Study title

A prospective cohort study for the intra-individual comparison of the performance characteristics of Gadoxetic Acid (**P**rimovist®)-enhanced M**RI** and **U**ltrasonography for the **S**urveillance of hepatocellular carcinoma in high-risk patients with liver cirrhosis **(PRIUS)**

Protocol Version	8.0
Date of Approval for the Original Protocol	August 16, 2011
Date of Approval for the Current Version Protocol	November 22, 2012
Clinical Study Type	Investigator-Initiated prospective cohort study
Principal Investigator	Young-Suk Lim, M.D., Ph.D. Professor, Department of Gastroenterology & Liver Center Asan Medical Center, University of Ulsan College of Medicine
Clinical phase	Biomarker Phase Ⅳ (Definition by US National Cancer Institute)

Confidentiality

The information contained in this document is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies described in the protocol. You should not disclose any of the information to others without written authorization from the investigator, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

Protocol Synopsis

Study Title	A prospective cohort study for the intra-individual comparison of the performance characteristics of Gadoxetic Acid (**P**rimovist®)-enhanced M**RI** and **U**ltrasonography for the **S**urveillance of hepatocellular carcinoma in high-risk patients with liver cirrhosis **(PRIUS)**
Trial sites and investigators-	Professor Young-suk Lim, Department of Gastroenterology, Asan Medical Center
Clinical phase	Biomarker Phase Ⅳ
Study design	An investigator-initiated, prospective cohort study
Number of Subjects planned	423 subjects in total
Target population	Patients with Liver Cirrhosis at High-Risk for developing hepatocellular carcinoma (HCC) ; 'High-Risk for HCC' will be defined by a model previously proposed by other investigators with some modifications as follows;[1] ● **Risk Index =** 1.65 (if the prothrombin activity is ≤75%) + 1.41 (if the age is 50 years or older) + 0.92 (if the platelet count is <100x10^3/mm^3) + 0.74 (if anti-HCV or HBsAg test is positive). ● The risk index greater than 2.33 is estimated to correspond to an annual risk of developing HCC >5%. **The primary indication to be enrolled to this study would be the patients with liver cirrhosis of any etiology with the Risk Index of higher than 2.33.**
Objectives	**Primary Study Objective** : The detection rate for HCC during three-rounds of paired evaluations with ultrasonography (US) and MRI enhanced with gadoxetic acid (Primovist-MRI) at 6-months intervals **Secondary Study Objective** 1) The detection rate of US and Primovist-MRI for very early stage HCC - Very early stage HCC is defined as a single HCC <2 cm in diameter, without gross vascular invasion or extra-hepatic metastasis 2) The detection rate of US and Primovist-MRI for early stage HCC - Early stage HCC is defined as a single HCC <5 cm or 3 lesions each <3 cm in diameter, without gross vascular invasion or extra-hepatic metastasis (Milan criteria) 3) The false referral rate, Positive predictive value
Duration of study planned	From the date of IRB approval to 31 DEC 2019
Study procedures	The first round of screening imaging tests will be performed at 6 months after their last clinical imaging study (US or dynamic-CT or MRI). All study subjects will be evaluated by 3 rounds of tests with both US and Primovist-MRI at the interval of 6 months. Whenever possible, both US and Primovist-MRI will be performed on the same day or within a time frame of 1 week. After the completion of the 3 strategic evaluation rounds, at least 6 months of clinical follow-up data with dynamic-CT images will be collected to record occurrence of HCC.
Eligibility criteria (Inclusion /Exclusion)	Patients with liver cirrhosis with high risk index (≥2.33) meeting all of following criteria; 1) The evidence of cirrhosis of any etiology within 12 months prior to screening - Definition of cirrhosis by any of following methods; (1) Histologically by liver biopsy (2) Non-histologically by evidence of morphologic changes of the liver and evidence of portal hypertension on US, CT, or MRI examinations including followings; ① The identification of hepatic surface nodularity and splenomegaly ② The identification of portal collaterals or ascites

	2) Older than 20 years of age 3) Absence of previous history or current suspicion of HCC - Absence of HCC should be identified by liver US, dynamic CT, or contrast-enhanced MRI within 6 months prior to screening 4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 5) Patient is able to comply with scheduled visits, evaluation plans, and other study procedures. 6) Patient is willing to provide written informed consent. → Exclusion criteria Patients will be excluded from the study for any of the following reasons: 1) History or suspected malignancy of any type 2) Significant medical comorbidities in which survival is predicted to be less than 3 years 3) Estimated GFR <30 mL/min/1.73m^2 4) Child-Pugh class C liver function 5) Precautions for MRI (cardiac pacemaker, ferromagnetic implants, etc.) 6) Severe claustrophobia that may interfere with protocol compliance. 7) Any other condition which, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with the completing the study.
Statistical Analyses	**Sample Size Justification** Sample size required for this study was estimated using PASS version 11 (Kaysville, Utah, USA) with following assumptions, - Estimated annual HCC incidence = 5% - HCC detection rate by US = 70% - HCC detection rate by Primovist-MRI = 92% - Power (1-beta) = 0.8 - Alpha error = 0.05 - Intra-individual analysis A total sample size of 380 (which includes 19 subjects with the disease) achieves 81% power to detect a change in detection rate from 0.7 to 0.92 using a one-sided binomial test. The target significance level is 0.05. If we consider the maximum drop out rate of 10%, the required sample size will be 423. **Statistical Analytic Plan** HCC detection rate will be defined as the number of patients with HCCs detected by a given modality divided by the total number of patients with HCCs detected by all two modalities plus interval cancers and cancers detected by follow-up CT scan. False referral rate (i.e., examinations leading to a negative recall process) will be defined as the number of false-positive results divided by the sum of true-negative and false-positive results. Differences in the relative HCC detection rate and false referral rate of each modality will be compared with McNemar test. The positive predictive value for each modality will be defined as the number of patients with confirmed HCCs divided by the number of positive tests. Person-years at risk will be calculated from the date of the first screening examination to the date of HCC diagnosis; the date that a patient stopped surveillance; or the date of follow-up CT scan at 6-month after the third round. Survival of the patients with HCC will be calculated from date of diagnosis of HCC to date of death or of last follow-up. A two-sided P value of less than 0.05 will be considered to indicate statistical significance. Statistical analyses will be performed using IBM SPSS software (IBMCorp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

Time & Event Table

	Latest Clinical Imaging	Recruitment	Evaluation Rounds[4]			Follow-up
Study visit window (weeks)	**W-26**	**W-26~W0**	**W0 (±1 weeks)**	**W26 (±1 weeks)**	**W52 (±1 weeks)**	**W78 (±6 weeks)**
Informed Consent		X				
Medical History		X	X	X	X	X
Physical Examination		X	X	X	X	X
Vital Signs		X	X	X	X	X
Hematology[1]		X	X	X	X	X
Chemistry[2]		X	X	X	X	X
Prothrombin Time		X	X	X	X	X
Alpha-fetoprotein		X	X	X	X	X
PIVKA-II[3]			X	X	X	X
Serum for storage			X	X	X	X
Clinical Imaging	X (US, CT or MRI)					
US Elastography			X			
US study			X	X	X	
Primovist-MRI study			X	X	X	
Dynamic 4-phase CT						X
Adverse Events			X	X	X	X

1. Hematology: Hemoglobin, red blood cell, white blood cell and differential white blood cell count, and platelet count
2. Chemistry: Sodium, potassium, BUN, creatinine, total protein, serum amylase, phosphorus, calcium, CPK, AST, ALT, albumin, ALP and total bilirubin
3. Protein induced by the absence of vitamin K or antagonist-II
4. Both US and MRI will be performed in pair on the same day whenever possible, or within 7 days of one another.

Table of Contents

1. Study Title and Phase

1.1. Study Title

A prospective cohort study for the intra-individual comparison of the performance characteristics of Gadoxetic Acid (**P**rimovist®)-enhanced M**RI** and **U**ltrasonography for the **S**urveillance of hepatocellular carcinoma in high-risk patients with liver cirrhosis **(PRIUS)**

1.2. Study Phase

Biomarker Phase IV (Definition by US National Cancer Institute)

2. Study Site and Investigator

	Investigator	Address
Asan Medical Center	Young-suk Lim	88, Olympic-ro 43-gil, Songpa-gu, Seoul, Korea

3. Study Objectives and Background

3.1. Study Objectives

The objective of this study is to evaluate the detection rate of ultrasonography (US) and Primovist-magnetic resonance imaging (MRI) for hepatocellular carcinoma (HCC)

3.1.1. Primary Endpoint

- The detection rate for HCC during three-rounds of paired evaluations with US and MRI at 6-months intervals

3.1.2. Secondary Endpoints

1) The detection rate of US and Primovist-MRI for very early stage HCC
   - Very early stage HCC is defined as a single HCC <2 cm in diameter, without gross vascular invasion or extra-hepatic metastasis
2) The detection rate of US and Primovist-MRI for early stage HCC
   - Early stage HCC is defined as a single HCC <5 cm or 3 lesions each <3 cm in diameter, without gross vascular invasion or extra-hepatic metastasis (Milan criteria)
3) The false referral rate, Positive predictive value

3.2. Background

HCC is the fifth most common cancer worldwide and accounts for 5.6% of all cancers, with an increasing incidence in Europe and the United States.[1-5] HCC has been the fastest-rising cause of cancer-related deaths in Western countries during the past two decades and is expected to increase further in the next decade.[4-6] Cirrhosis, particularly when related to viral hepatitis, is the most notable risk factor for HCC and is found in nearly 80–90% of cases.[2,6]

The stage of disease at the time of diagnosis largely determines the effectiveness of treatment. The treatment of advanced HCC continues to be primarily palliative; and curative options are only available for patients with early stage HCC. In patients with preserved hepatic function and single tumors, surgical resection has provided 5-year survival rates of 70%.[7] Similarly, liver transplantation for tumors meeting the Milan criteria (one nodule <5 cm or three nodules each <3 cm in diameter) has a 5-year survival rate of nearly 74%.[7-9] In patients with early-stage disease who are not amenable to resection or transplantation, radiofrequency ablation has demonstrated 5-year survival rates of 37%.[7] These survival rates are in stark contrast to the average survival of <1 year reported for advanced HCC.[10] Unfortunately, less than 30% of patients are diagnosed early enough to meet criteria for resection, transplantation, or local ablation.[11]

Surveillance strives to detect HCC at an early stage when it is amenable to curative therapy to reduce mortality. Current practice guidelines recommend surveillance of cirrhotic patients with US every 6 months.[12] However, few trials have prospectively evaluated the utility of US as a surveillance test. US has been reported to have a detection rate of between 65% and 80% and specificity of about 90% when used as a screening test.[12,13] However, with the advancement of cirrhosis, the detection rate of US decreases, while the risk for HCC increases.[12-14]

Gadoxetic acid (Primovist®)-enhanced MRI of the liver has already been demonstrated to be of

clinical value for local staging before HCC surgery and for the assessment of patients with inconclusive conventional imaging findings.[15-23] The detection rate of Primovist-MRI has been known to be as high as 90-95%, which is significantly higher than US or multiphase CT scan. Compared with CT, MRI does not have radiation exposure, which is a meaningful merit to be used as a surveillance test. However, MRI has never been considered for surveillance or screening of HCC.

Thus, the hypothesis to be proved by this study is as follows; Primovist-MRI should show significantly higher detection rate compared to US for HCC when both of these imaging modalities are used with the interval of 6 months in patients with cirrhosis at high risk of developing HCC.

4. Study Design

Prospective intra-individual comparative cohort study

5. Projected Duration of the Study

From the date of instuitional review board (IRB) approval to 31 DEC 2019
However, duration of the study could be extended.

6. Target Disease

Patients with Liver Cirrhosis at High-Risk for developing HCC
; 'High-Risk for HCC' will be defined by a model previously proposed by other investigators with some modifications as follows;[24]

- **Risk Index =** 1.65 (if the prothrombin activity is ≤75%) + 1.41 (if the age is 50 years or older) + 0.92 (if the platelet count is $<100x10^3/mm^3$) + 0.74 (if anti-HCV or HBsAg test is positive).
- **The risk index greater than 2.33** is estimated to correspond to an annual risk of developing HCC > 5%.
  The indication to be enrolled in this study would be the patients with liver cirrhosis of any etiology with the Risk Index of higher than 2.33.

7. Study Subjects Criteria (Inclusion/Exclusion)

7.1. Inclusion criteria

→ Patients with liver cirrhosis with high risk index (≥2.33) meeting all of following criteria;

1) The evidence of cirrhosis of any etiology within 12 months prior to screening
   - Definition of cirrhosis by any of following methods;
     (1) Histologically by liver biopsy
     (2) Non-histologically by evidence of morphologic changes of the liver and evidence of portal hypertension on US, CT, or MRI examinations including followings;;
       ① The identification of hepatic surface nodularity and splenomegaly
       ② The identification of portal collaterals or ascites
2) Older than 20 years of age
3) Absence of previous history or current suspicion of HCC
   - Absence of HCC should be identified by liver US, dynamic CT, or contrast-enhanced MRI within 6 months prior to screening
4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1
5) Patient is able to comply with scheduled visits, evaluation plans, and other study procedures.
6) Patient is willing to provide written informed consent.

7.2. Exclusion criteria

Patients will be excluded from the study for any of the following reasons:

1) History or suspected malignancy of any type
2) Significant medical comorbidities in which survival is predicted to be less than 3 years
3) Estimated GFR < 30 mL/min/1.73m^2
   :Estimated GFR by Modification of Diet in Renal Disease (MDRD) equation; GFR

(ml/min/1.73 m^2) = 175 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 1.212 (if black) × 0.742 (if female)

4) Child-Pugh class C liver function (Appendix 2)
5) Precautions for MRI (cardiac pacemaker, ferromagnetic implants, etc.)
6) Severe claustrophobia that may interfere with protocol compliance.
7) Any other condition which, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with the completing the study.

8. Study Procedures and Methods

8.1. Assignment of subjects

For this intra-individual comparative analysis, each study patient will be evaluated by both US and Primovist-MRI. Whenever possible, all 3 screening modalities will be performed on the same day or within a time frame of 1 week. All US examinations and MRI interpretations will be allocated by an independent research coordinator (D.K.K.) to different co-investigators who are board-certified abdominal radiologists (S.Y.K., S.J.L, H.J.W, or J.H.B) with substantial expertise in liver imaging.

8.2. Blinding

Observer-blind; Each imaging study will be read and scored independently by a different radiologist. The readers will be blinded to the findings of the other imaging modality of the same and previous screening rounds.

8.3 Evaluation Assessments

8.3.1. Time table of the study

	Latest Clinical Imaging	Recruitment	Evaluation Rounds[4]			Follow-up
Study visit window (weeks)	**W-26**	**W-26~W0**	**W0 (±1 weeks)**	**W26 (±1 weeks)**	**W52 (±1 weeks)**	**W78 (±6 weeks)**
Informed Consent		X				
Medical History		X	X	X	X	X
Physical Examination		X	X	X	X	X
Vital Signs		X	X	X	X	X
Hematology[1]		X	X	X	X	X
Chemistry[2]		X	X	X	X	X
Prothrombin Time		X	X	X	X	X
Alpha-fetoprotein		X	X	X	X	X
PIVKA-II[3]			X	X	X	X
Serum for storage			X	X	X	X
Clinical Imaging	X (US, CT or MRI)					
US Elastography			X			
US study			X	X	X	
Primovist-MRI study			X	X	X	
Dynamic 4-phase CT						X
Adverse Events			X	X	X	X

1. Hematology: Hemoglobin, red blood cell, white blood cell and differential white blood cell count, and platelet count
2. Chemistry: Sodium, potassium, BUN, creatinine, total protein, serum amylase, phosphorus, calcium, CPK, AST, ALT, albumin, ALP and total bilirubin
3. Protein induced by the absence of vitamin K or antagonist-II
4. Both US and MRI will be performed in pair on the same day whenever possible, or within 7 days of one another.

8.3.2. Study Procedures

1) Screening visit (W-26~W0)

- Review of inclusion/exclusion criteria
- Obtain written informed consent
- Basic information, Medical history
- Complete physical examination and vital signs
- Evaluate last clinical imaging (Liver US, CT or MRI)
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, AFP)

2) Evaluation Rounds (W0 ±1 weeks)

- Medical history
- Complete physical examination and vital signs
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, AFP, PIVKA-II, Serum for storage)
- Blood sampling for genomic DNA extraction
- US elastography
- Liver US
- Primovist-MRI
- Both US and MRI will be performed in pair on the same day whenever possible, or within 7 days of one another.
- Assessment of adverse events

3) Evaluation Rounds (W26 ±1 weeks)

- Medical history
- Complete physical examination and vital signs
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, AFP, PIVKA-II, Serum for storage)
- Liver US
- Primovist-MRI
- Both US and MRI will be performed in pair on the same day whenever possible, or within 7 days of one another.
- Assessment of adverse events

4) Evaluation Rounds (W52 ±1 weeks)

- Medical history
- Complete physical examination and vital signs
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, AFP, PIVKA-II, Serum for storage)
- Liver US
- Primovist-MRI
- Both US and MRI will be performed in pair on the same day whenever possible, or within 7 days of one another.
- Assessment of adverse events

5) Clinical Follow-up (W78 ±6 weeks)

- Medical history
- Complete physical examination and vital signs
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, AFP, PIVKA-II, Serum for storage)
- Dynamic 4-phase CT scan
- Assessment of adverse events

8.3.3. Details of Imaging Methods

1) Liver US

US examinations will be obtained using a convex broadband probe (SC6–1) of a US system (Supersonic Imagine SA; Aixplorer, Aix-en-Provence, France). One of co-investigators who are board-certified abdominal radiologists (S.Y.K., S.J.L, H.J.W, or J.H.B) with substantial expertise in liver imaging will evaluate the entire liver thoroughly and interpret the US study.

2) Primovist-MRI

Liver MRI will be performed on a 1.5 T MR imaging system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) with dedicated six-channel torso array coils.
Patients will undergo liver MRI using a widely used MRI protocol,[25,26] which consists of non-enhanced MRI (breath-hold dual gradient-echo T1-weighted imaging, breath-hold half-Fourier acquisition single shot TSE T2-weighted imaging, respiratory-triggered TSE T2-weighted imaging, and diffusion-weighted imaging with a respiratory-triggered single-shot echo planar sequence) and contrast-enhanced MRI. Contrast-enhanced MRI will be done using a fat-suppressed, three-dimensional, spoiled gradient echo T1-weighted sequence (volumetric interpolated breath-hold examination, VIBE; Siemens) at a 4mm-slice thickness. After intravenous injection of 0.1mL/kg body weight of Gd-EOB-DTPA at 1mL/sec followed by a 20-mL saline flush, the following four phases will be obtained: the arterial phase (determined using a test-bolus method), venous phase (25 seconds after completion of arterial phase images), delayed phase (three minutes following contrast injection), and hepatobiliary phase images (20 minutes after contrast injection).

3) Dynamic 4-Phase CT

CT scans will be obtained with a 64 multidetector CT scanner (LightSpeed VCT, GE medical Systems, Milwaukee, WI) in the unenhanced, arterial, portal venous, and delayed phases. Patients were given 2 mL/kg of iopromide (Ultravist 370; Schering, Berlin, Germany) intravenously at a rate of 4 mL/sec via the antecubital vein. Arterial phase images were obtained using a bolus tracking technique with a trigger enhancement threshold at the upper abdominal aorta of 100 HU. After the threshold is reached, a diagnostic delay time of 25 seconds will be used for the arterial phase. Portal and delayed phase images will be obtained 72 and 180 seconds, respectively, following contrast injection.

8.4. Interpretation and Recording of Results

All US examinations and MRI interpretations will be allocated by an independent research coordinator to different radiologists. The readers will be blinded to the findings of the other imaging modality of the same and previous screening rounds.

1) Liver US

The radiologist, who performs the US scan, will interpret the US study. Results of US exams will be scored according to a predefined structured report on a four-point scale indicating the likelihood of HCC (suspicious, category 4; equivocal, category 3; probably benign, category 2; or definitely benign, category 1) based on previous studies (Appedix 3).[27-29] The structured report system will be integrated in a picture archiving and communication system (PACS) and an electronic medical record system in our institution in order to automatically categorize the image interpretation (Appendix 4).

2) Primovist-MRI

Interpretation of MRI will be also scored using a predefined structured report on a five-point scale indicating the likelihood of HCC (highly suggestive, category 5; suspicious, category 4; equivocal, category 3; probably benign, category 2; or definitely benign, category 1), modified from the Liver Imaging Reporting and Data System (LI-RADS) Version1.0_March2011 proposed by the American College of Radiology (http://www.acr.org/Quality-Safety/Resources/Archive). The structured report system will be integrated in a PACS and an electronic medical record system in our institution in order to automatically categorize the image interpretation (Appendix 3 & 4).

8.5. Recall Process

When one of the US or MRI examinations detected a nodule scored as category 5 or 4, further investigation with dynamic 4-phase CT scan will be performed within3 months. A biopsy will be also tried whenever possible. If the findings on US and Primovist-MRI are different, the recall process will be followed by the higher grade in either imaging.
The diagnosis of HCC will be based on the results of a histologic examination. However, if the pathologic specimen will be unobtainable by any reason, the diagnosis of HCC will be made by CT images showing typical features of HCC, i.e., a nodule larger than 1 cm with arterial hypervascularity and portal- or delayed-phase washout.[10] Patients will not be offered subsequent surveillance tests unless the recall process confirmed the absence of HCC
Surveillance based on the protocol will be performed in next round if HCC is not diagnosed by recall process.

Patients with no suspicious lesion during the three screening rounds will undergo follow-up CT scan 6-month after the third screening round.

9. Safety Evaluation

Although Primovist has already been approved for MR contrast, any adverse events will be evaluated, recorded, and reported.

9.1. Definition of Adverse Events

All adverse events will be assessed and recorded on the adverse event (AE) case reporting form (CRF) page by the investigator. An AE is any untoward medical occurrence in a study patient, regardless of the potential relation with the use of a study drugs.

9.2. Assessment of AEs

All AEs occurring after initiation of clinical trial and until the end of follow-up/final visit should be recorded in the CRF.

9.3. Severe Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence that, at any dose:

- Death or life-threatening events
- Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Development of fetal anomalies

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered a SAE

9.4. Reporting Procedure

The principle investigator and sub-investigators have to notify IRB all SAEs during the study regardless of causal relationship. They must fax or e-mail the SAE form to the principal investigator and Asan medical center IRB within 24 hours of the investigator's acknowledgement of the event.
All the information about SAE should be reported to the principal investigator and IRB until they are completely resolved.

9.5. Intensity of AE

All AEs will be graded according to the Common Terminology Criteria of Adverse Event (CTCAE), version 4.0 grading scale.

9.6 Causal Relationship of AE

The following categories and definitions of causal relationship to the study drug should be used for any AE:

1) Definitely related
   - Event or laboratory test abnormality, with plausible temporal relationship to the drug intake
   - Cannot be explained by the disease or other drugs
   - Response by the withdrawal of the study drug (pharmacologically, pathologically)
   - Event definitive pharmacologically or clinically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
2) Probably related
   - Event or laboratory test abnormality, with reasonable time relationship to drug intake
   - Unlikely to be attributed by the disease or other drugs
   - Response to withdrawal clinically reasonable
3) Possibly related
   - Event or laboratory test abnormality, with reasonable time relationship to drug intake
   - Could also be explained by disease or other drugs
   - Response to withdrawal clinically reasonable
4) Probably not related
   - Event or laboratory test abnormality, could be explained by the disease or other drugs than the study drug intake

- Response to withdrawal unsatisfactory or vague

5) Definitely not related
- Event or laboratory test abnormality, with a temporal relationship to the drug intake unlikely
- The disease or other drugs provide plausible explanations

6) Unknown
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

10. Statistical Considerations

10.1. Efficacy Evaluation

10.1.1. Primary Endpoint

The primary endpoint of this study is HCC detection rate

: Number of patients with HCCs detected by a given modality divided by the total number of patients with HCCs detected by all two modalities plus interval cancers and cancers detected by follow-up CT scan

10.1.2. Secondary Endpoint

1) The detection rate of US and Primovist-MRI for very early stage HCC
2) The detection rate of US and Primovist-MRI for early stage HCC
3) The false referral rate, Positive predictive value
   - False referral rate (i.e., examinations leading to a negative recall process)
     : Number of false-positive results divided by the sum of true negative and false-positive results.

10.2. Sample Size Justification

Sample size required for this study was estimated using PASS version 11 (Kaysville, Utah, USA) with following assumptions,

- Estimated annual HCC incidence = 5%
- HCC detection rate by US = 70%
- HCC detection rate by Primovist-MRI = 92%
- Power (1-beta) = 0.8
- Alpha error = 0.05
- Intra-individual analysis

A total sample size of 380 (which includes 19 subjects with the disease) achieves 81% power to detect a change in detection rate from 0.7 to 0.92 using a one-sided binomial test. The target significance level is 0.05.
If we consider the maximum dropout rate of 10%, the required sample size will be 423.

10.3. Statistical Analyses

Event will be defined as the diagnosis of patients with HCC during the entire study period. Person-years at risk will be calculated from the date of the first screening test to the date of diagnosis of HCC; the date that a patient stopped surveillance; or the date of follow-up CT scan at 6-month after the third round. An interval cancer will be defined as a HCC detected between two screening rounds after negative findings on preceding screening.
HCC detection rate will be defined as the number of patients with HCCs detected by a given modality divided by the total number of patients with HCCs detected by all two modalities plus interval cancers and cancers detected by follow-up CT scan. False referral rate will be defined as the number of false-positive results divided by the sum of true negative and false-positive results. Differences in the relative HCC detection rate and false referral rate of each modality will be compared with McNemar test. The positive predictive value for each modality will be defined as the number of patients with true positive test results in patients with the positive tests in a specific imaging category.
A two-sided P value of less than 0.05 will be considered to indicate statistical significance. Statistical analyses will be performed using IBM SPSS software (IBMCorp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

11. Discontinuation and Withdrawal

Subjects may be withdrawn from the study at the investigator's discretion in any of the following instances:

- Development of a toxicity or adverse event which warrants drug discontinuation
- Vital violations of the clinical trial protocol
- The subjects refuse the administration of the study drugs or safety tests
- The subjects withdraw the agreement of participation of the trial

Treatment after discontinuation or withdrawal will be determined by the investigator. In case of discontinuation or withdrawal due to adverse events or safety issue, subjects should be followed until full recovery and the events should be recorded in CRFs.

12. Protection of the Subjects

The investigational institutions should make sure that the necessary personnel and facilities to conduct the study are appropriately provided. The investigators should do their best for the safety of the study subjects. If serious adverse events occur during the trial, the investigators should notify IRB after taking adequate therapeutic measures.
The responsible conduct of the study will be regularly monitored by the Human Research Protection Center of each participating sites.

13. Informed Consent, Agreement of Compensation, Post-Study Treatment

13.1 Patient Information and Informed Consent

The investigator is responsible for obtaining written informed consent from each participants after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the IRB-approved consent form for the written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent.
A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. If the subject or representative cannot read, an impartial witness is needed.

13.2. Compensation Available to the Patients in the Event of Trial Related Injury

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract.

13.3. Treatment of the Subjects after the End of the Clinical Trial

The subjects who have fulfilled the study would follow the standard treatment of liver cirrhosis. The subjects who are terminated in the middle of the study should receive other appropriate surveillance of HCC. After detection of HCC, treatment will be determined by the subjects' clinical status and at the physician's discretion.

14. Additional Considerations for the Study

14.1. Compliance and modification of the Clinical Trial Protocol

This study must be conducted according to the clinical trial protocol, including written informed consent approved by the IRB. All protocol modifications should be upfront discussed between the investigators. All protocol modifications, except those intended to reduce immediate risk to subjects, should be submitted to and approved by the IRB. Approvals must be obtained before changes can be implemented. In the event that modification applied to prevent immediate damage to the subjects before the IRB approval, they should be reported to the IRB as soon as possible.

14.2. Monitoring

Assigning the Data Safety and Monitoring Committee (DSMB) in charge of this trial, the DSMB will regularly visit and monitor the study sites before starting the study and during the whole study period. The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

14.3. Storage of the Documents and Data

The investigator must maintain all the documents and records of this study to be adequate and accurate, and should subsequently verify them. The investigator is responsible for maintaining and providing of the essential documents. The essential documents mean ones that allow evaluating conduct of the clinical trial. The clinical trial essential document will contain the protocol/amendments, CRF and query forms, IRB approval with correspondence, informed consent, and monitoring records and other appropriate documents and correspondence.
Subject clinical source documents contain all the observed date, the records of clinical trial activities and all the reports and records for assessment and reconstruction of the clinical trial. Therefore subject clinical source documents should include the records of all the procedures conducted by the clinical trial protocol.
All clinical study documents must be retained by the investigator until at least 3 years after the end of the study.

14.4. Confidentiality of the Data and Records of the Subjects

The investigator must assure that subjects' anonymity will be strictly maintained. The subjects should be accessed by only subject initials or an identification code. Their identities have to be protected from unauthorized parties. Only the investigators, study coordinators, those who conduct inspections, IRB, the director of Korea Food & Drug Administration (KFDA) can review the data of the subjects to verify the reliability and the study process within the range prescribed by the relevant provisions and without violating the confidentiality of research subjects.

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Appendix 1. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 2. Child-Pugh score

Measures	Points			
	1	2	3	
Total bilirubin	< 2 (<34)	2-3 (34-50)	> 3 (>50)	mg/dL (μmol/L)
Serum Albumin	> 35 (>3.5)	28-35 (2.8-3.5)	< 28 (<2.8)	g/L (g/dL)
PT (INR)	< 3 (< 1.70)	4-6 (1.71-2.20)	> 6 (>2.20)	sec
Ascites	None	Mild	Moderate to Severe	
Hepatic encephalopathy	None	Grade I-II	Grade III-IV	
Interpretation – class A : 5-6, B : 7-9, C : 10-15 points				

Appendix 3. Diagnostic Categories and Scoring Criteria for HCC

1) US categories and scoring criteria

Diagnostic Categories	**Scoring Criteria**
Suspicious (Category 4)	One of the followings
	Size ≥ 1cm AND one or more of the followings
	Discrete focal mass distinguishable from the adjacent parenchyma
	Peripheral low echoic halo
	Mosaic pattern
	Definite tumor thrombus
Equivocal (Category 3)	Size < 1cm AND one or more of the followings
	Peripheral halo
	Mosaic pattern
	Thrombus (equivocal for benign or malignant)
Probably benign (Category 2)	Imaging features suggestive of a benign entity including cyst, hemangioma, focal fat deposition, focal fat sparing, or hypertrophic pseudomass
Definitely benign (Category 1)	Imaging features diagnostic of a benign entity including cyst, hemangioma, focal fat deposition, focal fat sparing, or hypertrophic pseudomass

2) MRI categories and scoring criteria

Diagnostic Categories	Scoring Criteria
Highly suggestive (Category 5)	One of the followings
	Size ≥ 1cm AND arterial enhancement AND low SI on portal or delay phase
	Definite tumor thrombus
Suspicious (Category 4)	One of the followings
	Size ≥ 1cm AND one or more of the followings
	Arterial enhancement AND low SI on HB phase
	Arterial enhancement AND T2 moderate high SI
	T2 moderate high SI AND low SI on portal, delayed, or HB phase
	low SI on portal AND low SI on HB phase
	Size < 1cm AND arterial enhancement AND low SI on portal, delayed, or HB phase
	Equivocal tumor thrombus
	Increase in size ≥ 1cm on F/U imaging in the lesion previously classified as Category 3
Equivocal (Category 3)	One of the followings
	Size ≥ 1cm AND only one of the followings
	T2 moderate high SI
	Low SI on portal phase
	Low SI on delayed phase
	Low SI on HB phase,
	Containing fat
	Capsular enhancement on Portal or Delayed phase
Probably benign (Category 2)	Imaging features suggestive of a benign entity*
Definitely benign (Category 1)	Imaging features diagnostic of a benign entity †

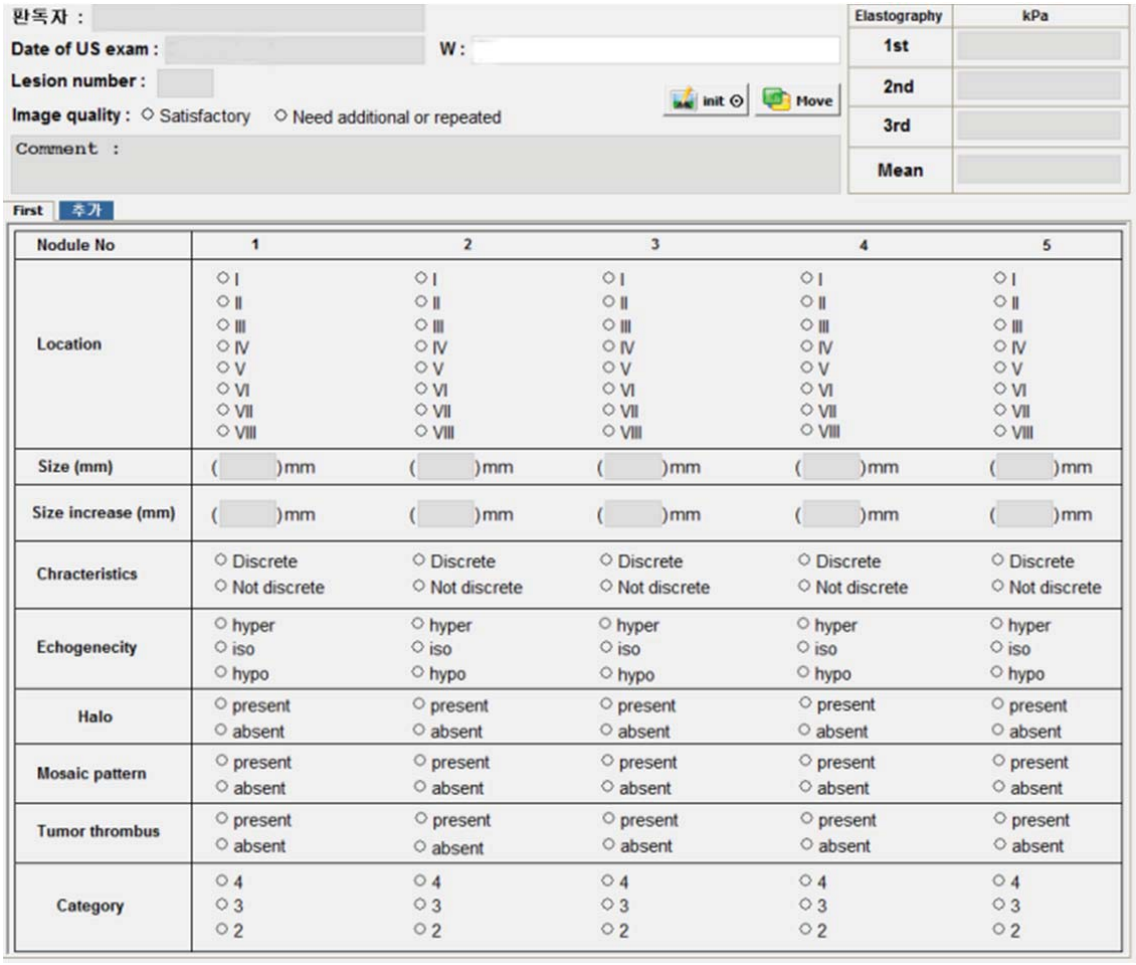
F/U, follow-up; HB, hepatobiliary; MRI, magnetic resonance imaging; SI, signal intensity
* Atypical cyst (or probable cyst), atypical hemangioma (or probable hemangioma), atypical focal fat deposition (or probable focal fat), atypical focal fat sparing (or probable focal fat sparing), hypertrophic pseudomass interpreted as probably benign, rounded perfusional alterations (nodular arterial phase hyperenhancement, NAPH), patchy (changed from "florid") perfusional alterations, atypical confluent fibrosis (probable confluent fibrosis), atypical focal scars (probable focal scars), some arterial-phase non-hyperenhancing atypical nodules progressively enhancing observations which do not meet the criteria in Category 3

† Cyst, hemangioma, focal fat deposition, focal fat sparing, hypertrophic pseudomass interpreted as definitely benign, wedge-shaped perfusional alterations, confluent fibrosis, focal scars, homogeneous siderotic nodules

Appendix 4. The structure report system integrated in a picture archive and communicating system (PACS)

1) The structured report system for US

The image interpretation will be automatically categorized after putting-in the individual findings.



판독자 :
Date of US exam : W :
Lesion number :
Image quality : ○ Satisfactory ○ Need additional or repeated
Comment :
init ⊙ Move

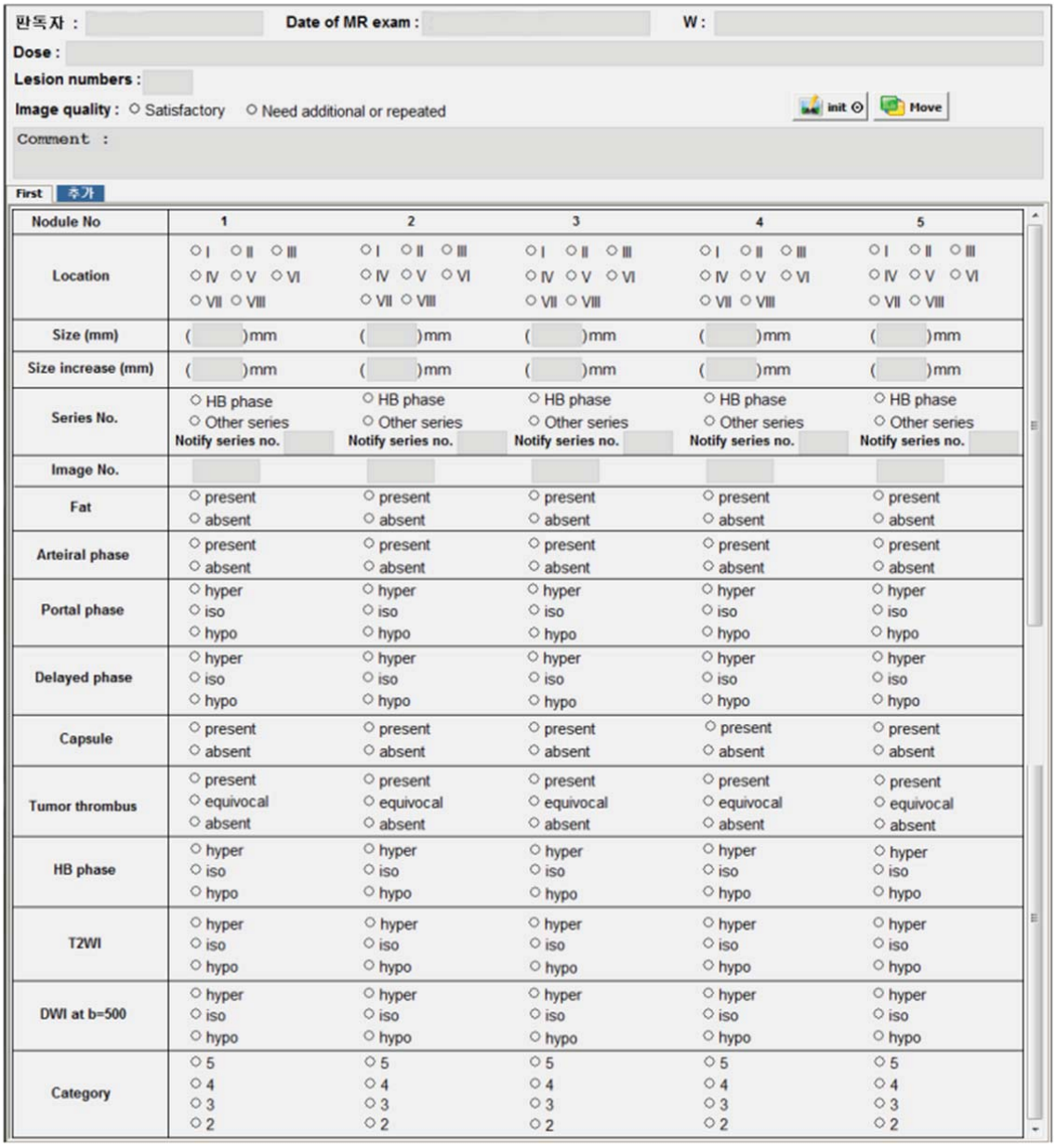
Elastography	kPa
1st	
2nd	
3rd	
Mean	

First 추가

Nodule No	1	2	3	4	5
Location	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII
Size (mm)	( )mm	( )mm	( )mm	( )mm	( )mm
Size increase (mm)	( )mm	( )mm	( )mm	( )mm	( )mm
Chracteristics	○ Discrete ○ Not discrete	○ Discrete ○ Not discrete	○ Discrete ○ Not discrete	○ Discrete ○ Not discrete	○ Discrete ○ Not discrete
Echogenecity	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
Halo	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Mosaic pattern	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Tumor thrombus	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Category	○ 4 ○ 3 ○ 2	○ 4 ○ 3 ○ 2	○ 4 ○ 3 ○ 2	○ 4 ○ 3 ○ 2	○ 4 ○ 3 ○ 2

2) The structured report system for MRI

The image interpretation will be automatically categorized after putting-in the individual findings.



판독자 : Date of MR exam : W :

Dose :

Lesion numbers :

Image quality : ○ Satisfactory ○ Need additional or repeated

init Move

Comment :

First 추가

Nodule No	1	2	3	4	5
Location	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII	○ I ○ II ○ III ○ IV ○ V ○ VI ○ VII ○ VIII
Size (mm)	( )mm	( )mm	( )mm	( )mm	( )mm
Size increase (mm)	( )mm	( )mm	( )mm	( )mm	( )mm
Series No.	○ HB phase ○ Other series Notify series no.	○ HB phase ○ Other series Notify series no.	○ HB phase ○ Other series Notify series no.	○ HB phase ○ Other series Notify series no.	○ HB phase ○ Other series Notify series no.
Image No.					
Fat	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Arteiral phase	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Portal phase	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
Delayed phase	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
Capsule	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent	○ present ○ absent
Tumor thrombus	○ present ○ equivocal ○ absent	○ present ○ equivocal ○ absent	○ present ○ equivocal ○ absent	○ present ○ equivocal ○ absent	○ present ○ equivocal ○ absent
HB phase	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
T2WI	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
DWI at b=500	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo	○ hyper ○ iso ○ hypo
Category	○ 5 ○ 4 ○ 3 ○ 2	○ 5 ○ 4 ○ 3 ○ 2	○ 5 ○ 4 ○ 3 ○ 2	○ 5 ○ 4 ○ 3 ○ 2	○ 5 ○ 4 ○ 3 ○ 2