



US Food and Drug Administration

Pulmonary-Allergy Drugs Advisory Committee Meeting June 23, 2011

Susan Limb, MD

Clinical Team Leader

Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drugs

Center for Drug Evaluation and Research

US Food and Drug Administration

Objective

- Discuss the New Drug Application (NDA) submitted by Jerini U.S./Shire Human Genetic Therapies, Inc. for icatibant for the treatment of acute attacks of hereditary angioedema

Hereditary angioedema (HAE)

- Rare disease
- Intermittent, unpredictable attacks of edema at various anatomic sites

Therapeutic options

- Prophylaxis
 - Androgenic steroids
 - C1 esterase inhibitor replacement (Cinryze®)
- Acute attacks
 - C1 esterase inhibitor replacement (Berinert®)
 - Kallikrein inhibitor (Kalbitor®)

Icatibant

- Bradykinin antagonist
- Dosage and administration
 - 30 mg subcutaneous injection
 - Two additional 30 mg injections may be administered in a 24 hour period
 - Administration by healthcare professional or patient

Original icatibant clinical program

Study	Year	Study type	N	Treatment
Original submission – 2007				
2101	2004	Proof-of-concept, dose-ranging	15	<ul style="list-style-type: none"> ●0.4mg/kg IV icatibant ●0.8mg/kg IV ●0.4mg/kg IV ●30 mg SC ●45 mg SC
2102 <i>FAST-2</i>	2006	Efficacy and safety	74	<ul style="list-style-type: none"> ●30 mg SC icatibant ●Tranexamic acid x 2d
		Open-label extension	54	
2103 <i>FAST-1</i>	2006	Efficacy and safety	56	<ul style="list-style-type: none"> ●30 mg SC icatibant ●Placebo
		Open-label extension	72	
4102	2007	Patient-reported outcome validation	60	<ul style="list-style-type: none"> ●No intervention

Original submission issues

- No statistically significant benefit seen in placebo-controlled trial (FAST-1)
- Second pivotal trial used an active comparator of uncertain efficacy in HAE (FAST-2)
- Post-hoc analyses supportive but insufficient
- No clinical data to support self-administration



Clinical program summary

Study	Year	Study type	N	Treatment
Original submission – 2007				
2101	2004	Proof-of-concept, dose-ranging	15	<ul style="list-style-type: none"> •0.4mg/kg IV icatibant •0.8mg/kg IV •0.4mg/kg IV •30 mg SC •45 mg SC
2102 <i>FAST-2</i>	2006	Efficacy and safety	74	<ul style="list-style-type: none"> •30 mg SC icatibant •TA x 2 days
		Open-label extension	54	
2103 <i>FAST-1</i>	2006	Efficacy and safety	56	<ul style="list-style-type: none"> •30 mg SC icatibant •Placebo
		Open-label extension	72	
4102	2007	Patient-reported outcome validation	60	<ul style="list-style-type: none"> •No intervention
Complete Response – 2011				
054 <i>FAST-3</i>	2010	Efficacy and safety	93	<ul style="list-style-type: none"> •30 mg SC icatibant •Placebo
		Open-label extension (ongoing)	76	
3101	2010	Self-administration trial (ongoing)	56	<ul style="list-style-type: none"> •30 mg SC icatibant⁸



Clinical program summary

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2102 <i>FAST-2</i>	2006	Efficacy and safety	74	<ul style="list-style-type: none"> •30 mg SC icatibant •TA x 2 days
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Complete Response – 2011				
054 <i>FAST-3</i>	2010	Efficacy and safety	93	<ul style="list-style-type: none"> •30 mg SC icatibant •Placebo
		Open-label extension (ongoing)	76	
3101	2010	Self-administration trial (ongoing)	56	<ul style="list-style-type: none"> •30 mg SC icatibant⁹

Major Issues

- Robustness of the efficacy data
- Adequacy of the safety data
- Self-administration

Questions for Discussion and Voting

- Total of 5
- Questions 2, 3, and 4 require voting
- Questions 1 and 5 are non-voting

Question 1

(Discussion question)

- Discuss the efficacy and safety data for icanatibant.

Question 2 (Voting Question)

- Does the data provide substantial and convincing evidence of a clinically meaningful benefit for icatibant in the treatment of acute attacks of hereditary angioedema?
 - *If not, what further data should be obtained?*

Question 3 (Voting Question)

- Has the safety of icatibant been adequately assessed for the treatment of acute attacks of hereditary angioedema?
 - *If not, what further data should be obtained?*

Question 4 (Voting Question)

- Do the efficacy and safety data provide substantial evidence to support approval of icatibant for the treatment of acute attacks of hereditary angioedema in patients 18 years of age and older?
 - *If not, what further data should be obtained?*

Question 5 (Discussion question)

- Discuss the potential impact of self-administration on the safety and efficacy of icanatibant, if any.

Objective

- Discuss the New Drug Application (NDA) submitted by Jerini U.S./Shire Human Genetic Therapies, Inc. for icatibant for the treatment of acute attacks of hereditary angioedema



Thank you



Icatibant (Firazyr) for the treatment of acute attacks of Hereditary Angioedema

Brian Oscar Porter, M.D., Ph.D., M.P.H.

Medical Officer

Division of Pulmonary, Allergy, and Rheumatology Products

PADAC Meeting: June 23, 2011

Icatibant Presentation Outline

Original NDA Submission (1st Review Cycle)

- Summary of clinical trials
- VAS validation studies
- Key efficacy findings of FAST-1 and FAST-2
- Not Approvable action letter

Post-NDA Follow-up

- No Agreement on Special Protocol Assessment for FAST-3

Complete Response Submission (2nd Review Cycle)

- Summary of clinical trials
- Phase 3 efficacy results: **Dr. Joan Buenconsejo (Biometrics)**

Safety Analysis

- Pooled safety findings
- Self-administration results

Summary

Efficacy: Do the data provide substantial and convincing evidence of a clinically meaningful benefit for icatibant in the treatment of acute attacks of HAE?

Points to consider:

- Clinical relevance of VAS-based results
- Adequacy of efficacy data



Original NDA Submission: Clinical Trials

Trial	Design	Duration	Tx Arms	ITT	Relevance
JE049-2101 Phase 2	OL, POC	Single dose, but 5 subjects re-enrolled at higher dose level	Icatibant 0.4 mg/kg IV (2 hr infusion)	4	PK, PD, limited dose-ranging information
			Icatibant 0.4 mg/kg IV (0.5 hr infusion)	4	
			Icatibant 0.8 mg/kg IV (0.5 hr infusion)	4	
			Icatibant 30 mg SC	4	
			Icatibant 45 mg SC	4	
JE049-2103 (FAST-1) Phase 3	R, DB, PC *24-wk OL EXT	Single dose, with 14-day observation	Icatibant 30 mg SC	27	Pivotal efficacy trial versus placebo
			Placebo	29	
JE049-2102 (FAST-2) Phase 3	R, DB, DD, AC *24-wk OL EXT	Single dose, with 14-day observation	Icatibant 30 mg SC Tranexamic acid 1 g PO q6-8hr x 2 days (up to 6 doses)	36 38	Pivotal efficacy trial versus tranexamic acid 4

Icatibant Dose Selection

- **Available dose-ranging information:**
 - Phase 1 PK studies in healthy adults
 - Limited Phase 2 dose-ranging information:
 - Time to subject-reported symptom relief ~30 min with SC dosing
 - Similar efficacy results: 30 mg SC vs 0.8 mg/kg IV
 - No added benefit of 45 mg SC over 30 mg SC
- **Dose-selection based on the following:**
 - Estimated bradykinin levels in acute HAE attacks
 - Human IV bradykinin challenge model in healthy adults

Primary Efficacy Endpoint

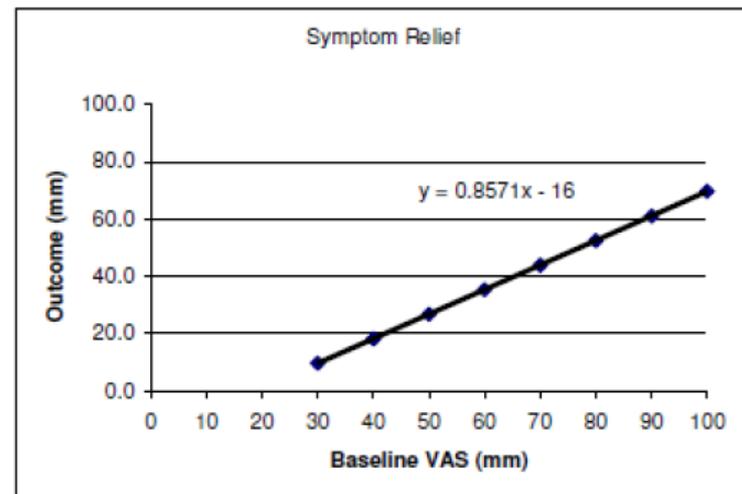
- Time to onset of primary symptom relief, based on self-reported Visual Analogue Scale ratings

Visual Analogue Scale (VAS)

100mm linear scale: 0mm = no symptom; 100mm = worst possible symptom

Primary Symptom Relief:

Time to onset of symptom relief based on the 1st of 3 consecutive non-missing ratings to the right and below this line:



VAS Validation Study

Trial	Subjects	Design	Tx Arms	Duration	Relevance
JE049-4102	Adults with HAE (80)	Observational	No intervention	PRO validation study	Correlation of VAS scores to VDS* to establish minimum clinically significant difference in VAS rating of 9 mm

*VDS = Visual Descriptor Scale: 5-point rating scale used as comparative standard for evaluating symptom change over time

Phase 3 Demographics: Key Considerations

- **Treatment groups generally well-balanced**
 - **Females (~ 60-70%) > Males (~ 30-40%)**
 - **Nearly exclusively Caucasian (~ 86-100%)**
 - **% Cutaneous > % Abdominal in FAST-2**
 - **Minimal discontinuations (0-3 per group)**

Key Phase 3 Efficacy Analyses: Median time to primary symptom relief onset

	Icatibant		Tranexamic Acid		Placebo		P value
	N	Time (h)	N	Time (h)	N	Time (h)	
FAST-1							
All HAE attacks	27	2.5			29	4.6	0.142
FAST-2							
All HAE attacks	36	2.0	38	12.0			<0.001

Median time to primary symptom relief onset by anatomic site of HAE attack

	Icatibant		Tranexamic Acid		Placebo		P value
	N	Time (h)	N	Time (h)	N	Time (h)	
FAST-1							
Cutaneous	14	3.4			13	10.0	0.221
Abdominal	13	2.0			16	3.0	0.159
FAST-2							
Cutaneous	24	2.5	23	18.2			<0.001
Abdominal	12	1.6	15	3.5			0.026

Original NDA Review: Not Approvable

After reviewing original clinical program (FAST-1 & FAST-2), DPARP issued **Not Approvable action letter** on April 23, 2008:

Clinical Deficiencies

- Substantial evidence of safety and efficacy not provided, given uncertainty of comparator drug (tranexamic acid) in FAST-2, as well as failure of FAST-1 to show statistically significant treatment difference from placebo.
 - Concerns also noted over validity of primary efficacy endpoint (based on Visual Analog Scale).
 - Data required to demonstrate safety of icatibant for self-injection.
 - Further definition of dose-selection needed in sufficient patients based on clinical endpoint or other validated related biomarkers.

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Post-NDA Follow-up

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- Phase 3 efficacy results: **Dr. Joan Buenconsejo (Biometrics)**

Safety Analysis

- Pooled safety findings
- Self-administration results

Summary

Post-NDA Follow-up: Additional Efficacy Data

- **12/15/08 NDA End-of-Review Meeting**

- Division recommended using the same primary efficacy endpoint in future Phase 3 trials, as for FAST-1 and FAST-2 (time to 1^o symptom relief)
- Composite HAE symptom scores recommended as informative efficacy measures

Request for Special Protocol Assessment for Third Pivotal Phase 3 Efficacy Trial: FAST-3

- **2/13/09 SPA Request from Applicant:**

- Similarly designed placebo-controlled Phase 3 trial with new primary efficacy endpoint of time to symptom relief based on 50% reduction from baseline in composite VAS-3 symptom score: *abdominal pain, skin pain, & skin swelling*

- **4/2/09 No Agreement SPA letter from Agency:**

- Concerns over proposed primary efficacy endpoint analysis (based on VAS-3) and key secondary analysis (based on primary symptom VAS)

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Icatibant Complete Response (February 25, 2011)

- **Safety and efficacy data**

- 3rd pivotal Phase 3 trial: FAST-3 (placebo-controlled)

- **Self-administration**

- Phase 3b safety and efficacy trial: FAST-4 (EASSI)

- **Dose-selection data (further justification)**

- Population PK data & PK/PD modeling

- HGT-FIR-061: Thorough QT study

- HGT-FIR-065: PK of repeated SC dosing in healthy adults



Complete Response: Phase 3 Clinical Trials

Trial	Design	Duration	Tx Arms	ITT	Relevance
*HGT-FIR-054 (FAST-3)	R, DB, PC *OL Ext (ongoing)	Single dose, with 14-day observation	Icatibant 30 mg SC Placebo	43 45	Pivotal efficacy trial versus placebo
*JE049-3101 (FAST-4, EASSI)	OL (ongoing)	Single self-administered dose in non-naïve subjects	Icatibant 30 mg SC	56	Safety/efficacy of self-administration

Key Elements of Phase 3 Efficacy Trial Design

- **Designs of FAST-1, FAST-2, and FAST-3 are similar:**
 - R, C, DB, PG, MC trial in adults \geq 18 yrs with Type I or II HAE (similar demographic distribution across all three trials)
 - FAST-1 & FAST-3: placebo comparator
 - FAST-2: tranexamic acid comparator
- **Randomized: icatibant 30 mg SC vs. comparator**
 - 1st moderate to severe cutaneous/abdominal HAE attack (all trials)
 - 1st mild to moderate laryngeal HAE attack (FAST-3 only: amended)
- **Open-label: icatibant 30 mg SC (up to 3 doses in 24 hr)**
 - All other laryngeal HAE attacks
 - All subsequent HAE attacks (automatically enrolled in EXT phase)

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Summary



Icatibant (Firazyr) for the treatment of acute attacks of Hereditary Angioedema

Joan Buenconsejo, Ph.D.

Acting Statistics Team Leader

Division of Pulmonary, Allergy, and Rheumatology Products

PADAC Meeting: June 23, 2011

Comparison of Phase 3 Efficacy Endpoints

- **Primary: FAST-1 & FAST-2**
 - Time to onset of primary symptom relief based on primary VAS symptom rating in acute moderate to severe cutaneous and abdominal HAE attacks

- **Primary: FAST-3**
 - Time to onset of composite symptom relief based on VAS-3 (average VAS symptom rating of *abdominal pain*, *skin pain*, and *skin swelling*) in acute moderate to severe cutaneous and abdominal HAE attacks

- **Post-hoc analyses for cross-trial comparisons**
 - Time to onset of VAS-3-based symptom relief for FAST-1 and FAST-2 (submitted to Division prior to Complete Response)
 - Time to onset of primary VAS-based symptom relief was key secondary efficacy endpoint for FAST-3

Key Phase 3 Efficacy Analyses:

Median time to composite (VAS-3) symptom relief

	Icatibant		Tranexamic Acid		Placebo		P value
	N	Time (h)	N	Time (h)	N	Time (h)	
FAST-3							
Non-laryngeal attacks	43	2.0			45	19.8	<0.001
FAST-1 (post-hoc)							
Non-laryngeal attacks	26	2.3			29	7.9	0.014
FAST-2 (post-hoc)							
Non-laryngeal attacks	35	2.0	38	12.0			<0.001

Key Phase 3 Efficacy Analyses: Median time to primary VAS symptom relief

	Icatibant		Tranexamic Acid		Placebo		P value
	N	Time (h)	N	Time (h)	N	Time (h)	
FAST-3 (key secondary)							
Non-laryngeal attacks	43	1.5			45	18.5	<0.001
FAST-1							
Non-laryngeal attacks	27	2.5			29	4.6	0.142
FAST-2							
Non-laryngeal attacks	36	2.0	38	12.0			<0.001

Median time to primary symptom relief by anatomic site of HAE attack

	Icatibant		Tranexamic Acid		Placebo		P value
	N	Time (h)	N	Time (h)	N	Time (h)	
FAST-3							
Cutaneous	26	2.0			26	22.5	<0.001
Abdominal	17	1.0			19	3.6	0.002
FAST-1							
Cutaneous	14	3.4			13	10.0	0.221
Abdominal	13	2.0			16	3.0	0.159
FAST-2							
Cutaneous	24	2.5	23	18.2			<0.001
Abdominal	12	1.6	15	3.5			0.026

Pooled Phase 3 Analyses: Laryngeal Attacks

- Limited number of subjects treated for laryngeal attacks (Initial attacks: N = 28; All attacks: N = 60)
- Data are uncontrolled (limited randomized comparisons)
- Demographics of pooled laryngeal population similar to ITT population
- **Generally consistent efficacy findings:**
 - Time to primary symptom relief: 2.2 hrs
 - Time to composite symptom relief: 2.2 hrs
 - Progressive reductions in laryngeal symptoms

Durability of Response: Primary symptom relief onset \leq 8 hr of dosing and lasting \geq 24 hrs

	Icatibant		Tranexamic Acid		Placebo		P value
	N	n (%)	N	n (%)	N	n (%)	
FAST-3							
All HAE attacks	43	37 (86)			45	19 (42)	<0.001
Cutaneous	23	22 (85)			26	7 (27)	<0.001
Abdominal	17	15 (88)			19	12 (63)	0.705
FAST-1							
All HAE attacks	27	14 (52)			28	14 (50)	1.000
Cutaneous	14	8 (57)			13	5 (39)	0.449
Abdominal	13	6 (46)			15	9 (60)	0.705
FAST-2							
All HAE attacks	35	24 (69)	36	14 (39)			0.017
Cutaneous	23	15 (65)	23	5 (22)			0.007
Abdominal	12	9 (75)	13	9 (69)			1.000

Secondary Endpoints Independent of VAS

- **Rescue Medication Use**
- **Clinical Global Assessment**
(5-point ordinal scale ranging from 0 = absence of symptoms to 4 = very severe)

Secondary Endpoints Independent of VAS

- **Rescue Medication Use**

- FAST-2: Icatibant = 19%; Tranexamic acid = 32%
- FAST-1: Icatibant = 22%; Placebo = 48%
- FAST-3: Icatibant = 7%; Placebo = 40%

- **Clinical Global Assessment (5-point ordinal scale)**

- Cutaneous symptoms were milder in icatibant vs placebo in FAST-2 and FAST-3, but not FAST-1
- Abdominal symptoms showed similar patterns

Summary

- Statistically significant treatment effects were observed in one active-controlled trial (FAST-2) and one placebo-controlled trial (FAST-3) for icatibant in the treatment of acute HAE attacks.
- There is a sharp contrast in placebo response between FAST-1 and FAST-3. Nonetheless, there is consistent evidence that median time to onset of symptom relief is about 2 hours when treated with icatibant regardless of how the primary endpoint is defined.
- The results over the use of rescue or on the clinical global assessments are consistent with the findings using VAS scores.

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- Not Approvable action letter

Post-NDA Follow-up

- No Agreement on Special Protocol Assessment for FAST-3

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- Summary of clinical trials
- Phase 3 efficacy results: **Dr. Joan Buenconsejo (Biometrics)**

Safety Analysis

- Pooled safety findings
- Self-administration results

Summary

Safety: Has the safety of icatibant been adequately assessed for the treatment of acute attacks of HAE?

Points to consider:

- Deaths, SAEs, Withdrawals
- Common AEs
- Local injection site reactions
- Safety of self-administration

Phase 3 Safety Analysis

- **Safety assessments**

- AEs/SAEs (MedDRA v 8.1), clinical laboratory tests (including immunogenicity), physical examination, vital signs, 12-lead ECG, local injection site reactions

- **Pooled randomized ITT Safety Population (similar demographics across all treatment arms)**

- Icatibant 30 mg SC (N=113): FAST-1, FAST-2, FAST-3
- Tranexamic Acid (N=38): FAST-2
- Placebo (N=75): FAST-1, FAST-3

- **Safety data for sequential HAE attacks**

- Combined blinded and open-label data from all trials

Phase 3 Safety Population: Icatibant exposure

Number of total icatibant exposures across all sequential HAE attacks		Number of Subjects				
0		42				
1		76				
2		50				
3		28				
4		20				
5		10				
>5		41				
Doses given per acute HAE attack	Attack 1 (N = 225)	Attack 2 (N = 146)	Attack 3 (N = 96)	Attack 4 (N = 67)	Attack 5 (N = 48)	
1 SC dose (30 mg)	217 (96)	137 (94)	86 (90)	65 (96)	41 (85)	
2 SC doses (60 mg)	8 (4)	7 (5)	10 (10)	1 (2)	7 (15)	
3 SC doses (90 mg)	0	2 (1)	0	1 (2)	0	

Deaths, SAEs, Withdrawals

- **No deaths** in icatibant-recipients
- **7 SAEs** in 5 icatibant-recipients (all from FAST-2)
 - Pregnancy (2), HAE worsening (2)
 - Viral gastroenteritis (1), Hypertensive crisis (1), Cystitis (1)
- **Withdrawals** of 2 icatibant-recipients (reason: other)
- **No hypersensitivity/anaphylactic** reactions
- **1 patient** with post-icatibant anti-drug antibodies: transient and non-neutralizing

Common Adverse Events (> 2%)

Preferred Term (n, %)	Treatment Group		
	Icatibant N = 113	Tranexamic Acid N = 38	Placebo N = 75
Acute period (within 24 hours post-dosing)			
Injection site reaction	110 (97)	10 (26)	25 (33)
Pyrexia	3 (3)	0	0
Observation period (Days 1 - 14 post-dosing)			
HAE (worsening ≤ 48 hr)	18 (16)	6 (16)	15 (20)
Abdominal pain	3 (3)	0	0
Pyrexia	4 (4)	0	0
Sinusitis	3 (3)	0	1 (1)

Severe AEs ↑ in placebo, except 1 dyspepsia (rare: only 2 cases) and 1 headache (but headache less common with icatibant) ³⁵

Local Injection Site Reactions:

Assessed separately from AEs as safety endpoint

Treatment Group	Icatibant N = 113	Tranexamic Acid N = 38	Placebo N = 75
Any injection site reaction (n, %):	110 (97)	10 (26)	25 (33)
Erythema	108 (96)	4 (11)	15 (20)
Swelling	93 (82)	6 (16)	12 (16)
Burning	41 (36)	2 (5)	3 (4)
Itching	35 (31)	0	0
Warm sensation	60 (53)	1 (3)	3 (4)
Cutaneous (skin) pain	29 (26)	0	3 (4)

Results from EASSI: Icatibant self-administration

Clinical Trial	FAST-1	FAST-2	FAST-3	EASSI
All icatibant-treated non-laryngeal HAE attacks (n)	27	36	43	56
<u>Primary</u> : Time (hrs) to symptom relief onset	2.5	2.0	1.5	2.0
<u>VAS-3</u> : Time (hrs) to symptom relief onset	2.3	2.0	2.0	2.6

- **AE profile similar to other Phase 3 trials:**
 - HAE most common AE (23%)
 - Injection site reactions in ~90%

Summary

- **FAST-1 failed to show significant treatment effect** of icatibant versus placebo
- **FAST-2 showed significant treatment effect** of icatibant versus tranexamic acid
- **FAST-3 showed significant treatment effect** of icatibant versus placebo
- **Safety and efficacy results of EASSI** self-administration trial were similar to those of other Phase 3 trials
- **Local injection site reactions** observed nearly universally



Thank you



Pulmonary-Allergy Drugs Advisory Committee June 23, 2011

Charge to the Committee

Susan Limb, MD

Clinical Team Leader

Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drugs

Center for Drug Evaluation and Research

US Food and Drug Administration

Approval of an Application

21 CFR 314.105 (c)

“FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.”

Efficacy standard

21 CFR 314.125

Refusal to approve an application

(b)(5) “...substantial evidence consisting of adequate and well-controlled investigations...that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Safety standard

21 CFR 314.125

Refusal to approve an application

- (b)(2) “...do not include adequate tests by all methods reasonably application to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”
- (b)(3) “The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.”
- (b)(4) “There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”

Questions for Discussion and Voting

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Question 5

(Discussion question)

- Discuss the potential impact of self-administration on the safety and efficacy of ibrutinib, if any.