NDA 211810 – Pexidartinib

Introductory Comments

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Office of Hematology and Oncology Products

Oncologic Drugs Advisory Committee Meeting

May 14, 2019

Approval Request: NDA 211810

- **Pexidartinib:**
  - small-molecule tyrosine kinase inhibitor of the colony-stimulating factor-1 receptor (CSF1R)

- **Proposed Indication:**

Pexidartinib is a kinase inhibitor indicated for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

Tenosynovial Giant Cell Tumor (TGCT)

- **Disease course**
  - Proliferative, rarely malignant disease
  - Tumor mass in synovium, bursae, tendon sheaths
  - Progressive, slow-growing
  - Presentation: pain, swelling, stiffness, functional impairment
- **Management**
  - Observation, symptom management
  - Surgical excision
    - Recurrence in 8-33% of patients
    - Interventions may include joint replacement, amputation
  - Radiation
  - No approved systemic therapies
- **Unmet medical need**

ENLIVEN Trial

	ENLIVEN
Design	Randomized, double-blind, multicenter, placebo-controlled
Study Population	tenosynovial giant cell tumor (TGCT; includes PVNS or GCT-TS)
Treatment	Pexidartinib/placebo 1000 mg/day x 2 weeks; then 800 mg/day
Primary Endpoint	ORR per RECIST v1.1 by BICR at Week 25
Secondary Endpoints	Measured at Week 25: • Range of motion (ROM) • ORR per tumor volume score • PROMIS® Physical Function • Worst Stiffness NRS item • Brief Pain Inventory-30 (BPI-30)
Statistical Analysis Plan	• ORR: 10% vs. 35% • 90% power, 2-sided α = 5% • Hierarchical testing of endpoints

PVNS=pigmented villonodular synovitis; GCT-TS=giant cell tumor of the tendon sheath; ORR=overall response rate; BICR=blinded independent review committee

Key Review Issues

- Assessment of Clinical Benefit
- Characterization of Liver Injury

ENLIVEN EFFICACY RESULTS

- Overall Response Rate per RECIST v1.1. BICR:
  - **38**% (95% CI: 26%, 50%) vs. **0%** (95% CI:0, 6); p-value <0.0001
  - Durability of Response (based on Week 25+)
    - DOR ≥ 6 months: 22/23 patients
    - DOR ≥ 12 months: 13/13 patients
- Clinical Outcome Assessments (COA)

	Difference from Placebo (95% CI)	p-value	Percent Missing at Week 25
Mean Δ From Baseline ROM	8.9% (2.9, 14.9)	0.0043	**27%**
Mean Δ From Baseline Physical Function	4.7 (2.5, 6.9)	<0.0001	**43%**
Mean Δ From Baseline Worst Stiffness	-2.2 (-3.0, -1.4)	<0.0001	**43%**
BPI-30 Response	16% (0.7, 30.2)	0.0521	**43%**

Issue 1: Assessment of Clinical Benefit

- **Estimating Clinical Benefit**
  - Measures of tumor burden (primary efficacy analysis- ORR)
    - Durability of response
  - Measures of symptoms & function (secondary efficacy- COA)
    - Impact of missing data
- **Interpreting Clinical Benefit (COA)**
  - Revised hierarchical order of testing secondary endpoints
  - Potential unblinding of clinical assessors
  - Establishing a clinically meaningful threshold of benefit

Issue 2: Risk of Liver Injury

- **Known risks**
  - Transaminase and bilirubin elevations : ALT (67%), AST (90%), total bilirubin (12%)
  - Severe drug induced liver injury: 4.9%
    - Biopsies: hepatocellular injury, injury to bile ducts, ductopenia
  - 2 cases of irreversible liver injury: liver transplantation, death

Issue 2: Risk of Liver Injury- Cont.

- **Uncertainties**
  - Effects of long-term exposure to pexidartinib
    - Liver injury in setting of clinically ‘normal’ or ‘improved’ serum aminotransaminase levels
    - Liver injury not detectable by laboratory monitoring

Summary

- TGCT can cause significant functional impairment
- No available systemic therapies for patients with severe morbidity from TGCT and which is not amenable to improvement with surgery
- Benefit:risk assessment different than for a fatal disease
- FDA considers evidence of clinical benefit in TGCT to include robust effects on tumor burden & on symptoms of the disease
  - ORR 38% provides evidence of tumor burden reduction
  - Limitations in estimating benefit based on COA data, & in the interpretation COA results
- Risk of hepatotoxicity can be managed with dose modifications and discontinuation of drug
  - Toxicity can be irreversible and fatal and uncertainties remain

NDA 211810 – Pexidartinib

FDA Presentation

Christy Osgood, MD
Medical Officer

Mallorie Fiero, PhD
Statistical Reviewer

Oncologic Drugs Advisory Committee Meeting

May 14, 2019

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Key Issues of Application

- **Assessment of Clinical Benefit**
  - Statistically significant improvement in overall response rate (ORR) and range of motion (ROM)
  - Estimation of treatment effect with missing clinical outcome assessment data
  - Interpretation of clinical benefit as measured by a within-patient change for ROM
- **Characterization of Liver Injury**
  - Pexidartinib causes liver injury
    - 2 to 5% experience severe liver injury
    - 2 of 768 patients experienced irreversible liver injury
  - Pattern of bile duct injury and ductopenia may be progressive, subacute or chronic leading to clinically important sequalae
  - Lack of understanding of the potential long-term effects of pexidartinib

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Outline

- **Background: Christy Osgood, MD**
  - Proposed Indication
  - Disease Background
  - Regulatory History
- **Efficacy Results and Issues: Mallorie Fiero, PhD**
  - Estimating and Interpreting Clinical Benefit
- **Safety Results and Issues: Christy Osgood, MD**
  - Liver Injury
- **Summary and Conclusions**
- **Discussion Topics and Questions for ODAC**

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Proposed Indication & Dosage

Proposed Indication:

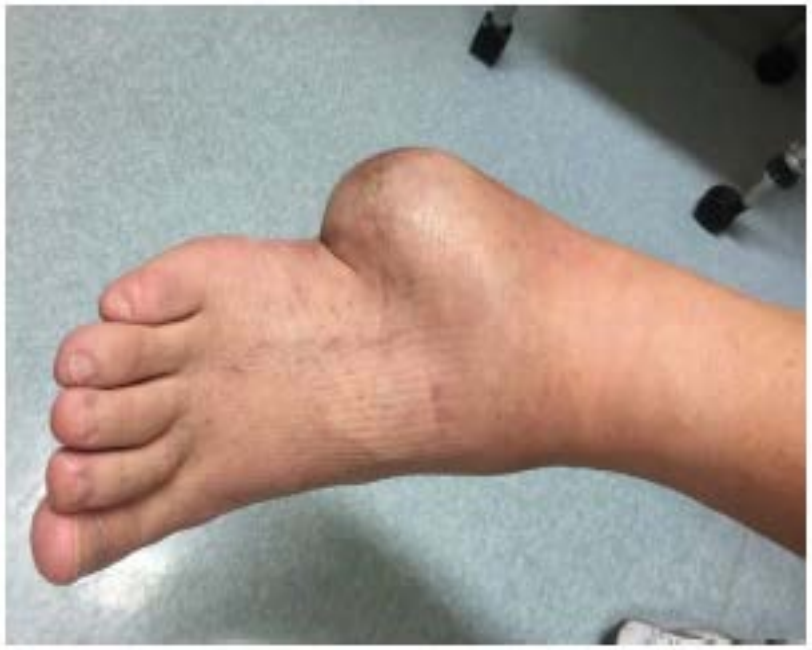
Pexidartinib is a kinase inhibitor indicated for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery

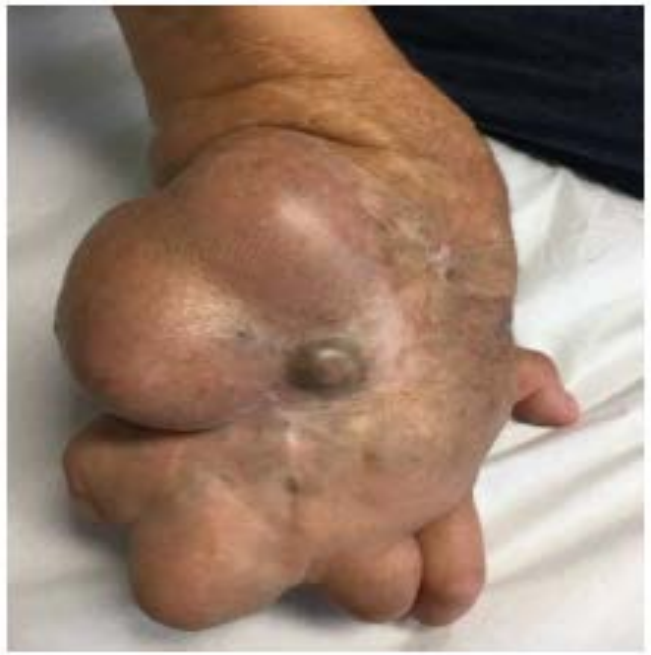
Proposed Dosing Regimen:

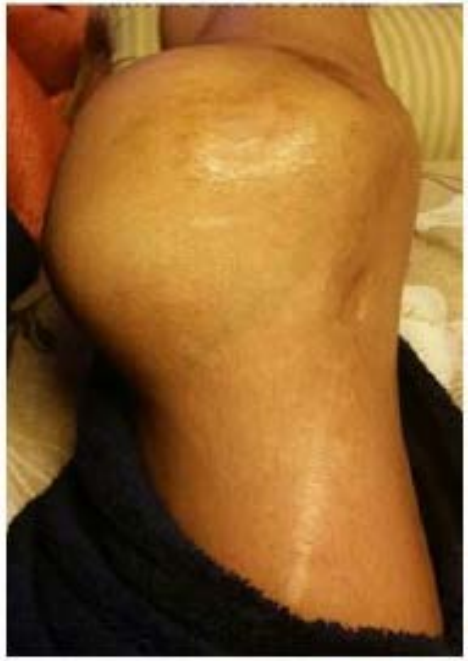
400 mg orally twice daily on an empty stomach (at least 1 hour before or 2 hours after a meal)

Tenosynovial Giant Cell Tumor (TGCT)

- Non-malignant tumor
- Progressive and debilitating
  - Pain
  - Stiffness
  - Functional impairment
- Treatment Options
  - Surgical resection
  - No approved systemic therapies

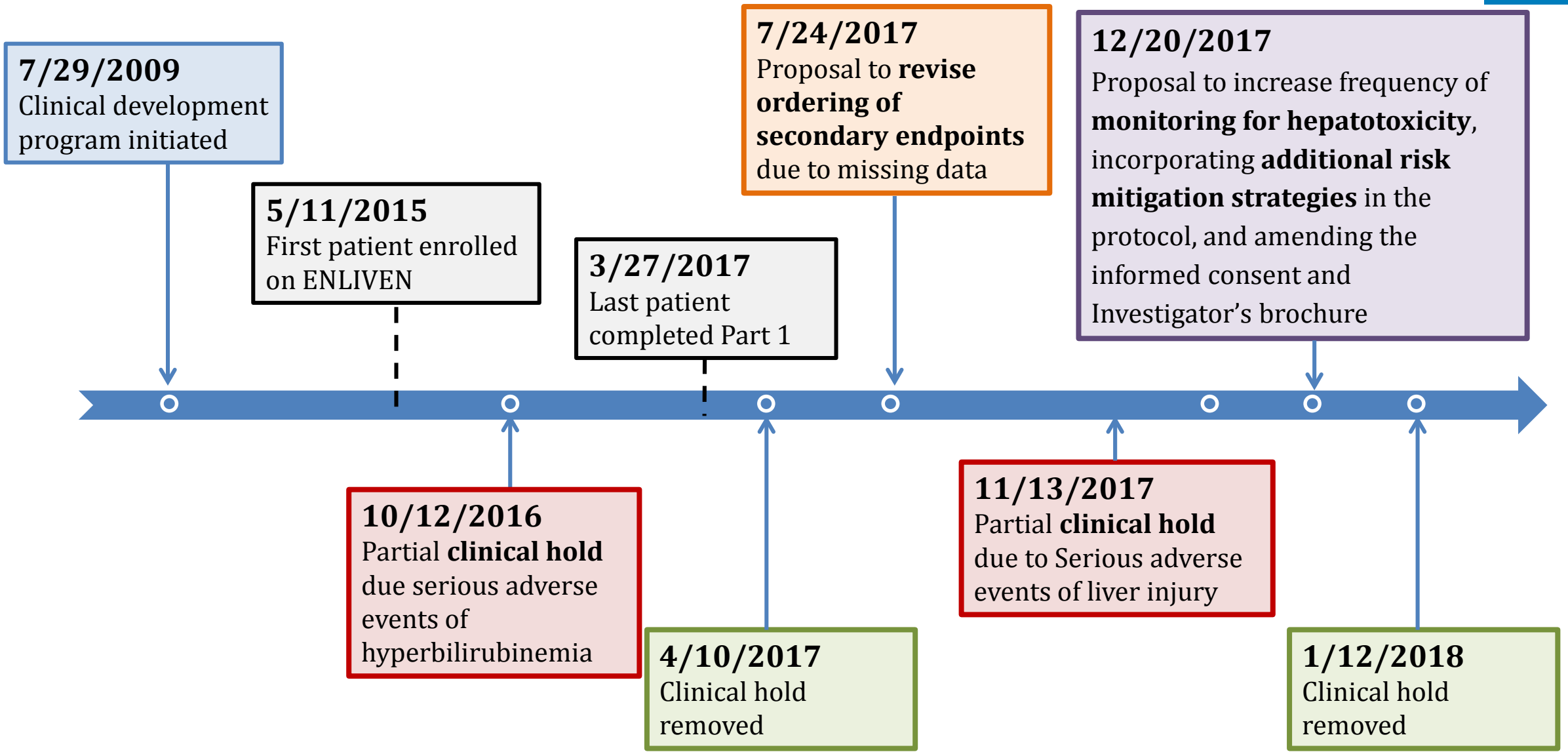






Pictures reproduced from PLX108-10-Study Report Addendum Version 1.0, October 23, 2018

Key Regulatory History



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Efficacy Results and Issues

- **Estimating Clinical Benefit**
  1. Primary efficacy results
  2. Timing of ORR assessments
  3. Impact of missing assessments of secondary endpoints
- **Interpreting Clinical Benefit of Secondary Endpoints**
  4. Revised hierarchical order of testing secondary endpoints
  5. Potential unblinding of clinical assessors
  6. Establishing a clinically meaningful threshold of benefit

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Estimating Clinical Benefit
Key Studies

	ENLIVEN	PLX108-01
Design	Randomized, double-blind, multicenter, placebo-controlled	Single arm, open-label, multicenter, dose escalation, dose expansion
Study Population	PVNS or GCT-TS	Advanced and metastatic solid tumors
Treatment	Pexidartinib/placebo 1000 mg/day x 2 weeks; then 800 mg/day	Pexidartinib 1000 mg/day
Primary Endpoint	ORR per RECIST v1.1 by BICR at Week 25	ORR per RECIST v1.1 by INV
Secondary Endpoints	• Range of motion (ROM) • ORR per tumor volume score • PROMIS® Physical Function • Worst Stiffness NRS item • BPI-30	• Not Applicable
Statistical Analysis Plan	• ORR: 10% vs. 35% • 90% power, 2-sided α = 5% • Hierarchical testing of endpoints	• Not Applicable (efficacy endpoint was descriptive only)

1. Primary Efficacy Results

	ENLIVEN[1] Pexidartinib N = 61	PLX108-01[2] TCGT N = 39
Overall Response Rate at Week 25		
Rate (%) (95% CI)	38%[3] (26%, 50%)	49%[4] (34%, 64%)
p-value[5]	<0.0001	--
Duration of Response[3]		
Range	(6.9+, 24.9+)	(1.8+, 53.2+)
DOR ≥ 6 months[6]	22/23	12/15
DOR ≥ 12 months[6]	13/13	12/14

[1] Response evaluated by BICR, [2] Response evaluated by investigator, [3] Data cut-off date: 1/31/2018, [4] Data cut-off date: 3/2/2017, [5] Compared to placebo arm in which no responses were observed 0% (95% CI: 0, 6), [6] Number of patients with ongoing DOR/Number of patients on follow-up for specified time (have not yet been censored)

2. Timing of ORR Assessments

	ENLIVEN Pexidartinib Part 1 and 2[1] n=61	ENLIVEN Crossover Part 2[1] n=30	PLX108-01 TGCT cohort[2] n=39	Pooled Pexidartinib TGCT Patients n=130
Confirmed ORR (%) (95% CI)	52% (40, 64)	53% (36, 70)	62% (45, 77)	54% (45, 62)

[1] Response evaluated by BICR, [2] Response evaluated by investigator

- With longer follow-up, increased tumor response rates were seen in all cohorts, including patients who crossed-over from placebo to pexidartinib in ENLIVEN

Estimating Clinical Benefit
Secondary Endpoints

- ENLIVEN demonstrated an improvement in ORR in a slow-growing & benign tumor
- Planned secondary endpoints of clinical outcome assessments (COA) could provide evidence of alleviation of symptomatic aspects of TGCT
  - However, prevalence of missing data for these assessments is high
- FDA Guidance for Industry: Patient-Reported Outcome (PRO) Measures (2009) – "Missing data can introduce bias and interfere with the ability to compare effects..."

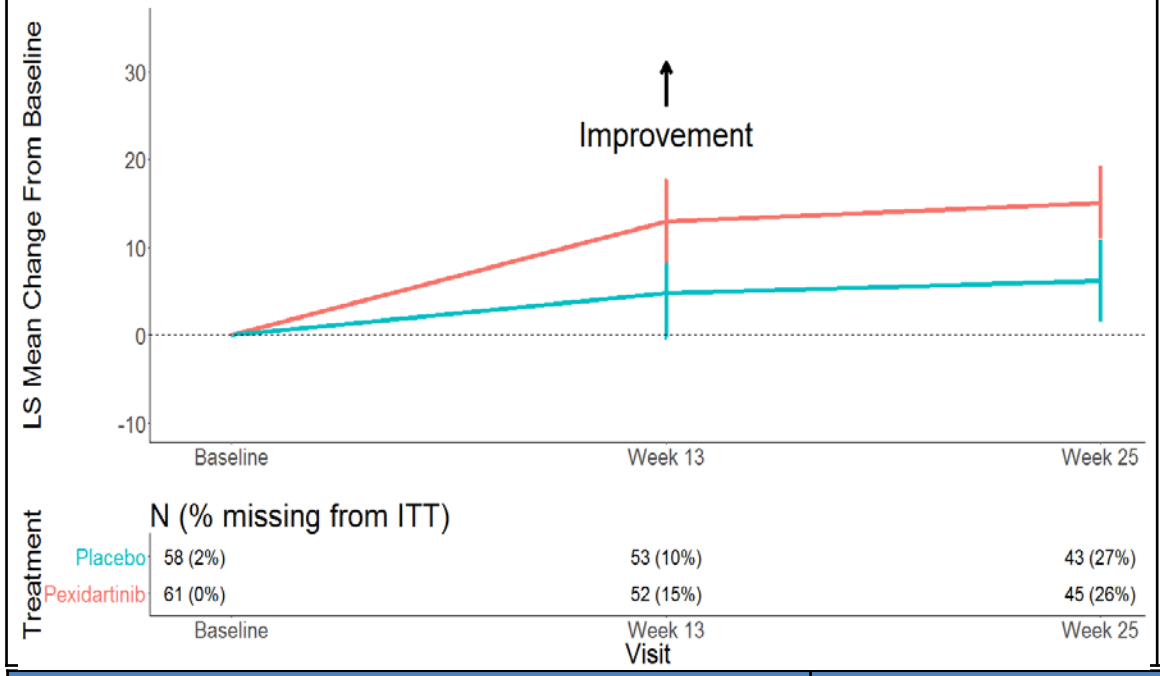
3. Impact of Missing Assessments Missing COA Data at Week 25

- COA endpoints of physical function, worst stiffness, and BPI-30 had missing proportion rates of >40%, which is much higher than acceptable

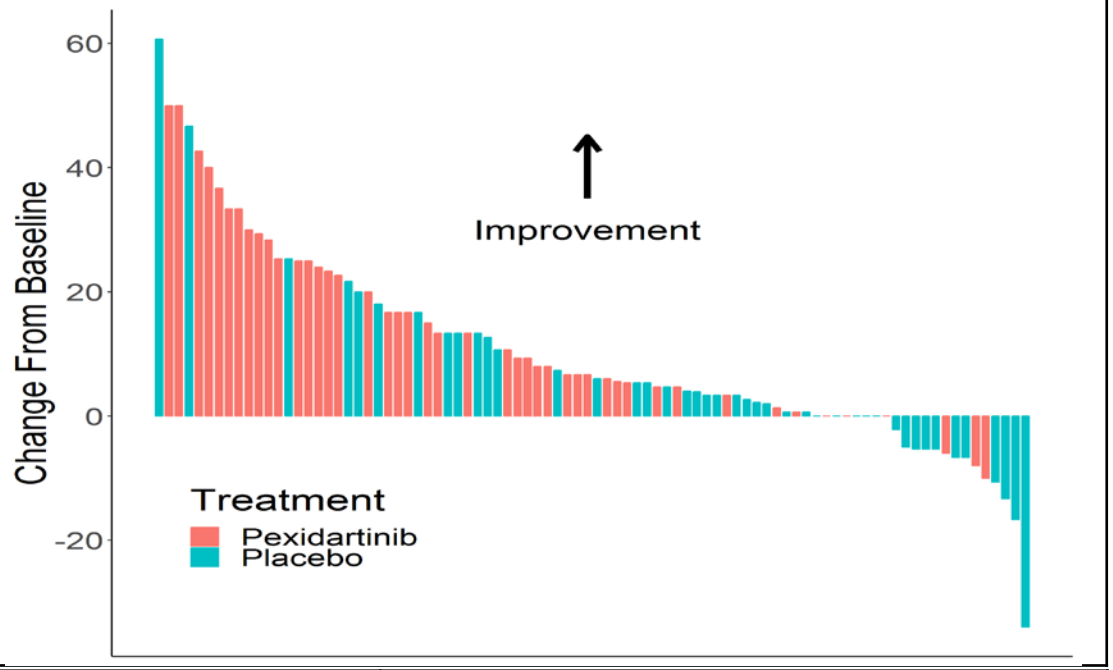
	Difference from Placebo (95% CI)	p-value	Missing at Week 25
Mean Δ From Baseline ROM	8.9% (2.9, 14.9)	0.0043	**27%**
Mean Δ From Baseline Physical Function	4.7 (2.5, 6.9)	<0.0001	**43%**
Mean Δ From Baseline Worst Stiffness	-2.2 (-3.0, -1.4)	<0.0001	**43%**
BPI-30 Response	16% (0.7, 30.2)	0.0521	**43%**

Estimating Clinical Benefit
Range of Motion

Adjusted Mean Change From Baseline



Change From Baseline at Week 25

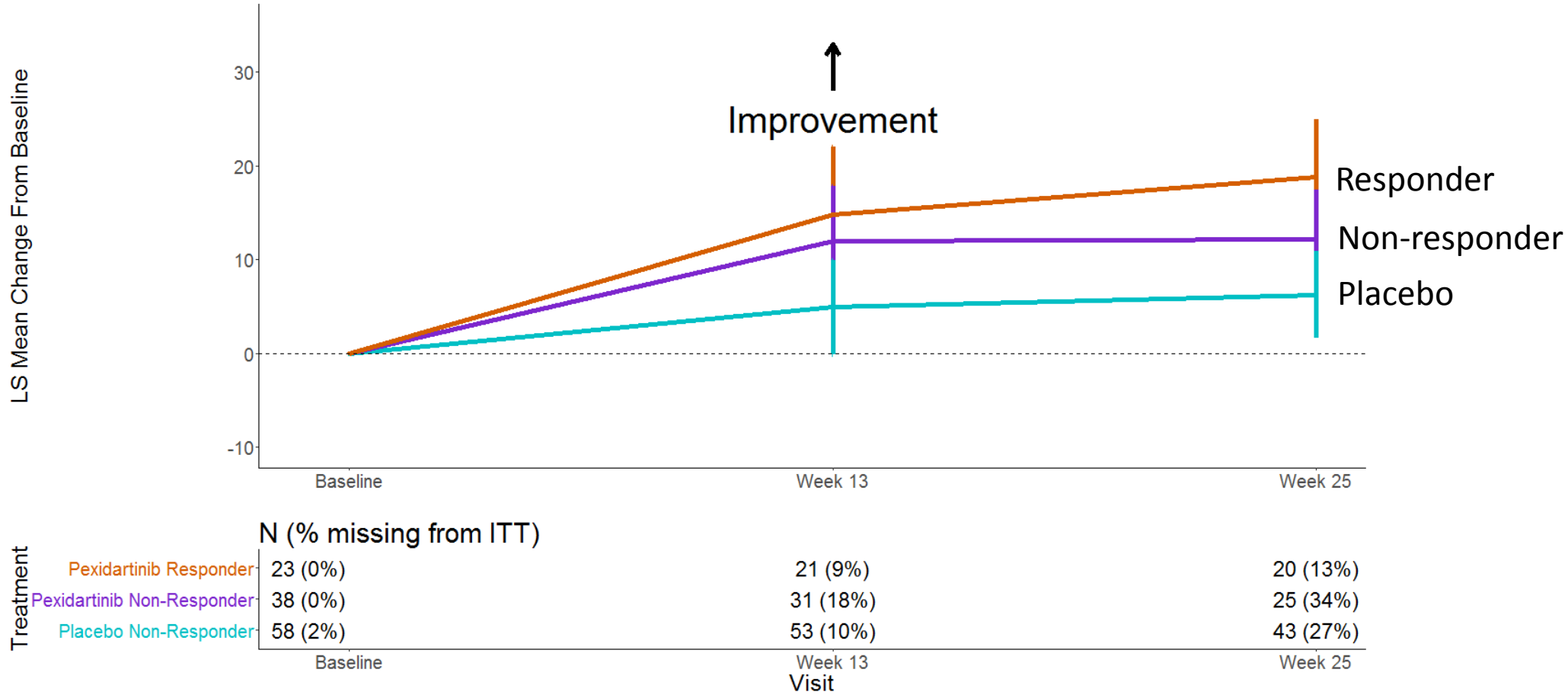


	Pexidartinib	Placebo
LS Mean Change[1] (95% CI)	15.1% (10.9, 19.2)	6.2% (1.5, 10.9)
Difference (95% CI)	8.9% (2.9, 14.9)	
P-value	0.0043	

[1] Estimated using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment arm, visit, baseline, region, joint type, treatment × visit, baseline × visit, treatment × joint type, baseline × joint type

Estimating Clinical Benefit
ROM by Tumor Response

- Greater ROM improvement for pexidartinib responders
- Missing for responders (13%) vs. non-responders (34%)



3. Impact of Missing Assessments Informative Missing ROM Data

- Informative missing data leads to biased estimates of treatment effect
  - Missingness may be indicative of worsening of symptoms while on treatment

- Example: The reason that a patient has a missing assessment- worsened ROM affects willingness or ability to complete the assessment

- Differential reasons for missing ROM data across treatment arms in ENLIVEN

3. Impact of Missing Assessments Sensitivity Analysis

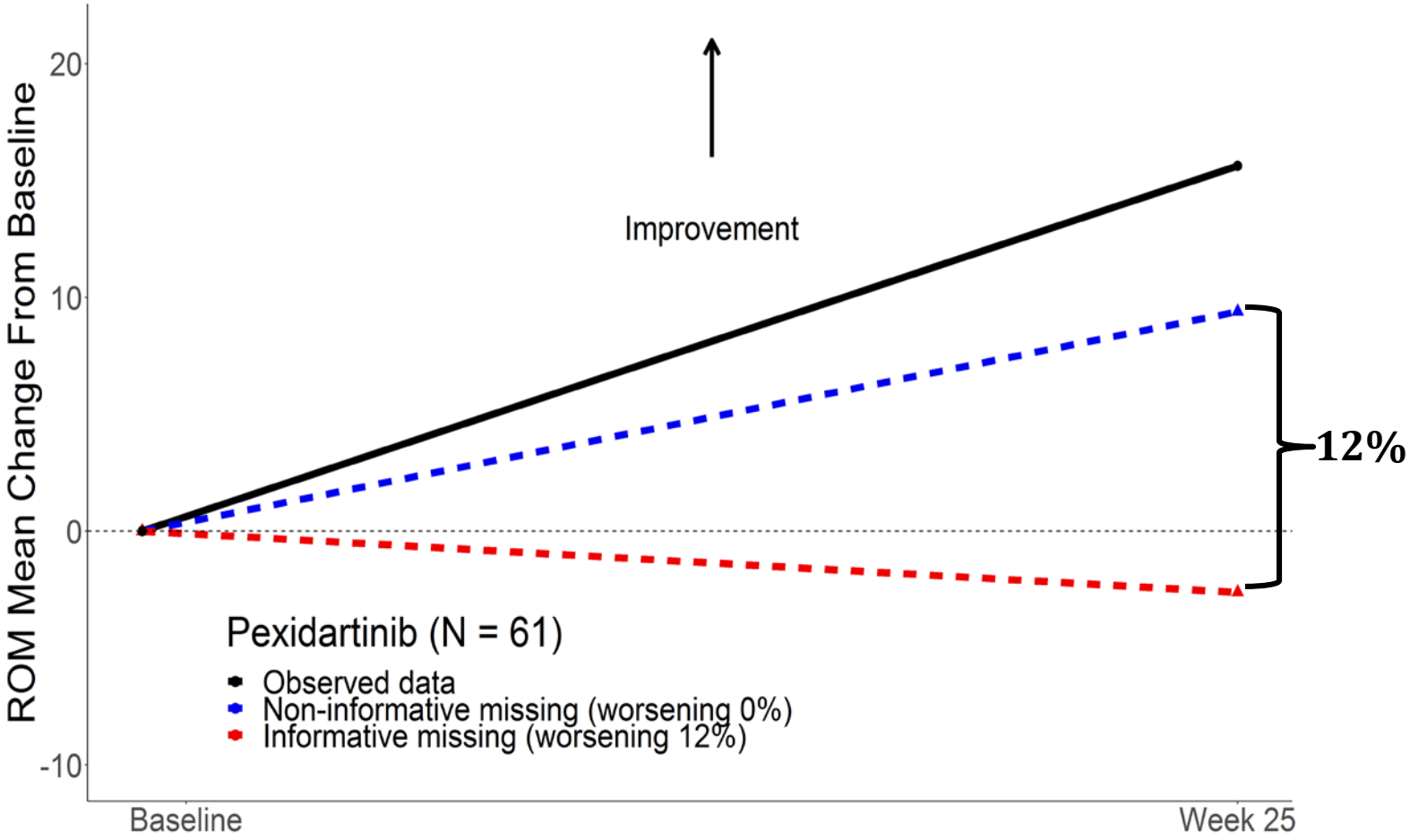
- Sensitivity analyses assess robustness of observed results due to different missing data assumptions

- **Tipping Point Analysis**
  - Conservative approach
  - Aim to determine how negative the missing responses must be to negate the observed finding

3. Impact of Missing Assessments Tipping Point Analysis

Question: What % worsening of ROM is needed for pexidartinib patients with missing assessments to reverse statistical significance (p-value > 0.05)?

Results: A **worsening of 12%** of ROM for patients with missing assessments would make ROM for pexidartinib not different from placebo



3. Impact of Missing Assessments

- There seems to be a treatment benefit of pexidartinib on ROM, but the magnitude is unclear

- Results of pre-specified and sensitivity analyses estimate the within-patient ROM improvement for patients on pexidartinib **may range from 7% - 19%**

Efficacy Results and Issues

- **Estimating Clinical Benefit**
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4. Revised Hierarchical Order of Secondary Endpoints

- **BPI-30 was originally the first secondary endpoint in the testing order**
  - Due to missing data, BPI-30 was moved to last in testing and ROM was moved from 3rd to 1st in hierarchy
- **Re-ordering prior to unblinding of results, but with knowledge of missing data**
  - Changing statistical analysis plan after completion of the trial is strongly discouraged as potential bias may be introduced
- **Results of BPI-30 were not found to be statistically significant**
  - Prior to re-ordering: ROM would not have been tested
  - After re-ordering: ROM was tested and determined to be statistically significant

5. Potential Unblinding of Clinical Assessors

- ENLIVEN was double-blind, and range of motion was measured by a blinded third party assessor
- High prevalence of adverse events (such as hair color changes) may have resulted in unblinding of assessors

	With Hair Color Change	No Hair Color Change
N	35	15
LS Mean Change 95% CI	14.4% (8.1, 20.7)	16.1% (9.0, 23.2)

6. Establishing a Clinically Meaningful Threshold of Benefit

- FDA requested a proposal of threshold(s) for a clinically meaningful within-patient change in score to help interpret results

- FDA Guidance for Industry: PRO Measures (2009) – Anchor-based methods to define threshold of clinical benefit
  - Anchor-based approach uses relationship between ROM and another independent measure to establish clinically meaningful benefit
  - Not feasible due to missing data in other COA measures

6. Establishing a Clinically Meaningful Threshold of Benefit

- **A threshold of +6.7% within patient change was proposed for the knee only (61% of patients)**
  - ➢+6.7% corresponds to 10° improvement in ROM for the knee
- No threshold for meaningful change was provided for other joints due to limited published literature
- Clinically meaningful thresholds not established

6. Establishing a Clinically Meaningful Threshold of Benefit: ROM of the Knee

Estimating and Interpreting Clinical Benefit

- **ENLIVEN demonstrated statistically significant improvement in ORR and ROM**
  - Magnitude of within-patient improvement of ROM for pexidartinib may range from 7-19%
    - 6-19% within-patient improvement of ROM for the knee
- **Limitations in interpreting clinical benefit as measured by ROM:**
  - There is little information what constitutes a clinically meaningful threshold for improvement

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Safety Analysis

- ENLIVEN Part 1 (N=61) provides the primary evidence of safety for pexidartinib in the TGCT population

- Evaluation of safety included
  - Adverse events
  - Laboratory assessments
  - Patient narratives
  - Case report forms
  - Liver biopsy reports when available

- Detailed evaluation of liver injury occurred for all patients in the proposed indicated population of TGCT (N=130)

Summary of Safety
ENLIVEN: Part 1

	Pexidartinib N = 61	Placebo N = 59
All Grade adverse events (AEs)	98%	93%
Grade 3-4 AEs	44%	12%
Serious AEs	13%	1.7%
Grade 3-4 serious AEs	12%	1.7%
AEs leading to discontinuation	13%	0
AEs leading to dose reductions	8%	0
AEs leading to dose interruptions	33%	10%

AEs in > 20% of Patients
ENLIVEN : Part 1

MedDRA Preferred Term	Pexidartinib N = 61		Placebo N = 59	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Any patient with an AE	98%	44%	93%	12%
Changes in hair color	67%	0	3.4%	0
Asthenia/fatigue	64%	0	41%	0
Increased AST	39%	10%	0	0
Facial Edema	34%	1.6%	7%	0
Increased ALT	28%	10%	1.7%	0
Rash	26%	1.6%	7%	0
Dysgeusia	25%	0	1.7%	0

Elevated ALT, AST and Total Bilirubin TGCT Population

Laboratory Test	Placebo in ENLIVEN N = 59	Pexidartinib in ENLIVEN N = 61	All TGCT Patients Treated with Pexidartinib N = 130
ALT > ULN	22%	67%	64%
≥3 × ULN	0	34%	22%
≥10 × ULN	0	7%	5%
AST > ULN	15%	90%	89%
≥3 × ULN	0	30%	22%
≥10 × ULN	0	3.3%	1.5%
Bilirubin > ULN	1.7%	12%	10%
≥2 × ULN	0	5%	3.8%
≥2 × baseline	29%	34%	27%
TBIL≥ 2 × ULN and AST or ALT ≥3 × ULN	0	4.9%	3.1%

ULN=Upper limit of normal

Elevated ALT, AST and Total Bilirubin TGCT Population

Laboratory Test	Placebo in ENLIVEN N = 59	Pexidartinib in ENLIVEN N = 61	All TGCT Patients Treated with Pexidartinib N = 130
ALT > ULN ≥3 × ULN ≥10 × ULN	22% 0 0	67% 34% 7%	64% 22% 5%
AST > ULN ≥3 × ULN ≥10 × ULN	15% 0 0	90% 30% 3.3%	89% 22% 1.5%
Bilirubin > ULN ≥2 × ULN ≥2 × baseline	1.7% 0 29%	12% 5% 34%	10% 3.8% 27%
TBIL≥ 2 × ULN and AST or ALT ≥3 × ULN	0	4.9%	3.1%

ULN=Upper limit of normal

Hy's Law

- Occurrence of Hy's Law identifies a drug likely to cause severe drug induced liver injury
- Identifies incidences of hepatocellular injury sufficient to impair bilirubin excretion
- Criteria include:
  - ALT or AST >3xULN
  - Total Bilirubin >2xULN
  - No increase in alkaline phosphatase
  - No other reason found to explain the combination of increased ALT or AST and total bilirubin (e.g., viral hepatitis or pre-existing liver disease)

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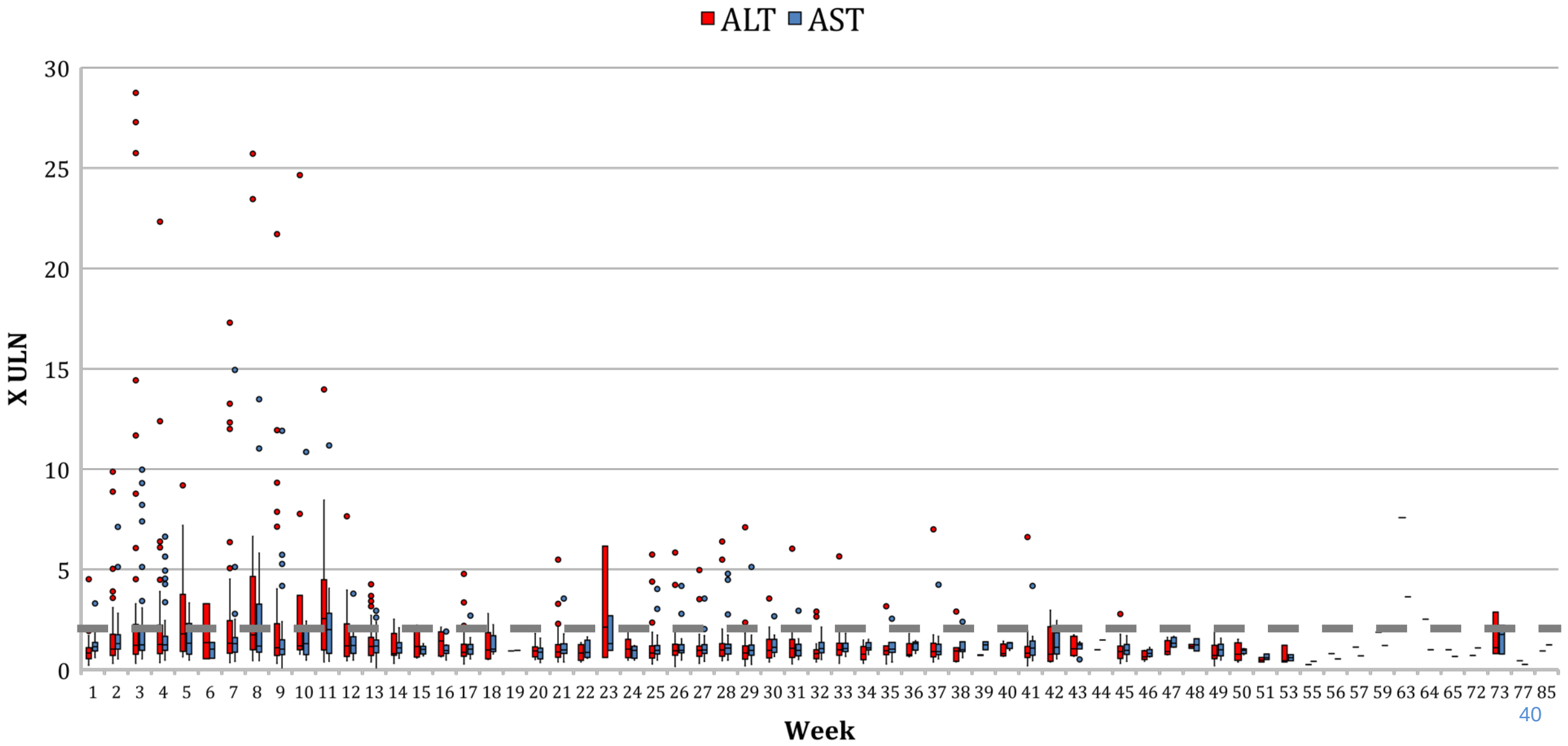
ALT > ULN	22%	67%	64%
≥3 × ULN	0	34%	22%
≥10 × ULN	0	7%	5%
AST > ULN	15%	90%	89%
≥3 × ULN	0	30%	22%
≥10 × ULN	0	3.3%	1.5%
Bilirubin > ULN	1.7%	12%	10%
≥2 × ULN	0	5%	3.8%
≥2 × baseline	29%	34%	27%
TBIL≥2 × ULN and AST or ALT ≥3 × ULN	0	4.9%	3.1%

ULN=Upper limit of normal

Majority of AST/ALT Elevations Occur Early ENLIVEN: Part 1



Management Guidelines for Hepatotoxicity

Toxicity	Action	Outcome
ALT or AST 3-5 x ULN No increase in bilirubin	Hold drug Monitor weekly	Resolve to baseline or < 3.0 x ULN Resume at reduced dose
ALT or AST 5-20 x ULN No increase in bilirubin	Hold drug Monitor 2 x weekly	Resolve to baseline or <3.0 x ULN Resume at a reduced dose
ALT or AST >20 x ULN No increase in bilirubin	Discontinue drug Monitor 2 x weekly	Discontinue drug Follow until resolution
ANY ALT or AST increase with ANY bilirubin increase	Discontinue drug Monitor 2 x weekly	Discontinue drug Follow until resolution

Actions Taken for AST/ALT & Bilirubin Elevations

- 55 patients (90%) in Part 1 of ENLIVEN experienced elevated transaminases and bilirubin
- No intervention: 40 patients (73%)
- Dose interruption: 8 patients (15%)
  - 4 resumed pexidartinib successfully
  - 4 had recurrence of transaminase elevation following re-challenge, leading to permanent discontinuation
- Permanent discontinuation: 4 patients (7%)
  - No re-challenge
- Dose reduction: 3 patients (5%)

Outcomes of Transaminase & Bilirubin Abnormalities

- After action was taken with pexidartinib, all 55 patients who experienced elevated transaminases and bilirubin improved
- Resolved to within normal limits or baseline: 37 patients (67%)
- Improved to 1.1-2.0xULN: 15 patients (27%)
- Improved to 2.1-2.7xULN: 3 patients (5%)

Outcomes for Patients with Severe Liver Injury ENLIVEN: Part 1

Age/Gender Study	Peak Laboratory	Action Taken	Outcome
67 yo/ F ENLIVEN	ALT 8 × ULN AST 5 × ULN ALP 3 × ULN TBIL 7 × ULN DBIL 4 × ULN	Permanently discontinued	• **Hospitalization** • Antibiotic treatment • Biochemical resolution in 3.9 months
52 yo/M ENLIVEN	ALT 9 × ULN AST 5 × ULN ALP 2 × ULN TBIL 7 × ULN DBIL 18 × ULN	Permanently discontinued	• Biochemical improvement to <2 x ULN in 1.9 months
75 yo/F ENLIVEN	ALT 6 × ULN AST 6 × ULN ALP 2 × ULN TBIL 15 × ULN DBIL 84 x ULN	Permanently discontinued	• Liver biopsy • **Hospitalization** • Bilirubin dialysis • Biochemical improvement to <2 x ULN after **7.1 months**

Overall Safety Database

- Safety database (N=768) submitted as part of the application
  - Commercial-sponsored trials (N=630)
  - Investigator-initiated trials (N=138)

- 2.5% of patients who received pexidartinib in the commercial-sponsored trials had labs consistent with liver injury (TBIL ≥2 x ULN and AST or ALT ≥ 3 x ULN)

- 2 cases of liver failure were identified (N=768)

Irreversible Liver Injury

Age/Gender Study Diagnosis	Dose	Peak Laboratory	Action Taken	Outcome
60 yo/F Early-Stage Breast CA[1]	1200 mg/day BID and paclitaxel 155 mg weekly	ALT 12 × ULN AST 8 × ULN ALP 4 × ULN TBIL 25 × ULN DBIL 5 × ULN	Permanently discontinued both pexidartinib, paclitaxel	• Liver biopsy • Cholecystectomy for cholecystitis • **Liver transplant** after 20 months
66 yo/F Metastatic Melanoma[2]	1000 mg/day, cisplatin, temozolomide, and recombinant human endostatin	ALT 10 × ULN AST 11 × ULN ALP 5 × ULN TBIL 18 × ULN DBIL 60 × ULN	Permanently discontinued	• Silbyum marianum and ursodeoxycholic acid • **Hospitalization** • Unspecified Chinese herbal remedies • Bilirubin absorption • "Liver protecting" therapy • **Died** after 4 months

[1] Enrolled in an Investigator-Initiated Trial [2] Enrolled in Trial PLX108-13

Findings from Liver Biopsies

- 8/768 patients had liver biopsy
  - 7 patients had evidence of cholestasis and bile duct injury
  - 1 patient had mild apoptotic hepatocellular injury with minimal inflammation and no fibrosis
- None of these patients had a second biopsy to evaluate for progression or resolution

Summary of Hepatotoxicity

- **Irreversible liver injury occurred in patients who received pexidartinib (N=768)**
  - 0.3% (upper 95% confidence interval: 0.9%)
- **Pexidartinib development Program**
  - Liver injury (TBIL ≥2 x ULN and AST or ALT ≥ 3 x ULN)
    - 2.5% in the pooled safety data set (n=630)
    - 3.1% in TGCT population (n=130)
    - 4.9% in ENLIVEN (n=61)
- **ENLIVEN Trial**
  - Liver test elevations: ALT-67% , AST-90%, and total bilirubin-12%
  - All patients improved with no interventions, dose reductions/interruptions/discontinuations
  - 2 TGCT patients had a prolonged time to recovery requiring more intervention

Uncertainties of Liver Injury

- **Unknown mechanism of action causing bile duct injury**
- **Pattern is predominantly cholestatic**
  - Severity ranges from liver enzyme elevations to ductopenia and liver failure
  - Unknown if injury to bile duct is progressive, even in the setting of normalized biochemical labs
  - Unknown whether pexidartinib causes subacute or chronic injury, which may result in cirrhosis and liver failure
- **Small number of patients had long-term exposure to pexidartinib; potential long-term effects unknown:**
  - 69 patients received ≥ 18 months of pexidartinib
  - 55 patients received ≥ 24 months of pexidartinib
  - 8 patients received ≥ 48 months of pexidartinib

Risk Evaluation and Mitigation Strategies (REMS)

- FDA Amendments Act (FDAAA) of 2007 authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.

- A REMS with elements to assure safe use (ETASU) can be required for a drug, if FDA determines that the product is effective but is associated with serious risk and be approved only if, or would be withdrawn from the market, unless such a strategy is in place to ensure the benefits outweigh the risks.

Rationale regarding the need for a REMS for Pexidartinib

- The risks of hepatotoxicity with pexidartinib are serious, severe and potentially fatal
- TGCT is associated with severe morbidity and/or functional limitations but is not imminently life-threatening
- Risk mitigation measures must be performed that may prevent the risk or severity of the risk, however less is known about the risks of chronic hepatotoxicity associated with long-term use
- This is a new molecular entity; there is no experience with this drug class

Daiichi Sankyo's Proposed REMS

- Communication plan
  - Require prescriber education on the risk of hepatotoxicity and the need for frequent monitoring prior to prescribing pexidartinib
- Elements to assure safe use
  - Prescriber education and certification
  - Patient Registry
  - Pharmacy certification (ensure elements met prior to dispensing pexidartinib; no more than 30 day supply)
  - Implementation system
- Timetable for submission of assessments

Purpose of a Patient Registry Required by the REMS

- To assess post-marketing safe use and further characterize acute, chronic and irreversible hepatotoxicity

- The registry enables the collection of:
  - Baseline information (e.g., biochemical laboratory values, concomitant medications)
  - Periodic status reports on each patient and diagnostic work-up for patients that experience acute, long-term, and/or irreversible liver toxicity

Outline

- **Background**
  - Proposed Indication
  - Disease Background
  - Regulatory History
- **Efficacy Results and Issues**
  - Estimating and Interpreting Clinical Benefit
- **Safety Results and Issues**
  - Liver Injury
- **Summary and Conclusions**
- **Discussion Topics and Questions for ODAC**

Conclusions

- Patients with symptomatic TGCT which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery have **no available therapies**

- Pexidartinib demonstrated a **statistically significant improvement in ORR and ROM**
  - However, there **are limitations in interpreting the results for ROM** due to missing data and insufficient evidence to establish a clinically meaningful threshold for improvement

- Pexidartinib causes **liver injury that may be severe and/or irreversible** and this liver injury has not been fully characterized

Outline

- **Background**
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Discussion Topic

- **Benefit**
  - ENLIVEN demonstrated statistically significant improvement in ORR and ROM
  - ORR is 38% and ROM improvement magnitude may range from 7-19%
  - There is little information what constitutes a clinically meaningful threshold for improvement in ROM
- **Risk**
  - Irreversible liver injury occurred in 0.3% of patients who received pexidartinib
  - Severe liver injury (TBIL 2 x ULN and AST or ALT ≥ 3 x ULN) occurred in 2.5%-4.9%
  - Long-term effects uncertain

- **Discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatoxicity**.

Voting Question

Does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication?


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