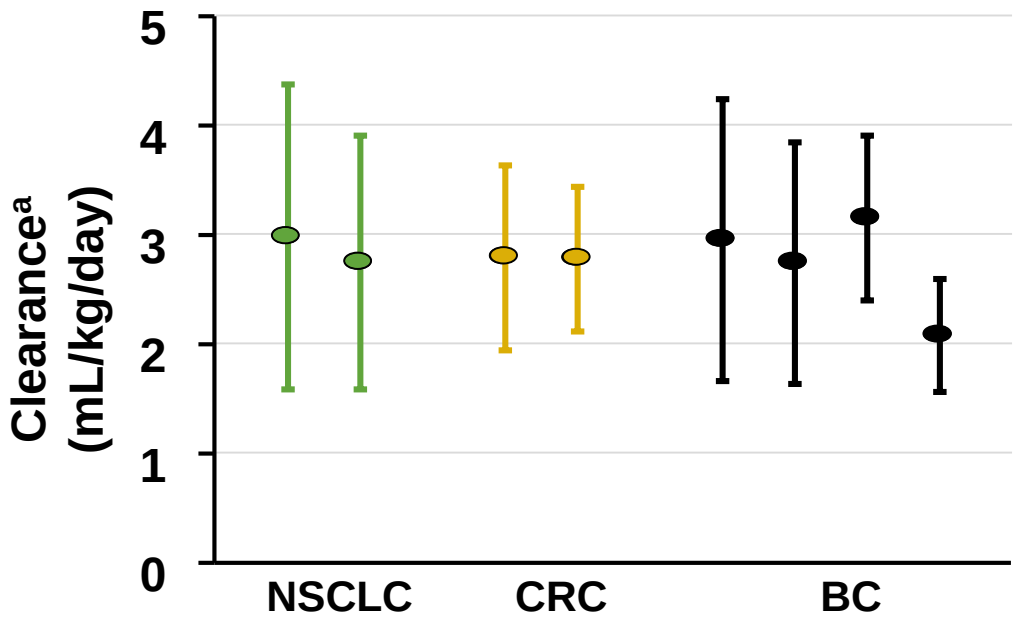

## Advanced NSCLC (15 mg/kg)




| | Week 13 | Week 19 |
|---|---|---|
| ABP 215, n= | 235 | 195 |
| Bev, n= | 233 | 208 |

# Similar PK Distribution and Clearance of Bevacizumab Across Different Tumor Types




- **Consistent PK properties also demonstrated in population PK analysis of bevacizumab (in NSCLC, CRC, GBM, BC, RCC, other tumors)[b]**

a. US and EMA prescribing information, Mean ± SD, BC approved in EU only.
b. Han et al, *Cancer Chemother Pharmacol* 2016. CRC=Colorectal Carcinoma, GBM=Glioblastoma Multiforme, BC=Breast Cancer, RCC=Renal Cell Carcinoma.

# Similar Pharmacokinetics

## Product Exposure

PK characteristics consistent with any dose or tumor type:

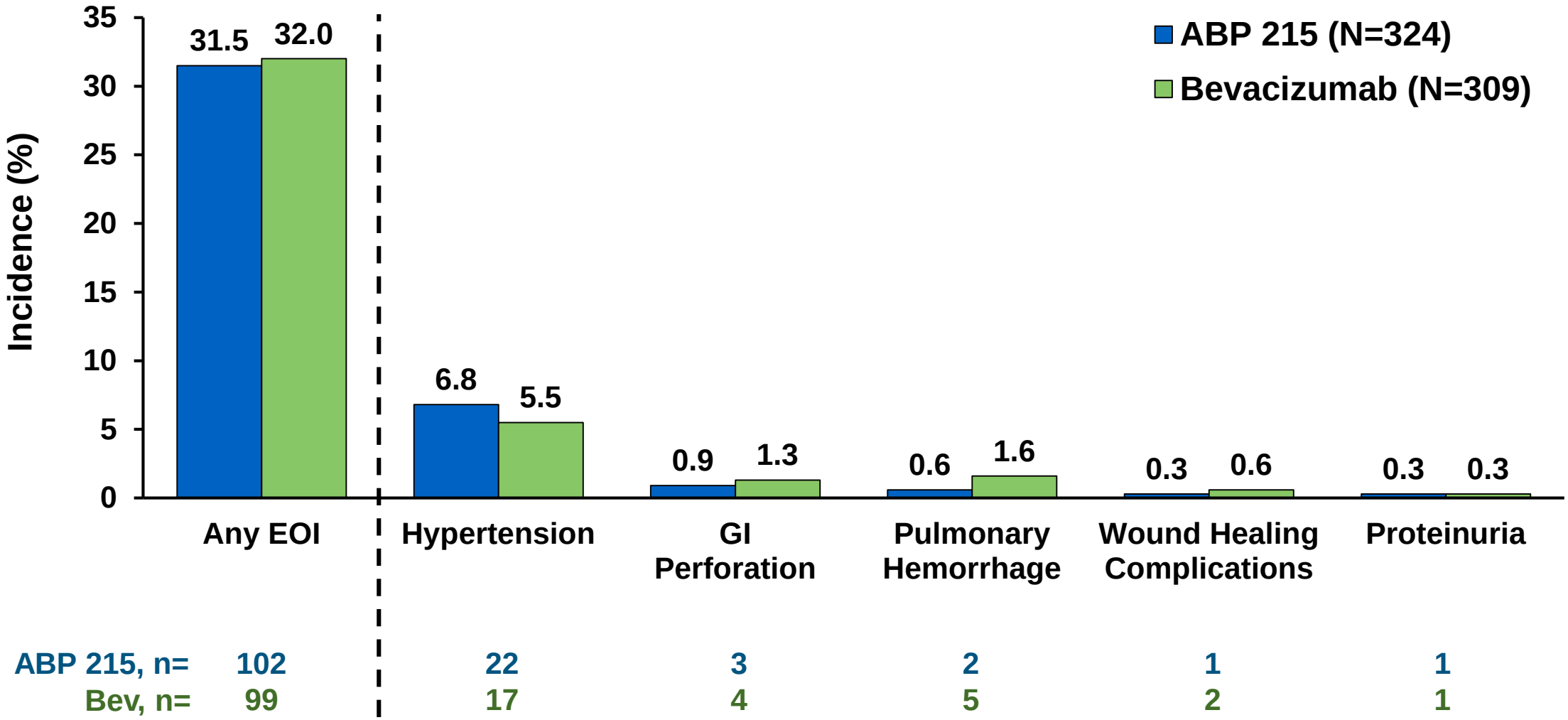
- Volume of distribution
- Clearance
- Half-life

✓Similar PK

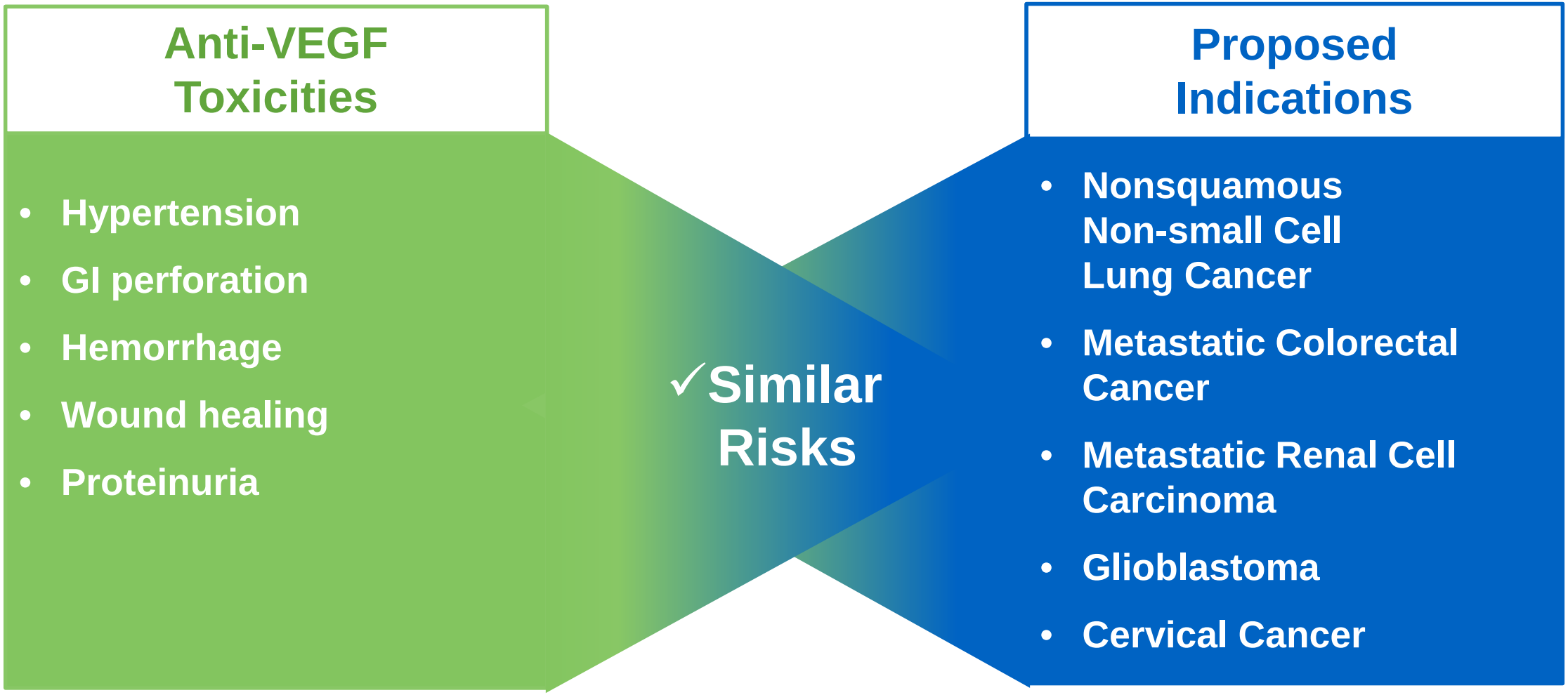
## Proposed Indications

- Nonsquamous Non-small Cell Lung Cancer
- Metastatic Colorectal Cancer
- Metastatic Renal Cell Carcinoma
- Glioblastoma
- Cervical Cancer

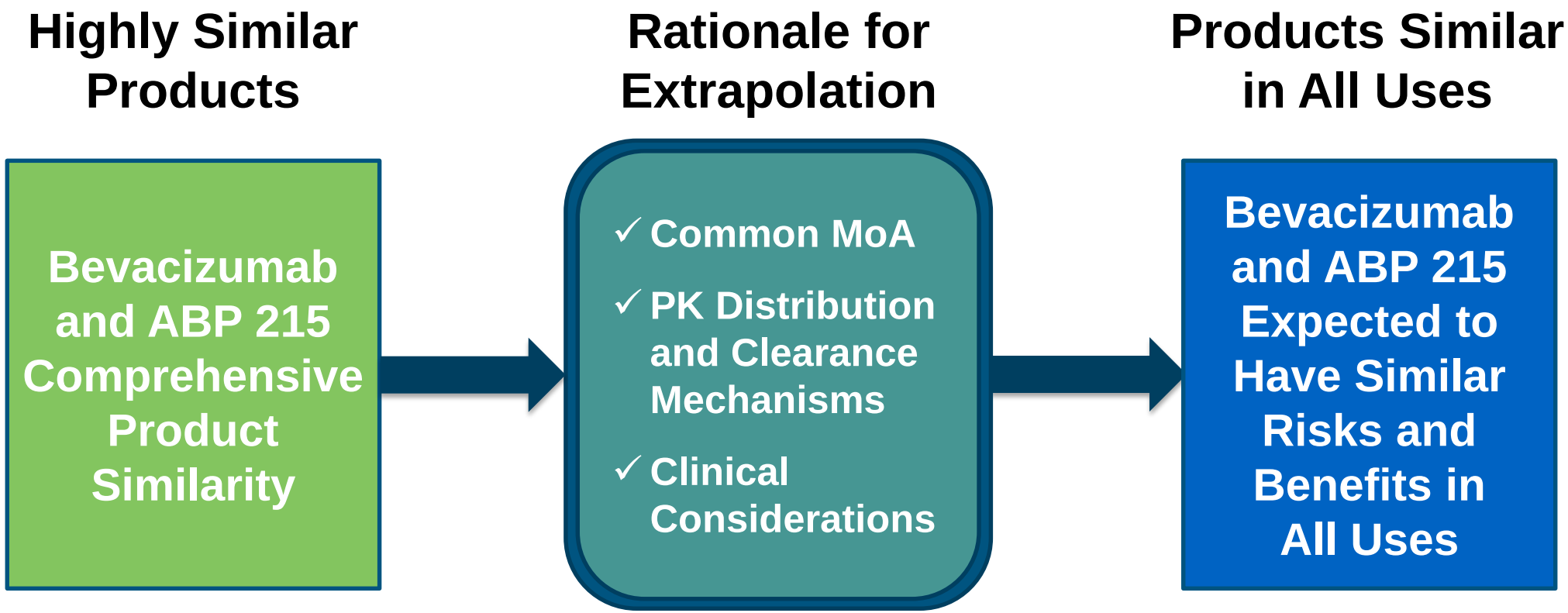
# Anti-VEGF Toxicities: AEs Grade ≥3 in NSCLC Study



# Similar Safety Profiles



# Extrapolation of Indications



# ABP 215 Proposed Indications of Use

- Nonsquamous Non-small Cell Lung Cancer
- Metastatic Colorectal Cancer
- Metastatic Renal Cell Carcinoma
- Glioblastoma
- Cervical Cancer

# Agenda

| | |
|---|---|
| **Introduction** | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| **Analytical Similarity** | **Simon Hotchin**<br>*Regulatory Affairs, Amgen* |
| **Non-Clinical and Clinical Similarity and Extrapolation to All Indications** | **Richard Markus, MD, PhD**<br>*Global Development, Amgen* |
| **Conclusion** | **Lisa Bollinger, MD**<br>*Regulatory Affairs and Safety, Amgen* |

# Conclusions

**Lisa Bollinger, MD**

*VP Regulatory Affairs & Safety*

# Statutory Requirements: Biosimilarity

**Section 351(i) of the PHS Act defines biosimilarity to mean**

- "that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components" and

  √ *Structural and functional similarity demonstrated*

- that "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product."

  √ *Equivalent PK, efficacy, similar safety and immunogenicity demonstrated*

# Statutory Requirements: Extrapolation

**PHS Act allows biosimilar sponsor to seek licensure for one or more conditions of use if:**

- Biosimilarity supported by data from one or more clinical study in an appropriate condition of use
  - √ *Double blind, randomized study in patients with NSCLC (n=642)*

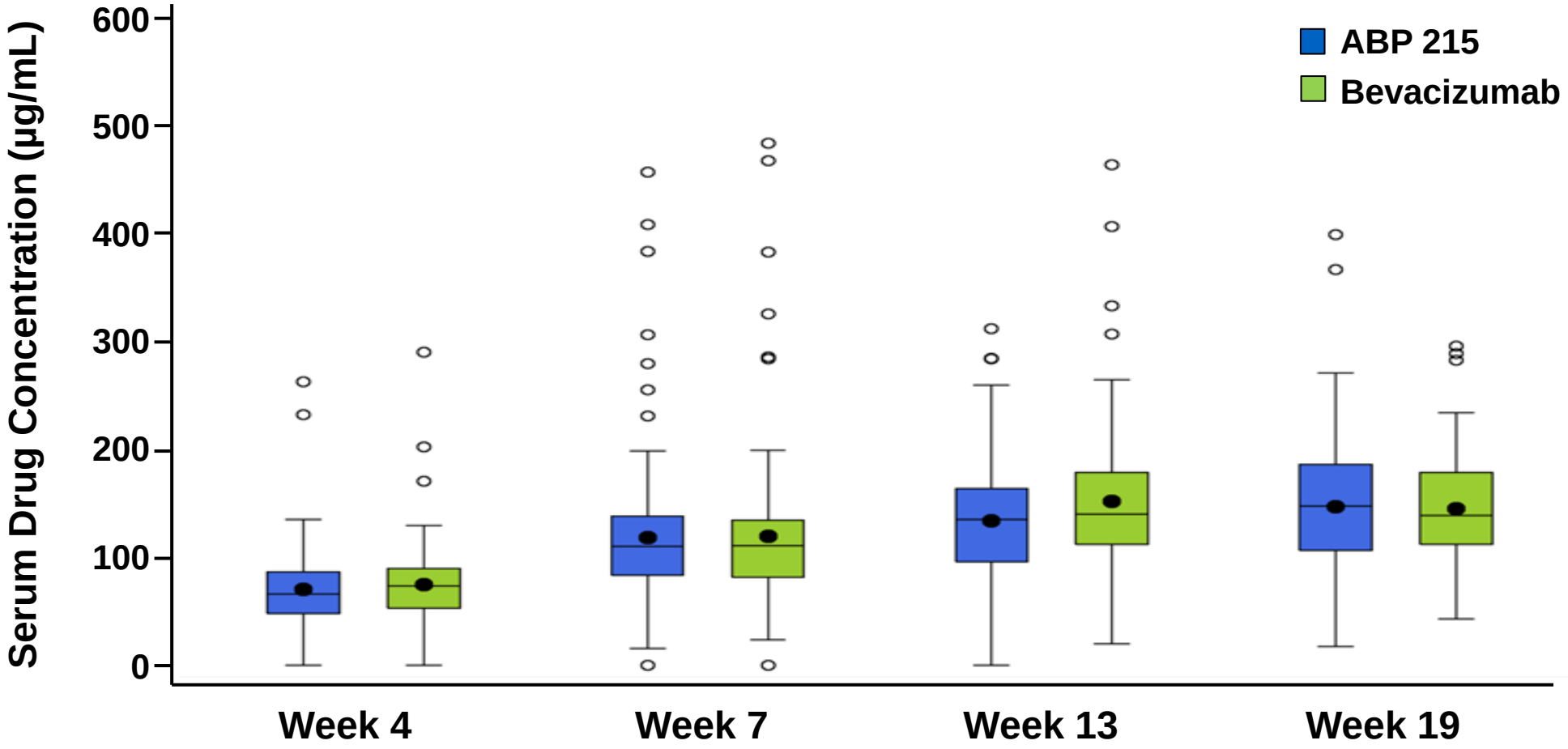
- **Scientific justification for extrapolation of biosimilarity to each condition of use is provided**
  - √ *Mechanism of Action (VEGF neutralization)*
  - √ *PK distribution and clearance*
  - √ *Clinical considerations*

# Amgen’s Commitment

- Increased access to an important oncology therapy
- Same pharmacovigilance system and manufacturing as other Amgen products
- High quality biosimilar option for patients

# Supporting Slides

# NSCLC: PK Trough Concentrations by Visit (Female)




| | Week 4 | Week 7 | Week 13 | Week 19 |
|---|---|---|---|---|
| ABP 215, n= | 111 | 109 | 96 | 78 |
| Bev, n= | 113 | 112 | 95 | 87 |

# NSCLC: Exposure Summary – IP

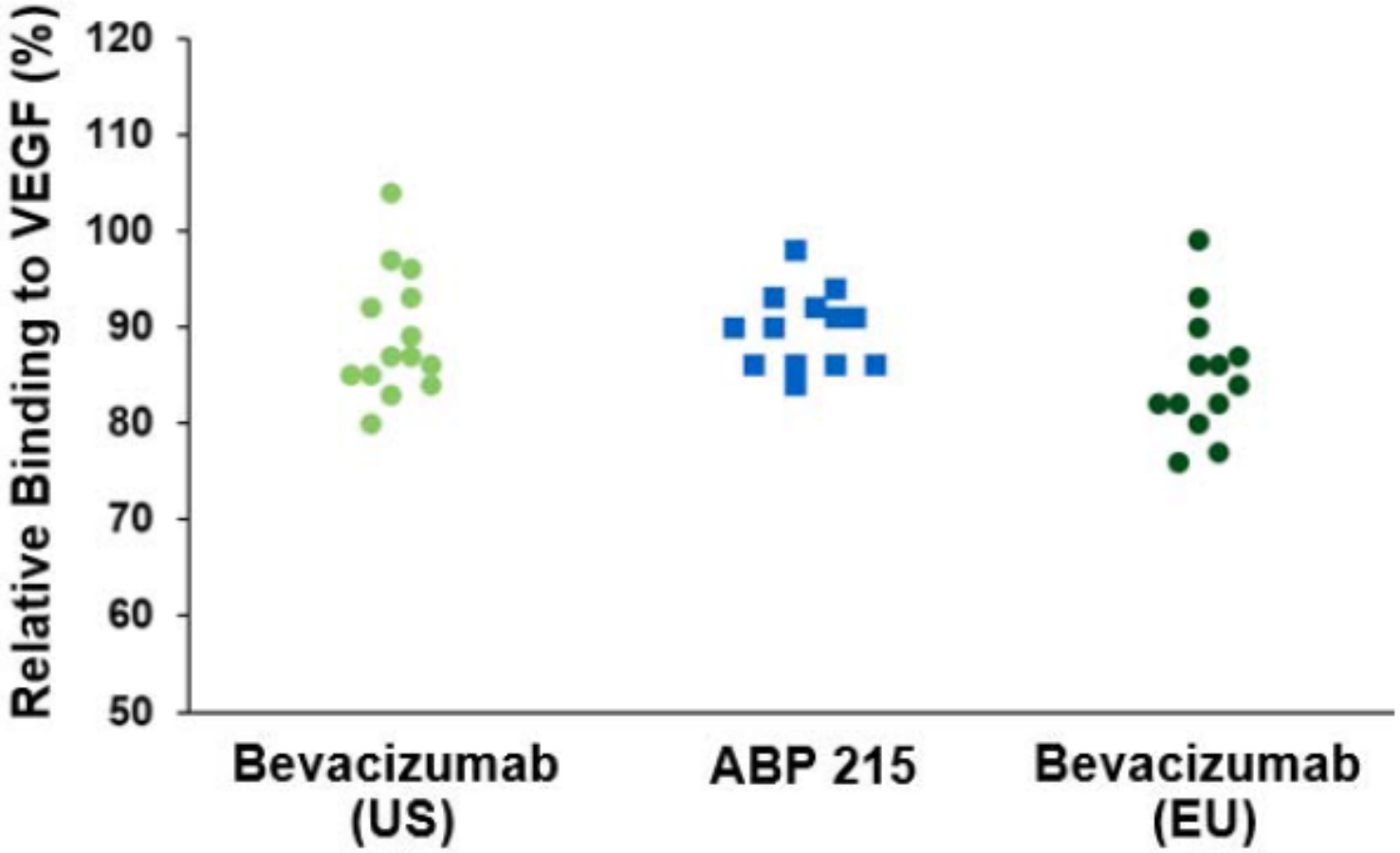
| | ABP 215 N=324 | Bevacizumab N=309 |
|---|---|---|
| **Total number of IP doses administered** | | |
| Mean (SD) | 4.8 (1.76) | 5.0 (1.61) |
| Median | 6.0 | 6.0 |
| Q1, Q3 | 4.0, 6.0 | 4.0, 6.0 |
| Min, Max | 1, 7 | 1, 6 |
| **Cumulative total dose of IP administered (mg/kg)[a]** | | |
| Mean (SD) | 71.3 (26.32) | 74.8 (24.22) |
| Median | 90.0 | 90.0 |
| Q1, Q3 | 60.0, 90.0 | 60.0, 90.0 |
| Min, Max | 15, 105 | 15, 90 |

a. Four subjects received partial dose and were therefore excluded.

# NSCLC: Exposure Summary – Chemotherapy

| | ABP 215 N=324 | Bevacizumab N=309 |
|---|---|---|
| Subjects receiving ≥1 dose of paclitaxel, n | 323 | 309 |
| Total number of doses administered | | |
| Mean (SD) | 4.5 (1.69) | 4.7 (1.56) |
| Median | 5.0 | 5.0 |
| Q1, Q3 | 4.0, 6.0 | 4.0, 6.0 |
| Min, Max | 1, 7 | 1, 6 |
| Subjects receiving ≥1 dose of carboplatin, n | 320 | 309 |
| Total number of doses administered | | |
| Mean (SD) | 4.6 (1.67) | 4.7 (1.57) |
| Median | 5.0 | 5.0 |
| Q1, Q3 | 4.0, 6.0 | 4.0, 6.0 |
| Min, Max | 1, 7 | 1, 6 |

# F2. pg 9. Relative Binding to VEGF




VEGF = vascular endothelial growth factor.

Binding was calculated relative to the ABP 215 reference standard.