Rituximab and Hyaluronidase injection, for subcutaneous use *(rituximab SC)*

BLA 761064

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Proposed Indications for Rituximab SC

a. Follicular Lymphoma (FL)

… indicated for the treatment of patients with:

- Relapsed or refractory, FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to *TRADENAME™* for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

Proposed Indications for Rituximab SC

b. Diffuse Large B-Cell Lymphoma (DLBCL)

… indicated for the treatment of patients with previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline-based chemotherapy regimens.

c. Chronic Lymphocytic Leukemia (CLL)

… indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CLL.

Comparison between rituximab intravenous (IV) and rituximab SC

Characteristics	Rituximab IV	Rituximab SC
Administration	IV infusion over 1.5 to 2.5 hours	SC injection over 5 minutes
Rituximab Concentration	10 mg/mL	120 mg/mL
Co-formulation	none	Hyaluronidase
Dosing regimen	Body surface area - based	Fixed
Doses	375 mg/m^2 → 1400 mg 500 mg/m^2 → 1600 mg	

Regulatory Considerations

Regular Approval as a 351(a) biologic

- Public Health Service Act
- Biologic must be shown to be “safe, pure, and potent” to be approved.
  - The concept of potency has long been interpreted to include effectiveness.
- Requires the conduct of adequate and well-controlled clinical trials

Regulatory Considerations

FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

"In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form."

Regulatory Considerations

FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

"It may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic (PK) data without an additional clinical efficacy trial."

BLA 761064 Rituximab SC

- **PK-bridging approach**
  - targeted a trough concentration (C_{trough}) for the rituximab SC product that would be at least as high as that achieved with IV rituximab
- **Additional changes**
  - Use of fixed-dose regimen
  - Use of hyaluronidase to facilitate drug absorption

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Rituximab and Hyaluronidase

BLA 761064

FDA Presentation Outline

a. Clinical Pharmacology	Lanre Okusanya, PharmD, MS
b. Efficacy	Jingjing Ye, PhD
c. Safety	Alexandria Schwarsin, MD
d. Patient Preference and Conclusion	Vishal Bhatnagar, MD

Clinical Pharmacology

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Clinical Pharmacologist
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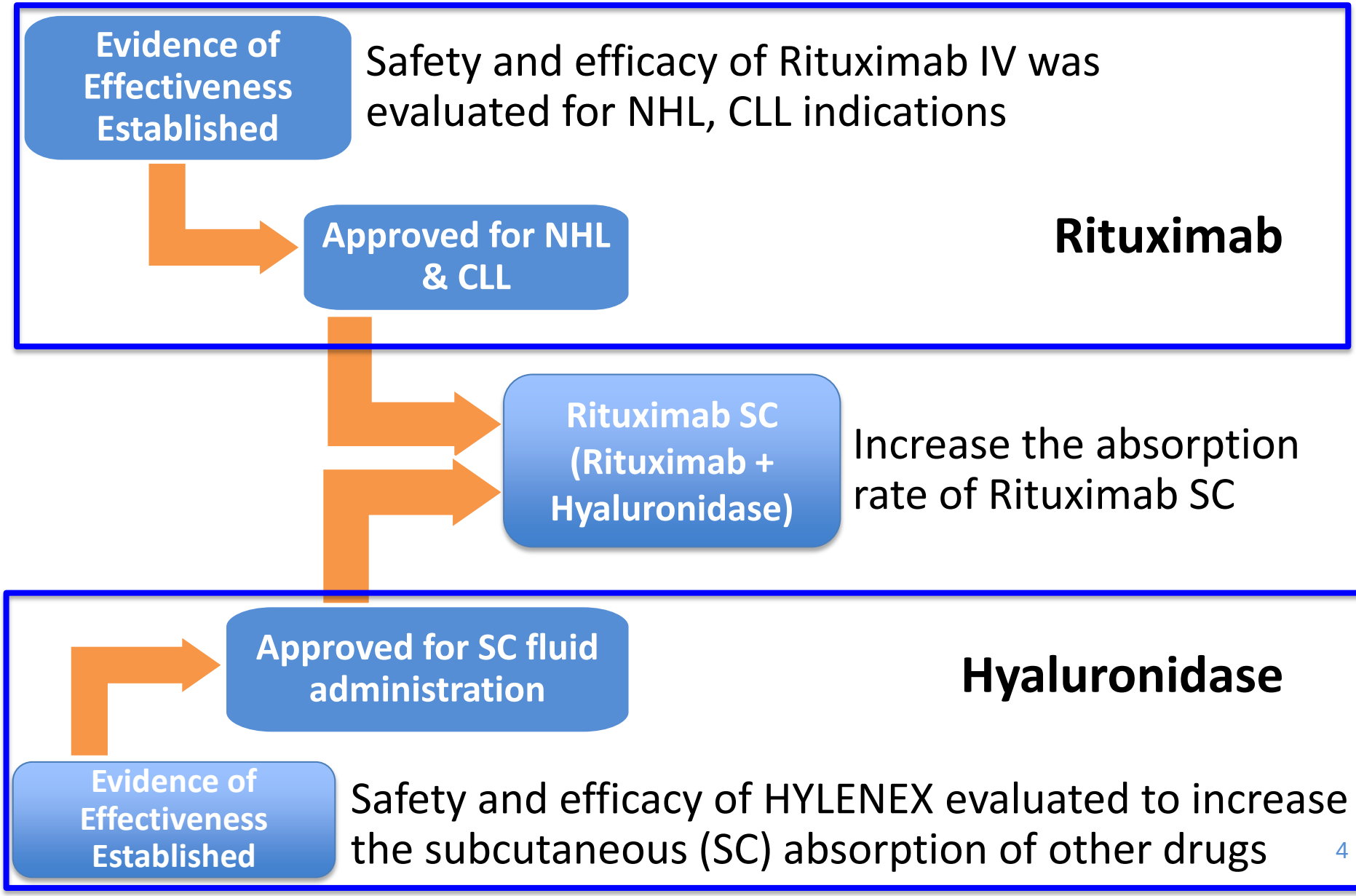
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS), CDER, FDA

Clinical Pharmacology Outline

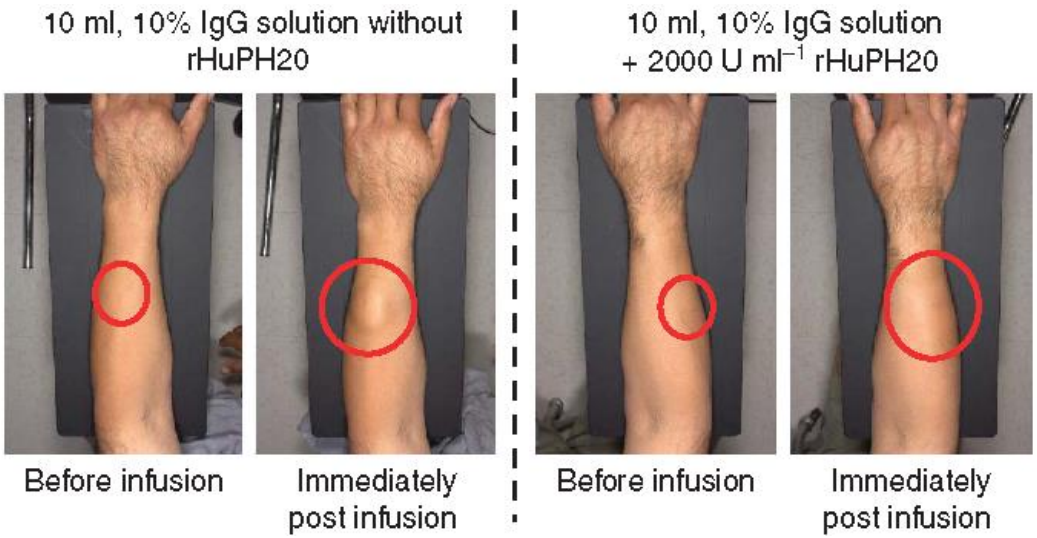
- Background
  - Rituximab and hyaluronidase (Rituximab SC) Development Pathway
  - Pharmacokinetic (PK) Bridging Strategy for Rituximab SC
- Studies Supporting PK bridging for Rituximab SC
- Key Questions
  - Efficacy
    - Do the proposed fixed doses of 1400 mg for Non Hodgkin's Lymphoma (NHL) and 1600 mg for Chronic Lymphocytic leukemia (CLL) provide adequate exposures relative to that following intravenous (IV) doses?
    - Do the proposed fixed doses provide adequate exposure to replace body surface area (BSA)-based dosing regimen?
  - Safety
    - Do differences in C_{trough} between rituximab SC and rituximab IV influence safety?

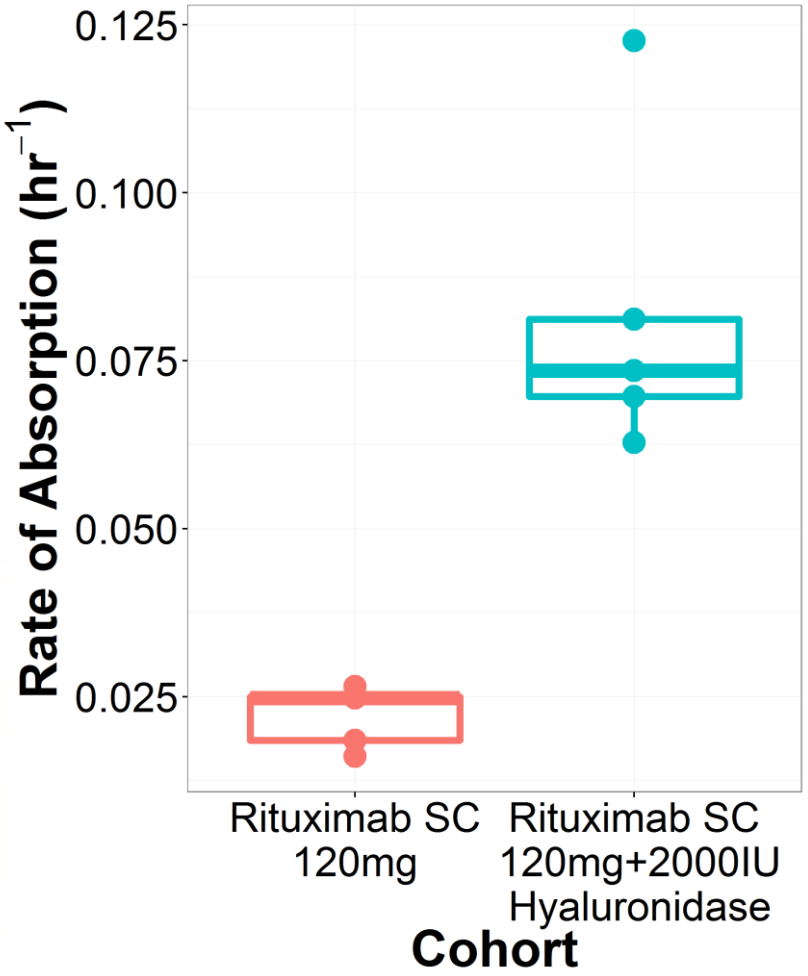
Rituximab SC Development



Hyaluronidase Increases the Rate of SC Absorption

- Hyaluronidase was shown to increase the rate of rituximab absorption in minipigs
- Facilitates the SC absorption of large volumes





British Journal of Cancer (2013) 109, 1556–1561

Rituximab SC Development

- Rituximab SC development is based on the predicate that it is "*a different dose, regimen, or dosage form*" of rituximab IV
  - PK data can be used to bridge the 2 formulations
- Safety and efficacy of rituximab IV has been established
- Effectiveness may be shown without the use of efficacy trials in certain cases

FDA Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998

Precedent for Using PK Bridging

- Examples
  - Addition of IV route of administration to labeling
    - Asparaginase *Erwinia chrysanthemi*
  - Oral to IV
    - Temozolomide intravenous from temozolomide capsules
  - Immediate release to Extended release for once daily dosing
    - Extended-release carvedilol (carvedilol phosphate) from carvedilol immediate release tablets
  - Spray to Powder
    - Nitroglycerin powder from Nitrolingual pumpspray

PK Bridging for Rituximab SC

- C_{trough} and the area under the drug concentration-time curve (AUC) are correlated with the efficacy and safety of chronically administered drugs

- Rituximab concentrations after IV administration have been correlated with efficacy (Overall response rate (ORR) and Progression Free survival (PFS))

- Achieving a equal or higher rituximab exposures after SC administration is expected to result in similar efficacy

Rituximab C_{trough} is Appropriate for PK Bridging

- The rituximab C_{trough} after IV doses can serve as reference threshold required for efficacy

- Rituximab SC C_{trough} equal to or greater than that following rituximab IV is an acceptable endpoint for PK bridging

Key Questions

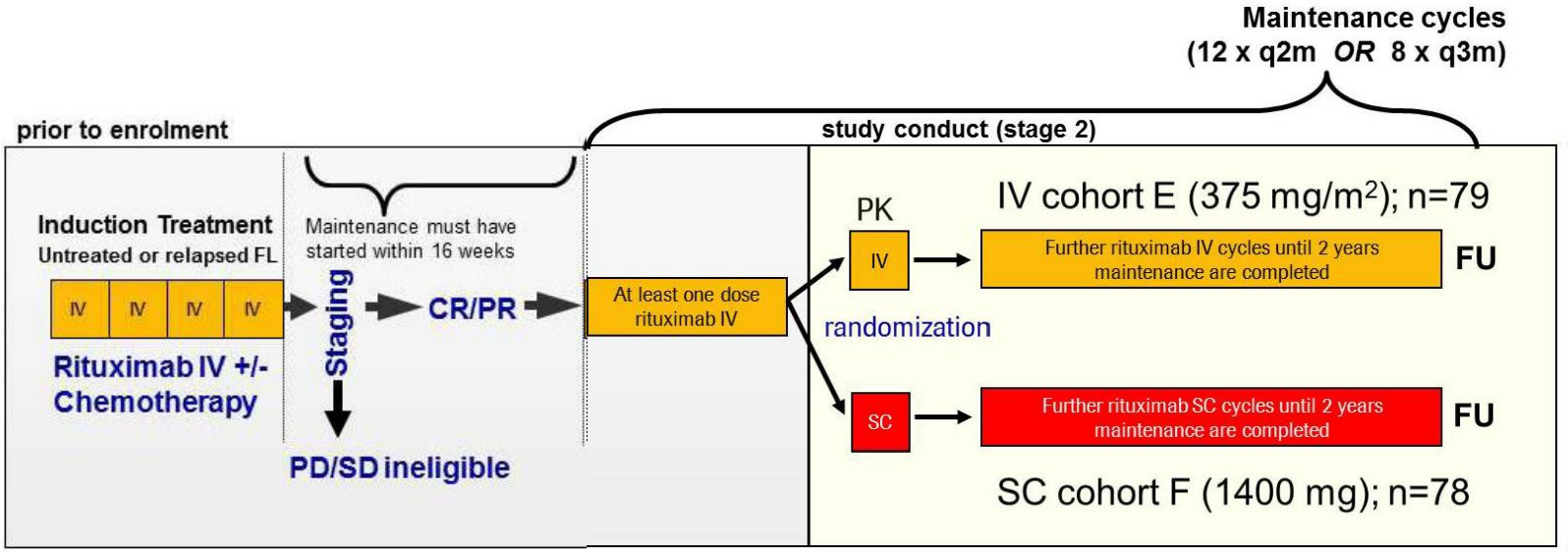
- Efficacy
  - Do the proposed fixed doses of 1400 mg for NHL and 1600 mg for CLL provide adequate exposures relative to that following IV doses?
  - Do the proposed fixed doses provide adequate exposure to replace BSA-based dosing regimen?

- Safety
  - Do differences in C_{trough} between rituximab SC and rituximab IV influence safety

Studies Used to Support Dose Selection and Dose Confirmation

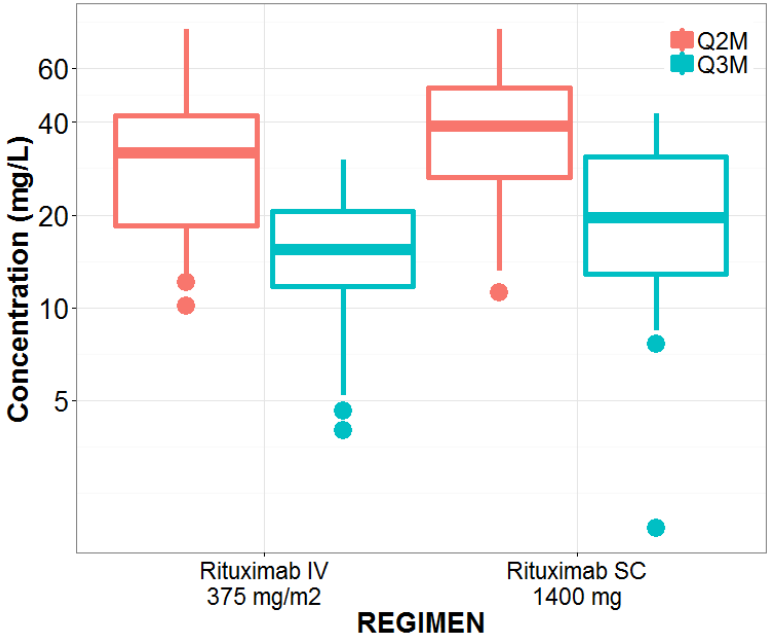
	STUDY	
	DOSE SELECTION STAGE OBJECTIVE	DOSE CONFIRMATION STAGE OBJECTIVE
SparkThera Follicular Lymphoma (FL)	Determine a SC dose that yielded comparable C_{trough} to IV dose	Demonstrate C_{trough} non-inferiority of SC dose in FL maintenance
SABRINA FL		Demonstrate C_{trough} non-inferiority compared to 375 mg/m^2 IV
SAWYER CLL	Determine a SC dose that yielded comparable C_{trough} to IV dose	Demonstrate C_{trough} non-inferiority compared to 500 mg/m^2 IV

Dose Selection in SparkThera (FL)



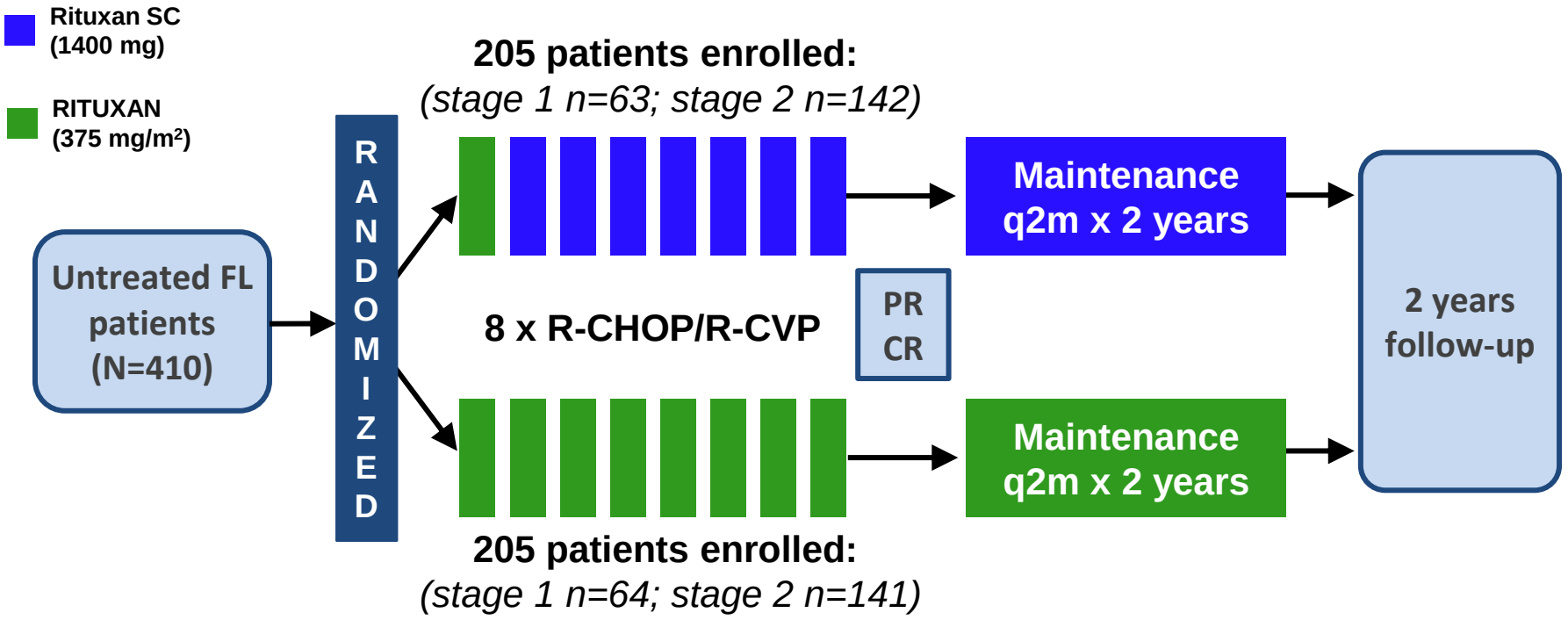
- The 800 mg/m^2 SC dose showed equal/higher C_{trough} as rituximab 375 mg/m^2 IV

- The 1400 mg SC achieved C_{trough} equal/higher than 375 mg/m^2 IV



Source: Applicant BLA submission

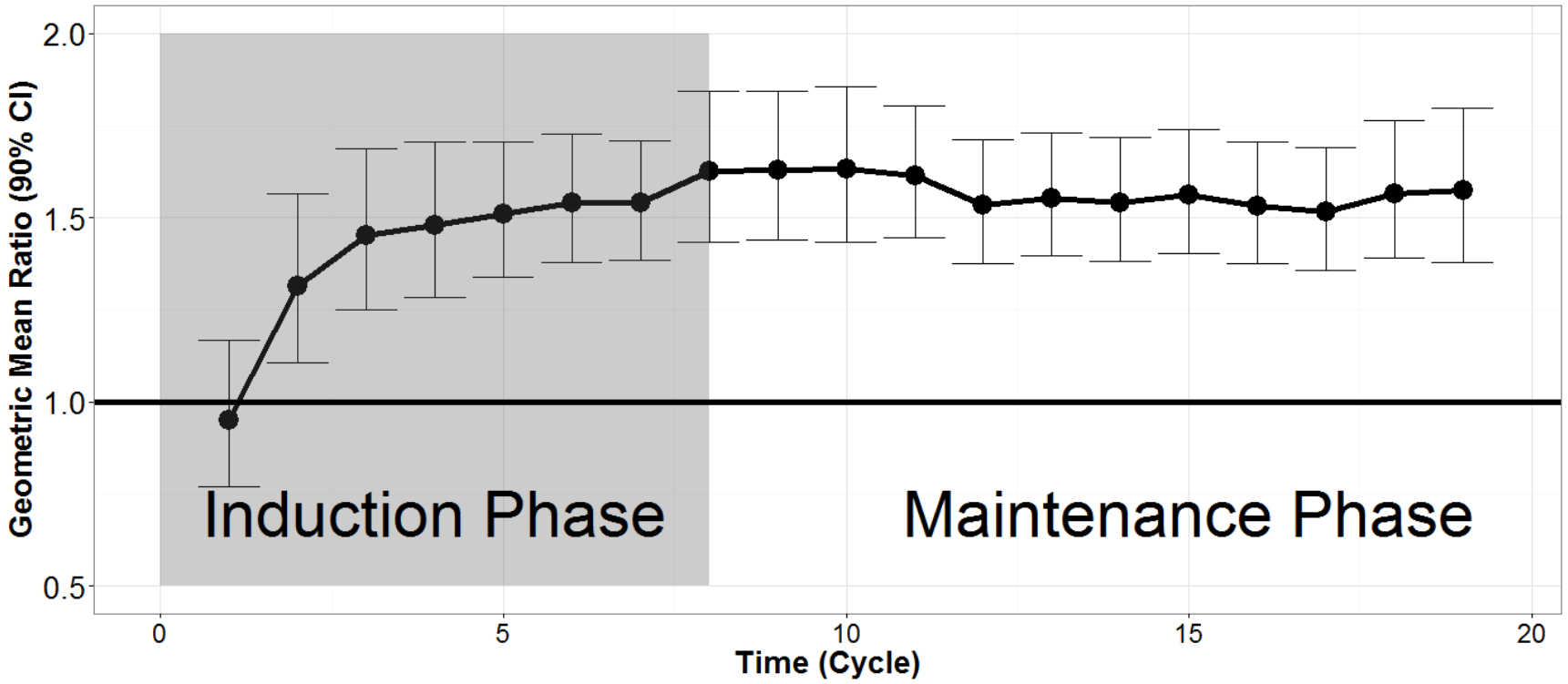
Dose Confirmation in SABRINA (FL)



Goal: C_{trough} comparison after IV and SC administration in the NHL induction setting

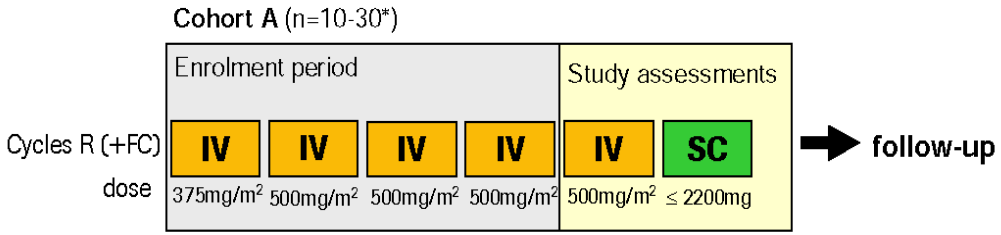
Source: Applicant BLA submission

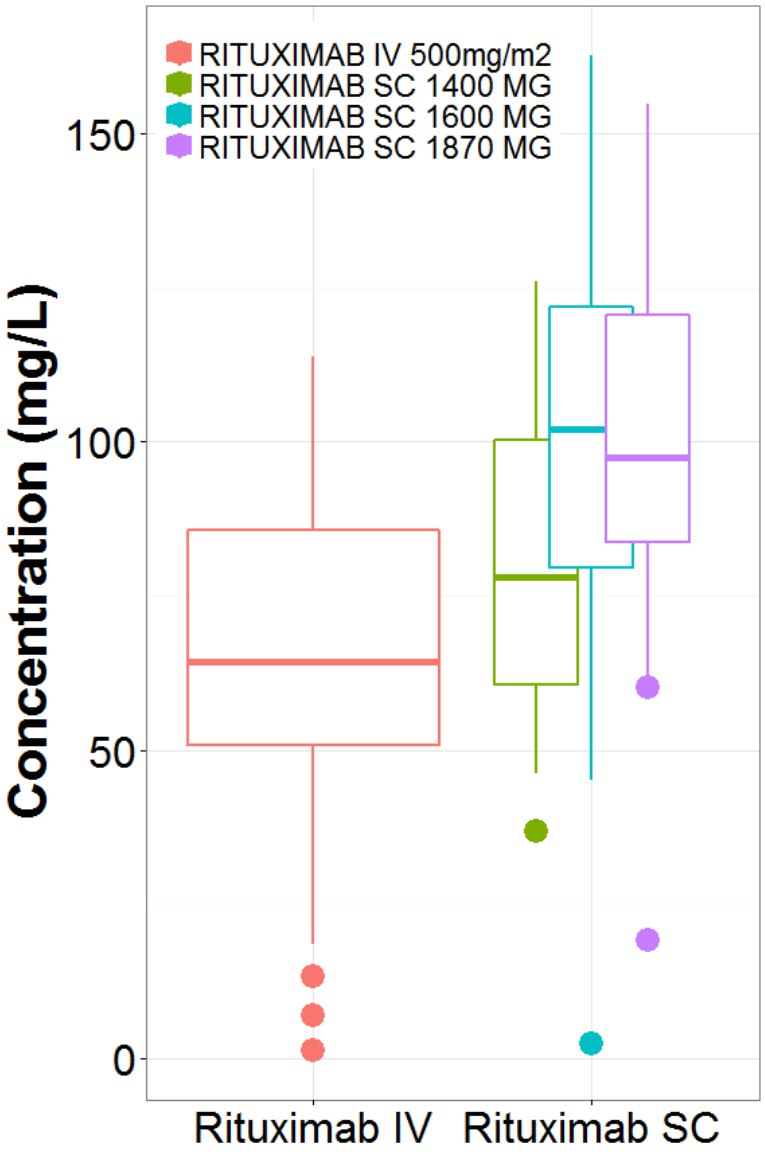
Dose Confirmation in SABRINA (FL)



The 1400 mg SC dose achieved equal or higher C_{trough} than then 375 mg/m^2 IV for induction and maintenance phases

Dose Selection in CLL (SAWYER - Part 1)

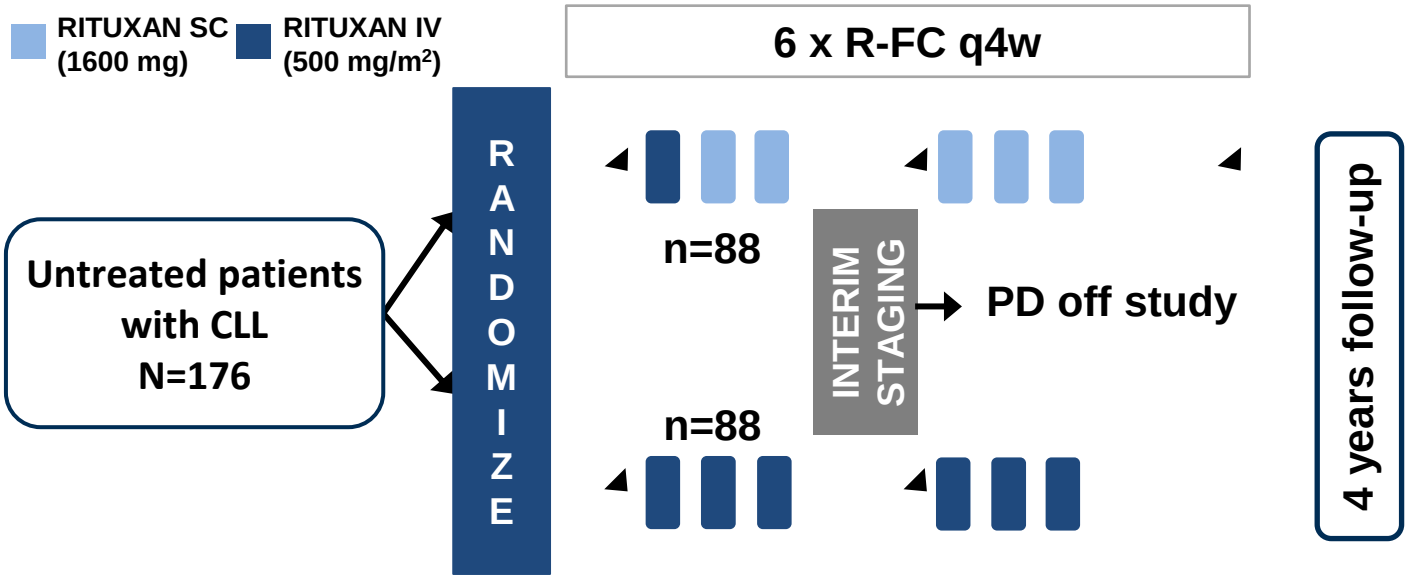




The 1600 mg SC dose achieved C_{trough} equal/higher than the 500 mg/m² IV dose

Source: Applicant BLA submission

Dose Confirmation in CLL (SAWYER –Part 2)

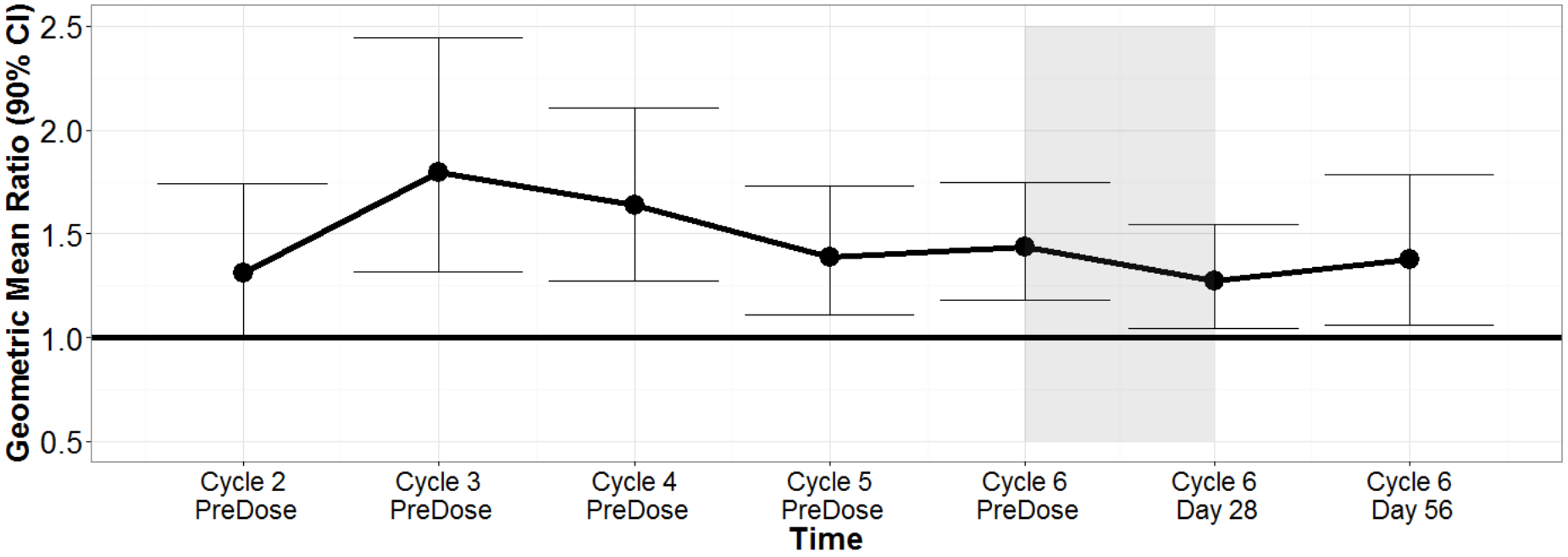


R-FC = Rituximab, Fludarabine and cyclophosphamide

Goal: C_{trough} comparison after IV and SC administration

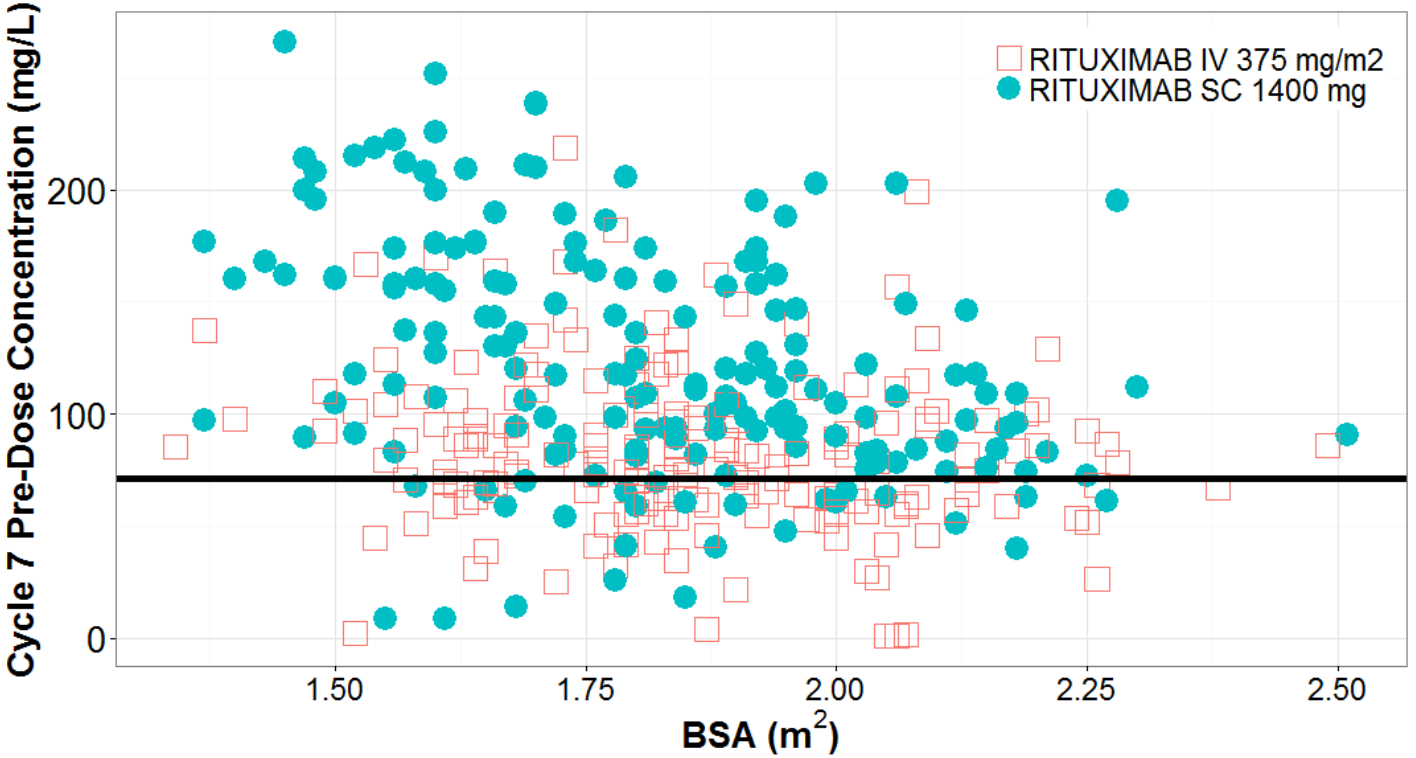
Source: Applicant BLA submission

Dose Confirmation in CLL (SAWYER)



The 1600 mg SC dose achieved equal/higher C_{trough} than the 500 mg/m^2 IV over the course of the study

1400 mg and 1600 Doses Provide Consistent Exposure Across all BSA Sizes



- Relative to the rituximab IV, the C_{trough} after the 1400 mg dose resulted in consistent exposure across all BSA sizes
- A similar result was observed for the 1600 mg dose compared to the 500 mg/m^2 IV dose for CLL

No Exposure-Safety Relationships Observed

- No significant relationships between exposure and neutropenia was observed based on data from either the FL or CLL studies

- No significant relationships between exposure and adverse events (AE), serious AE, Grade 3+ AE were observed based on data from the FL or CLL

- Numerical differences in AE were observed and will be addressed by the clinical reviewer

Clinical Pharmacology Summary

- Dose
  - Do the proposed fixed doses of 1400 mg for NHL and 1600 mg for CLL provide adequate exposures relative to that following IV doses?
    Fixed 1400 and 1600 mg SC doses of Rituximab lead to equal or higher rituximab C_{trough} than Rituximab IV
  - Do the proposed fixed doses provide adequate exposure to replace BSA-based dosing regimen?
    The fixed SC doses provide consistent exposure relative to the BSA-based IV doses
- Safety
  - Do differences in C_{trough} between rituximab SC and rituximab IV influence safety
    No significant exposure-safety relationships were observed.

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Efficacy

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Mathematical Statistician
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Office of Biometrics (OB), OTS, CDER, FDA

Overview

- Four randomized clinical trials
- No pre-specified hypothesis to test for efficacy- the objective only to describe the observed data
- Primary efficacy endpoint– Response rate
- Multiple secondary endpoints – no adjustment for multiplicity

Randomized Clinical Studies

Study	Patient Population	Ratio	Treatment Arms/ # Subjects	Primary Endpoint	Secondary Endpoints
BO22334/ **SABRINA**	FL	1:1	SC+CHOP or CVP / **205** IV+CHOP or CVP / **205**	Investigator-assessed ORR, induction	ORR, CRR, induction ORR, CRR, maintenance PFS, EFS, OS
MO28107/ **MabEase**	DLBCL	2:1	SC+CHOP / **381** IV+CHOP / **195**	Investigator-assessed CR/CRu, induction	PFS, DFS, EFS,OS
MO28457/ **PrefMab**	FL/DLBCL	1:1	Arm A: SC->IV / **372** Arm B: IV->SC / **371**	% patients who preferred SC over IV, cycle 8	CR/CRu PFS, DFS, EFS, OS
BO25341/ **SAWYER**	CLL	1:1	SC+FC / **88** IV+FC / **88**	Non-inferiority in Ctrough between SC vs IV	CR, CRi, PR

CRR: Complete Response Rate; EFS: Event-Free Survival; DFS: Disease-Free Survival; OS: Overall Survival
PFS: Progression-Free Survival; PR: Partial Response; CRu: Complete Response Unconfirmed
CRi: Complete Response with incomplete bone marrow recovery

FDA's Evaluation of Efficacy

- To ensure that efficacy is not compromised by using SC compared to IV

Primary Endpoint: Response Rates

- Comparable results in response rates between arms

Study	Endpoints	IV	SC	Diff: SC-IV, 95% CI	Response Rate Ratio: SC/IV, 95% CI
SABRINA (FL)	ORR, Induction	84.9%	84.4%	-0.5% [-7.7, 6.8]	0.99 [0.92, 1.08]
MabEase (DLBCL)	CR, Induction	42.1%	47%	4.9% [-3.6, 13.5]	1.12 [0.92, 1.36]

Response rate ratio > 1 favors SC
CI = Confidence Interval

SABRINA (FL), 2º Endpoints

- Response rates comparable

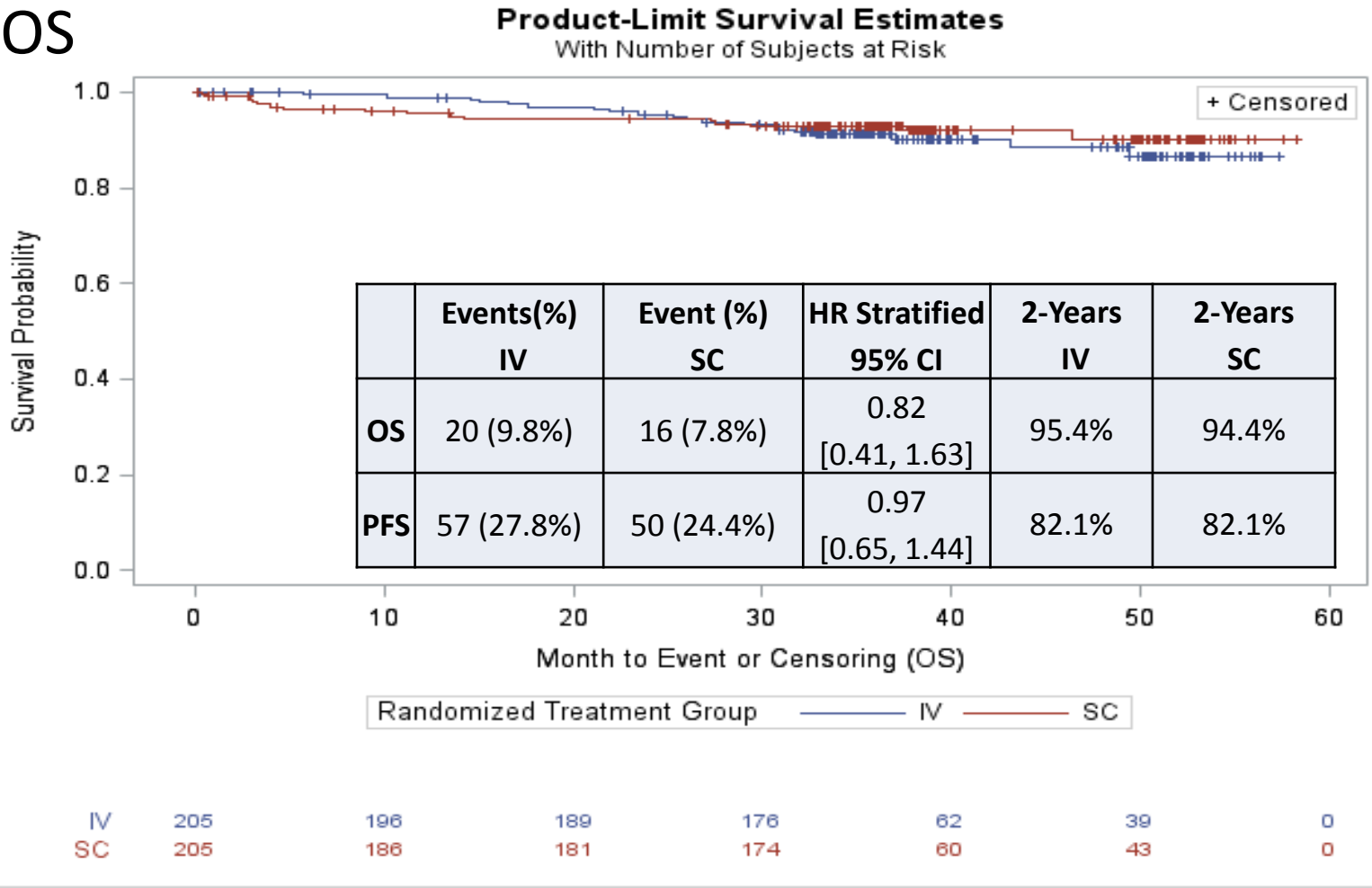
Endpoints	IV	SC	Diff: SC-IV, 95% CI	Response Rate Ratio: SC/IV, 95% CI
CR/CRu, induction	32.2% (66/205)	32.2% (66/205)	0.0% [-9.3, 9.3]	1.00 [0.76, 1.32]
ORR, Maintenance	78.1% (139/178)	77.9% (134/172)	-0.2% [-9.2, 8.8]	1.00 [0.89, 1.12]
CR/CRu, maintenance	56.2% (100/178)	50.6% (87/172)	-5.6% [-16.4, 5.2]	0.90 [0.74, 1.10]

Response rate ratio > 1 favors SC

SABRINA (FL), 2º Endpoints

Comparable results between treatment arms

OS



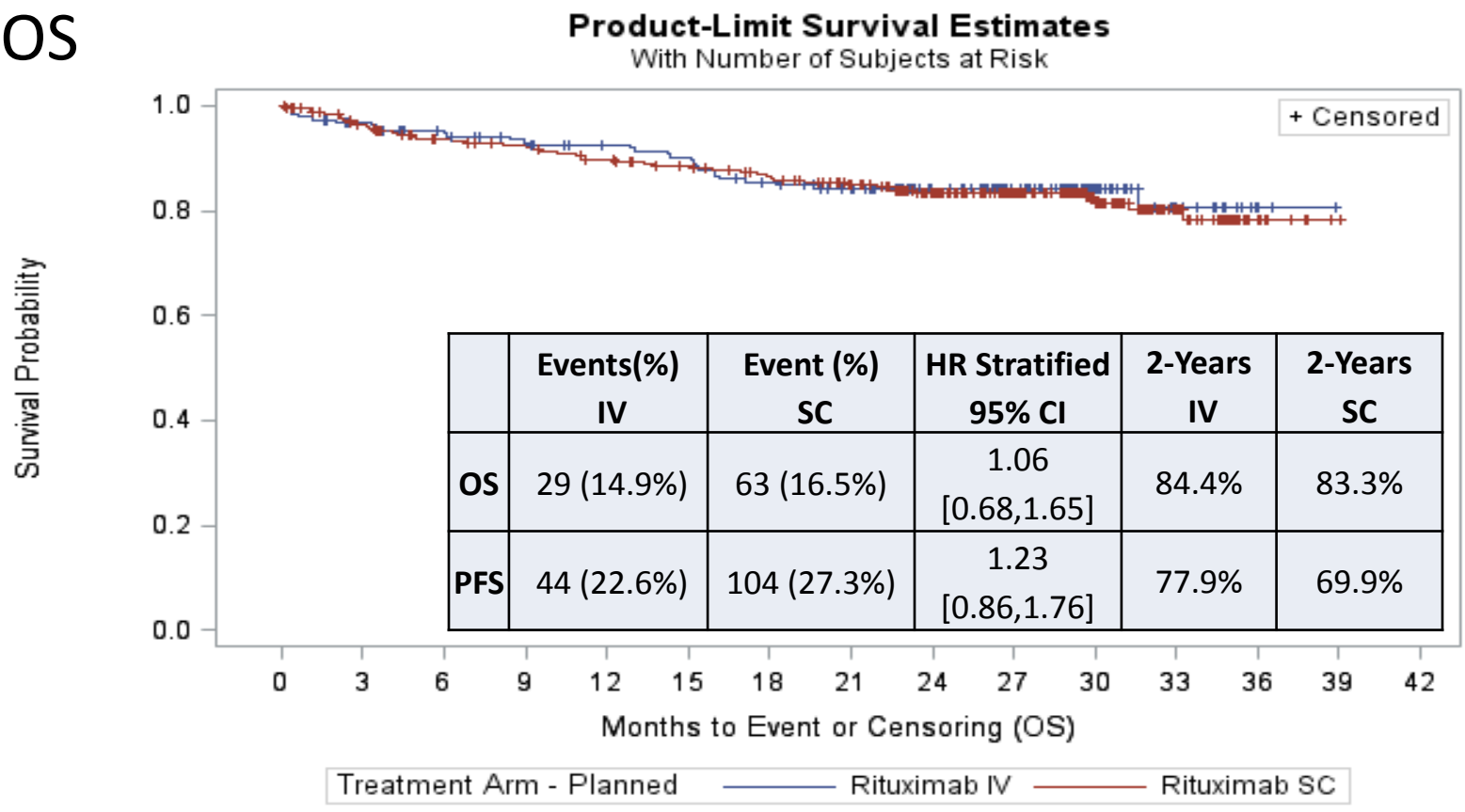
	Events(%) IV	Event (%) SC	HR Stratified 95% CI	2-Years IV	2-Years SC
OS	20 (9.8%)	16 (7.8%)	0.82 [0.41, 1.63]	95.4%	94.4%
PFS	57 (27.8%)	50 (24.4%)	0.97 [0.65, 1.44]	82.1%	82.1%

Hazard Ratio (HR) < 1 favors SC

MabEase (DLBCL), 2º Endpoints

- Comparable results between arms

OS



	Events(%) IV	Event (%) SC	HR Stratified 95% CI	2-Years IV	2-Years SC
OS	29 (14.9%)	63 (16.5%)	1.06 [0.68,1.65]	84.4%	83.3%
PFS	44 (22.6%)	104 (27.3%)	1.23 [0.86,1.76]	77.9%	69.9%

SAWYER (CLL) Results

Endpoints	IV (95% CI)	SC (95% CI)	Diff: SC-IV (95% CI)	Response Rate Ratio: SC/IV (95% CI)
Response Rate	80.7% [70.9, 88.3]	85.2% [76.1, 91.9]	4.6% [-7.2, 16.3]	1.06 [0.92,1.21]

Comparable results between arms

	Events (%) IV	Events (%) SC	
	N=88	N=88	HR, 95% CI
PFS	23 (26.1%)	19 (21.6%)	0.89 [0.49, 1.64]
OS	12 (13.6%)	7 (8%)	0.60 [0.24, 1.52]

Time-to-event data not provided; Results reported by the applicant

Response rate ratio > 1 favors SC

Efficacy Summary

- All efficacy results are descriptive
- IV and SC arms appear to be comparable
- Efficacy results are similar across studies

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Safety

Alexandria Schwarsin, MD
Medical Officer
DHP, OHOP, OND, CDER, FDA

Treatment Emergent Adverse Events (TEAE)

- Common TEAE (≥25%)
  - FL: neutropenia, nausea
  - DLBCL: neutropenia
  - CLL: neutropenia, nausea, pyrexia, injection site erythema

TEAE with a >5% increase on the rituximab SC arm compared to rituximab IV arm (SC – IV)		
SABRINA (FL) N=407	**MabEase (DLBCL) N=572**	**SAWYER (CLL) N=174**
Nausea (9.6%)	None overall	Neutropenia (6.3%)
Injection site erythema (6.4%)		Injection site erythema (25.9%)
Pneumonia (6.4%)		Injection site pain (16.5%)
Cough (9.5%)		Erythema (8.6%)
		Pyrexia (7.1%)

Non-fatal Serious Adverse Events

- Febrile neutropenia
  - rituximab IV vs rituximab SC
  - SABRINA (FL): 4.8% vs 5.1% (0.3% increase)
  - MabEase (DLBCL): 10.8% vs 13.0% (2.2% increase)
  - SAWYER (CLL): 4.5% vs 10.6% (6.1% increase)
- Pyrexia increased 2.4% in the CLL trial
- No other SAE increased greater than 2%

Non-fatal Serious Adverse Events

- Is the risk of having a non-fatal serious adverse events increased given higher drug concentrations with rituximab SC?

Nonfatal SAE (%)	SABRINA (FL) 1400 mg			MabEase (DLBCL) 1400 mg			SAWYER (CLL) 1600 mg		
	IV N=210	SC N=197	(SC-IV)	IV N=203	SC N=369	(SC-IV)	IV N=89	SC N=85	(SC-IV)
% with at least 1 SAE	31.4%	35.0%	**+3.6%**	34%	39.6%	**+5.6%**	32.6%	29.4%	**-3.2%**

Neutropenia laboratory values

- Neutropenia was increased across all 3 trials
  - rituximab IV vs rituximab SC
  - SABRINA (FL): 64.8% vs 68.0% (3.1% increase)
  - MabEase (DLBCL): 13.3% vs 18.4% (5.1% increase)
  - SAWYER (CLL): 50.6% vs 60.0% (9.4% increase)
- Neutropenia grades 3 and 4
  - SABRINA (FL): 30.0% vs 37.6% (7.6% increase)
  - MabEase (DLBCL): 4.9% vs 7.0% (2.1% increase)
  - SAWYER (CLL): 37.1% vs 42.4% (5.3% increase)

Infections

- System Organ Class Infections and infestations
  - rituximab IV vs rituximab SC
  - SABRINA (FL): 62.9% vs 67.0% (4.1% increase)
  - MabEase (DLBCL): 34.0% vs 40.7% (6.7% increase)
  - SAWYER (CLL): 48.3% vs 55.3% (7.0% increase)
- Serious Infections and infestations
  - SABRINA (FL): 10.0% vs 15.2% (5.2% increase)
  - MabEase (DLBCL): 6.9% vs 13.0% (6.1% increase)
  - SAWYER (CLL): 10.1% vs 11.8% (1.7% increase)

Administration Site Reactions

- Local cutaneous reactions including injection site erythema and injection site pain, were increased in the rituximab SC arms.
- These adverse events did not occur on the rituximab IV arms.

	SABRINA (FL)	MabEase (DLBCL)	SAWYER (CLL)
Injection site erythema	13.2%	2.7%	25.9%
Injection site pain	8.1%	1.9%	16.5%

Safety Summary

- No major differences between the SC and IV arms aside from administration site reactions
- An increased risk of neutropenia associated with a possible increased risk of infection
- The safety of rituximab SC given with subsequent lines of therapy is unknown.

Patient Preference and Patient Reported Outcomes

Vishal Bhatnagar, MD
Medical Officer
DHP, OHOP, OND, CDER, FDA

PrefMab

- **Dedicated**, open label, multicenter study to evaluate patient preference SC vs. IV Rituximab
- Patient population: **743** previously untreated patients with DLBCL or FL receiving R-CHOP, R-CVP or R-Bendamustine
- 201 enrolling sites in 32 countries (all ex-US)
- Primary objective: To evaluate the proportion of patients indicating an overall preference using the Patient Preference Questionnaire (PPQ) for either the SC or the IV route of rituximab administration

Three Questionnaires

- **PPQ:** Patient Preference Questionnaire
- **CTSQ:** Cancer Therapy Satisfaction Questionnaire
- **RASQ:** Rituximab Administration Satisfaction Questionnaire

All instruments were self-administered.

Patient Assessments

- **PPQ:** Patient Preference Questionnaire

Please answer the following questions about your experiences and your preferences. There are not any right or wrong answers.

1) All things considered which method of administration did you prefer?

☐ IV ☐ SC ☐ No preference

2) If you have a preference for one of the administration routes, how strong is this preference?

☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the **TWO** main reasons for your preference?

☐ Feels less emotionally distressing

☐ Requires less time in the clinic

☐ Lower level of injection-site pain

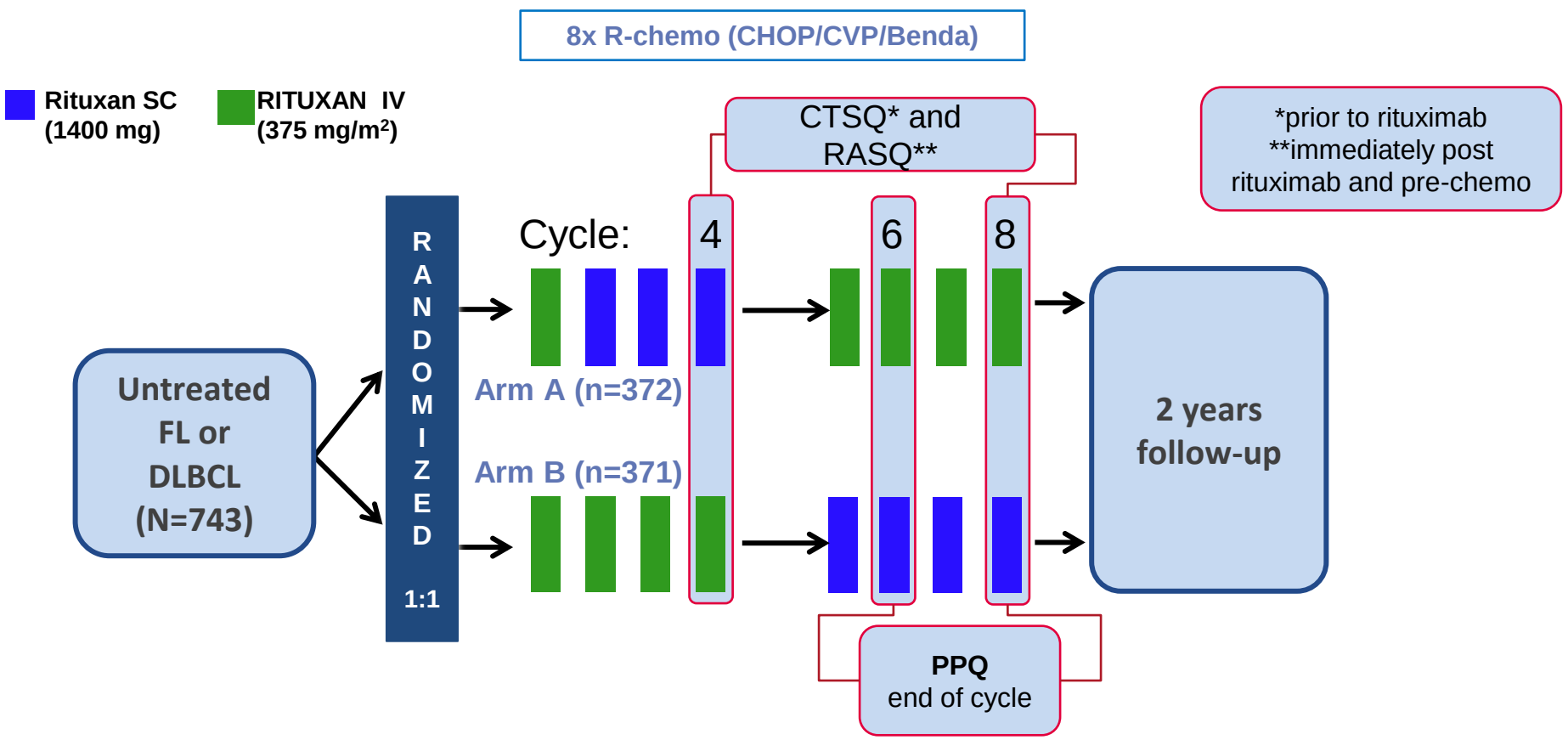
☐ Feels more comfortable during administration

☐ Other reason; please specify: .....

Patient Assessments

- **CTSQ:** Cancer Therapy Satisfaction Questionnaire
  - Sixteen-item Patient-Reported Outcome (PRO) instrument developed from interviews with patients with breast, colorectal and lung cancer
  - Three domains: expectations of therapy, feelings about side effects, satisfaction with therapy
- **RASQ:** Rituximab Administration Satisfaction Questionnaire
  - Twenty-item PRO instrument developed from interviews with patients with DLBCL and indolent lymphoma (n=10)
  - Five domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction

PrefMab Design



Primary endpoint	Secondary endpoints	
• Patient Preference for IV or SC using Questionnaire (PPQ) Question #1	• Administration time • CTSQ • RASQ	• Safety • CR, EFS, DFS, PFS, OS

Source: Applicant BLA submission

PrefMab Results

- **Patient Preference Questionnaire:**
  - After cycle 6: **80%** (CI: 77%, 83%) **prefer SC**
  - After cycle 8: **81%** (CI: 77%, 84%) **prefer SC**
  - Retained preference between cycle 6 and 8: **83%**
  - Reasons after cycle 8 for preferring SC:
    - Requires less time in the clinic (69%)
    - Feels more comfortable during administration (37%)
    - Feels less emotionally distressing (29%)
    - Lower level of injection site pain (16%)

    (Note: percentages add up to >100% as subjects were asked to pick two reasons)

PrefMab Results

- **CTSQ** results were similar in all domains

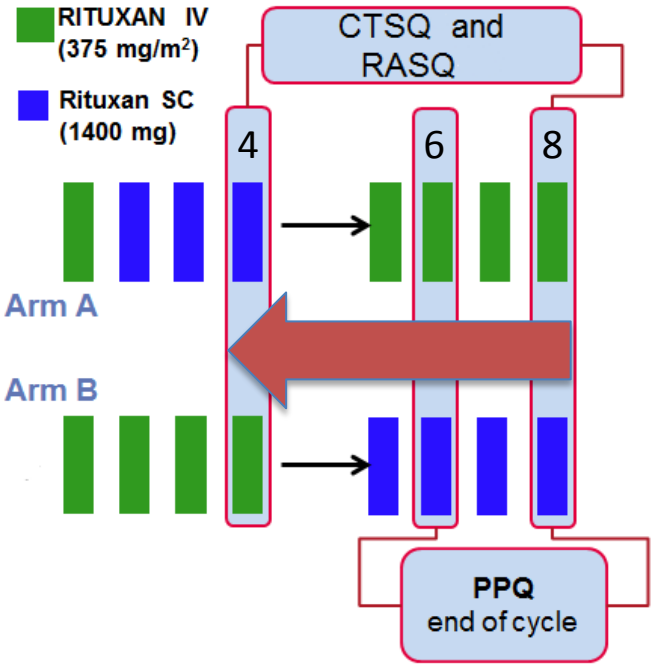
Domain	CTSQ Score after IV n=743 (SD)	CTSQ Score after SC n=687 (SD)
Expectation of therapy	81 (18.3)	82 (17.9)
Feelings about side effects	61 (22.3)	62 (22.3)
Satisfaction with therapy	85 (12.2)	85 (11.3)

- **RASQ** results: SC favored in 4 out of 5 domains

Domain	RASQ Score after IV n=743 (SD)	RASQ score after SC n=687 (SD)
Physical Impact	82 (15.6)	82 (15.9)
Psychological Impact	78 (16.4)	84 (14.4)
Impact on ADLs	58 (25.2)	84 (16.5)
Convenience	59 (20.8)	81 (13.1)
Satisfaction	75 (19.4)	87 (15.0)

Design Issues

- **CTSQ and RASQ results were disparate despite content overlap and timing (Cycles 4 and 8)**
  - RASQ and CTSQ results could be confounded by a multi-agent regimen
  - RASQ was NOT developed using input from subjects who had received rituximab SC
- **Long recall period for Cycle 8 PPQ**



Source: Applicant BLA submission

Patient Preference and PRO Summary

- **The PPQ appears to be fit-for-purpose and accurately measures patient preference for routes of administration**
  - Strengths of PPQ and preference results:
    - Brevity and clarity of PPQ (3 questions)
    - Large magnitude of effect and consistency of findings

- **The evidence submitted by the applicant is insufficient to demonstrate that the RASQ and CTSQ are adequate to measure satisfaction**
  - Limitations of the instrument
  - Disparate results between similar surveys
  - RASQ and CTSQ results could be confounded by a multi-agent regimen
  - Satisfaction is complex: What factors do patients consider when thinking about satisfaction?

FDA Overall Summary

- Rituximab SC achieved equal or higher C_{trough} relative to rituximab IV.
- A fixed-dosing strategy lead to consistent C_{trough} across all BSA sizes relative to BSA-based dosing regimen of rituximab IV.
- Efficacy results were comparable between IV and SC arms in all clinical studies.
- There were no major differences in safety findings between rituximab SC and rituximab IV.
- PrefMab trial was adequate to determine preference for rituximab SC.

BLA 761064 Rituximab SC

ODAC Discussion Objectives:

- Provide feedback and insights on the development approach
- Assess whether the results of the clinical trials support the approval of the rituximab SC product for the proposed indications in FL, DLBCL, and CLL