10th Anniversary

Sumitomo Dainippon Pharma

R&D Meeting

December 9, 2015

Sumitomo Dainippon Pharma Co., Ltd.

Development products topics

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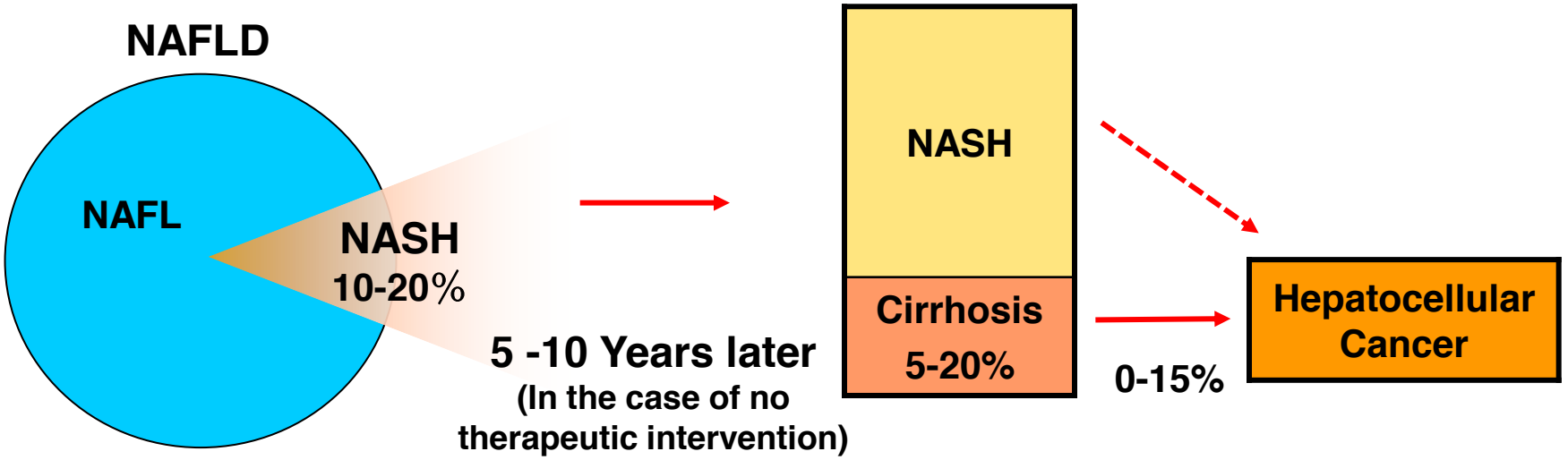
Obeticholic acid (DSP-1747) and NASH

- **Mode of Action for DSP-1747: FXR agonist**
  - ✓ **Improvement on NASH is expected by improvement of liver accumulation, anti-inflammatory effect, and anti-fibrosis effect**
- **Prognosis of NASH/NAFLD[1)]**



NASH

- **Number of NASH patients in Japan: approximately 200 to 300 millions (estimate 2 to 3% of adult population)[1)]**
- **Five to 20 % of NASH progress to cirrhosis in 5 to 10 years.**
- **The 5-year survival rates of NASH cirrhosis is comparable to that of Hepatitis C[2)]**

NAFLD: Non-Alcoholic Fatty Liver Disease
NAFL: Non- Non-Alcoholic Fatty Liver
NASH: Non-Alcoholic Steatohepatitis

1) Japan Society of Hepatology : NASH/NAFLD practice guideline 2015
2) The Journal of the Japan Medical Association: 2010; 139(9); 1880

DSP-1747 Phase II study

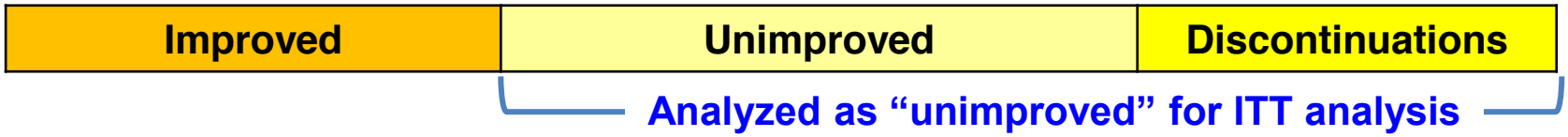
- **Study Design**
  - ✓ Randomized, Double-blind, Parallel-group, Placebo-controlled Study of DSP-1747 in Patients with NASH
  - ✓ The number of dosed subjects: 200 (50 subjects/arm)
  - ✓ Arms: DSP-1747 10mg/day, 20mg/day, 40mg/day, and Placebo
  - ✓ Primary endpoint: Improvement of liver pathological findings from baseline to week 72
    The improvement was defined as: a) No worsening of Kleiner's fibrosis staging, and b) Decrease in NAFLD activity score (NAS) by 2 or more points.
    - Factors of NAS are steatosis (3 points), inflammation (3 points) and ballooning (2 points); total NAS is 8 points at maximum
    - Evaluating liver fibrosis with Kleiner's fibrosis staging (stage 0-4). Stage 4 was excluded from the study because stage 4 is liver cirrhosis.

DSP-1747 Phase II study: Results

- **Efficacy: The percentages of improvement increased dose dependently**
  [Primary analysis with Stratified Cochran-Armitage test with multiple contrast coefficients: p=0.053]

＜Primary endpoint＞

Arms（ITT）	Placebo（N=50）	10mg/day（N=50）	20mg/day（N=50）	40mg/day（N=50）
Improved[*1]	10（20%）	11（22%） p=0.807[*2]	14（28%） p=0.338[*2]	19（38%） p=0.0496[*2]
Decrease in NAS by 2 or more points	12	13	17	20
No worsening of liver fibrosis	31	30	29	28
Unimproved ( ): number of discontinuations	40（5）	39（6）	36（6）	31（13）



< Analyzed with the subjects who conducted 2nd biopsy at 72 W >

Arms	Placebo	10mg/day	20mg/day	40mg/day
Improved	10/45 (22.2%)	11/44 (25.0%) P=0.764[*2]	14/44 (31.8%) P=0.291[*2]	19/37 (51.4%) P=0.006[*2]

[*1] The subjects for whom the fibrosis stage or NAS or both at Week 72 were missing were classified as “unimproved”
[*2] vs placebo, CMH test stratified by baseline fibrosis stage, There is no adjustment for multiplicity.

DSP-1747 Phase II study：Efficacy (liver fibrosis)

Arms (ITT)	Placebo	10mg/day	20mg/day	40mg/day
No worsening of liver fibrosis	**31/50 (62%)**	**30/50 (60%)**	**29/50 (58%)**	**28/50 (56%)**
Fibrosis improvement (1 stage or more improvement of liver fibrosis)*1	**12/50 (24.0%)**	**12/44 (27.3%)**	**15/49 (30.6%)**	**10/49 (20.4%)**

＜Analyzed with the subjects who conducted 2nd biopsy at 72 W*2＞

Arms	Placebo	10mg/day	20mg/day	40mg/day
No worsening of liver fibrosis	31 / 45 (68.9)	30 / 44 (68.2%)	29 / 44 (65.9%)	28 / 37 (75.7%)
Fibrosis improvement (1 stage or more improvement of liver fibrosis)*3	12 / 45 (26.7%)	12 / 38 (31.6%)	15 / 43 (34.9%)	10 / 36 (27.8%)

*1 Percentages are based on the number of ITT subjects for whom the Kleiner's fibrosis stage at baseline are not stage 0.
*2 Post-hoc analyses.
*3 Percentages are based on the number of the subjects, who conducted 2nd biopsy at 72 W , for whom the Kleiner's fibrosis stage at baseline are not stage 0.

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DSP-1747 Phase II study：Efficacy (NASH resolution, ITT)

Arms (ITT)	Placebo (N=50)	10mg/day (N=50)	20mg/day (N=50)	40mg/day (N=50)
Non-NASH in Matteoni classification*1	0 (0%)	1 (2%)	3 (6%)	3 (6%)
p value (vs placebo)*2		p=0.317	p=0.075	p=0.079
Resolution of hepatocyte ballooning and residual inflammation (0-1)*3	2 (4%)	2 (4%)	4 (8%)	7 (14%)
p value (vs placebo)*2		p=1.000	p=0.379	p=0.082
Resolution of hepatocyte ballooning	3 (6%)	4 (8%)	7 (14%)	9 (18%)
p value (vs placebo)*2		p=0.694	p=0.163	p=0.064*4

*1 NASH diagnosis method which is used in Japan widely. NAFLD (Non-Alcoholic Fatty Liver Diseases) patients are classified in type 1 to 4 and type 3 and 4 are diagnosed as NASH.

*2 vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity.

*3 As a part of surrogate histological primary endpoint of pivotal Phase 3 study planned by Genfit, NASH resolution is defined as “ballooning = 0, inflammation = 0-1” (press release by Genfit on Nov.16, 2015)

*4 Analyzed with the subjects who conducted 2nd biopsy at 72 W as post-hoc analysis: placebo 3/45 (6.7%) vs 40mg/day 9/37 (24.3%), p=0.030 (vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity)

DSP-1747 Phase II study: Safety

Adverse events reported more than 10% incidence in any DSP-1747 arms

Adverse events (PT; Preferred Terms)	Placebo N=50 n (%)	10 mg/day N=50 n (%)	20 mg/day N=50 n (%)	40 mg/day N=50 n (%)
Constipation	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Dental caries	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Nasopharyngitis	27 (54%)	21 (42%)	23 (46%)	21 (42%)
Influenza	4 (8%)	2 (4%)	8 (16%)	4 (8%)
Diabetes mellitus	2 (4%)	3 (6%)	6 (12%)	3 (6%)
Insomnia	2 (4%)	0	5 (10%)	0
Pruritus	4 (8%)	10 (20%)	12 (24%)	25 (50%)

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NASH Diagnostic Marker: Exploratory Study

- **Original article "Identification of novel noninvasive markers for diagnosing nonalcoholic steatohepatitis and related fibrosis by data mining" ("Hepatology" accepted on Sep. 21)**
  http://onlinelibrary.wiley.com/doi/10.1002/hep.28226/abstract;jsessionid=42FA284E0BD5D00BE38F2B50947DB3BC.f01t03

  - ✓ **Collaborative study with Saiseikai Suita Hospital**
  - ✓ **The purpose of the study was to identify noninvasive diagnosing marker differentiating NASH or NASH-related liver fibrosis from NAFLD patients.**
  - ✓ **261 blood molecules were examined for 132 Japanese NAFLD patients.**
  - ✓ **The two markers by using combinations of a few molecules respectively appropriate to diagnosing NASH and NASH-related liver fibrosis were established.**
  - ✓ **Reproducibility of diagnosis by the NASH-related liver fibrosis marker has been confirmed by examinations of an independent validation group at the same hospital consisting of 62 Japanese NAFLD patients.**
  - ✓ **While the novel markers seem promising, the study has several limitations due to single institution and limited number of subjects => Additional multicenter study is needed**

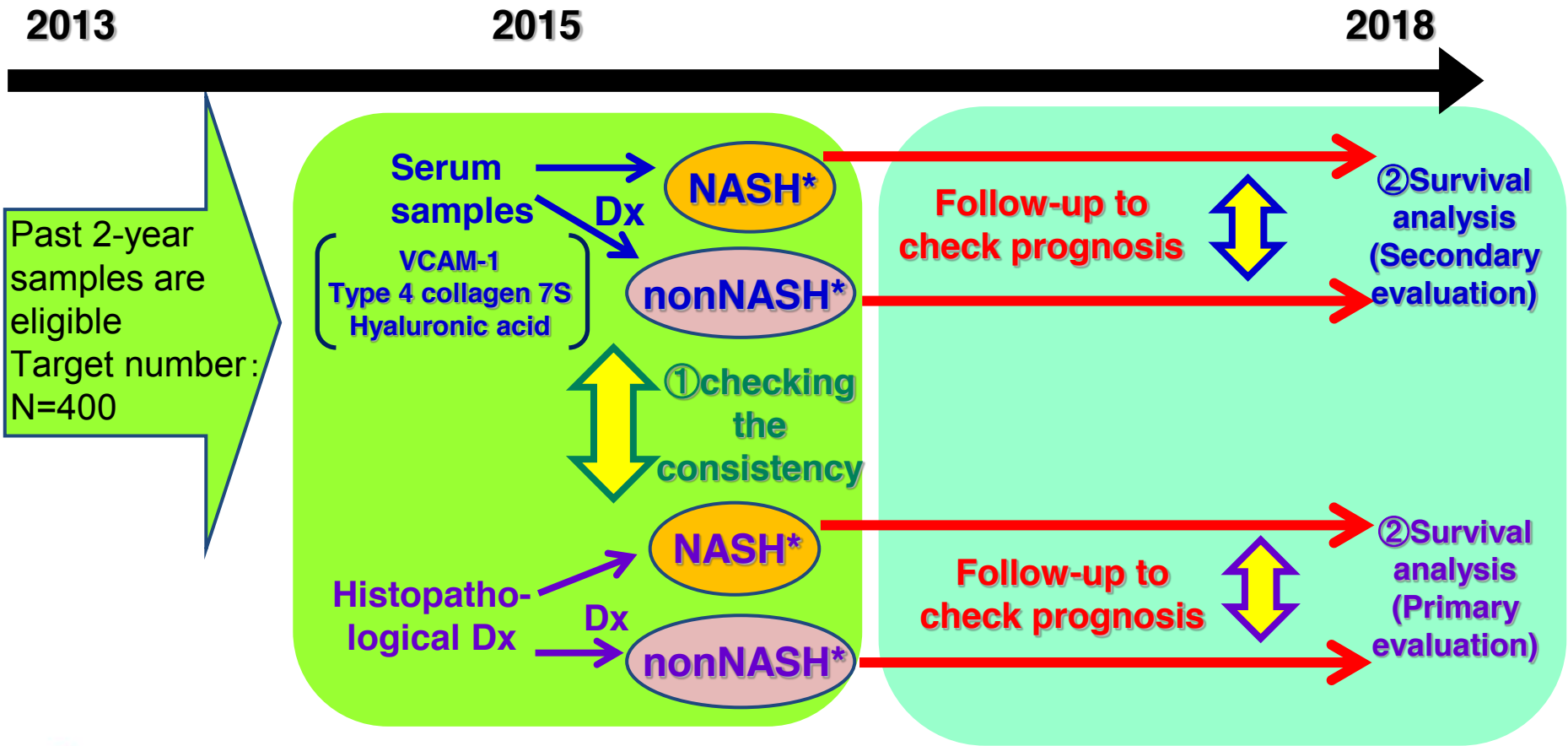
Markers for diagnosing NASH related liver fibrosis	Clinical Parameters/Blood molecules	AUROC of Exploratory Group	AUROC of Validation Group
FM-fibro Index (Novel)	VCAM1, Type IV collagen 7S	**0.896**	**0.852**
	VCAM1, Hyaluronic acid	**0.867**	**0.878**
	Hyaluronic acid, Type IV collagen 7S	**0.917**	**0.892**
FIB4 Index (Existing)	Age, AST, ALT, Platelet	**0.809**	**0.831**

AUROC: Area Under the Receiver Operator Characteristic curve; which is used as a basis for evaluation of diagnostic markers.
If the value is closer to "1" , it means more sensitive marker for diagnosis.

Clinical Research on NASH diagnosis markers

① External validation study of diagnostic accuracy for NASH by the serum biomarkers vs histopathological Diagnosis (Dx): cross-sectional, retrospectively collected samples

② Investigation on the prognosis of NASH/NAFLD



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* NASH here means “NASH with fibrosis (type 4 patients of Matteoni’s classification)”

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Innovation today, healthier tomorrows