

# Summary of MID-NET<sup>®</sup> Study: No.2018-001

February 25, 2020

## Study title

Study on the effect of hepatitis C drugs on blood coagulability in patients on warfarin

## Products investigated

The following direct-acting antivirals (DAAs) against hepatitis C or compensated cirrhosis-C:

- Daclatasvir hydrochloride
- Asunaprevir
- Ombitasvir hydrate/paritaprevir hydrate/ritonavir
- Sofosbuvir
- Ledipasvir acetate/sofosbuvir
- Elbasvir
- Grazoprevir hydrate
- Daclatasvir hydrochloride/asunaprevir/beclabuvir hydrochloride
- Glecaprevir hydrate/pibrentasvir
- Telaprevir
- Vaniprevir
- Simeprevir sodium

## Background

- The Pharmacovigilance Risk Assessment Committee of the European Medicine Agency (EMA) recommended<sup>1</sup> in September 2016 that a precaution regarding the

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[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/PRAC\\_recommendation\\_on\\_signal/2016/09/WC500212809.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2016/09/WC500212809.pdf)

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effects of hepatitis C drugs on the blood coagulability in patients treated with vitamin K antagonists<sup>2</sup> be added to the European package inserts of DAAs citing as the basis the post-marketing case reports and the risk associated with the potential changes in liver function in such patients. The European DAA package inserts were revised in succession following the recommendation. Similar precautions were also added to the U.S. DAA package inserts from November to December 2017.

- In the report of a US database study on changes in warfarin dose response following DAA administration<sup>3</sup> (hereinafter, "the preceding study"), the changes in warfarin dose response observed in the study were discussed for 3 possibilities that the changes may indicate: 1. Changes in the blood coagulability of the patients as a result of improved liver function derived from the elimination of hepatitis C virus, 2. a drug-drug interaction between warfarin and DAA or ritonavir co-administered with DAA, or 3. ribavirin co-administered with DAA being the primarily cause of the changes in blood coagulability. However, liver function data that could support these discussions were unavailable in the study. Furthermore, no data on changes in blood coagulability specific to individual DAA dosing regimens including presence or absence of co-administered ritonavir or ribavirin used in Japan have been collected.

### **Purpose of the study**

To descriptively investigate the relationship between DAA prescription and changes in blood coagulability and liver functions in patients prescribed warfarin.

### **Reason to select MID-NET<sup>®</sup> for the study**

Reason to select: To perform evaluation with laboratory test results as an index.

Data from 22 hospitals at 10 healthcare organizations cooperating with MID-NET<sup>®</sup> whose data were available during the data period

Data period: January 1, 2010 to December 31, 2017

### **Outline of method**

The warfarin dose response was investigated in patients prescribed warfarin during the

<sup>2</sup> Only warfarin is available in Japan.

<sup>3</sup> Ann Pharmacother. 2016; 50: 909-17, Ann Pharmacother. 2017; 51: 439-40

treatment with DAA at 3 time points: Before DAA treatment (T1), at the completion of DAA treatment (T2), and at Week 12 after the completion of DAA treatment (T3), based on the prothrombin time international normalized ratio (PT-INR) and warfarin daily doses.

Laboratory test values related to liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP],  $\gamma$ -glutamyl transpeptidase [ $\gamma$ -GTP], index of hepatic fibrosis [FIB-4 index], and platelet counts) and changes in hepatitis C viral load were also investigated.

## Outline of results

### ■ Study population

➤ The study population included 16 patients who could be followed up from the initiation to 12 weeks after the completion of DAA administration, continued receiving warfarin during the follow-up period, and had their PT-INR, warfarin daily doses and liver function test values at the 3-time points: T1, T2, and T3 recorded.

### ■ Changes in warfarin dose response while co-administered warfarin with DAA.

➤ The PT-INR, warfarin daily dose, and WSI (warfarin sensitivity index)<sup>4</sup> (calculated by dividing PT-INR by warfarin daily dose) were identified for the patients at the 3 time-points, T1, T2, and T3 and means of the entire study population were calculated at respective time-points. In addition, the percentage of the 3 values at T2 and T3 against T1 as 100% was calculated for individual patients, and the mean of their values was obtained for the entire study population at respective time-points. Results are presented in the table below. Changes in PT-INR and WSI both slightly decreased at T2 compared to T1 and increased at T3 compared to T2. On the other hand, changes in warfarin daily dose increased at T2 compared to T1 and decreased at T3 compared to T2.

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<sup>4</sup> Thrombosis and haemostasis. 1999; 81; 396-9.

*This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

Table of Mean ( $\pm$  standard deviation) PT-INR, warfarin daily dose, and WSI at each time point (n = 16)

	Before DAA treatment (T1)	At the completion of DAA treatment (T2)	Week 12 after the completion of DAA treatment (T3)
<b>PT-INR</b>			
Mean (value)	1.96 ( $\pm$ 0.88)	1.72 ( $\pm$ 0.64)	1.96 ( $\pm$ 0.80)
Mean (proportion)	100%	96.7% ( $\pm$ 38.7%)	108.2 ( $\pm$ 40.4%)
<b>Warfarin daily dose</b>			
Mean (value)	2.36 ( $\pm$ 1.54)	2.48 ( $\pm$ 1.58)	2.39 ( $\pm$ 1.72)
Mean (proportion)	100%	116.4% ( $\pm$ 40.6%)	108.9% ( $\pm$ 43.6%)
<b>WSI</b>			
Mean (value)	1.06 ( $\pm$ 0.60)	0.84 ( $\pm$ 0.41)	1.23 ( $\pm$ 1.08)
Mean (proportion)	100%	93.8% ( $\pm$ 54.5%)	115.2% ( $\pm$ 60.1%)

■ **Changes in liver function-related laboratory test values and hepatitis C viral load when co-administered warfarin with DAA**

- Liver function-related test value also indicated that  $\gamma$ -GTP and FIB-4-index decreased at T2 compared to T1 by approximately 20% and increased at T3 to the level at T1. AST and ALT decreased at T2 by approximately 40% but changed at T3 by approximately 5% and did not increase at T3 to the level at T2. Platelet counts and ALP exhibited only a few percent of changes from T1 to T3 time-point.
- Hepatitis C virus load was markedly reduced at T2 compared to T1, and the marked decreases were maintained from T2 to T3 time-points.

■ **Discussion based on the results**

- Although the small sample size limits the interpretation of the results, the WSI mean values decreased at T2 compared to T1 and increased at T3 compared to T2, which suggested a tendency that is not inconsistent with the preceding study. In addition, considering the changes observed in liver function-related laboratory test values, the possibility for the changes in liver function in patients as the cause of the changes in warfarin dose-response could not be ruled out. Therefore, we could not determine that the changes in warfarin dose response were caused by the interaction between DAA and warfarin. Changes in blood coagulability specific to individual DAA regimens could not be assessed due to the limited number of eligible patients.