HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Lancet Infect Dis. 2015 September ; 15(9): 1049–1054. doi:10.1016/S1473-3099(15)00157-7.

Ledipasvir and Sofosbuvir for Hepatitis C Genotype 4: A Proof of Concept Phase 2a Cohort Study

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AUTHOR CONTRIBUTIONS

SK and AK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AK and ZS performed the literature search. AK, SK, AN, MP, and HM contributed to the study design. AK, ZS, RK, SS, AN, CK, CG, GT, KS, and DK collected data. AK, ZS, RK, Sand MP analyzed data. AK, AO, SK, RK, PP, GT, KS, PP, JM, MP, BL and HM interpreted data. ZS, AK, and RK contributed to figure design. AK wrote the first draft of the manuscript and all authors participated in the review and critique of the manuscript.

CONFLICT OF INTEREST STATEMENT

Anu Osinusi is an employee of Gilead Pharmaceuticals. Gebeyehu Teferi serves on the Gilead and Merck Advisory Boards and as a speaker for Gilead. No other conflicts of interest.

DISCLAIMER

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Research in context

Systematic review

We searched PubMed on Feb 11, 2015, for articles in published between January 1, 2000 and Feb 11, 2015 using a combination of the MeSH search terms “HCV treatment”, “antiviral agent” and “genotype 4” and consulted the hepatitis C virus (HCV) treatment guidelines for phase 2 or 3 clinical trials of treatments for patients with genotype-4 hepatitis C virus. We also searched the reference list of articles from our search for additional reports that met our inclusion criteria of phase 2 and phase 3 clinical trials of interferon-free regimens for treatment of HCV genotype 4.

5 clinical trials[12,13,21-23] have been published (one journal article and four in abstract form) of interferon-free regimens for patients with HCV genotype 4. These trials have shown promising safety and efficacy (SVR12 84-100%) using combination direct-acting antiviral drugs, with or without ribavirin for 12–24 weeks. Few patients with cirrhosis or who have been previously treated with interferon containing regimens have been included.

Added value of this study

Although our study is small, we showed high rates of sustained viral response at 12 weeks with use of sofosbuvir and ledipasvir for 12 weeks, which supports the possibility that this simple regimen might be effective for some patients.

Implications of all the available evidence

Further development of this efficacious, simple, well tolerated, regimen is warranted and studies in patients with cirrhosis and previously treated patients should be pursued.

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Abstract

Background—Chronic hepatitis C (HCV) genotype 4 (GT-4) represents up to 13% of HCV infections globally, concentrated in resource limited countries in the Middle East and Africa. In patients with HCV GT-1, the combination of ledipasvir and sofosbuvir has shown high cure rates with excellent tolerability but has not been examined for HCV GT-4. We evaluated, the efficacy, safety and tolerability of 12 weeks of combination therapy with ledipasvir and sofosbuvir in patients infected with HCV GT-4.

Methods—In this single center, open-label cohort, phase 2a trial, twenty-one HCV GT-4 treatment naïve or interferon treatment-experienced patients (HIV negative) were sequentially enrolled and treated with 12 weeks of ledipasvir (aNS5A inhibitor and nucleotide polymerase inhibitor, respectively) and sofosbuvir (*n*=21). The primary efficacy endpoint was SVR12 (HCV RNA less than the level of quantification 12 weeks after treatment completion).

Findings—Twenty of 21 patients treated with a two drug combination (ledipasvir and sofosbuvir) for 12 weeks achieved SVR12 (95%CI: 76-100%), including seven patients with cirrhosis. One patient was identified as non-adherent to study medications and withdrew from the study, but is included in the intention to treat analysis. There were no discontinuations of treatment due to adverse events and no grade 3 or 4 adverse events related to study medications.

Interpretation—In this small proof of concept study, ledipasvir and sofosbuvir for 12 weeks in HCV GT-4 patients was well tolerated and resulted in 100% SVR on all patients who took 12 weeks of study drugs regardless of previous treatment status and underlying liver fibrosis. This is the first report of a single pill, all oral interferon and ribavirin free therapy for patients with HCV GT-4.

Funding—NIAID, National Cancer Institute and Clinical Center Intramural Program. Clinical Trials.gov number NCT01805882. The study was also supported in part a Cooperative Research and Development Agreement between NIH and Gilead Sciences.

INTRODUCTION

An estimated 185 million people in the world are infected with hepatitis C (HCV), which is associated with the progression to end stage liver disease and hepatocellular carcinoma[1,2]. Of these infections, HCV genotype 4 (GT-4) accounts for up to 8-13% of HCV infections, primarily concentrated in Sub-Saharan Africa, North Africa, the Middle East and Southeast Asia.[3,4] Within Europe, HCV GT4 is found in a significant proportion of HCV infected patients in countries including France, Belguim and Greece.[5] In Egypt, GT-4 HCV is particularly common, with approximately 15% of the population is infected with this subtype.[4]

While the development of interferon and ribavirin free regimens for HCV GT-1 has been progressing rapidly, simple, well-tolerated therapies for the treatment of HCV GT-4 is particularly crucial given the concentration of this genotype in resource limited countries, where laboratory monitoring for adverse events may not be feasible.[4] In 2014, sustained viral response (SVR) rates for HCV GT-4 dramatically improved with the introduction of the directly acting antivirals (DAA), sofosbuvir or simeprevir in combination in this population with pegylated interferon and ribavirin for 12 weeks. An alternative regimen for interferon-ineligible patients utilizing sofosbuvir and ribavirin for 24 weeks was also recommended.[6] While these regimens are associated with high SVR rates of 59-100% in treatment naïve or treatment experienced patients, they require multiple pills, and injections as well as long treatment durations.[6] In addition, both interferon and ribavirin are associated with toxicities including fatigue, anemia and teratogenicity and require frequent laboratory monitoring.[6]

Ledipasvir and sofosbuvir, two novel DAAs have been approved in the United States for combination use for the treatment of hepatitis C GT-1. Recent studies of this combination, given as one pill per day for 12 weeks, demonstrated high SVR rates of 91-100 in HCV GT-1 treatment naïve and treatment experienced patients, with few adverse events.[7,8] In vitro, both ledipasvir and sofosbuvir exhibit anti-HCV activity against HCV GT-4 that is similar to that seen against HCV GT-1. The clinical efficacy of this regimen in-vivo for HCV GT-4, however, has not been established.

Historically, SVR rates for patients with HCV GT-4 treated with interferon containing therapy have been between those of HCV GT-1 and HCV GT-2/3.[9,10] Further, the in-vitro efficacy of ledipasvir and sofosbuvir for HCV GT-4 suggests that the combination of the potent DAAs ledipasvir and sofosbuvir without ribavirin for 12 weeks may be effective for the treatment of HCV GT-4, in both treatment naïve and interferon treatment experienced patients. Thus, we conducted a clinical trial in a predominantly immigrant population, to evaluate the two drug combination of ledipasvir and sofosbuvir for 12 weeks.

METHODS

Patients and Study Design

Patients were enrolled at a single center, the Clinical Center of the National Institutes of Health (NIH), Bethesda, MD, USA (NCT01805882). Patients were enrolled and followed from September 2013 to November 2014. Eligible participants were men and women, 18 years of age or older, infected with chronic HCV GT-4 infection (serum HCV RNA ≥ 2000 IU/mL), compensated liver disease, who were treatment naïve or treatment experienced (previous exposure to directly acting antivirals was exclusionary). Patients with HIV or HBV infection were excluded. The stage of liver disease was determined by liver biopsy or by a Fibrosure test. Fibroscan was not used given its limited availability at most U.S. medical care centers at the time of study initiation. Full eligibility criteria are included in the Supplementary Appendix 1. Written or oral informed consent was obtained from all participants.

Study Design

Twenty-one patients were enrolled to be treated with ledipasvir and sofosbuvir. Ledipasvir at a dose of 90 mg and sofosbuvir at a dose of 400 mg and were administered as a single combination tablet taken once daily for 12 weeks. Criteria for stopping study medications were failure to achieve a >2 $\log_{10}$ decline in HCV RNA by week 4, unless > 2 $\log_{10}$ decline would be below the lower limit of HCV quantification (LLOQ). All patients who took at least one pill were included in the final analysis. The protocol permitted participants who failed treatment the option of treatment with the current standard of care, which at the time of the study was pegylated-interferon and ribavirin or ribavirin alone with sofosbuvir. Neither patient nor investigators were blinded. Patients were contacted for screening visits in the order in which they initially contacted the study team for participation and enrolled in the order in which they completed screening requirements. All eligible participants were invited to enroll.

Study Oversight

The study was approved by the Institutional Review Board of the National Institute of Allergy and Infectious Diseases (NIAID) and was conducted in compliance with the Good Clinical Practice guidelines, the Declaration of Helsinki and regulatory requirements. The Regulatory Compliance and Human Participants Protection Branch of NIAID served as the study sponsor and medical monitor. Gilead Sciences Inc. provided drug and scientific advice.

Efficacy Assessments

Plasma HCV RNA levels were measured using the real time HCV Assay (Abbott), with a lower limit of quantification (LLOQ) of 12 IU/mL and lower limit of detection (LLOD) of 3 IU/mL at the start of study medication, week 4, 8 and 12 on treatment, as well as at 2, 4, 8 and 12 weeks post-treatment . Serum HCV RNA levels were also measured using the COBAS TaqMan HCV RNA assay, version1.0 (Roche), with a LLOQ of 43 IU/mL and a LLOD of 15 IU/mL at select time points.

Safety Assessments

Adverse events and clinical laboratory results were recorded throughout the study. Adverse events were graded from 1 (mild) to 4 (severe) according to the NIAID Division of AIDS (DAIDS) toxicity table (version 1.0).[11]

Clinical End Points

The primary efficacy end point was the proportion of participants with plasma HCV viral load below the LLOQ of the Roche COBAS TaqMan HCV RNA Assay 12 weeks after treatment completion (SVR_{12}). The LLOQ is the represents the lowest HCV RNA concentration that is within the linear range of detection of the HCV RNA assay.

The primary safety endpoint was the frequency and severity of adverse events. Secondary endpoints that have been completed and included are the proportion of participants with unquantifiable HCV viral load at specified time points during and after treatment,

discontinuations, adverse events and safety laboratory changes. Data through SVR12 is included here with follow up through 48 weeks post-treatment ongoing.

Statistical Analysis

The primary efficacy and safety analyses were based on an intention to treat population (all patients who received at least one dose of study medication). Sample size was calculated to provide both a sufficiently high probability of observing at least one adverse event of probability ≥10% and with pre-specified confidence intervals (CI) for estimates of efficacy assuming 20 patients. Given that one patient dropped out and was replaced, post-hoc CIs were calculated for 21 patients. With 21 patients in the treatment group, if the true probability of an adverse event due to a regimen is 10% or more, a sample size of 21 provides an 88% chance of observing at least one such adverse event. With a sample size of 21 if all patients achieved SVR12, the 95% confidence interval for that estimate is 87-100% and if 19 patients achieved SVR 12 the 95% confidence interval for that estimate is 76-100%. The proportion of patients with an SVR12 weeks after completion of therapy was calculated. Analyses were performed using PRISM 6.0.

Role of the funding source

Data collection, review and analysis were performed by NIH and University of Maryland investigators. AK and SK participated in the study design and all authors in the writing of the report. NIH and University of Maryland affiliated investigators had full access to all data in the study, and A.K. and the corresponding author had final responsibility for the decision to submit for publication.

RESULTS

Twenty-four participants were screened and 21 were enrolled in this study (Figure 1).

Baseline Characteristics of Patients

Of the patients enrolled, 38% (8/21) were treatment experienced, and 43% had advanced stage 3 or 4 fibrosis (9/21). Twenty-nine percent (6/21) of patients were of Egyptian origin, and 38% (8/21) were from other African countries.

The majority of participants were male [67%; (14/21)] and had high baseline plasma HCV RNA levels (>800,000 IU/mL) [62%; (13/21)]. Nine percent (2/21) of patients had Histologic Activity Index (HAI) Stage 3 liver disease and 33% (7/21) had cirrhosis. (Table 1)

Virologic Response

Twenty of 21 patients (20/21; 95%CI: 76-100%) treated with ledipasvir and sofosbuvir had an unquantifiable HCV RNA (Roche CobasTaqman Assay) 12 weeks after the completion of therapy. One patient treated with ledipasvir and sofosbuvir had an HCV VL of 1,533,291 IU/mL at week 4. On further questioning the patient reported non-adherence and by pill count had taken a maximum of 18 doses by week 4. The patient withdrew from the study, but is included in the intention to treat analysis.

Ninety-five percent (20/21) of participants treated with ledipasvir and sofosbuvir had an unquantifiable level of HCV RNA by both weeks 4 and week 8 of treatment (Table 2). Complete results of HCV RNA and changes in ALT and AST are included in the Supplemental Figure and Tables.

Safety

Twenty of 21 (95%) of patients completed treatment. The most common adverse events were diarrhea, fatigue, nausea and upper respiratory infections (Table 3). Most adverse events were mild in severity. No deaths, serious adverse events, grade 3 or 4 adverse events occurred. Five grade 3 laboratory abnormalities occurred: decreased absolute neutrophil count in a patient who took only one dose of study medication four weeks prior, hyperglycemia in two patients with type 2 diabetes mellitus and a hemoglobin A1C of 7.6% and 8.7% at screening, hypophosphatemia in a patient with a history of grade 3 hypophosphatemia prior to starting study medications, thrombocytopenia (41 K/mL) in a patient with cirrhosis, and thrombocytopenia (45 K/mL) prior to starting study medications.

DISCUSSION

In the present study, treatment with sofosbuvir and ledipasvir for 12 weeks resulted in an SVR12 rate of 95% in chronic HCV genotype 4 infected treatment-naïve and interferon treatment-experienced patients. The regimen was well tolerated, able to rapidly suppress HCV viremia and dramatically simplifies treatment for HCV GT4, while achieving 100% SVR in all patients who received 12 weeks of therapy, including those who failed previous therapy and with cirrhosis.

Treatment for HCV infection is changing rapidly.[9] Initial studies demonstrated that sofosbuvir or simeprevir could be used in combination with pegylated interferon and ribavirin for the treatment of HCV GT4 infection. Subsequently sofosbuvir and ribavirin alone for 12-24 weeks was shown to result in SVR rates of 59-100% in HCV GT4 treatment naïve and experienced patients.[12] Most recently, paritaprevir and ombitasvir, with or without RBV, was evaluated for treatment naïve GT4 patients, and with RBV for GT 4 previous IFN non-responders, resulting in SVR rates of 90.9-100%.[13]

While numerous interferon and ribavirin free regimens are in development for HCV GT-1, development of interferon and ribavirin free regimens for HCV GT4 has been slower. In this present proof of concept study, the use of ledipasvir and sofosbuvir in HCV GT4 treatment naïve and experienced, mostly immigrant patients, resulted in high cure rates similar or exceeding those seen with the current standard of care,[12-14] with excellent tolerability. Over half of patients had a high baseline viral load, were treatment experienced and/or had advanced stage 3 or 4 liver disease, factors previously associated with treatment failure in HCV GT-1 patients.[15,16] Despite lower EC50 values in replicons for ledipasvir against HCV GT4 (0.39 nm for GT4 versus 0.031 nm and 0.004 nm against GT1a and 1b respectively) 100% of patients who completed therapy achieved SVR thus attesting to the potency of NS5A inhibitors.[17]

While 12 weeks of therapy was effective in all patients, one patient in this trial was non-adherent to study medications and discontinued the study at week 7. The patient was treatment naïve and had stage 1-2 liver disease by Fibrosure and APRI.

This study suggests, pending validation by larger trials, that the use of 12 weeks ledipasvir and sofosbuvir is effective for the treatment of HCV GT-4. A safe and simple, single pill regimen will be ideal to treat large number of patients and impact the global hepatitis GT4 epidemic. It remains to be determined whether therapeutic regimens could be shortened further for patients with specific host or viral parameters and comorbidities. Further reductions in treatment duration may decrease the cost of treatment, which are high.[18] In addition licensing agreements in some resource limited countries may also allow for further reductions in medication prices.[19]

Limitations of the study include the sequential, non-randomized enrollment which was chosen given the toxicity and low rate of SVR associated with the standard of care at time of study initiation (pegylated interferon and ribavirin)[20], which would have been the comparator arm. In addition, this is a single site trial, which was thought to be sufficient given the exploratory nature of this study. Confidence in the estimates of efficacy are limited by the small numbers of patients included and ability to use only historical comparisons for efficacy. Patients with and without cirrhosis as well as those who are treatment naïve and experienced are included, however the study was not powered to compare these groups. The majority of patients included had early stage liver fibrosis (less than Stage 3) with other studies suggesting these patients may have a more favorable response to DAA therapy compared to patients with cirrhosis liver fibrosis.[16] Further studies in patients with advanced Stage 3 or 4 liver disease should be performed. While IL28B genotype has not been shown to be useful predictor of treatment outcome sofosbuvir and ledipasvir when used to treat HCV GT1[8], it was not examined in this study of HCV GT4. In addition, patients received intensive nursing support and monitoring which may not be replicated in community-based treatment programs for hepatitis C.

In conclusion, 12 week regimens of oral combination direct acting agent therapy with ledipasvir and sofosbuvir appears to be effective in treating patients with HCV GT4. This simple, well-tolerated therapy for HCV GT4 holds promises to dramatically improve and simplify the treatment of HCV in the resource-limited countries where it is concentrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We would like to acknowledge the contributions of the following individuals: Katie Watkins BS, Erin Rudzinski BS, and Susan Vogel RN, BSN (clinical monitoring support), Judith Starling PharmD and Lori Gordon (pharmacy), Vanessa Eccard, Jerome Pierson PhD, John Tierney BSN, MPM (Regulatory support); William Ronnenberg JD/MIP, MS, Richard Williams PhD and Mike Mowatt PhD (technology transfer support), Marc Teitelbaum MD, CPI (sponsor medical monitor), John Powers MD (oversight), Mary Hall (protocol support), Cathy Rehm, Sarah Jones, Kerry Townsend B.S. (clinical support), Senora Mitchell (clinic support).

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E.

This research was supported in part by the National Institute of Allergy and Infectious Diseases as well as in part by a Cooperative Research and Development Agreement between NIH and Gilead Sciences. These entities did not have a role in the writing of the manuscript or decision to submit for publication.

AO was an employee of Gilead Sciences and participated in the writing of the manuscript.

The data from this study have been partially presented at the 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver meeting, Boston, Massachusetts, USA 2015. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

ROLE OF THE SPONSOR

The Regulatory Compliance and Human Participants Protection Branch of the National Institute of Allergy and Infectious Diseases (NIAID) served as the study sponsor and were involved in the review and approval of the study via the usual peer-review process as well as the study management. The Regulatory Compliance and Human Participants Protection Branch did not play a role in the design of the study, data collection and analysis, interpretation of the data, preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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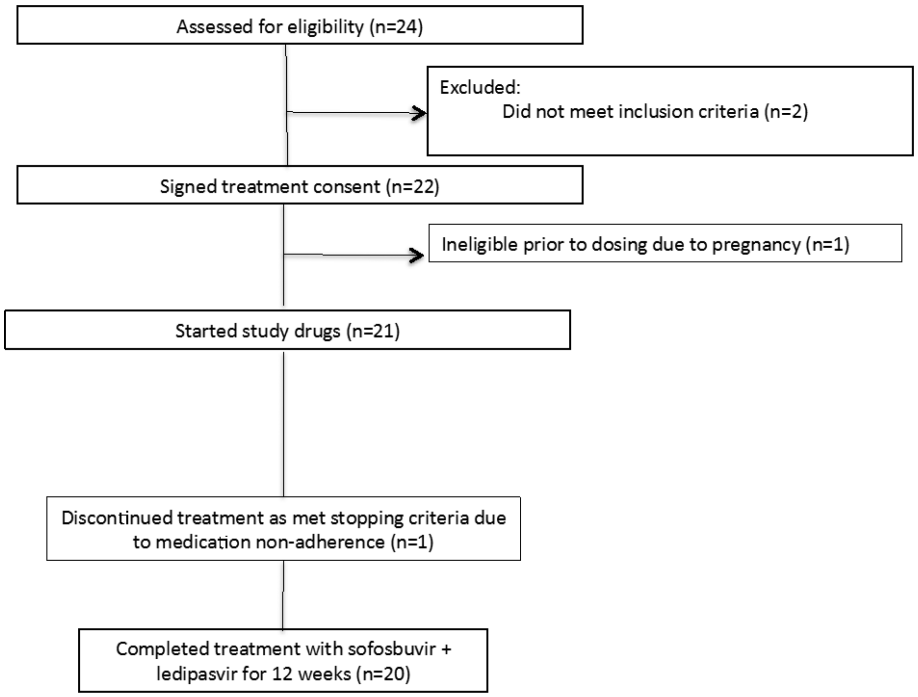

Figure 1. Patient Disposition

Screening and enrollment of the study. One subject discontinued the study after starting study drugs and was replaced.

Table 1

Baseline demographics and clinical characteristics of study participants

	Sofosbuvir + Ledipasvir n=21 12 wk
Age ± mean SD	55 ± 10
Male – n(%)	14 (67)
Race[+] –n(%)	
Black	9 (43)
White	11 (52)
Indian/Alaska Native	1 (5)
Country of Origin[+]–n(%)	
Egypt	6 (29)
United States	5 (24)
Ethiopia	4 (19)
Cameroon	3 (14)
Sudan	1 (5)
Pakistan	1 (5)
Greece	1 (5)
BMI – mean ± SD	31 ± 6
HCV RNA >800,000 IU/mL – *n*(%)	13 (62)
Stage of Liver Fibrosis[*]	
0-2	12 (57)
3	2 (10)
4	7 (33)
Treatment history –*n*(%)	
Treatment naïve	13 (62)
Treatment experienced	8 (38)
•Pegylated interferon + RBV	
Relapser	2 (10)
Null responder	1 (5)
Non-responder	1 (5)
•Interferon + RBV	
Relapser	1 (5)
Non-responder	2 (10)
•Interferon + RBV + Nitazoxanide	1 (5)

Abbreviations: BMI: Body mass index, IFN: interferon, SD: standard deviation, HCV: hepatitis C virus

[+]Race and Ethnicity was self-reported.

[*]14 patients had liver biopsies and seven patients had Fibrosure tests used for staging of liver disease (Fibrosure F0-F2: < 0.44 cutoff with 76% and 70% sensitivity and specificity respectively, F3: >0.60 cutoff with 47% and 90% sensitivity and specificity respectively, F4: >0.75 cutoff with 50% and 93% sensitivity and specificity respectively).[24,25]

Table 2

Patients with HCV RNA levels below the level of quantification at various times of treatment and follow up*

Time Point	Ledipasvir + Sofosbuvir *n*=21 12 wk
Week 4 n (%[95% CI**])	20 (95[76-100])
Week 8	20 (95[76-100])
Week 12	20 (95[76-100])
Post Treatment Period	
Week 12	20 (95[76-100])

*The limit of HCV RNA quantification was 43 IU/mL

**CI: confidence interval

Table 3
Adverse events profile of all study participants

All adverse events reported at a frequency of more than 10% are reported here.*

	Sofosbuvir + Ledipasvir for 12 Weeks (N=21)
Any serious adverse event during treatment –n (%)	0
Any adverse event –n (%)	10 (48)
Common adverse events** - n (%)	
Diarrhea	2 (10)
Fatigue	3 (14)
Nausea	2 (10)
Upper respiratory infection	2 (10)
Laboratory abnormalities	
Grade 3 abnormality	5 (24)
Decreased absolute neutrophil count	
Grade 3	1 (5)
Hyperglycemia	
Grade 3	2 (10)
Hypophosphatemia	
Grade 3	1 (5)
Decreased platelets	
Grade 3	1 (5)

* Treatment period includes time on study medication and 30 days after discontinuation

** Occurring in ≥10% of patients