NDA 22465: VOTRIENT™ (pazopanib) Tablets Applicant: GlaxoSmithKline

FDA Presentation
ODAC Meeting
Oct. 5, 2009

Key NDA Information

Submission: Dec. 18, 2008

Product Information: Pazopanib, a new tyrosine kinase inhibitor, targets VEGFR, PDGFR and c-Kit tyrosine kinases.

Proposed Indication: VOTRIENT™ is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Presentation Outline

- Recently Approved Products for RCC
- Regulatory History of Pazopanib
- Studies in RCC
- Efficacy in the Key Study
- Safety Evaluation Results
- Hepatotoxicity of Pazopanib
- Summary
- Question to ODAC

Recently Approved Therapies for RCC

Product Name	Trial Type	Endpoint	Key Findings
Sorafenib (Dec. 2005)	Randomized, double-blind, compared to placebo	**PFS**	HR: 0.44 (0.35-0.55) Median PFS 5.5 vs. 2.8 mos. with placebo
Sunitinib (Jan. 2006)	Randomized, double-blind, compared to IFN-α	**PFS**	HR: 0.42 (0.32-0.54) Median PFS 10.8 vs. 5.1 mos. with IFNα
Temsirolimus (May 2007)	Randomized, open-label, compared to IFN-α, in patients with poor prognostic factors	**OS (2^{nd} PFS)**	HR: 0.73 (0.58-0.92) Median OS 10.9 vs. 7.3 mos. with IFNα
Everolimus (Mar. 2009)	Randomized, double-blind, compared to placebo, in RCC pts previously treated with sorafenib or sunitinib	**PFS**	HR: 0.33 (0.25-0.43) Median PFS 4.9 vs. 1.9 mos. with placebo
Bevacizumab+ IFNα (July 2009)	Randomized, double-blind, compared to IFNα alone	**PFS**	HR: 0.60 (0.49-0.72) Median PFS 10.2 vs. 5.4 mos. with IFNα

Regulatory History of Pazopanib

Sep 2002	IND 65747 submitted
Jul 2005	EoP1 Meeting: Proposed development for RCC
Sep 2005- Feb 2006	SPA Submitted: To study patients with advanced RCC who have progressed following cytokine-based therapy
Mar 2006	Meeting to Discuss a Protocol Amendment: Proposal to include treatment-naïve patients and allow for crossover. FDA expressed concerns. No agreement reached.
Dec 2008	NDA submission

Regulatory History of Pazopanib

The Agency's Concerns Expressed in March 2006:

"Control patients with no prior therapy should receive either sorafenib, sunitinib, or a cytokine. The use of placebo in a second line patient population will be problematic unless patients have received one of these drugs"

Regulatory History of Pazopanib

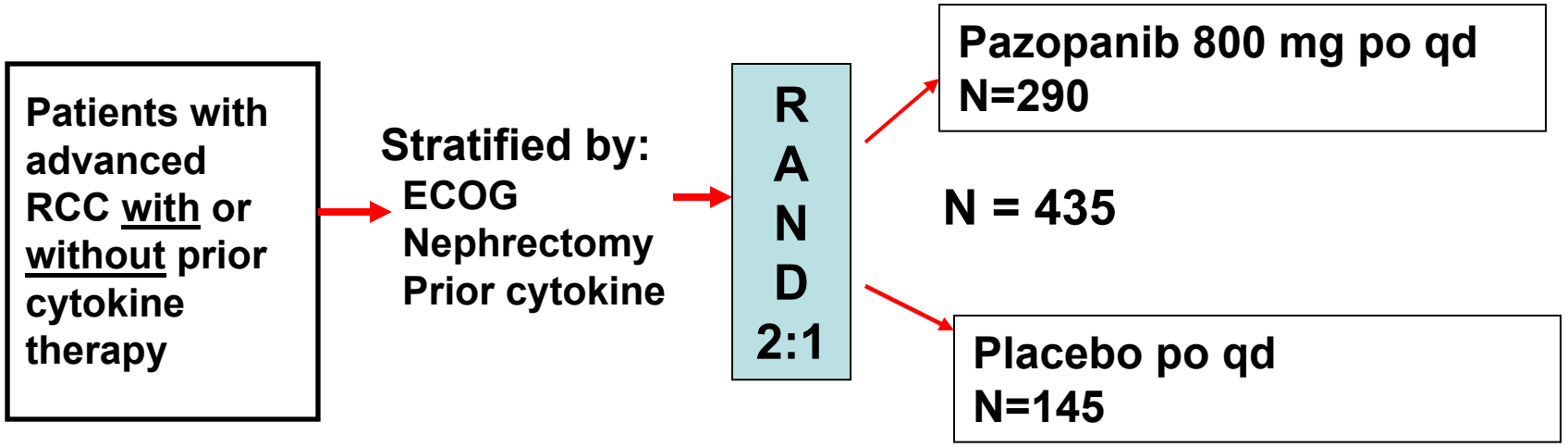
The Agency's position on the proposed primary endpoint in RCC:

"The acceptability of PFS as an endpoint for approval depends on the magnitude of the difference, risk benefit ratio and whether any drugs are approved based on survival."

Evidence for the Proposed Indication

Study Number	Study Design	Primary Endpoint	Dose Groups	Status at Submission
VEG105192 (Key Study)	Randomized, Double-blind, placebo-controlled (N=435)	PFS	Pazopanib 800 mg vs. placebo	Complete (follow-up)
VEG102616 (Supportive)	Double-blind, placebo-controlled, randomized discontinuation design (Revised to single arm) (N=225)	RR	Pazopanib 800 mg vs. placebo (Revised to single arm)	Primary analysis complete
VEG107769 (Supportive)	A single-arm study of patients (placebo) previously enrolled on the key study (N=71) (48% crossover)	Safety	Pazopanib 800 mg	Primary analysis complete (study ongoing)

VEG105192 Study Design



Endpoints

- Primary: PFS
- Secondary: OS, ORR (CR + PR), safety

Assessment q 6 wks, q 8 wks after 24 wks
Treatment until:

- disease progression
- death
- unacceptable toxicity
- withdrawal

The first patient enrolled in April 2006.

Study Accrual

No patients from the US

Country	Placebo N=145	Pazopanib N=290	Total N=435
Poland	36	72	108
Russian	10	22	32
UK - CMD	6	22	28
Argentina	11	14	25
Tunisia-France	12	10	22
Korea	8	14	22
Chile	8	13	21
Lithuania	8	11	19
Slovakia	4	14	18
Italy	4	12	16
Pakistan	4	11	15

Baseline Characteristics

- **Baseline Demographics:** balanced between the two arms
- **Disease Characteristics:** balanced between the two arms
  - 90% with prior nephrectomy
  - 53% with no prior cytokine-based therapy
  - MSKCC risk factors*: 55% intermediate, 39% favorable, 3% poor

*one factor "<1 year from diagnosis to systemic treatment" was replaced with "no prior nephrectomy" in the applicant's classification.

Disposition at the Data Cut-off

	Placebo N=145	Pazopanib N=290
Off Treatment	**90%**	**78%**
Disease Progression	77%	51%
Death*	6%	4%
Adverse Events	3%	14%
Lost to Follow-up	1%	1%
Withdrawal	1%	5%
Other	1%	4%
On Treatment	**10%**	**22%**

*not including death after disease progression

Efficacy Results

Efficacy Outline

- Study Endpoints
- Statistical Analysis Plan
- Efficacy Results
- Efficacy Summary

Study Endpoints

- **Primary Endpoint**
  - Progression-Free Survival by IRC
  - Censoring Rules:
    - No progression prior to clinical cutoff
    - Another anti-cancer therapy was initiated prior to progression
    - Event occurred after ≥12 wks of inadequate assessment
    - Without an adequate baseline assessment

- **Secondary Endpoints**
  - OS
  - ORR, Duration of Response

Statistical Analysis Plan

- **Planned Size**: N = 350, powered for OS (287 events)
  - stratification factors: ECOG PS, prior nephrectomy, prior cytokine treatment

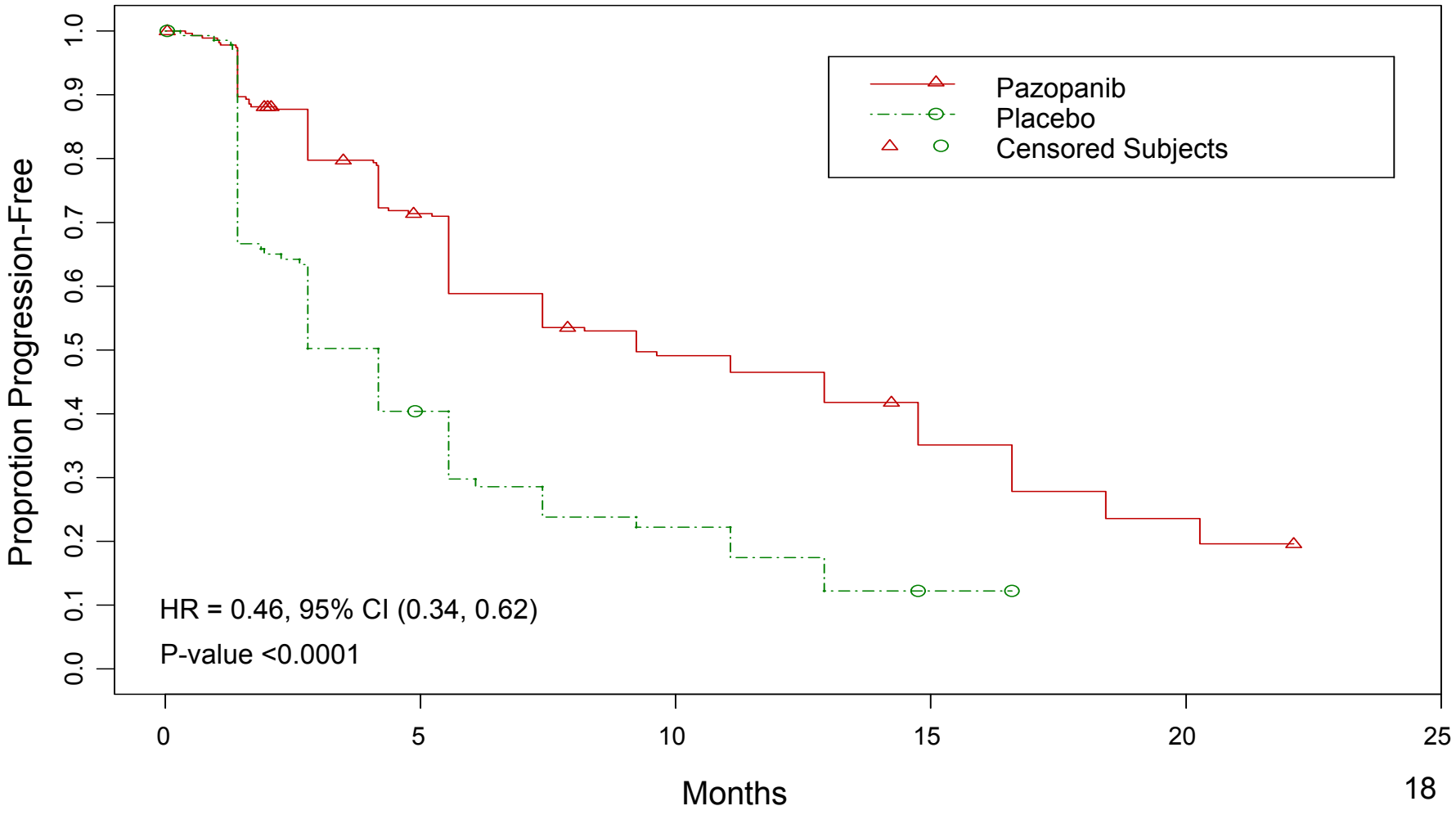
- **Primary PFS Analysis (IRC)**: Stratified log-rank test with one-sided alpha of 0.025
  - 435 patients enrolled
  - 246 PFS events observed

- **Interim OS Analysis**: Stratified log-rank test with one-sided alpha of 0.004
  - 176 events observed (61% of required 287 events)

Primary PFS Results (IRC)

	Placebo	Pazopanib
	N=145	N=290
Subject Status, n (%)		
Progressed or Died (event)	98 (68)	148 (51)
Censored	47 (32)	142 (49)
Kaplan-Meier Estimates for PFS (months)		
Median (95% CI)	**4.2** (2.8, 4.2)	**9.2** (7.4, 12.9)
Adjusted Hazard Ratio (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-Rank p-value	<0.0001	

Progression-Free Survival (IRC)



Subgroup Analyses

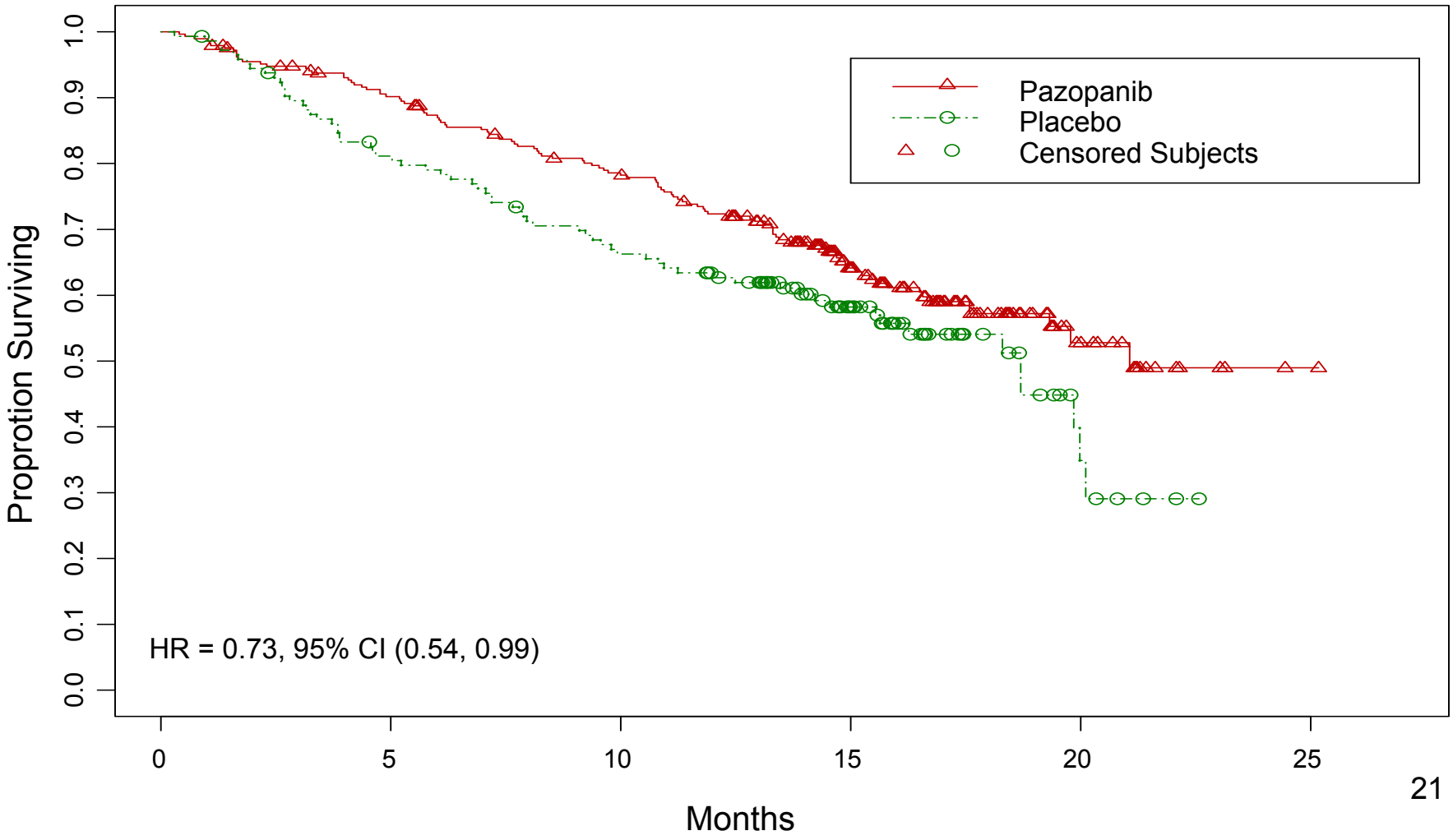
Treatment-Naïve	**Placebo N=78**	**Pazopanib N=155**
*PFS (months) Median (95% CI)	2.8 (1.9, 5.6)	11.1 (7.4, 14.8)
Unadjusted Hazard Ratio (95% CI)	0.40 (0.27, 0.60)	
Cytokine Pre-treated	**Placebo N=67**	**Pazopanib N=135**
*PFS (months) Median (95% CI)	4.2 (2.8, 5.6)	7.4 (5.6, 12.9)
Unadjusted Hazard Ratio (95% CI)	0.54 (0.35, 0.84)	
*Based on Kaplan-Meier Estimates		

Interim Overall Survival Results

	Placebo	Pazopanib
	N=145	**N=290**
Subject Status, n (%)		
Died (event)	67 (46)	109 (38)
Censored	78 (54)	181 (62)
Kaplan-Meier Estimates for OS (months)		
Median (95% CI)	18.7 (14.6, 20.1)	21.1 (19.3, NC)
Adjusted Hazard Ratio (95% CI)	0.73 (0.53, 1.00)	
Stratified Log-Rank p-value	0.02*	

*Required Significance Level at Interim Analysis = 0.004; 48% of patients in the placebo crossed over to pazopanib

Overall Survival



Response Rate

	Placebo N=145	**Pazopanib N=290**
Overall RR (CR+PR) (95% CI)	3% (1% - 6%)	30% (25% - 36%)
Duration of Response (months) (95% CI)	--*	13.5 (12,15.7)

*The number of patients is too small to provide a meaningful estimate.

Efficacy Summary

- Statistically Significant Improvement in PFS compared to Placebo
  - In ITT population, estimated 5 mo. improvement in median PFS
  - In treatment-naïve subgroup, estimated 8.3 mo. improvement in median PFS
  - In cytokine-pretreated subgroup, estimated 3.2 mo. improvement in median PFS
- Overall Survival Not Statistically Significant
  - Interim analysis
- Overall Response Rates 30% for Pazopanib with a Median DoR of 13.5 Months and 3% for placebo

Safety Outline

- Safety Overview of the Key Study (N=290/145)
- Hepatic Safety in the Pazopanib Monotherapy Population (N=990)
- Safety Overview of Important Adverse Events in both Key and All RCC Studies (N=593)

Safety Results in the Placebo-Controlled Study

Safety Overview

	Placebo N=145	Pazopanib N=290
All Grade AEs	74%	93%
Grade 3/4 AEs	20%	40%
Serious Adverse Events	20%	26%
Fatal SAEs	3%	4%
Discontinuations Due to AEs	5%	16%
Deaths not Due to Study Disease	7%	7%

Median Duration of Exposure: Pazopanib-7.4 mos., Placebo-3.8 mos.

Common Adverse Reactions

Adverse Event n (%)	Placebo N=145		Pazopanib N=290	
Grade	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	9%	<1%	52%	5%
Hypertension	11%	<1%	40%	5%
Hair Color Change	3%	0	38%	**
Nausea/Vomiting	16%	2%	36%	3%
Fatigue	9%	2%	20%	2%

Laboratory Abnormalities

	Placebo N=145		Pazopanib N=290	
Grade	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
ALT	32%	<1%	67%	12%
Bilirubin	14%	2%	37%	3%
Neutrophils	9%	0	36%	2%
Hemoglobin	26%	2%	55%	2%
Platelets	9%	<1%	35%	2%

Grade 3/4 Hepatic Injury

Parameter	Grade 3/4 ALT N=36 of 290 on Pazopanib
Timing of Occurrence ≤6 weeks after treatment initiation >6 weeks after treatment initiation	 72% 28%
Dose Modification Interruption Reduction Neither	 55% 55% 39%
Discontinuation	19%
Recovery (Grade 0-2)	92%
Deaths Associated with Hepatic Insufficiency	2 patients

Hepatic Safety

(Monotherapy Population ~1000 Patients)

1) **Incidence of Abnormalities in ALT and Bilirubin**

2) Identification of Hy's Law Cases

3) Examination of Possible Liver-Related Deaths

Abnormalities in ALT and Bilirubin

	Pazopanib N=990
ALT > 3xULN	14%
Bilirubin > 2xULN	5%
ALT > 3xULN and Bilirubin > 2xULN	1.3%

Hepatic Safety
(Monotherapy Population)

1) Incidence of Abnormalities in ALT and Bilirubin

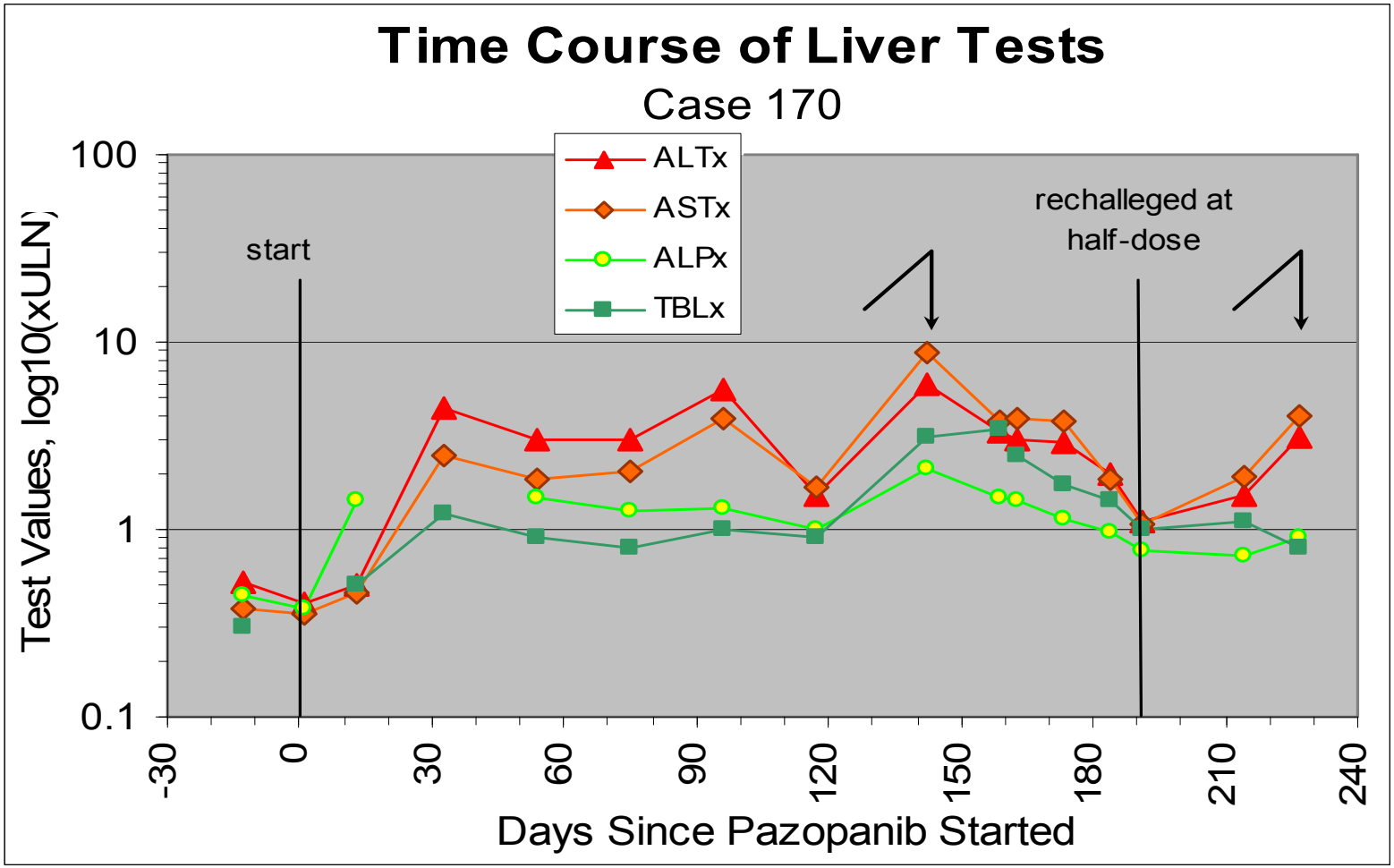
2) Identification of Hy's Law Cases

3) Examination of Possible Liver-Related Deaths

Hy's Law

- Definition
  - ALT > 3xULN
  - Bilirubin > 2xULN
  - No Other Cause
- Predictive of Hepatic Failure/Death
  - Hepatic Failure/Deaths ≥ 1/10 Hy's Law Cases
  - ≥ 2 Hy's Law Cases per 1000: Unacceptable in Non-Oncologic Drugs

Hy's Law Case
Recurrence Following Rechallenge



Rate of Hy's Law Cases: 4 per ~ 1000

Patient ID	Recovery	Occurrence of Severe Hepatic Injury	Applicant's Assessment	FDA's Assessment
Pt 170	No	**Death with Hepatic Injury**	Included	Probably Related
Pt 386	No	**Death**	Not Excluded	Possibly Related
Pt 152	Yes	**No** (discontinued)	Included	Probably Related
Pt 410	Yes	**No** (adapted)	Included	Probably Related

Hepatic Safety
(Monotherapy Population)

1) Incidence of Abnormalities in ALT and Bilirubin

2) Identification of Hy's Law Cases

3) Examination of Possible Liver-Related Deaths

Deaths Associated with Pazopanib

Patient ID	Onset of Hepatic Abnormality	Hepatic Abnormality to Death	Applicant's Assessment	FDA's Assessment
Pt 386	Day 28	**4 days**	Possibly Related	Possibly Related
Pt 233	Day 9	**4 days**	Unrelated	Possibly Related
Both patients had no hepatic metastases and normal hepatic function at study initiation				

Summary of Pazopanib Hepatotoxicity

1) Evidence of Hepatic Injury: **excess and marked ALT elevations with pazopanib**

2) Estimated Rate of Hy's Law Cases**: 4 per ~1000 patients in the monotherapy population**

3) Estimated Rate of Hepatic Failure/Death Based
   on the 2 deaths: **20 per ~ 10,000 patients**
   on the 4 Hy's Law cases: **4 per ~10,000 patients**

Rate of Severe Pazopanib Hepatotoxicity Likely Underestimated

- Several Patients Were Eliminated Due to Confounding Factors.
- Identification of Hy's Law Cases from Patients Enrolled in the Pazopanib Combination Studies Represents a Challenge.
- One Hepatic Death, Supported by Autopsy, Probably Related to Pazopanib in a Combination Study.

Important Adverse Events* Associated with Pazopanib Compared to Placebo

Adverse Event n (%)	Placebo N=145		Pazopanib N=290	
Grade	**≥ Grade 3**	**Deaths**	**≥ Grade 3**	**Deaths**
Hemorrhage	0	0	7 (2%)	4 (1%)
Arterial Thrombotic Events	0	0	9 (3%)	2 (<1%)
Perforation/Fistula	0	0	2 (1%)	1 (<1%)
Torsades de Pointes	0	0	1 (<1%)	0

*Recognized in other VEGF/VEGFR Inhibitors

Important Adverse Events in the RCC Studies

Adverse Event n (%)	Pazopanib N=593	
Grade	**≥ Grade 3**	**Deaths**
Hepatotoxicity	63 (11%)	2 (<1%)
Hemorrhage	14 (2%)	6 (1%)
Arterial Thrombotic Events	14 (2%)	3 (<1%)
Perforation/Fistula	5 (1%)	2 (<1%)
Torsades de Pointes	2 (<1%)	0

Life-Threatening Adverse Reactions Associated with Pazopanib in Premarketing Studies

	Pazopanib
Hepatotoxicity	YES
Hemorrhage	YES
Arterial Thromboembolic Events	YES
Hypertensive Crisis	YES
Torsades de Pointes	YES
Fistula/Perforation	YES

Summary

- A 5-Month Improvement in Median PFS Was Seen with Pazopanib Compared to Placebo.
- In an Interim Analysis of OS, a Trend Was Seen in Favor of Pazopanib.
- Pazopanib Is Associated with Hepatotoxicity that Has Resulted in Death.
- Pazopanib Is Associated with Important Adverse Reactions Recognized in Products that Act Through the VEGF Pathway.

Question to ODAC

Background Summary: The randomized, placebo-controlled Phase 3 trial of pazopanib in advanced RCC showed a 5 month improvement in median PFS (HR 0.46 (0.34-0.62), without a statistically significant improvement in OS. The safety results showed an excess incidence of hepatotoxicity in addition to the occurrence of important adverse reactions known to VEGF inhibitors, including hypertension, hemorrhage, arterial thrombo-embolic events, and gastrointestinal perforation. It is also associated with torsades de pointes and a prolonged QTc interval.

Question to ODAC

VOTE: Is the benefit-to-risk profile demonstrated for pazopanib acceptable for the treatment of patients with advanced RCC?