CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Original article

A Novel Validated RP-HPLC Method Development for the Quantitative Determination of Rimegepant in Bulk Form and Marketed Pharmaceutical Dosage Form

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ARTICLE INFO:
Received: 28 May 2023
Accepted: 16 June 2023
Published: 30 June 2023

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ABSTRACT:
A rapid and precise reverse phase high performance liquid chromatographic method has been developed for the validated of Rimegepant, in its pure form as well as in tablet dosage form. Chromatography was carried out on a Symmetry C18 (4.6 x 150mm, 5µm) column using a mixture of Methanol and water (45:55% v/v) as the mobile phase at a flow rate of 0.8ml/min, the detection was carried out at 260nm. The retention time of the Rimegepant was 2.379 ±0.02min respectively. The method produce linear responses in the concentration range of 24-120mg/ml of Rimegepant. The method precision for the determination of assay was below 2.0%RSD. The method is useful in the quality control of bulk and pharmaceutical formulations. The method was validated for accuracy, precision, linearity, robustness, ruggedness and LOD & LOQ of standard solution. The developed RP-HPLC method was found to be accurate, precise, linear, and robust and was successful applied to a pharmaceutical tablet formulation for qualitative estimation of Rimegepant in Bulk form and Marketed Pharmaceutical Dosage forms.

Keywords: Rimegepant, RP-HPLC, Method Development, Validation, Accuracy.

1. INTRODUCTION

Rimegepant is a small molecule inhibitor of the calcitonin gene-related peptide (CGRP) receptor that blocks the action of CGRP, a potent vasodilator believed to play a role in migraine headaches. Rimegepant[1] is approved for treatment of acute migraine attacks. In clinical trials, Rimegepant was generally well tolerated with only rare instances of transient serum aminotransferase elevations during therapy and with no reported instances of clinically apparent liver injury. Rimegepant is an oral antagonist of the CGRP receptor developed by Biohaven Pharmaceuticals. It received FDA approval on February 27, 2020 for the acute treatment migraine headache, and was subsequently approved by the European Commission in April 2022 for both the treatment and prevention of migraines. While several parenteral antagonists of CGRP and its receptor have been approved for migraine therapy (e.g. [erenumab], [fremanezumab], [galcanezumab]), Rimegepant [1, 2] and [ubrogepant] were the only CGRP antagonists that possessed oral bioavailability until the approval of [Atogepant] in 2021. The current standard of migraine therapy involves abortive treatment with "triptans", such as [sumatriptan], but these medications are contraindicated in patients with pre-existing cerebrovascular and cardiovascular disease due to their vasoconstrictive properties. Antagonism of the CGRP pathway has become an attractive target for migraine therapy as, unlike the triptans, oral CGRP antagonists have no observed vasoconstrictive properties and are therefore safer for use in patients with contraindications to standard therapy. Rimegepant [3] is a Calcitonin Gene-related Peptide Receptor Antagonist. The mechanism of action of Rimegepant is as a Calcitonin Gene-related Peptide Receptor Antagonist. The IUPAC Name of Rimegepant is [(5S, 6S, 9R)-5-amino-6-(2, 3-difluorophenyl)-6, 7, 8, 9-tetra hydro-5H-cyclo hepta [b] pyridin-9-yl] 4-(2-oxo-3H-imidazo [4, 5-b] pyridin-1-yl) piperidine-1-carboxylate. The Chemical Structure of Rimegepant is as following

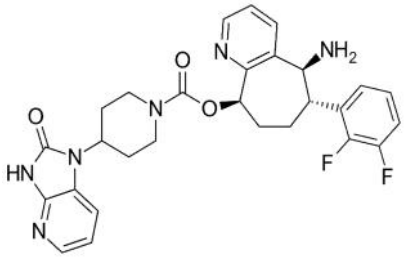

Fig 1: Chemical Structure of Rimegepant

A thorough literature survey of Rimegepant revealed that very few analytical methods had been reported for

estimation of Rimegepant. Majority of methods for determination of Rimegepant in biological fluids and pharmaceutical dosage forms includes LC-MS/MS, LC-MS, and HPTLC-LC, HPTLC, UPLC-MS, HPLC-MS, RPHPLC and UV-Visible Spectrophotometric methods. This novel proposed method contributes quick estimation, correct peak shape, precise, simple, and quick, use of smaller sample volumes and utilizing Suitable Solvent System as a mobile phase which is economical when compared with other existing methods. So, it is necessary to develop a simple, precise, and rapid RP-HPLC method for the quantitative determination of Rimegepant. This work describes the validation parameters [4] stated by the International Conference on Harmonization [ICH] guidelines Q2 (R1).

2. EXPERIMENTAL

Table 1: Instruments Used

S.No.	Instruments and Glasswares	Model
1	HPLC	WATERS Alliance 2695 separation module, Software: Empower 2, PDA 996 Detector.
2	pH meter	LabIndia
3	Weighing machine	Sartorius
4	Volumetric flasks	Borosil
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil
7	Digital ultra sonicator	Labman

Table-2: Chemicals Used

S.No.	Chemical	Brand names
1	Rimegepant (Pure)	Local Market
2	Water and Methanol for HPLC	LICHROSOLV (MERCK)
3	Acetonitrile for HPLC	Merck

HPLC METHOD DEVELOPMENT:

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 0.72ml of the above Rimegepant stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Procedure:

Inject the samples by changing the chromatographic conditions and record the chromatograms, note the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

Mobile Phase Optimization:

Initially the mobile phase tried was methanol: Water and Acetonitrile: Water with varying proportions. Finally, the mobile phase was optimized to Methanol and Water in proportion 45:55 v/v respectively.

Optimization of Column:

The method was performed with various C18columns like ODS column, Xterra, and X Bridge C18 column. Symmetry C18 (4.6 x 150mm, 5µm) was found to be ideal as it gave good peak shape and resolution at 1ml/min flow.

Preparation of Mobile Phase:

Accurately measured 450 ml (45%) of HPLC Methanol and 550 ml of HPLC Water (55%) were mixed and degassed in a digital ultrasonicator for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation:

The Mobile phase was used as the diluent.

METHOD VALIDATION PARAMETERS

System Suitability

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.72ml of the above Rimegepant stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure:

The standard solution was injected for five times and measured the area for all five injections in HPLC. The % RSD for the area of five replicate injections was found to be within the specified limits.

Specificity:

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent (Stock solution).

Further pipette 0.72ml of the above Rimegepant stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Preparation of Sample Solution:

Take average weight of the Tablet and crush in a mortar by using pestle and weight 10 mg equivalent weight of Rimegepant sample into a 10mL clean dry volumetric flask and add about 7mL of Diluent [5] and sonicate to dissolve it completely and make volume up to the mark with the same solvent.

Further pipette 0.72ml of Rimegepant above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure:

Inject the three replicate injections of standard and sample solutions and calculate the assay [6] by using formula:

$$\%\,ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

Linearity:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Preparation of Level – I (24ppm of Rimegepant):

Pipette out 0.24ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – II (48ppm of Rimegepant):

Pipette out 0.48ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – III (72ppm of Rimegepant):

Pipette out 0.72ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – IV (96ppm of Rimegepant):

Pipette out 0.96ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – V (120ppm of Rimegepant):

Pipette out 1.2ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Procedure:

Inject each level into the chromatographic system and measure the peak area. Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

Precision

Repeatability

Preparation of RimegepantProduct Solution for Precision:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.72 ml of the above Rimegepant stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

Intermediate Precision:

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different days by maintaining same conditions.

Procedure:

Day 1:

The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Day 2:

The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Accuracy:

For Preparation of 50% Standard Stock Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.36ml of the above Rimegepant stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

For Preparation of 100% Standard Stock Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent (Stock solution).

Further pipette 0.72ml of the above Rimegepant stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

For Preparation of 150% Standard Stock Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 1.08ml of the above Rimegepant stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure:

Inject the Three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculate the Amount found and Amount added for Rimegepant and calculate the individual recovery and mean recovery values.

Robustness:

The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results.

For Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Rimegepant working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.72ml of the above Rimegepant stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Effect of Variation of Flow Conditions:

The sample was analyzed at 0.7 ml/min and 0.9 ml/min instead of 0.8ml/min, remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded

Effect of Variation of Mobile Phase Organic Composition:

The sample was analyzed by variation of mobile phase i.e. Methanol: Water was taken in the ratio and 40:60, 50:50 instead of 45:55, remaining conditions are same.10µl of the above sample was injected and chromatograms were recorded.

3. RESULTS AND DISCUSSION

Development of Analytical Method:

Optimized Chromatographic Conditions:

Mobile phase ratio : Methanol: water (45:55 v/v)
Column : Symmetry C18 (4.6×150mm) 5µm
Column temperature : 40ºC
Wavelength : 260nm
Flow rate : 0.8ml/min
Injection volume : 10µl
Run time : 6minutes

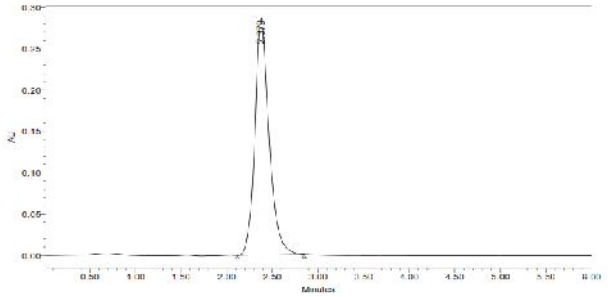

Fig 2: Optimized Chromatographic Condition of Rimegepant

Observation: In this trail it shows well peak shape and proper plate count and tailing under limit in the chromatogram. So it's optimized chromatogram.

Method Validation

Once the chromatographic and the experimental conditions were established, the method was validated by the determination of the following parameters such as specificity, system suitability, linearity, precision, accuracy, robustness, limit of detection (LOD) and limit of quantitation (LOQ) as per ICH Q2 (R1) guidelines.

System Suitability:

The chromato-graphic systems used for analysis must pass system suitability [7] before going to start the experiment. At first HPLC system is stabilized for forty minutes. Inject blank preparation (single injection) and standard preparation (five replicates) and record the chromatograms to evaluate the system suitability parameters such as tailing factor (NMT 1.5), theoretical plate count (NLT 3000) and retention time. The % RSD for the peak area of five replicate injections of Rimegepant standard NMT 2.0. The parameters, such as tailing factor, % RSD, and theoretical plates, were studied.

Table 3: Results of System Suitability for Rimegepant

S.No.	PeakName	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Rimegepant	2.317	2274631	239458	5728	1.2
2	Rimegepant	2.302	2284721	239582	5093	1.2
3	Rimegepant	2.323	2238127	236493	5391	1.2
4	Rimegepant	2.343	2259349	249482	6139	1.2
5	Rimegepant	2.321	2204850	239452	5281	1.2
Mean			2252336			
Std.Dev.			31827.08			
%RSD			1.41307			

Specificity

The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components.

Analytical method was tested for specificity [8] to measure accurately quantitates Rimegepant in drug product.

$$\%\,ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

The % purity of Rimegepant in pharmaceutical dosage form was found to be 99.7%.

Linearity: Standard stock solution of the Dasatinib (72 mg/ml) was prepared with the mobile phase. To study the linearity range [9] of drugs, serial dilutions were made from a standard stock solution in the range of 24-120 µg/ml.

Table 4: Linearity Data of Rimegepant

Concentration Level (%)	Concentration «g/ml	Average Peak Area
33	24	791554
66	48	1647073
100	72	2283804
133	96	3058339
166	120	3839630

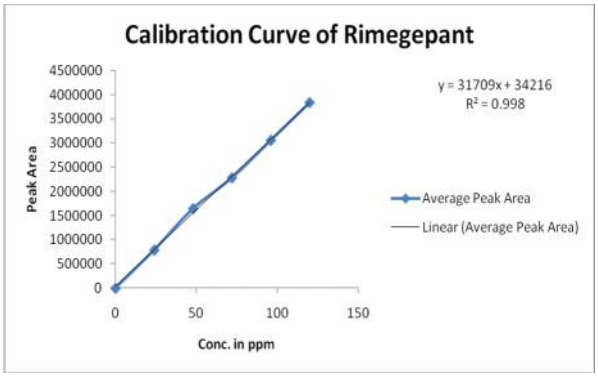

Fig 3: Calibration Curve of Rimegepant

Linearity Plot: The plot of Concentration [10] (x) versus the Average Peak Area (y) data of Rimegepant is a straight line.

Y = mx + c

Slope (m) = 31709

Intercept (c) = 34216

Correlation Coefficient (r) = 0.998

Validation Criteria: The response linearity is verified if the Correlation Coefficient is 0.99 or greater.

Conclusion: Correlation Coefficient (r) is 0.99, and the intercept is 34216. These values meet the validation criteria [11].

Precision:

The precision [12] of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Repeatability: Obtained Five (5) replicates of 100% accuracy solution as per experimental conditions. Recorded the peak areas and calculated % RSD [13-15]. The results were shown in Table-5.

Table 5: Results of Repeatability for Rimegepant:

S. No.	Peak Name	Retention time	Area(µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Rimegepant	2.356	2259464	245362	5938	1.2
2	Rimegepant	2.356	2275915	248293	5827	1.2
3	Rimegepant	2.357	2282117	240795	5032	1.2
4	Rimegepant	2.358	2278675	230139	5978	1.2
5	Rimegepant	2.359	2282448	249605	6183	1.2
Mean			2275724			
Std. Dev			9476.485			
%RSD			0.416416			

Intermediate Precision:

Analyst1:

Table 6: Results of Intermediate Precision for Rimegepant

S.No.	PeakName	RT	Area (µV*sec)	Height (µV)	USPPlate count	USPTailing
1	Rimegepant	2.380	2236184	202188	5472	1.2
2	Rimegepant	2.383	2238020	201837	6193	1.2
3	Rimegepant	2.385	2239352	201273	5980	1.2
4	Rimegepant	2.385	2242466	203923	7163	1.2
5	Rimegepant	2.389	2244692	202938	6182	1.2
6	Rimegepant	2.389	2247654	201982	7684	1.2
Mean			2241395			
Std.Dev.			4333.851			
%RSD			0.193355			

Analyst 2:

Table 7: Results of Intermediate Precision Analyst 2 for Rimegepant

S.No.	PeakName	RT	Area (µV*sec)	Height (µV)	USPPlate count	USPTailing
1	Rimegepant	2.380	2236184	217363	5928	1.2
2	Rimegepant	2.383	2238020	218467	6183	1.2
3	Rimegepant	2.385	2239352	218346	5927	1.2
4	Rimegepant	2.385	2242466	221736	5163	1.2
5	Rimegepant	2.389	2244692	228361	4827	1.2
6	Rimegepant	2.346	2263431	217553	5019	1.2
Mean			2244024			
Std.Dev.			9988.458			
%RSD			0.445114			

Accuracy:

Accuracy at different concentrations (50%, 100%, and 150%) was prepared and the % recovery[14] was calculated.

Table 8: The accuracy Results for Rimegepant

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	1172485	36	35.8	99.4	99.5%
100%	2314753	72	71.6	99.4	
150%	3480210	108	107.9	99.9	

Limit of Detection

The detection limit [15] of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

LOD= 3.3 × σ / s

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result:

=5.5µg/ml

Quantitation Limit

The quantitation limit [16] of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.

LOQ=10×σ/S

Where

σ = Standard deviation of the response

S = Slope of the calibration curve [17]

Result:

=16.7µg/ml

Robustness

The robustness [18] was performed for the flow rate variations from 0.7 ml/min to 0.9ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for Rimegepant. The method is robust only in less flow condition and the method is robust even by change in the Mobile phase ±5%. The standard and samples of Rimegepant were injected by changing the conditions of chromatography [19]. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Table 9: Results for Robustness of Rimegepant

Parameter Used for Sample Analysis	Peak Area	Retention Time	Theoretical Plates	Tailing Factor
Actual Flow rate of 0.8mL/min	3119086	2.379	5837	1.2
Less Flow rate of 0.7mL/min	2640811	2.763	5361	1.2
More Flow rate of 0.9mL/min	2640354	2.234	5231	1.2
Less organic phase	2640758	2.765	4503	1.5
More organic phase	2640125	2.236	4491	1.5

Stability Studies

The API (Rimegepant) was subjected to worry conditions in numerous ways that to look at the speed and extent of degradation that's seemingly to occur within the course of storage and/or when administration to body. This is often one style of accelerated stability studies that helps United States deciding the fate of the drug that's seemingly to happen when on time storage, at intervals a awfully short time as compare to the important time or future stability testing. The various degradation pathways studied are acid chemical reaction, basic chemical reaction, thermal degradation, and photolytic degradation and Oxidation degradation.

Results of Degradation Studies: The results of the strain studies indicated the specificity of the tactic that has been developed. Rimegepant was stable in all stress conditions except thermal stress condition. The results of forced degradation studies [20-22] are given in the following table-10.

Table 10: Results of Forced Degradation Studies of Rimegepant API

Stress Condition	Time in hrs	Assay of active substance	Assay of degraded products	Mass Balance (%)
Acid Hydrolysis (0.1 M HCl)	24Hrs.	92.985	7.015	100.0
Basic Hydrolysis (0.1 M NaOH)	24Hrs.	91.062	8.938	100.0
Wet heat	24Hrs.	89.749	10.251	100.0
UV (254nm)	24Hrs.	95.625	4.375	100.0
3 % Hydrogen peroxide	24Hrs.	96.548	3.452	100.0

4. SUMMARY

The analytical method was developed by studying different parameters. First of all, maximum absorbance was found to be at 260nm and the peak purity was excellent. Injection volume was selected to be 10µl which gave a good peak area. The column used for study was Symmetry C_{18} because it was giving good peak.40 º C temperatures was found to be suitable for the nature of drug solution. The flow rate was fixed at 0.8ml/min because of good peak area and satisfactory retention time. Mobile phase is Methanol: water was fixed due to good symmetrical peak. So this mobile phase was used for the proposed study. Methanol: water was selected because of maximum extraction sonication time was fixed to be 10min at which all the drug particles were completely soluble and showed good recovery. Run time was selected to be 6min because analyze gave peak around 2.3 and also to reduce the total run time. The percent recovery was found to be 98.0-102 was linear and precise over the same range. Both system and method precision was found to be accurate and well within range. The analytical method was found linearity over the range of 24-120 ppm of the Rimegepant target concentration. The analytical passed both robustness and ruggedness tests. On both cases, relative standard deviation was well satisfactory [23-26].

5. CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of Rimegepant in bulk drug and pharmaceutical dosage forms. This method was simple, since diluted samples are directly used without any preliminary chemical derivatization or purification steps. Methanol: water was chosen as the mobile phase. The solvent system used in this method was economical. The %RSD values were within 2 and the method was found to be precise. The results expressed in tables for RP-HPLC method was promising. The RP-HPLC method is more sensitive, accurate and precise compared to the Spectrophotometric methods. This method can be used for

the routine determination of Rimegepant in bulk drug and in Pharmaceutical dosage forms.

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ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable