the mean CDAI was 7.5 (84.5% patients with low disease activity, and 2.8% in clinical remission). While switching to tofacitinib 11mg QD for 3 months, no significant difference was observed in terms of the ratio of DAS28-ESR LDA or CDAI LDA, but numerically more patients achieved DAS28-ESR LDA or CDAI LDA (32 and 64, respectively). During the 3-month follow-up period, no new adverse events were present.

Conclusion: Our study showed that RA patients switching from tofacitinib 5mg BID to tofacitinib 11mg QD sustained the effectiveness with no adverse clinical impact.

Table 1. Clinical demographics and laboratory variables

	Baseline	Before Switching to 11mg QD	After switching to 11mg QD
Age, mean (SD)	57.4 (12.7)		
Female proportion (%)	85		
RF positivity (%)	78.9		
ACPA positivity (%)	80.3		
Bio-exposed (%)	70.1		
DAS28-ESR, mean (SD)	5.0 (1.1)	3.3 (0.3)	3.2 (0.4)
CDAI, mean (SD)	23.0 (8.7)	7.5 (2.8)	6.9 (2.7)
DAS LDA (n,%)		21 (29.6)	32 (45.0)
CDAI LDA (n,%)		60 (84.5)	64 (90.1)

REFERENCES:

- [1] Lamba M, Wang R, Fletcher T, et al. J Clin Pharmacol. 2016 Nov;56(11):1362-1371
- [2] Kuo CF, Luo SF, See LC, et al. Rheumatol Int. 2013 Feb;33(2):355-60.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2924

FRI0160

PREPARATION AND PROPERTY OF IGURATIMOD NANOSCALE SUSTAINED-RELEASE SYSTEM

Zhenzhen Ma¹, Cheng Tao², Lin Sun¹, Jianjun Zhang², Jinxia Zhao¹. ¹Peking University Third Hospital, Department of Rheumatology and Immunology, Beijing, China; ²Beijing University of Chemical Technology, College of Chemical Engineering, Beijing, China

Background: Iguratimod, a methanesulfonanilide, has obvious anti-inflammatory function and has been developed exclusively in Asia-Pacific countries. As a novel disease-modifying anti-rheumatic drug, iguratimod is effective in the treatment of RA, but some side effects, such as liver damage and gastrointestinal discomforts are the main concerns in clinical application^[1]. Currently, iguratimod is practically insoluble in aqueous solvents and only available in oral dosage forms. The low solubility of drugs leads to incomplete absorption and bioavailability, which affects the clinical efficacy and increases the gastrointestinal side effects of drugs^[2].

Objectives: In order to improve the bioavailability and alleviate the side effect of gastrointestinal reaction, we changed the dosage form of iguratimod to Nanoliguratimod-loaded Hydrogel Composite.

Methods: Iguratimod nanoparticles (Nanoliguratimod) were prepared by using the high-gravity anti-solvent precipitation (HGAP) technique, and its properties were tested. The Nanoliguratimod-loaded Hydrogel Composite was prepared and the delivery of the payload was demonstrated. In vitro, the biological effects of Nanoliguratimod@Hydrogel on fibroblast-like synoviocytes (RA-FLS) were evaluated. In vivo, the pharmacokinetics of oral raw iguratimod or subcutaneous injection of Nanoliguratimod@Hydrogel was carried out in the healthy rats. Further, we evaluated the efficacy of Nanoliguratimod@Hydrogel in treating collagen-induced arthritis (CIA) rats.

Results: By the HGAP technique, we acquired the amorphous form Nanoliguratimod with an average size of 295nm, which had higher dissolution rates and higher stability. The release of iguratimod from hydrogel composite in PBS was gradual and sustained for up to 48h compared with Nanoliguratimod. Nanoliguratimod@Hydrogel inhibited the proliferation, migration, and invasion of RA-FLS in a doses dependent manner. The pharmacokinetic parameters showed better bioavailability and longer half-life time with Nanoliguratimod@Hydrogel by subcutaneous administration than oral raw iguratimod. Animal experiments confirmed that subcutaneous injection of Nanoliguratimod@Hydrogel (10mg/kg every three days) and oral raw iguratimod (10mg/kg daily) showed similar efficacy in decreasing arthritis index score, pathological score, and expression of cytokines (IL-6, TNF- α and IL-1 β).

Conclusion: Overall, our data suggested that Nanoliguratimod@Hydrogel provided new administration routes and extended the administration interval, it may serve as a promising drug delivery approach for the treatment of RA.

REFERENCES:

- [1] Hara M, Abe T, Sugawara S, et al. Long-term safety study of iguratimod in patients with rheumatoid arthritis[J]. Mod Rheumatol., 2007, 17(1):10-16.
- [2] Zhou T, Ding L, Li X, et al. Determination of iguratimod in rat plasma by high performance liquid chromatography: method and application[J]. Biomed Chromatogr, 2010, 22(3):260-264.

Figure: Preparation and Property of Iguratimod Nanoscale Sustained-Release System. (A): Synthesis scheme of Hyaluronic acid-acrylate (HA-AC). (B): Brief production process of Nanoliguratimod@Hydrogel. (C): TEM images of Nanoliguratimod. (D): Dissolution profiles of raw iguratimod, Nanoliguratimod and Nanoliguratimod-loaded Hydrogel. (E): Plasma concentrations and pharmacokinetic parameters of raw iguratimod and Nanoliguratimod-loaded Hydrogel. (F): Changes of arthritis index (AI) score in rats during drug intervention. (G): Results of HE staining and saffron O-fixing green staining on the ankle joints of rats. *p<0.05, **p<0.01, ***p<0.001, n=7 per group. Scar bar =200 μ m.

Acknowledgement: No

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.3436

FRI0161

PHARMACOKINETICS AND SAFETY OF A SINGLE ORAL DOSE OF PEFICITINIB (ASP015K) IN SUBJECTS WITH NORMAL AND IMPAIRED HEPATIC FUNCTION

Daisuke Miyatake¹, Tomohisa Shibata¹, Junko Toyoshima¹, Yuichiro Kaneko¹, Kazuo Oda², Tetsuya Nishimura¹, Masataka Katashima¹, Masashi Sakaki³, Kazuaki Inoue⁴, Takayoshi Ito⁵, Naoki Uchida⁶, Kenichi Furihata⁷, Akino Urae⁸. ¹Astellas Pharma, Inc., Tokyo, Japan; ²Astellas Research Institute of America LLC, Northbrook, United States of America; ³Showa University School of Medicine, Tokyo, Japan; ⁴Showa University Fujigaoka Hospital, Yokohama, Japan; ⁵Showa University Koto Toyosu Hospital, Tokyo, Japan; ⁶Clinical Research Institute of Clinical Pharmacology and Therapeutics, Showa University, Tokyo, Japan; ⁷P-One Clinic, Keiokai Medical Corporation, Tokyo, Japan; ⁸Mediscience Planning Inc., Tokyo, Japan

Background: Peficitinib (ASP015K), a novel oral Janus kinase inhibitor, demonstrated efficacy as once-daily therapy for moderate-severe rheumatoid arthritis in a phase 2b study (NCT01649999)¹ and 2 phase 3 studies (NCT02308163²; NCT02305849).³ Mean urinary excretion of peficitinib accounted for 9–15% of the oral dose.⁴ It produces 3 conjugated metabolites (H1, H2, H4), which show very weak in-vitro pharmacological action.

Objectives: To assess pharmacokinetics (PK) and safety of a single oral dose of peficitinib 150 mg in subjects with normal and impaired hepatic function.

Methods: This phase 1, open-label, single-dose, parallel-group study was conducted at six centres in Japan. Eligible subjects were aged 20–75 years, with body mass index ≥ 17.0 – <30.0 kg/m². Hepatic impairment was defined at screening using Child-Pugh classification: Class A, mild (5–6 points); Class B, moderate (7–9 points). Subjects with severe hepatic impairment (Child-Pugh classification Class C, 10–15 points) were excluded. Subjects received a single oral dose of peficitinib 150 mg under fasting conditions, based on daily dose in the 2 phase 3 studies. Blood samples for plasma PK analysis of peficitinib and its metabolites were collected before and up to 72 h post dose. Safety was assessed throughout the study.

Results: 24 subjects were enrolled (70.8% male): 16 with impaired and 8 with normal hepatic function (Table 1); all received study medication

according to protocol. The peficitinib concentration-time profiles from dosing to 72 h (Fig. 1), extrapolated to infinity (AUC_{inf}), and maximum concentration (C_{max}) were similar in subjects with normal and mildly impaired hepatic function; however, AUC_{inf} and C_{max} were increased in subjects with moderate hepatic impairment (Table 2). There was a trend of greater exposure to H1, H2 and H4 metabolites in subjects with mild or moderate hepatic impairment, except for H2 in moderate hepatic impairment, although geometric mean ratios versus subjects with normal function were variable (Table 2). One subject in each group experienced a total of 5 TEAEs (Table 3), all of which were considered drug-related except back pain. No serious TEAEs, deaths or clinically significant mean changes from baseline in clinical laboratory parameters were reported during the study.

Table 1 Demographic characteristics (PKAS)

Parameter	Normal hepatic function (n=8)	Mild hepatic impairment (n=8)	Moderate hepatic impairment (n=8)	Total (n=24)
Male, n (%)	6 (75.0)	5 (62.5)	6 (75.0)	17 (70.8)
Median (min, max) age, y	60.0 (55, 64)	69.0 (48, 75)	60.5 (49, 67)	63.0 (48, 75)
Median (min, max) weight, kg	65.3 (48.8, 76.3)	69.0 (51.7, 81.2)	73.0 (43.3, 75.1)	71.3 (43.3, 81.2)
Median (min, max) BMI, kg/m ²	24.2 (20.8, 28.4)	27.3 (20.0, 29.7)	23.8 (18.6, 29.2)	24.5 (18.6, 29.7)
Median (min, max) postmenstrual time, %	-	97.0 (76.2, 120.0)	65.2 (52.2, 101.0)	86.0 (52.2, 120.0) ^a

^aTotal number of subjects for which postmenstrual time was calculated was 20.
^bHepatic impairment was defined at screening according to Child-Pugh classification: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.

Table 2 Plasma PK parameters of peficitinib and its metabolites H1, H2 and H4 (PKAS)

Parameter		Normal hepatic function (n=8) ^a	Mild hepatic impairment (n=8)	Moderate hepatic impairment (n=8)
Peficitinib				
AUC_{inf} , ng.h/mL	Mean (SD)	1149 (231.1)	1435 (525.1)	2332 (895.6)
	GMR (90% CI)	—	1.19 (0.86, 1.64)	1.92 (1.39, 2.66)
C_{max} , mg/mL	Mean (SD)	350.4 (129.1)	371.6 (146.5)	673.8 (331.6)
	GMR (90% CI)	—	1.04 (0.71, 1.53)	1.82 (1.24, 2.69)
$t_{1/2}$, h	Mean (SD)	10.43 (6.215)	13.70 (9.934)	11.16 (8.881)
H1				
AUC_{inf} , ng.h/mL	Mean (SD)	372.1 (111.8)	887.9 (453.0)	1138 (1259)
	GMR (90% CI)	—	2.15 (1.01, 4.56)	1.65 (0.78, 3.50)
C_{max} , ng/mL	Mean (SD)	44.79 (23.87)	90.64 (50.46)	110.3 (107.2)
	GMR (90% CI)	—	1.95 (0.97, 3.92)	1.71 (0.85, 3.45)
$t_{1/2}$, h	Mean (SD)	12.50 (7.983)	9.939 (5.496)	14.11 (7.024)
H2				
AUC_{inf} , ng.h/mL	Mean (SD)	2707 (557.4)	4393 (2075)	2489 (2358)
	GMR (90% CI)	—	1.52 (0.86, 2.68)	0.62 (0.35, 1.10)
C_{max} , ng/mL	Mean (SD)	641.3 (174.0)	808.9 (247.1)	485.0 (426.3)
	GMR (90% CI)	—	1.25 (0.75, 2.09)	0.55 (0.33, 0.91)
$t_{1/2}$, h	Mean (SD)	10.77 (6.098)	7.743 (5.093)	12.24 (9.027)
H4				
AUC_{inf} , ng.h/mL	Mean (SD)	357.2 (143.1)	571.8 (281.1)	1346 (1011)
	GMR (90% CI)	—	1.51 (0.91, 2.49)	3.17 (1.92, 5.24)
C_{max} , ng/mL	Mean (SD)	35.57 (26.23)	53.46 (34.03)	110.5 (80.01)
	GMR (90% CI)	—	1.55 (0.85, 2.83)	3.05 (1.67, 5.56)
$t_{1/2}$, h	Mean (SD)	12.24 (6.956)	10.71 (4.767)	15.13 (7.502)

^aNumber of subjects available for AUC_{inf} and $t_{1/2}$ was 7.

^bHepatic impairment was defined at screening according to Child-Pugh classifications: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.

AUC_{inf} , area under the concentration-time curve from the time of dosing extrapolated to infinity; C_{max} , maximum concentration; GMR, geometric mean ratio; PKAS, pharmacokinetic analysis set (all subjects who received the study drug and provided at least one estimable PK parameter); SD, standard deviation; $t_{1/2}$, terminal elimination half-life; t_{max} , time of C_{max} .

Table 3 Treatment-emergent adverse events (SAE), by Preferred Term

n (%)	Normal hepatic function (n=8)	Mild hepatic impairment (n=8)	Moderate hepatic impairment (n=8)	Total (n=24)
Overall	1 (12.5) ^a	1 (12.5) ^b	1 (12.5)	3 (12.5)
Diarrhoea	0	1 (12.5)	0	1 (4.2)
Nausea	1 (12.5)	0	0	1 (4.2)
Blood urine present	0	1 (12.5)	0	1 (4.2)
Back pain	1 (12.5)	0	0	1 (4.2)
Hypotension	0	0	1 (12.5)	1 (4.2)

^aHepatic impairment was defined at screening according to Child-Pugh classification: Class A, mild, 5–6 points; or Class B, moderate, 7–9 points.

^bAdverse events of nausea and back pain were observed in a single subject with normal hepatic function.

^cAdverse events of diarrhoea and presence of blood urine were observed in a single subject with mild hepatic impairment.

SAE, safety analysis set (all subjects who received the study drug).

Conclusion: Peficitinib exposure in subjects with mild hepatic impairment was similar to that in subjects with normal hepatic function; subjects with moderate hepatic impairment had greater exposure. A single dose of peficitinib was well tolerated.

Figure 1 Mean plasma peficitinib concentration over time by degree of hepatic impairment (semi-log scale PKAS)

REFERENCES:

- Takeuchi T, et al. Ann Rheum Dis 2016; 75: 1057–64; 2. Tanaka Y, et al. ACR/ARHP Annual Meeting 2018: Abstract 887; 3. Takeuchi T, et al. ACR/ARHP Annual Meeting 2018: Abstract 888; 4. Cao YJ, et al. Clin Pharmacol Drug Dev 2016;5:435–49

Acknowledgement: This study was sponsored by Astellas Pharma, Inc. Medical writing support was provided by Iona Easthope of Cello Health MedErgy and funded by Astellas Pharma, Inc.

Disclosure of Interests: Daisuke Miyatake Employee of: Astellas Pharma, Inc., Tomohisa Shibata Employee of: Astellas Pharma, Inc., Junko Toyoshima Employee of: Astellas Pharma, Inc., Yuichiro Kaneko Employee of: Astellas Pharma, Inc., Kazuo Oda Employee of: Astellas Pharma, Inc., Tetsuya Nishimura Employee of: Astellas Pharma, Inc., Masataka Katashima Employee of: Astellas Pharma, Inc., Masashi Sakaki Grant/research support from: Astellas Pharma, Inc., Kazuaki Inoue Grant/research support from: Astellas Pharma, Inc., Takayoshi Ito Grant/research support from: Astellas Pharma, Inc., Naoki Uchida Grant/research support from: Astellas Pharma, Inc., Kenichi Furihata Grant/research support from: Astellas Pharma, Inc., Akinori Urae Grant/research support from: Astellas Pharma, Inc.

DOI: 10.1136/annrheumdis-2019-eular.2443

FRI0162

BASELINE CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH ANAEMIA IN CLINICAL STUDIES OF TOFACITINIB IN RHEUMATOID ARTHRITIS

Burkhard Moeller¹, Axel Finckh², Jose-Maria Alvaro-Gracia³, Godehard Scholz¹, Daniel Aletaha⁴, Francesca Biondo⁵, Sander Strehgolt⁶, Jose Luis Rivas⁷, Carol A. Connell⁸, Harry Shi⁹. ¹Inselspital-University Hospital, Bern, Switzerland; ²University Hospital of Geneva, Geneva, Switzerland; ³Hospital Universitario de La Princesa, Madrid, Spain; ⁴Medical University of Vienna, Vienna, Austria; ⁵Pfizer Inc, Rome, Italy; ⁶Pfizer Inc, Capelle aan den IJssel, Netherlands; ⁷Pfizer SLU, Madrid, Spain; ⁸Pfizer Inc, Groton, CT, United States of America; ⁹Pfizer Inc, Collegeville, PA, United States of America

Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).

Objectives: To describe the profile of patients (pts) with RA and clinically significant anaemia and the impact of treatment with tofacitinib on those with anaemia.

Methods: In this post hoc analysis, data were pooled from Phase (P)2, P3 and P3b/4 studies across the tofacitinib RA clinical programme. Pts received tofacitinib 5 or 10 mg twice daily (BID) with/without background conventional synthetic disease-modifying antirheumatic drugs, or placebo (PBO). Pts with grade ≥ 2 anaemia (G2A; haemoglobin [Hgb] < 10 g/dL) at baseline (BL) were compared with pts without G2A (Hgb ≥ 10 g/dL) at BL. Demographic and BL characteristics, Hgb levels and efficacy (Disease Activity Score in 28 joints, erythrocyte sedimentation rate [DAS28-4(ESR)]) at Month (M)6 and treatment-emergent adverse events (TEAEs) were summarised descriptively.

Results: The proportion of pts with G2A at BL was similar for tofacitinib (3.2%, 152 of 4736 pts) and PBO (2.4%, 27 of 1125 pts) groups. Pts with G2A at BL were more often female, Asian, younger, had never smoked and had a lower body mass index (BMI) and higher C-reactive protein (CRP) and ESR vs pts without G2A at BL; RA duration was generally similar across groups (Table). Tofacitinib seemed to improve anaemia more rapidly than PBO: in pts with G2A at BL, a lower proportion of those receiving tofacitinib had G2A at M1 and M3 vs those receiving PBO (48.8% vs 75.0%, respectively, at M1 and 36.1% vs 57.1%, respectively, at M3), while the proportions were similar at M6 (28.9% vs 30.6%, respectively). In pts receiving tofacitinib, mean Hgb levels gradually increased from BL to M6 in those with G2A at BL (1.25 g/dL change), but were relatively stable in those without G2A at BL (0.15 g/dL change). In tofacitinib-treated pts, DAS28-4(ESR) scores decreased from BL to M6 by -2.40 in those with G2A at BL and -2.42 in those without G2A at BL. DAS28-4(ESR) low disease activity (≤ 3.2) rate at M6 was lower in tofacitinib-treated pts with G2A at BL vs those without G2A at BL (18.3% vs 28.4%, respectively). Among pts receiving tofacitinib,