

Analyses of Markers of Liver Injury in Phase 2 and 3 Controlled Clinical Trials of Peramivir in Subjects with Influenza Infection

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INTRODUCTION

- Patients with influenza have been reported to develop transient collateral liver injury.^{1,2}
- There have also been reports of liver enzyme abnormalities in influenza patients treated with neuraminidase inhibitors (NAI).^{3,4}
- Many patients with influenza are treated with neuraminidase inhibitors, but the potential influence of these therapies on liver function has not been systematically assessed.
- Peramivir is an intravenous neuraminidase inhibitor in Phase 3 trials in the US and approved in Japan and South Korea for treatment of influenza.
- Peramivir has been studied in over 2400 influenza patients and volunteers in a multinational development program.
- We conducted an analysis of data from five Phase 2 and 3 clinical trials to evaluate the potential association of peramivir exposure with liver injury in influenza patients.

METHODS

Study Designs and Treatments

- Five controlled studies of peramivir treatment for influenza were conducted in adult patients from 2006-2009

Peramivir Phase 2 and 3 Clinical Trials in Adult Subjects

Study	BCX1812-211	BCX1812-212	0722T0621	0815T0631	BCX1812-201
Peramivir	150 mg IM	300 mg IM	300 mg IV	300 mg IV	200 mg IV
Control	300 mg IM	600 mg IM	600 mg IV	600 mg IV	400 mg IV
Control	Placebo	Placebo	Placebo	Osetamivir 75 mg BID	Osetamivir 75 mg BID
Treatment	Single dose	Single dose	Single dose	Peramivir: Single dose	Osetamivir: 5 days
Duration	5 days	5 days	5 days	5 days	5 days
Subjects	344 outpatients	405 outpatients	300 outpatients	1099 outpatients	137 inpatients
Design	R, DB, PG	R, DB, PG	R, DB, PG	R, DB, DD, PG	R, DB, DD, PG

IV=intravenous, IM=intramuscular, R=randomized, DB=double blind, PG=parallel group, DD=double dummy

Subjects

- Enrolled subjects had
 - Positive RAT test for influenza A or B
 - Onset of acute illness 36-72 hr before presentation
 - ≥ 1 respiratory (e.g., cough) and ≥ 1 constitutional (e.g., fever) symptom
 - No recent antiviral treatment

Study Assessments

- Blood samples were drawn for determination of ALT, AST, bilirubin (BIL), and alkaline phosphatase (AP) levels at screening (baseline) and approximately 48 hr and 14 days (312 hr) after initiation of treatment
- Additional blood samples were drawn at 96, 168, or 192 hr in some trials
- In Study 0815T0631, all subjects were evaluated at 192 hr and only those with abnormalities were evaluated again at 312 hr
- ALT, AST, BIL, and AP elevations were graded using DAIDS Grading Scale (2004)
- Multiple logistic regression analyses with stepwise selection were performed to identify potential predictors of increases in markers of liver injury

RESULTS

Analyses of Markers of Liver Injury

- 2119 adults with confirmed influenza were assessed for liver injury

Analyses of Markers of Liver Injury in Combined Peramivir Studies

ALT, median U/L (min, max)	Baseline	48 hr	96 hr	168 hr	192 hr	312 hr*
Placebo	22 (6, 298)	25 (6, 216)	25 (7, 190)	NA	28 (6, 551)	22 (4, 636)
Peramivir	20 (1, 415)	22 (2, 336)	25 (7, 225)	20 (5, 236)	30 (8, 172)	21 (2, 242)
Osetamivir	18 (5, 129)	20 (5, 131)	35 (8, 350)	20 (5, 129)	NA	22 (7, 120)

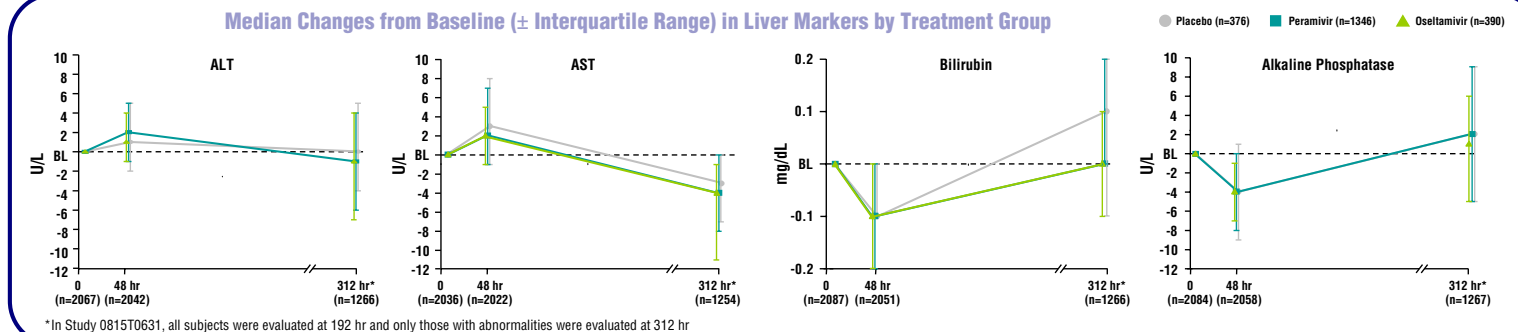
AST, median U/L (min, max)	Baseline	48 hr	96 hr	168 hr	192 hr	312 hr*
Placebo	24 (10, 179)	27 (12, 182)	25 (12, 137)	NA	24 (10, 257)	20 (9, 248)
Peramivir	22 (9, 410)	24 (9, 379)	25 (10, 191)	18 (8, 110)	24 (11, 116)	20 (9, 95)
Osetamivir	21 (12, 101)	23 (11, 134)	27 (13, 219)	19 (10, 57)	NA	19 (10, 66)

Bilirubin, median mg/dL (min, max)	Baseline	48 hr	96 hr	168 hr	192 hr	312 hr*
Placebo	0.4 (0.1, 3.4)	0.3 (0.1, 1.5)	0.4 (0.2, 1.6)	NA	0.4 (0.2, 1.7)	0.5 (0.1, 3.3)
Peramivir	0.4 (0.0, 2.5)	0.3 (0.1, 2.0)	0.3 (0.2, 1.2)	0.4 (0.2, 1.8)	0.4 (0.1, 1.3)	0.4 (0.2, 2.3)
Osetamivir	0.4 (0.2, 1.8)	0.4 (0.2, 1.2)	0.4 (0.2, 1.3)	0.4 (0.2, 1.4)	NA	0.5 (0.2, 1.2)

Alkaline Phosphatase, median U/L (min, max)	Baseline	48 hr	96 hr	168 hr	192 hr	312 hr*
Placebo	79 (25, 370)	76 (23, 310)	63 (31, 154)	NA	71 (30, 189)	80 (30, 411)
Peramivir	67 (21, 410)	62 (18, 452)	65 (33, 209)	57 (18, 181)	68 (32, 147)	75 (31, 388)
Osetamivir	61 (29, 148)	55 (27, 186)	71 (36, 163)	56 (27, 104)	NA	66 (29, 133)

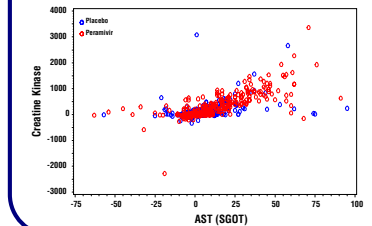
*In Study 0815T0631, all subjects were evaluated at 192 hr and only those with abnormalities were evaluated at 312 hr

- Liver marker levels were similar across treatment groups at baseline and all post-treatment timepoints
- Across all trials, pre-therapy baseline median (range) liver marker levels were as follows: ALT = 20 (1, 415) U/L; AST = 22 (9, 410) U/L; BIL = 0.4 (0, 3.4) mg/dL; AP = 67 (21, 410) U/L



- Median changes from baseline to 48 hr and 14 days (312 hr) were similar among treatment groups for ALT, AST, BIL, and AP

Scatter Plot of Change from Baseline in AST vs Creatine Kinase at Day 3 in Peramivir IM Studies



- AST elevations in the two peramivir IM studies (BCX1812-211 and 212) correlated with elevations in creatine kinase (peramivir: r=0.75, p<0.001; placebo: r=0.382, p<0.001), suggesting muscle injury at the injection site

Treatment Emergent Graded Increases in Markers of Liver Injury* in Combined Peramivir Studies†

Parameter	Placebo (n=383)	Peramivir (n=1346)	Osetamivir (n=390)
ALT			
48 hr Post-Treatment			
Grade 1	12 (3%)	32 (2%)	8 (2%)
Grade 2	3 (1%)	19 (1%)	3 (1%)
Grade 3	0	1 (0.1%)	0
Grade 4	0	0	0
312 hr [§] (Day 14) Post-Treatment			
Grade 1	10 (3%)	14 (1%)	4 (1%)
Grade 2	0	8 (0.6%)	1 (0.3%)
Grade 3	1 (0.3%)	0	0
Grade 4	1 (0.3%)	0	0
AST			
48 hr Post-Treatment			
Grade 1	26 (7%)	90 (7%)	7 (2%)
Grade 2	6 (2%)	14 (1%)	1 (0.3%)
Grade 3	0	1 (0.1%)	0
Grade 4	0	1 (0.1%)	0
312 hr [§] (Day 14) Post-Treatment			
Grade 1	3 (1%)	6 (0.4%)	1 (0.3%)
Grade 2	1 (0.3%)	1 (0.1%)	0
Grade 3	0	0	0
Grade 4	0	0	0
Bilirubin			
48 hr Post-Treatment			
Grade 1	2 (1%)	1 (0.1%)	0
Grade 2	0	2 (0.1%)	0
Grade 3	0	0	0
Grade 4	0	0	0
312 hr [§] (Day 14) Post-Treatment			
Grade 1	5 (1%)	14 (1%)	0
Grade 2	1 (0.3%)	3 (0.2%)	0
Grade 3	1 (0.3%)	0	0
Grade 4	0	0	0
Alkaline Phosphatase			
48 hr Post-Treatment			
Grade 1	1 (0.3%)	3 (0.2%)	0
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
312 hr [§] (Day 14) Post-Treatment			
Grade 1	1 (0.3%)	2 (0.1%)	1 (0.3%)
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0

*Elevated liver marker following initiation of treatment and increased by ≥ 1 grade from baseline level
 †BCX1812-201, BCX1812-211, BCX1812-212, 0722T0621, 0815T0631
 ‡ALT, AST, AP: Grade 1 = 1.25 - 2.5 x ULN, Grade 2 = 2.6 - 5.0 x ULN, Grade 3 = 5.1 - 10.0 x ULN, Grade 4 = >10.0 x ULN
 §In Study 0815T0631, all subjects were evaluated at 192 hr and only those with abnormalities were evaluated at 312 hr

- 48 hr post-treatment, most increases in ALT, AST, BIL, and AP were Grade 1 or 2
- By 14 days post-treatment, the proportions of patients with elevations in liver markers had declined substantially

Percentage of Subjects with Treatment-Emergent Grade 2, 3, or 4 Increases in Markers of Liver Injury in Combined Peramivir Studies

Parameter	Placebo (n=383)	Peramivir (n=1346)	Osetamivir (n=390)
Any Liver-Related Toxicity	3.1%	4.0%	1.8%
ALT	1.8%	2.7%	1.3%
AST	2.3%	1.9%	1.0%
Bilirubin	0.5%	0.5%	0
Alkaline Phosphatase	0	0	0

*Elevated liver marker at any timepoint following initiation of study treatment and increased by ≥ 1 grade from baseline level
 †BCX1812-201, BCX1812-211, BCX1812-212, 0722T0621, 0815T0631

- The percentages of subjects with increases in markers of liver injury at any post-treatment timepoint across the combined peramivir studies was low and similar across treatment groups
- Treatment-emergent Grade 2 or higher levels of bilirubin were found in very few subjects, and no subject had treatment-emergent AP elevations

Hepatic Adverse Events

- In this population of 2119 subjects across 5 studies, there was 1 report of a mild treatment-emergent hepatobiliary disorder in the peramivir treatment group (0.1%).

Predictors of Increased Markers of Liver Injury

ALT

Risk Factors for Treatment Emergent Grade 2, 3, or 4 ALT* in Combined Peramivir Studies†

Parameter	Present (n=180)	Absent (n=1928)	Odds Ratio (95% CI)	P value
Baseline ALT, median (range)	33 (10 - 298)	19 (1 - 415)	1.02 (1.01, 1.03)	<0.001
Baseline TCID ₅₀ ‡, median (range)	3.8 (0.5 - 8.2)	3.8 (0.5 - 8.8)	1.21 (1.01, 1.44)	0.035

*Elevated ALT at any timepoint following initiation of study treatment and increased by ≥ 1 grade from baseline level
 †BCX1812-201, BCX1812-211, BCX1812-212, 0722T0621, 0815T0631
 ‡50% Tissue Culture Infective Dose

- The risk for elevated ALT was increased in those subjects who
 - had Grade 2, 3, or 4 ALT at baseline
 - had higher baseline TCID₅₀
- Factors that did not significantly increase the risk for elevated ALT were
 - peramivir treatment
 - oseltamivir treatment
 - age
 - race
 - gender
 - influenza strain
 - influenza season
 - time from symptom onset to enrollment (<48 hr vs ≥48 hr)
 - route of peramivir administration (IM vs IV)

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AST

Risk Factors for Treatment Emergent Grade 2, 3, or 4 AST* in Combined Peramivir Studies†

Parameter	Present (n=200)	Absent (n=1903)	Odds Ratio (95% CI)	P value
Baseline AST, median (range)	30 (10 - 170)	21 (9 - 410)	1.02 (1.01, 1.03)	<0.001
Influenza Strain (A INDI vs B), n (%)	2 (1%) vs 30 (15%)	57 (3%) vs 191 (10%)	12.85 (1.84, 89.99)	0.010
Influenza Season (Northern 2008/9 vs Southern 2007), n (%)	72 (36%) vs 35 (18%)	1128 (59%) vs 197 (10%)	0.22 (0.07, 0.72)	0.013
Baseline TCID ₅₀ ‡ median (range)	3.75 (0.5 - 8.5)	4.0 (0.5 - 8.8)	1.26 (1.00, 1.59)	0.050

*Elevated AST at any timepoint following initiation of study treatment and increased by ≥ 1 grade from baseline level
 †BCX1812-201, BCX1812-211, BCX1812-212, 0722T0621, 0815T0631
 ‡Influenza A indeterminate
 §50% Tissue Culture Infective Dose

- The risk for elevated AST was increased in those subjects who
 - had Grade 2, 3, or 4 AST at baseline
 - had influenza during the Northern 2008/9 season (vs Southern 2007)
 - had an indeterminate strain of influenza A
 - had higher baseline TCID₅₀
- Factors that did not significantly increase the risk for elevated AST
 - peramivir treatment
 - oseltamivir treatment
 - age
 - race
 - gender
 - infection with influenza A H1N1 vs influenza B
 - infection with influenza A H3N2 vs influenza B
 - time from symptom onset to enrollment (<48 hr vs ≥48 hr)
 - route of peramivir administration (IM vs IV)

Bilirubin

- The only significant predictor of Grade 2 or higher bilirubin levels was the baseline bilirubin level (OR=14.18; 95% CI=4.94, 46.60; p<0.001)

DISCUSSION

- Concerns have been raised about potential liver injury associated with influenza or its treatment with NAIs
- This analysis of subjects enrolled in 5 controlled peramivir studies found that increases in markers of liver injury were very uncommon, especially for bilirubin and alkaline phosphatase
- Most increases in liver markers were Grade 1 (mild) or Grade 2 (moderate)
- Grade 2 or higher treatment-emergent increases in ALT and AST were transient and the incidence was similar between peramivir, oseltamivir, and placebo treatment groups
- By 14 days post-treatment, only 0-0.6% of subjects across peramivir, oseltamivir, and placebo treatment groups continued to have Grade 2 or higher increased markers of liver injury
- In IM peramivir studies, increases in AST levels across both peramivir and placebo groups correlated with increased creatine kinase, suggesting a relationship to muscle injury at the injection site
- No difference was observed in the reported rates of hepatic adverse events between the neuraminidase inhibitor and placebo-treated subjects, with only one report among 2119 subjects
- These safety data in subjects with influenza are consistent with those reported for human volunteers in three Phase 1 IV studies.⁵
- The only consistent predictors of Grade 2 or higher ALT, AST, or BIL levels were their corresponding baseline levels
- Treatment with peramivir or oseltamivir was not a predictor of increased markers of liver injury

CONCLUSIONS

- Increases in markers of liver injury were uncommon in patients with influenza enrolled in controlled clinical studies
- Changes in such markers were characterized by mostly mild to moderate initial increases followed by recovery
- Changes were similar regardless of treatment with placebo or NAIs, suggesting that underlying viral illness was the major contributor
- These data suggest that treatment of influenza infection with NAIs is not associated with hepatotoxicity

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