ORAL PRESENTATIONS: SESSION IBD AND GASTROENTEROLOGY

IBD-1

Benefits of high versus low dose upadacitinib as maintenance treatment in ulcerative colitis patients who were responders to 8-week induction with upadacitinib: Results from the U-ACHIEVE phase 3 maintenance trial

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Introduction: The benefits of high (30 mg) versus low (15 mg) dose Upadacitinib (UPA) as maintenance treatment in UC remains to be established.

Aims and Methods: The percentage of pts in each group with mild (Adapted Mayo score (AMS) <5), moderate (AMS 5 to ≤7), or severe (AMS >7) UC was assessed at Weeks 0 and 52 of maintenance. For each UPA dose, area under the curve (AUC) analysis on the proportion of pts in clinical remission per Partial Adapted Mayo score at Weeks 0, 4, 8, 12, 20, 28, 36, 44 and 52 of maintenance was used to calculate the number of weeks pts were in clinical remission.

Results: Based on AUC analysis, pts in the PBO, UPA 15 mg and UPA 30 mg groups were in clinical remission for 15.8 (95% CI: 12.2, 19.5), 30.5 (95% CI: 26.4, 34.6), and 34.4 (95% CI: 30.5, 38.3) weeks, respectively. Pts in the UPA 30 mg group were in clinical remission for an additional 3.8 weeks (26.9 days) over a year of maintenance compared to the UPA 15 mg group.

Conclusions: After 52-weeks of maintenance treatment with UPA 30 mg QD, pts had less severe disease and were in clinical remission for approx. 1 additional month/year vs pts treated with UPA 15 mg QD indicating an important clinical benefit of high dose UPA as maintenance treatment in UC.

Patients with mild, moderate, and severe UC at Weeks 0 and 52 and weeks in clinical remission

		Week 0			Week 52[a]			Weeks in Clinical Remission[b]
n (%)	**N**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mean (95% CI)**
PBO	149	137 (92.0)	12 (8.1)	0	34 (22.8)	70 (47.0)	45 (30.2)	15.8 (12.2, 19.5)
UPA 15 mg	148	136 (91.9)	11 (7.4)	0	94 (63.5)	25 (16.9)	28 (18.9)	30.5 (26.4, 34.6)
UPA 30 mg	154	141 (91.6)	13 (8.4)	0	114 (74.0)	24 (15.6)	15 (9.7)	34.4 (30.5, 38.3)

[a] Patients with Adapted Mayo scores collected at or after initiation of UC-related rescue medications through the end of the maintenance study or who prematurely discontinued from the study were assumed to have Week 52 Adapted Mayo score return to baseline. Pts with missing data for reasons other than UC-related rescue medications or premature discontinuation were handled by last observation carried forward. Disease severity was defined by Adapted Mayo score: mild (Adapted Mayo <5), moderate (Adapted Mayo 5 to ≤7), and severe (Adapted Mayo >7).

[b] Clinical remission was defined as Partial Adapted Mayo score ≤2 with no subscore >1.

IBD-2

IBD and therapeutic drug monitoring of upadacitinib to streamline induction and maintenance treatment

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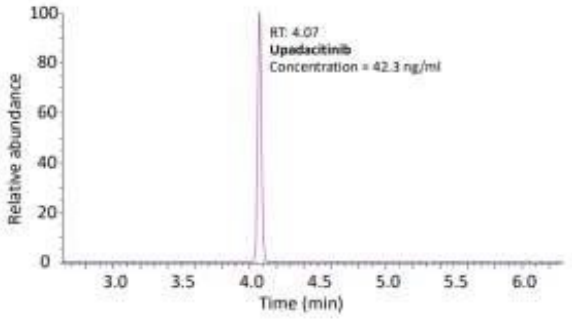
Background: A highly sensitive and selective analytical method based on multiplex high-performance liquid-chromatography coupled to tandem mass spectrometry (HPLCMS/MS) was developed and validated for the simultaneous plasma quantification of the oral selective JAK kinase inhibitor, Upadacitinib (UPA; Rinvoq®). The goal of the TDM is to identify the most appropriate dosing (between 15mg and 45mg) by addressing dose-dependent efficacy and tolerability issues.

Methods: The method was validated according to SFTSP and ICH-M10 guidelines, The MS/MS parameters of the upadacitinib and its respective stable isotope-labelled IS were established, as well as a chromatogram based on plasma sample of patients. Analytical range of UPA and its limit of detection were validated.

Results: Limit of detection was 0.05 ng/ml, lower limit of quantification 0.5, and upper limit of quantification 200 ng/ml. Chromatogram abundance was provided from a patient on upadacitinib 15 mg QD (Fig 1.). Accuracy profile related to updadacitinib concentration is shown on Fig. 2.



Chromatogram of plasma sample from a patient with atopic dermatitis and vitiligo treated with upadacitinib 15 mg QD.

Figure 1

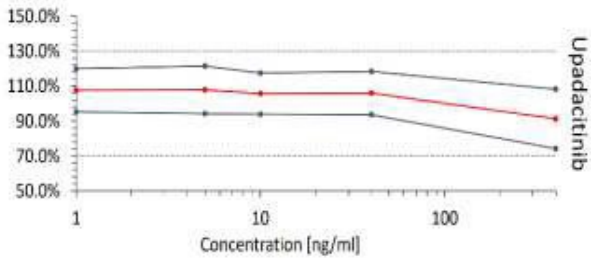


Figure 6. Accuracy profile. Limits = ± 30% risk, α = 0.05

Figure 2

Conclusion: We developed and validated a highly sensitive method to quantify in human plasma. This essay will be implemented for clinical guidance to improve upadacitinib effectiveness and safety. Population pharmacokinetics and Physiological based pharmacokinetic modeling with simulation are planned to leverage TDM of upadacitinib as a novel monitoring biomarker to streamline precision medicine in IBD.

IBD-3

A prospective interventional study to evaluate the effect of hypoxia on healthy volunteers and patients with inflammatory bowel disease: The Altitude IBD study

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Background: It is unknown how high-altitude exposure causes inflammatory bowel disease (IBD) flares. We assessed disease activity in healthy controls, IBD patients after 3h exposure in a hypobaric pressure chamber (imitating an altitude of 4000m).

Methods: In a prospective study, 11 Crohn's disease (CD, 6 males, 35.6y ± 13.7), 9 ulcerative colitis (UC, 3 males, 31.4y ± 10.8) patients and 10 healthy controls (7 males, 27.7y ± 4.9) underwent rectosigmoidoscopy in our outpatient clinic (490m, baseline) and after 3h exposure in a hypobaric pressure chamber (follow-up day 1 and day 7). Disease activity was further assessed by symptom scores, CRP levels and fecal calprotectin. Intestinal mucosa-associated microbial composition was analyzed using high-throughput sequencing.

Results: The 3h exposure in a hypobaric pressure chamber was well tolerated in all subjects. Mean oxygen saturation decreased from 97.5% ± 1.3 to 80.9% ± 4.1, and increased back to normal levels after the hypobaric intervention (p <0.0001). Clinical and endoscopic disease activity were not significantly changed before vs. after intervention. However, mild flare was seen in 2 UC patients and another UC patient was lost to follow-up due to a disease flare. New endoscopic lesions were detected in one healthy subject and one UC patient. Fecal calprotectin levels significantly increased in CD patients during the follow-up period (p = 0.031), but not in UC and healthy controls. No changes in CRP levels were observed. Percentage of calprotectin- based disease remission (fecal calprotectin <100ug/g) decreased in all groups after hypobaric pressure chamber exposure, and increased thereafter with a significant decrease in the control group (100% at baseline vs. 50% at day 1, p = 0.029) and all patients combined (73.3% at baseline vs. 36.7% at day 7, p = 0.013). No differences in alpha and beta diversity of stool microbiota composition before vs. after hypobaric pressure chamber exposure were observed.

Conclusion: A 3h exposure in a hypobaric pressure chamber did not result in higher disease activity. However, mild flares and development of endoscopic lesions were seen in a subset of patients. Calprotectin-based remission rates significantly decreased between baseline and day 7 suggesting a subclinical effect of short-term hypoxia.

IBD-4

Real-life efficacy and safety of tofacitinib to treat moderate- to-severe ulcerative colitis in Switzerland

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Background and aims: Due to the paucity of data we aimed to assess the real-life safety and efficacy of tofacitinib (Xeljanz®) to treat adults with moderate-to-severe ulcerative colitis (UC) in Switzerland.

Methods: In accordance with the OCTAVE study design, we assessed clinical and endoscopic activity at baseline and weeks 8, 26, and 52. Following the label, tofacitinib was given during the 8 week induction phase with 2x10mg a day and 2x5mg during the maintenance period.

Results: We included 104 adults (mean age 41±14.4yrs, median disease duration 6yrs [IQR 3-11, range 1-44yrs], 48.1% females). Disease location was as follows: proctitis 3.9%, left-sided colitis 34.6%, extensive colitis 11.5%, pancolitis 50%. The former drug treatment history was as follows: mesalazine 100%, topical budesonide 100%, prednisone 100%, azathioprine 70.2%. Before tofacitinib was started, patients had a median of 2 failed biologic therapies (IQR 1-3, range 0-6). 21/104 (20.2%) of patients were treated with prednisone at the moment tofacitinib was started. A significant decrease of the full Mayo score was observed over time (week 0: median 10, IQR 9-11, range 8-12; week 8: median 7, IQR 6-9, range 2-12; week 26: median 1, IQR 1-4, range 0-10; week 52: median 1, IQR 0-12, range 0-10; p <0.05 trend test). Adherence to tofacitinib was as follows: week 8: 104/104 (100%); week 26: 77/104 (74%); week 52: 63/104 (60.6%). No deep vein thrombosis, pulmonary embolism, major advanced cardiovascular event, or neoplasia were observed. Four patients had herpes zoster reactivation during induction phase and two during maintenance period.

Conclusions: In this Swiss UC population, characterized by a complicated disease course and multiple failures to biologic therapies, 60% of patients were still under tofacitinib at week 52 due to continued clinical benefit.

