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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev capsules			
Name of active ingredient: List pharmacotherapeutic Nintedanib			
Report date: 26 SEP 2025	Study number: 1199.402	Version/Revision: Version 1.0	Version/Revision date: NA
Title of study:	Post-marketing Surveillance of Ofev Capsules in Progressive Fibrosing Interstitial Lung Disease in Japan		
Keywords:	Ofev Capsules, Japan, PMS, Progressive Fibrosing Interstitial Lung Disease (PF-ILD)		
Rationale and background:	<p>This post marketing surveillance (PMS) plan was proposed as additional pharmacovigilance plan of the Japanese risk management plan (RMP). In Japan, post-approval execution of PMS is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and effectiveness data for re-examination.</p> <p>Re-examination period is defined by J-PMD Act. Five years and ten months after approval for new indication of orphan drugs, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW).</p> <p>Collected data from PMS is included in the Japanese periodic safety reports and submitted to Pharmaceuticals and Medical Devices Agency (PMDA) on designated dates until the end of re-examination period.</p> <p>The INBUILD (1199.247) trial was completed and INBUILD-ON (1199.248) trial was conducted as Phase III trials that evaluated the efficacy and safety of nintedanib in patients with progressive fibrosing interstitial lung disease (PF-ILD). IPF patients were excluded in these trials.</p> <p>As the number of Japanese patients treated with nintedanib in INBUILD trial was limited (52, total: 332), confirmation of the safety profile of nintedanib treatment for PF-ILD patients in the real world clinical setting was required.</p>		
Research question and objectives:	To evaluate the frequency of adverse drug reactions (focus on hepatic function disorders including liver enzyme elevation) of Ofev Capsules under the real world setting in patients with PF-ILD.		
Study design:	Non-interventional cohort study with new data collection (NISnd)		

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Observational & Non-Interventional Study (NIS) Report

Study number: 1199-0402

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	<p>Patients newly initiated Ofev Capsules were enrolled and followed up to 104 weeks (2 years) or until discontinuation of administration.</p> <p>The main analysis was to show frequency, proportion and its corresponding CI because the primary endpoint was the frequency of adverse drug reactions (ADRs). An ADR was defined as an adverse event (AE) for which either the physician who had reported the AE or the sponsor could not rule out its causal relationship.. As this PMS was an observational study with no control group, statistical analysis was limited to descriptive statistics.</p>		
Setting:	<p>Sites throughout entire country were equally listed according to the size of the hospitals or general clinics at which Ofev Capsules were available for prescription.</p> <p>Planned number of sites: Approximately 100 Sites</p> <p>A medical representative explained the objective and design of this study to investigators at each study site and concluded a written contract with the head of the study site (e.g., hospital director).</p> <p>This study was conducted in 102 sites in Japan.</p> <p>Study period: Oct 2020 – Jan 2025</p> <p>Enrollment period: Oct 2020 – Sep 2022</p>		
Subjects and study size, including dropouts:	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> - Patients in Japan with PF-ILD who were prescribed with Ofev Capsules and had never been treated with Ofev Capsules before enrolment was included. <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> - Diagnosis of IPF - Patients with PF-ILD due to systemic scleroderma as the underlying disease <p><u>Patient disposition</u></p> <p>In this PMS, a total of 425 patients were registered. Case report forms (CRFs) were collected from 409 patients.</p>		
Variables and data sources:	<p>Outcomes:</p> <p><u>Primary outcome:</u></p>		

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		<p>Frequency of adverse drug reactions (ADRs) by overall, each individual (especially focus on the safety specification on J-RMP: hepatic function disorders)</p> <p><u>Secondary outcome:</u> None</p> <p><u>Further outcomes:</u> Other safety outcomes were;</p> <ul style="list-style-type: none"> - Frequency of serious adverse events (SAEs) - Frequency of AEs leading to death - Frequency of AEs leading to treatment discontinuation - Frequency of liver enzyme elevations (aspartate transaminase [AST] and/or alanine transaminase [ALT] $\geq 3x$ to $< 5x$ ULN, $\geq 5x$ ULN) - Incidence of acute ILD exacerbations related to Ofev Capsules (ADR) <p>Other effectiveness outcomes were;</p> <ul style="list-style-type: none"> - Annual rate of decline in forced vital capacity (FVC) (mL/year) over 52 and 104 weeks - Annual rate of decline in FVC in percent predicted over 52 and 104 weeks - Change from baseline in FVC in percent predicted at 52 and 104 weeks - Time to first acute ILD exacerbation over 52 and 104 weeks <p><u>Others: characteristics associated with ADRs</u> Demographics, baseline characteristics, labs and vitals as baseline, concomitant therapy and medications etc.</p> <p><u>Data Sources</u> Patients' data were collected by electronic CRF on electronic data capture (EDC) system</p>	
Results:	Total of 425 patients were registered. Of the 425 patients who registered, 16 patients were only registration and their CRFs were not collected. In the		

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<p>409 patients whose CRFs were collected, 1 patient was excluded due to “Multiple registration”. A total of 157 patients completed the study, 252 patients did not. The reason why the study was not completed included “Multiple registration” (1 patient), “Adverse event” (130 patients), “Adverse event/ Patient's wish” (15 patients), “Adverse event/ Other personal reasons” (2 patients), “Patient's wish” (38 patients), “Improved” (2 patients), “No visit after last visit” (17 patients), “No visit after last visit/ Other personal reasons” (3 patients), “Other personal reasons” (36 patients), “Lost to follow up” (8 patients). The safety set included 408 patients. The effectiveness set also included 408 patients.</p> <p><u>Baseline characteristics</u></p> <p>In the safety set (N=408 patients), 51.96% (212 patients) of patients were men. The mean age (mean ± SD) was 71.9 ± 10.2 years. The minimum age was 26 years old. A total of 80.88% (330 patients) were aged 65 and above, while 19.12% (78 patients) were under 65. Among them, 45.83% (187 patients) were 75 years or older. For the indication of PF-ILD, 100.00% (408 patients) were reported as having PF-ILD, and none of them was reported as not having PF-ILD or "Other". The duration of assessment on progression class was ≤2 years for 365 patients (89.46%), >2 to 5 years for 29 patients (7.11%), >5 to 10 years for 6 patients (1.47%) and >10 years for 1 patient (0.25%).</p> <p>A total of 28.92% (118 patients) had any medical histories, while 69.12% (282 patients) did not. Similarly, 78.68% (321 patients) had any concomitant diseases, whereas 20.34% (83 patients) did not. Previous medication of any disease was reported in 10.54% (43 patients), whereas 76.96% (314 patients) did not. Concomitant medication was presented in 86.52% (353 patients), while 9.56% (39 patients) did not. A total of 35.05% (143 patients) had concomitant therapy, compared to 63.73% (260 patients) who did not.</p> <p><u>Exposure</u></p> <p>In the safety set (N=408), 39.95% (163 patients) were treated with Ofev Capsules for 728 days or over. Other patients were treated for <28 days (4.90%, 20 patients), 28 to <84 days (9.56%, 39 patients), 84 to <168 days (10.29%, 42 patients), 168 to 252 days (7.60%, 31 patients), 252 to <364 days (6.13%, 25 patients), 364 to <504 days (8.58%, 35 patients), 504 to</p>			

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<p><588 (5.15%, 21 patients), 588 to <672 days (3.43%, 14 patients) , and 672 to <728 days (4.41%, 18 patients).</p> <p>A total of 53.92% (220 patients) and 37.01% (151 patients) received 150 mg bis in die (twice a day, bid) and 100 mg bid as the first dose of Ofev Capsules, respectively. In contrast, 6.62% (27 patients) and 2.45% (10 patients) had 100 mg quaque die (once a day, qd), and 150 mg qd of Ofev Capsules, respectively. The median dose was 209.58 mg per day.</p> <p><u>Primary outcome</u></p> <p>Of 408 patients, 246 patients (60.29%) experienced at least 1 ADR. The frequently reported ADRs (in 2 patients or more) throughout the PMS were diarrhoea (30.88%, 126/408 patients), nausea (8.82%, 36/408 patients), hepatic function abnormal (8.33%, 34/408 patients), decreased appetite (6.62%, 27/408 patients), liver disorder (5.64%, 23/408 patients), vomiting (2.94%, 12/408 patients), hypertension and gamma-glutamyltransferase increased (2.21%, 9/408 patients each), platelet count decreased (1.47%, 6/408 patients), hepatic enzyme increased (1.23%, 5/408 patients), interstitial lung disease, rash, and proteinuria (0.98%, 4/408 patients each), pneumothorax, abdominal discomfort, abdominal pain, stomatitis, faeces soft, and pruritus (0.74%, 3/408 patients each), herpes zoster, hypokalaemia, abdominal distension, constipation, diverticulum intestinal haemorrhagic, enterocolitis, gastritis, upper gastrointestinal haemorrhage, drug-induced liver injury, pyrexia, alanine aminotransferase increased, weight decreased, and contusion (0.49%, 2/408 patients each).</p> <p>Of 408 patients, 29 patients (7.11%) experienced at least 1 serious ADR. The reported serious ADRs (in 2 patients or more) were interstitial lung disease and diarrhoea (0.98%, 4/408 patients each), pneumothorax (0.74%, 3/408 patients), diverticulum intestinal haemorrhagic, hepatic function abnormal, drug-induced liver injury, and platelet count decreased (0.49%, 2/408 patients each).</p> <p>The categories for which the 95% confidence interval (CI) of the odds ratio for the ADRs frequency by patients' demographics/baseline characteristics did not include 1 were Weight class, Hepatic dysfunction (based on standardised MedDRA queries [SMQ]), Concomitant diseases,</p>			

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<p>Concomitant medication, Concomitant medication (Corticosteroids), Concomitant medication for PF-ILD and Mean dose class.</p> <p>In the PMS, hepatic function disorders were focused as safety specification items on J-RMP. Of 408 patients, 79 patients (19.36%) experienced ADRs categorised into hepatic function disorders. The most frequently reported ADR categorised into hepatic function disorders was hepatic function abnormal (8.33%, 34/408 patients).</p> <p>The reported serious ADRs categorised into hepatic function disorders were hepatic function abnormal and drug-induced liver injury (0.49%, 2/408 patients, each), hepatic encephalopathy (0.25%, 1/408 patients). The outcomes for hepatic function abnormal was fatal and for all others were recovered/resolved.</p> <p>The categories for which the 95% CI of the odds ratio for the ADRs (the events relevant to hepatic function disorders) frequency by patients' demographics/baseline characteristics did not include 1 were BMI class, Smoking History, Concomitant diseases, Concomitant medication (Corticosteroids), Concomitant medication for PF-ILD and Mean dose class.</p> <p>The frequency of ADRs in elderly patients (≥ 65 years) (60.61%, 200/330 patients) showed no difference compared to other patients (< 65 years) (58.97%, 46/78 patients).</p> <p>Ofev Capsules were not administered to pregnant women in this PMS.</p> <p>The frequency of ADRs in patients with renal dysfunction (66.67%, 22/33 patients) showed no difference compared to patients without renal dysfunction (59.73%, 224/375 patients).</p> <p>The frequency of ADRs was higher in patients with hepatic dysfunction (based on SMQ) (82.61%, 19/23 patients) compared to that in patients without hepatic dysfunction (58.96%, 227/385 patients). The odds ratio (95% CI) was 3.31 (1.10, 9.90).</p> <p><u>Safety summary</u></p> <p>Of 408 patients, 308 patients (75.49%) experienced at least 1 AE under the treatment. Severe AEs were reported in 96 patients (23.53%). ADRs were</p>			

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<p>reported in 246 patients (60.29%), and severe ADRs were reported in 11 patients (2.70%). Deaths were reported for 59 patients (14.46%). Serious AEs were reported from 139 patients (34.07%) and serious ADRs were reported from 29 patients (7.11%).</p> <p><u>Further outcomes</u></p> <p>As for other safety outcomes, of 408 patients, 139 patients (34.07%) experienced at least 1 serious adverse event (SAE). The most frequently reported SAEs were interstitial lung disease (16.42%, 67/408 patients). AEs leading to deaths were reported for 59 patients (14.46%). AEs leading to discontinuation were reported 145 patients (35.54%).</p> <p>The frequency of ADRs relevant to liver enzyme elevations was 4.90% (20/408 patients). The changes in AST from baseline to Weeks 12, 52, and 104 had the highest proportion of patients remaining Normal (66.96% at Weeks 12, 66.24% at Weeks 52, 69.13% Weeks 104). The proportion of patients that were Normal at baseline and High at Week 12 was 13.45% (46/342 patients). The proportion of patients that were High at both baseline and Week 12 was 10.82% (37/342 patients). The changes in ALT from baseline to Weeks 12, 52, and 104 had the highest proportion of patients remaining Normal (64.91% at Weeks 12, 67.51% at Weeks 52, 73.15% Weeks 104). The proportion of patients that were Normal at baseline and High at Week 12 was 14.62% (50/342 patients). The proportion of patients that were High at both baseline and Week 12 was 10.53% (36/342 patients). Although the proportion of High patients of AST and ALT decreased at Weeks 52 and 104, it is speculated that discontinuation patients affected the results. The changes in total bilirubin (TBILI) from baseline to Weeks 12, 52, and 104 had the highest proportion of patients remaining Normal (85.41% at Weeks 12, 84.18% at Weeks 52, 82.40% Weeks 104). No notable changes were observed from baseline through Weeks 12, 52, and 104. The subgroup analysis showed generally similar results in all subgroups, and no factors influencing AST, ALT and TBILI were detected.</p> <p>Incidence of acute ILD exacerbations (AEs) was 16.42% (67/408 patients, 95% CI: 12.96, 20.38%). Incidence of acute ILD exacerbation related to Ofev Capsules (ADRs) was 0.98% (4/408 patients, 95% CI: 0.27, 2.49%).</p>			

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	<p>The subgroup analysis by underlying diagnosis class and chest high-resolution computed tomography (HRCT) pattern showed no differences between categories.</p> <p>As for other effectiveness outcomes, adjusted annual rate of decline in FVC was -104.4 mL/year (SE: 73.3, 95% CI: -249.6, 40.9) over 52 weeks and -93.2 mL/year (SE: 65.6, 95% CI: -223.1, 36.8) over 104 weeks. Adjusted annual rate of decline in FVC% predicted was -3.776% (SE: 3.249, 95% CI: -10.216, 2.665) over 52 weeks and -3.265% (SE: 2.979, 95% CI: -9.162, 2.632) over 104 weeks.</p> <p>Absolute change from baseline in FVC% predicted was $-1.444 \pm 11.376\%$ (mean \pm SD) at 52 weeks (72 patients), $-4.136 \pm 11.436\%$ (mean \pm SD) at 104 weeks (44 patients). The absolute change at last observation (208 patients) was $-3.351 \pm 10.780\%$ (mean \pm SD).</p> <p>Incidence of patients with acute ILD exacerbation was 11.76% (48/408 patients) over over 52 weeks and 16.42% (67/408 patients) over 104 weeks. The median (range) of time to first acute ILD exacerbation was 167.0 days (4, 416) over 52 weeks and 278.0 days (4, 799) over 104 weeks.</p> <p>No interim analyses were planned or performed.</p>		
Discussion:	There was no notable difference in the safety profile observed in the PMS and the information provided in the Japanese package insert. The study does not indicate any changes on Risk and Benefit concerning Ofev Capsules treatment.		
Marketing Authorisation Holder(s):	[REDACTED]		
Names and affiliations of principal investigators:	[REDACTED]		