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Application of the QbD Principles in the Development of the Casopitant Mesylate Manufacturing Process. Process Research Studies for the Definition of the Control Strategy of some Drug Substance-CQAs for Stages 2a, 2b, and 2c

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Abstract:

Casopitant was identified as a potent NK_1 antagonist by GlaxoSmithKline (GSK). It was selected as part of a wide drug discovery programme within GSK for its potential activities on a number of therapeutic targets such as inflammatory bowel disease, overactive bladder, CNS disorders, and others. The mesylate salt of casopitant was selected for full development. The manufacturing process to casopitant mesylate was developed and optimised by following a Quality by Design approach, whereby a control strategy was developed, underpinned by process understanding and risk analysis, for an enhanced level of quality assurance. Quality process parameters and specifications levels for the Stages 2a, 2b, and 2c are the elements of the control strategy of the manufacturing process discussed in detail in this paper. The Design of Experiment approach has been extensively used to support the definition of the proven acceptable ranges for the process. The aim is to show the process development studies carried out to ensure quality control for the final drug substance.

1. Introduction

In the past years, a number of regulatory guidelines (ICH Q8, ICH Q9, and ICH Q10)[1] have been issued, describing a new approach to process development where the quality is built-in rather than tested in the product. This approach is called "Quality by Design" (QbD).

These guidelines are focused on different aspects of QbD.[1] For example, ICH Q8 describes an enhanced approach by the use of process understanding. ICH Q9 describes the risk management tools that can be used to successfully manage the risk, and ICH Q10 introduced the concept of a control strategy, defined as a set of controls, derived from current product and process understanding that assures process performance and obtaining drug substance that meets the critical quality attributes (drug substance-CQAs, the measurable properties that are critical to ensuring patient safety and efficacy).

The development of a robust control strategy supported by process understanding and by using the appropriate risk assessment tools is therefore key to ensuring that the quality of the drug substance or drug product is appropriate and consistent.

Regulatory agencies[2] fully support this approach and encourage its adoption during the development of drug substance and drug product manufacturing processes. More details on this approach as applied by GSK have been recently reported in a previous paper,[3] where a detailed description of the elements of control (the attributes of the input materials, the process parameters, and the procedure) is also given.

A QbD approach has recently been applied to the development of the manufacturing process for casopitant mesylate **1**, a potent neurokinin receptor (NK_1) antagonist.

In this contribution, some of the process understanding studies carried out on Stages 2a, 2b, and 2c for the definition of the control strategy are described. The elements of control discussed are the quality process parameters (the parameters that have an impact on drug substance-CQAs) and the specifications levels for starting materials and one intermediate of the manufacturing process. The Design of Experiment (DoE) approach has been extensively used to support the development work in all the stages and in particular in the definition of the proven acceptable ranges (PARs) (the upper and/or lower limits for process parameter between which the parameter is known to produce a process output that meets the CQAs) for Stage 2a.

For the reader's benefit, a Glossary with the definitions of the terms used within this text is included.

2. Synthetic Route

The commercial process to synthesise casopitant mesylate **1**, is a multistage convergent process, summarised in Scheme 1.

In Stage 1, the dihydropyridone **10** is converted into the piperidone **8** by reduction of the double bond and hydrogenolysis of the carbobenzyloxy protecting group. The piperidone **8** is resolved *via* dynamic kinetic resolution (DKR) using L-mandelic acid to yield the (*R*)-piperidone as the L-mandelate salt **7**.

In Stage 2, the (*R*)-amine **5** is converted into the carbamoyl chloride **4** by reaction with carbon dioxide and thionyl chloride.

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(1) *ICH Q8 Pharmaceutical Development*; *ICH Q9 Quality Risk Management*; *ICHQ 10 Pharmaceutical Quality System*.

(2) See for example: Pharmaceutical cGMPs for the 21st century - A risk based approach, Final Report; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Silver Spring, MD, U.S.A., 2004.

(3) Cimarosti, Z.; Bravo, F.; Stonestreet, P.; Tinazzi, F.; Vecchi, O.; Camurri, G. *Org. Process Res. Dev.* ASAP - DOI: 10.1021/op900242x.

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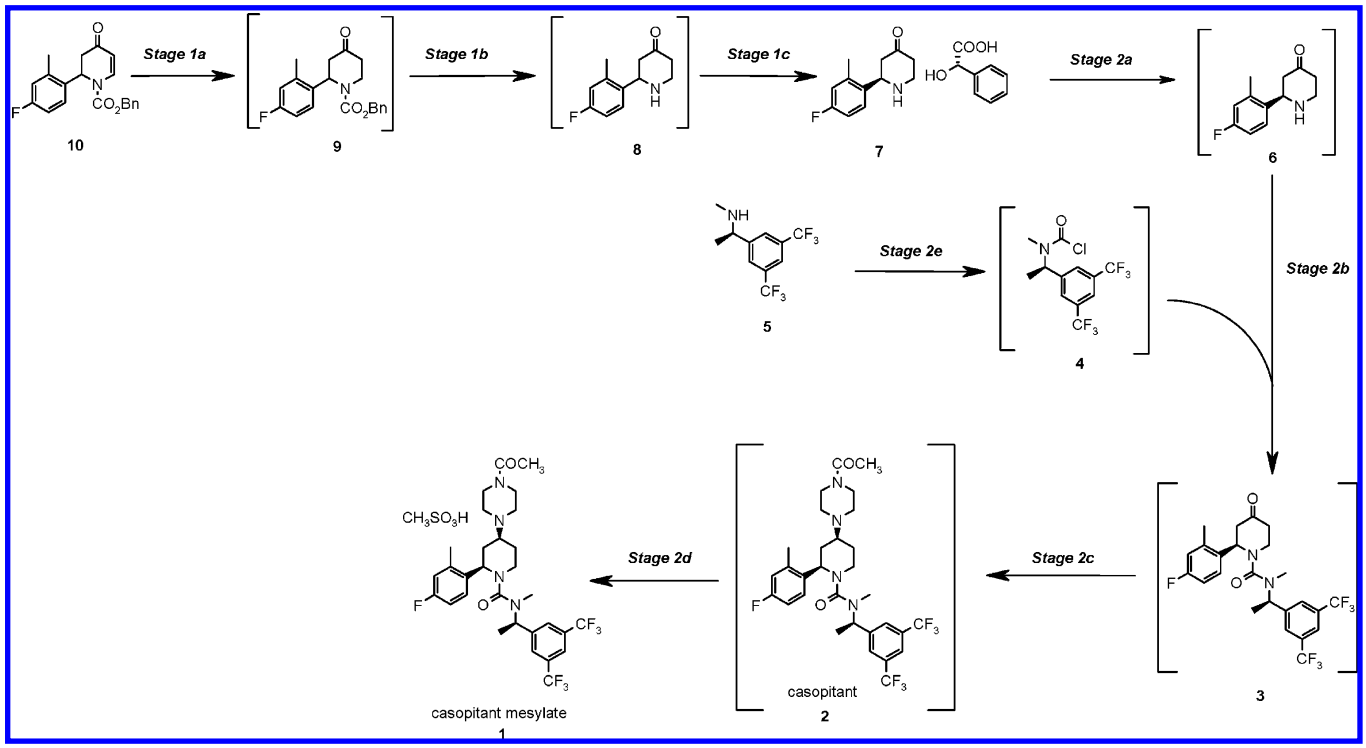
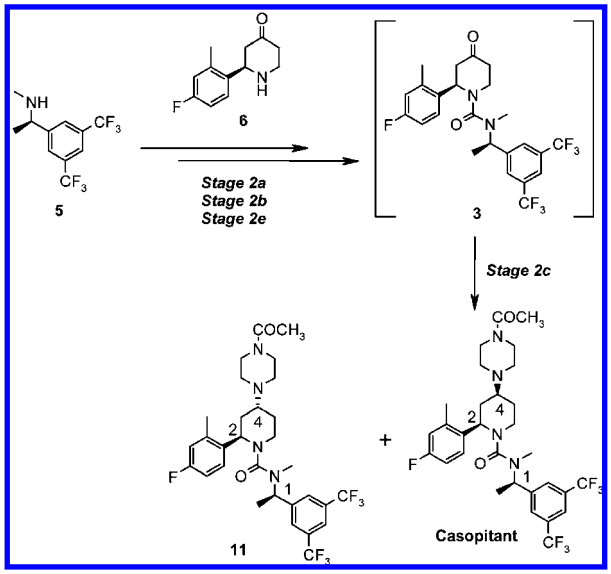
Scheme 1. **Commercial route for casopitant mesylate**[a]



[a] **Stage 1a:** ethyl acetate, Rh/C, hydrogen. **Stage 1b:** ethyl acetate, Pd/C, hydrogen. **Stage 1c:** i) 2-propanol, water, L-mandelic acid; ii) **7** seed; iii) 2-propanol, cyclohexane. **Stage 2e:** i) ethyl acetate, carbon dioxide, triethylamine; ii) chloro(trimethyl)silane; iii) pyridine; iv) thionyl chloride; v) malic acid (aq); vi) water; vii) Na_2CO_3 (aq) or K_2HPO_4 (aq); viii) ethyl acetate. **Stage 2a:** i) ethyl acetate; ii) Na_2CO_3 (aq); iii) NaCl (aq) or water; iv) ethyl acetate. **Stage 2b:** i) triethylamine; ii) 1-acetylpiperazine; iii) malic acid (aq); iv) Na_2CO_3 (aq); v) NaCl (aq) or water; vi) acetonitrile. **Stage 2c:** i) acetonitrile, 1-acetylpiperazine, $NaBH(OAc)_3$/HCOOH; ii) ethyl acetate; iii) NH_4OH (aq); iv) Na_2CO_3 (aq); v) NaCl (aq) or water or K_2HPO_4 (aq); vi) ethyl acetate. **Stage 2d:** i) ethyl acetate; ii) acetone; iii) methanesulfonic acid; iv) casopitant mesylate seed; v) isooctane; vi) ethyl acetate.

Scheme 2. **Formation of casopitant stereoisomers**



Acylation of the (*R*)-piperidone **6** (obtained by basification of its corresponding L-mandelate salt **7**) with an excess of the carbamoyl chloride **4** yields the piperidone-urea **3**, followed by addition of l-acetylpiperazine to react with the excess of carbamoyl chloride. The piperidone-urea **3** is subjected to reductive amination with additional 1-acetylpiperazine in the presence of the reducing system sodium triacetoxyborohydride [$NaBH(OAc)_3$]/formic acid to afford a mixture of casopitant **2** and its *anti*-isomer **11** (showed in Scheme 2) in a ratio of approximately 2:1. Casopitant mesylate **1** is obtained after a seeded, selective precipitation by addition of methanesulfonic acid in a mixture of ethyl acetate, acetone, and isooctane.

In this contribution the process research studies carried out for the definition of the control strategy for Stages 2a, 2b, and 2c of some drug substance-CQAs are reported.

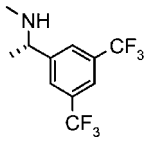
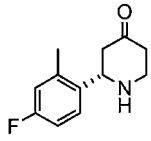
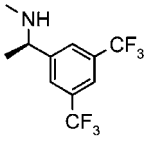
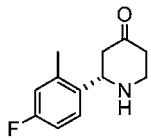
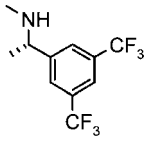
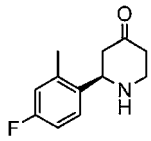
3. Drug Substance-CQAs Discussed for Stages 2a, 2b, and 2c

The drug substance-CQAs discussed in this paper in the context of Stages 2a, 2b, and 2c are impurities with the potential to contaminate the drug substance, and they are the stereoisomers of the casopitant and the impurities coming from the contaminants of the starting material 1-acetylpiperazine. The structures and the rationale for their formation are reported below.

3.1. Casopitant Stereoisomers. The synthetic route introduces three stereogenic centres, so that in principle a total of eight stereoisomers can be formed. In addition to casopitant mesylate **1** and its enantiomer, there are six other isomers: three diastereoisomers and each diastereoisomer can exist as an enantiomeric pair. The formation of each individual stereoisomer is summarised in Scheme 2 and Table 1; all of them might be present in the drug substance. For this reason all of them are drug substance-CQAs, and their control has to be ensured according to the ICH guideline on impurities.

Considering Stages 2a, 2b, and 2c that are discussed in this contribution, the sources of these stereoisomers are in the

Table 1. **Formation of casopitant stereoisomers**

Amine	Piperidone	Casopitant stereoisomers*
 (*S*)-12	 (*S*)-13	(1*S*,2*S*,4*R*)-**14** and (1*S*,2*S*,4*S*)-**15**
 (*R*)-5	 (*S*)-13	(1*R*,2*S*,4*S*)-**16** and (1*R*,2*S*,4*R*)-**17**
 (*S*)-12	 (*R*)-6	(1*S*,2*R*,4*R*)-**18** and (1*S*,2*R*,4*S*)-**19**

[a] The configuration of the stereocentres according to Scheme 2 is reported.

Scheme 3. **Drug substance-CQAs from 1-acetylpiperazine impurities**

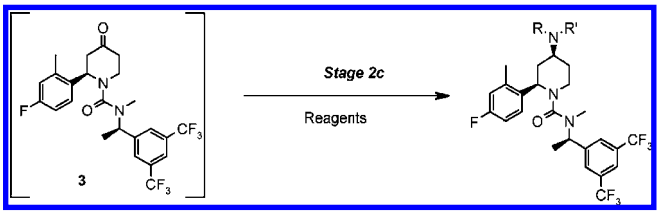
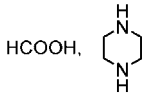
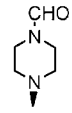
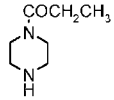
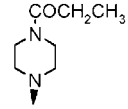
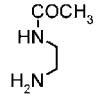
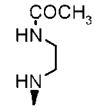


Table 2. **Structures of the 1-acetylpiperazine impurities**

Reagents	NRR'	Compound Number
 HCOOH,		**20**
		**21**
		**22**

stereoselectivity of the Stage 2c reaction (the reductive amination) and in the enantiomer contamination of the (*R*)-piperidone mandelate salt **7** and the (*R*)-amine **5**, as summarised in Scheme 2 and Table 1.

The same synthetic path is followed also by the enantiomers of the compounds (*R*)-amine **5** and (*R*)-piperidone **6**, (*S*)-amine **12** and (*S*)-piperidone **13**, respectively, leading to the formation of the other casopitant stereoisomers as detailed in Table 1.

It is worth noting that the compounds belonging to the following pairs **11** and **15**, **16** and **18**, **17** and **19** and casopitant and **14** are enantiomers.

3.2. 1-Acetylpiperazine Impurities. Process understanding studies highlighted also that one of the reagents, 1-acetylpiperazine, could contain piperazine, 1-propanoylpiperazine, and *N*-(2-aminoethyl)acetamide as impurities. Process understanding studies showed that these impurities could react in Stage 2c chemistry by generating three impurities with the potential to contaminate the drug substance (compounds **20**, **21**, and **22**). These potential impurities were defined drug substance-CQAs. Details of their formation are given in Scheme 3 and Table 2.

4. Setting of the Appropriate Specification Limits for the Key Input Materials of Stages 2a, 2b, and 2c

The experiments that allowed the definition of the specification for the (*R*)-piperidone **6**, the (*R*)-amine **5**, and 1-acetylpiperazine are reported in this section. These data in combination with the chemical data reported in the following sections allowed the definition of the control strategy for Stages 2a, 2b, and 2c with respect to the drug substance-CQA to be introduced.

4.1. (*R*)-Piperidone 6 and (*R*)-Amine 5. These input materials are considered together as they are both linked with the drug substance-CQA reported in Scheme 2 (casopitant stereoisomers **11**, **14**, **15**, **16**, **17**, **18**, and **19**). Thus, a spiking study by using (*R*)-piperidone mandelate salt **7** [contaminated with 2% a/a of (*S*)-piperidone **13**], and (*R*)-amine **5** [contaminated with 0.9% a/a of the (*S*)-amine **12**] was carried out. The final casopitant mesylate was within specification as shown in Table 3.

Table 3. **Spiking experiment for the definition of the specification limits for 5 and 6**

impurity	level of impurity (% a/a)	level of drug substance-CQA in the drug substance (% w/w)[a]		specification limit of drug substance-CQA in the drug substance (% w/w)
(*S*)-piperidone **13** in (*R*)-piperidone salt **7**	2	**16** and **18**	0.25	NGT[b] 0.4
		17 and **19**	<0.05	NGT 0.1
(*S*)-amine **12** in (*R*)-amine **5**	0.9	**11** and **15**	0.14	NGT 0.6
		14	<0.05	NGT 0.15

[a] Casopitant stereoisomers **16** and **18**, **17** and **19**, and **11** and **15** are reported together as the analytical method was not chiral. **14** is the casopitant enantiomer, and a dedicated chiral method was used for its detection. [b] NGT = Not Greater Than.

In addition, the process research studies carried out in the initial phase of the development made it possible to clarify the following points:

- Epimerisation of the stereogenic centre coming from the (*R*)-amine **5** and its derivatives (piperidone-urea **3**, carbamoyl chloride **4** and casopitant **2**) do not occur in the process conditions so, no QCPPs/QPPs are linked to the level of (*S*)-amine **12** in (*R*)-amine **5** and derivatives.
- Epimerisation of the stereogenic centre coming from (*R*)-piperidone **6** does not occur in:
  - (*R*)-piperidone **6** itself in ethyl acetate in presence of triethylamine in Stage 2b

Table 4. **Spiking of piperazine, 1-propanoylpiperazine and *N*-(2-aminoethyl)acetamide in 1-acetylpiperazine**

impurity in 1-acetylpiperazine	level of impurity in 1-acetylpiperazine (% a/a)	drug substance-CQA affected	level of drug substance-CQA in the drug substance (% w/w)	specification limit of drug substance-CQA in the drug substance (% w/w)
piperazine	0.29	**20**	<0.05	0.3
1-propanoylpiperazine	0.44	**21**	0.33	0.15
N-(2-aminoethyl)acetamide	0.5	**22**	0.34	0.15

- piperidone-urea **3** under Stage 2b or 2c conditions
- casopitant **2** under Stage 2c conditions

- Epimerisation has been seen in (*R*)-piperidone **6**, and it is due to thermal or acidic instability of the molecule as a consequence of a retro-Michael/Michael mechanism (see Scheme 5). The epimerisation of the (*R*)-piperidone **6** is further discussed in section 5.

These data from process research studies and the spiking experiments reported in Table 3 allowed setting the appropriate specifications for the two input materials considered above. In particular, limits of 1.5% a/a (*S*)-piperidone **13** in (*R*)-piperidone mandelate salt **7** and 0.7% a/a (*S*)-amine **12** in (*R*)-amine **5** have been set. The limits set on these compounds represent an element of control over the control strategy.

4.2. 1-Acetylpiperazine. The contaminants of 1-acetylpiperazine are described in section 3.2; considering these impurities and the conditions of Stage 2c, the only approach to ensure their control was to set appropriate limits of piperazine, 1-propanoylpiperazine, and *N*-(2-aminoethyl)acetamide in 1-acetylpiperazine.

Spiking experiments have been performed to define the level of each of these impurities that can be tolerated by the process, and the results are shown in Table 4. It is worth noting that the level of these drug substance-CQAs was detected on casopitant mesylate after Stage 2d. As Stage 2d and its control strategy will be the subject of a separate discussion, only the general procedure is reported in this paper (see the Experimental Section).

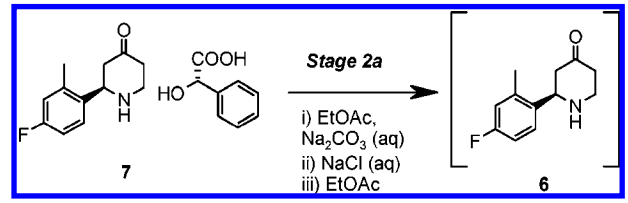
On the basis of the data presented in Table 4, and the specification limits of the corresponding drug substance-CQAs, the following limits of piperazine, 1-propanoylpiperazine, and *N*-(2-aminoethyl)acetamide in 1-acetylpiperazine specification are proposed:

- 0.3% a/a of piperazine in 1-acetylpiperazine.
- There is approximately a 1:1 ratio between the level of 1-propanoylpiperazine in 1-acetylpiperazine and the level of **21** in drug substance. Therefore, a limit of 0.10% a/a of 1-propanoylpiperazine in 1-acetylpiperazine specification is proposed.
- There is approximately a 1:1 ratio between the level of *N*-(2-aminoethyl)acetamide in 1-acetylpiperazine and the level of **22** in drug substance. Therefore, a limit of 0.15% a/a of *N*-(2-aminoethyl)acetamide in the 1-acetylpiperazine specification is proposed.

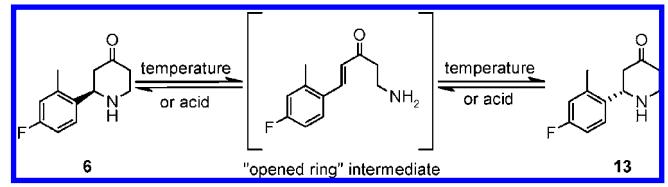
5. Process Studies and Control Strategy for Stage 2a

This process step consists of the free basing of the Stage 1 product, this is carried out by adding a solution of sodium carbonate to a suspension of the (*R*)-piperidone mandelate salt **7** in ethyl acetate. Sodium carbonate was selected over sodium bicarbonate for its higher water solubility (to allow more concentrated solutions) and ethyl acetate was selected as in common with Stages 2b and 2e.

Scheme 4. **(*R*)-piperidone 6 formation**



Scheme 5. **Mechanism of racemisation of (*R*)-piperidone 6**



5.1. Process Understanding Studies. Process studies were carried out to understand the stability of the (*R*)-piperidone **6** during the free basing (Scheme 4) as previous knowledge has highlighted that the stereocentre was not stable chemically and thermally and racemisation could have occurred.

The mechanism of racemisation is proposed in Scheme 5; the "opened ring" intermediate was never isolated due to its transient nature and its reactivity. As stated in the previous paragraph, this would have had an impact on the further steps of the synthesis. In particular, the enantiomer of **6** (compound **13**) could have reacted in downstream chemistry to give the diastereoisomers of casopitant reported in Scheme 2 and Table 1.

An initial risk assessment was carried out, taking into account the available process knowledge and the reaction mechanism proposed. Temperature and volumes of ethyl acetate were identified as potential QCPPs.

These parameters were considered in the context of all the Stage 2a substeps, in particular:

1. (*R*)-Piperidone L-mandelate salt **7** was suspended in ethyl acetate.
2. Aqueous sodium carbonate solution was added, and the mixture was stirred until dissolution was complete.
3. The two phases were separated.
4. The organic phase was washed with aqueous sodium chloride solution or water.
5. The two phases were separated.
6. The organic phase was concentrated under vacuum.

Steps 3−5 were not explicitly studied since the chemistry would not suggest any impact on drug substance-CQAs.

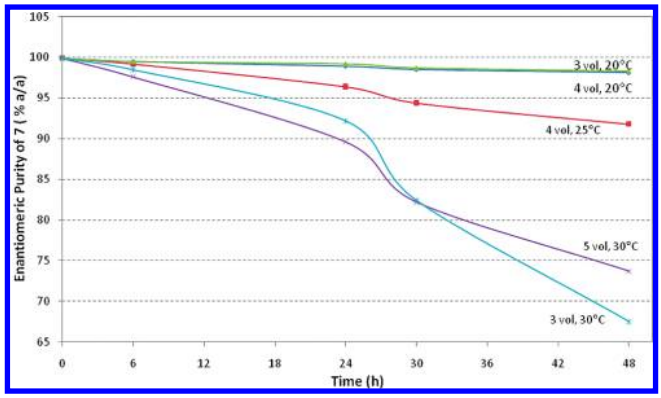


Figure 1. **Enantiomeric purity of (*R*)-piperidone L-mandelate salt 7 in ethyl acetate over time.**

5.1.1. Studies on Substep 1. The impact of temperature and volume of ethyl acetate on the racemisation time course was investigated using a two-level, full factorial experimental design with one centre point, comprising five experiments. The experiments were carried out in the absence of aqueous sodium carbonate solution. The ranges of these parameters studied were from 20 to 30 °C for the temperature and 3 to 5 for the volumes of ethyl acetate.

Data were collected for 48 h. The degree of racemisation was determined by monitoring the enantiomeric purity of the (*R*)-piperidone L-mandelate salt **7** over time. The data are graphically presented in Figure 1.

The rate of racemisation of (*R*)-piperidone L-mandelate salt **7** in ethyl acetate at 20 °C is very low, as can be seen by the small extent of racemisation over 48 h, and furthermore is independent of dilution (volume of ethyl acetate). At 25 °C and 4 volumes, there is an increased rate of racemisation, but (*R*)-piperidone L-mandelate salt **7** has acceptable stability for at least 6 h, based on the moderate extent of racemisation at this time point (the amount of **13** only increased by 0.4% a/a after 5 h at this temperature). At 30 °C there is a further increase in the rate of racemisation, resulting in an unacceptable level of (*S*)-piperidone **13** at the 6-h time point.

The PAR for temperature of the suspension of (*R*)-piperidone L-mandelate salt **7** in ethyl acetate was accordingly set at no more than (NMT) 25 °C. Note that on a full manufacturing scale, aqueous sodium carbonate solution is added within a few hours, well within the time limit for stability. Once the sodium carbonate solution has been added, (*R*)-piperidone **6** is stable in ethyl acetate, giving a very wide margin of control in manufacture. The PAR for the temperature is summarised in Table 5.

5.1.2. Studies on Substep 2. Substep 2 was studied by following the same approach used for Substeps 1 and 6 (see sections 5.1.1 and 5.1.3, respectively). Initial risk assessment identified temperature and ethyl acetate volumes as potential QCPPs; some studies have been carried out (by using the same ranges used for substep 1), and it was confirmed that the (*R*)-piperidone **6** was stable after basic wash. The knowledge from these experiments, the additional knowledge gained in the production plant, and performance of representative batches produced on scale were then used in a failure mode and effects analysis (FMEA) risk assessment, and the result of the assessment showed that these parameters had no impact on drug substance-CQA. Thus, these parameters were neither QPPs nor QCPPs, and they were not considered in the definition of the control strategy.

Table 5. **Potential QCPPs and PARs for Stage 2a**

potential QCPP	PAR	target value
intermediate **7** suspension temperature	NMT[a] 25 °C	20 °C
intermediate **6** distillation temperature	NMT[a] 25 °C	20 °C
intermediate **6** distillation endpoint volume	NLT[b] 2 vol	2.5 vol

[a] NMT = Not More Than. No impact on quality from use of lower temperature. [b] NLT = Not Less Than. No impact on quality from use of higher volume.

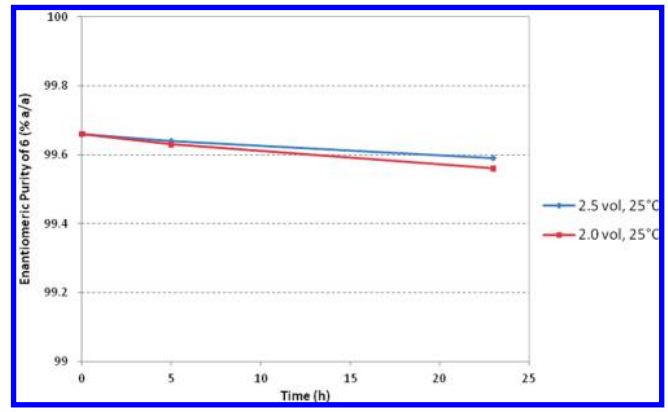


Figure 2. **Enantiomeric purity of (*R*)-piperidone 6 in ethyl acetate.**

5.1.3. Studies on Substep 6. (*R*)-Piperidone **6** solution is subjected to a vacuum distillation to azeotropically remove water prior to the Stage 2b. A two-level, full factorial experimental design with two centre points, comprising six experiments was carried out. For the temperature the range 20−30 °C and for the distillation endpoint, volumes in the range 2−10 were selected. The study showed that the interaction of high distillation temperature and low distillation endpoint volume increases the racemisation of (*R*)-piperidone **6**. In order to define the PARs for these potential QCPPs, the stability of the (*R*)-piperidone **6** was monitored at 2.5 and 2.0 volumes at 25 °C for 23 h. These values were investigated to achieve a minimum final volume, to maximise the reactor capacity for the subsequent Stage 2b. Data are graphically presented in Figure 2.

These results show that (*R*)-piperidone **6** is acceptably stable to racemisation for up to 23 h at 25 °C at 2.0 volumes. The PARs for the distillation temperature and distillation end point volume are summarised in Table 5.

5.2. PARs Determination. Table 5 summarises the PARs for the potential QCPPs for Stage 2a, along with the proposed target values. These PARs were further demonstrated in stressed, verification experiments as explained in section 5.3.

Running Stage 2a within the PARs of the potential QCPPs listed above is required to ensure that the levels of the drug substance-CQAs **14**, **15**, **16**, **17**, **18**, and **19** (see Scheme 2 and Table 1) will meet the specification criteria for casopitant mesylate.

5.3. Verification of the PARs. *5.3.1. Details on the Equipment.* The PARs listed in section 5.2 were defined on small-scale laboratory equipment.

In order to confirm that these PARs are applicable to reactions at scale, and unless otherwise specified, verification studies were performed using extremes of the Design Space in 2-L-scale equipment configured to mimic full-scale plant equipment. This was achieved through maintaining geometric similarity and operating under conditions scaled according to accepted chemical engineering principles, e.g., using the constant power-per-unit volume (*P*/*V*) principle for scaling agitation speed.

In addition, parameters that were previously investigated using a univariate approach were introduced in this study to ensure any interaction with other process parameters was identified.

5.3.2. Details on the Experiments. The verification experiments were done by carrying out two experiments. The parameter settings that were selected can be defined as "mild" or "forcing", depending on the impact expected on the drug substance-CQAs.

The "forcing" conditions were identified as those combinations of extremes of the PARs which, on the basis of knowledge of the process, would have a higher impact on drug substance-CQAs (high temperature and low volumes), whereas the "mild" conditions represent the other extreme of the PARs (low temperature and high volumes). These conditions were used to ensure that there was no failure of the drug substance quality at these extremes.

Casopitant mesylate derived from these experiments met the specifications, confirming that the PARs selected were appropriate.

5.4. Summary of the PARs and Criticality Assignment of Potential QCPPs Identified in Stage 2a. The Design Space knowledge derived from sections 5.1 and 5.3, the intended operating ranges in the production plant, knowledge gained from process models established in the laboratory, and performance of representative batches produced on scale were then used in a FMEA risk assessment to identify failure modes within the process that may lead to drug substance-CQAs failure.

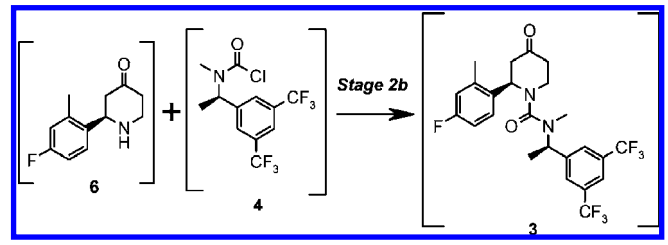
The outcome of this risk assessment was that all the parameters summarised in section 5.2 had very low risks of failing drug substance-CQAs, and therefore, no QCPPs are identified within the process; only QPPs remain. Accordingly, the current PARs for all the QPPs, as well as their target values and the drug substance-CQAs linked with the parameter, are summarised in section 5.2.

6. Process Studies for Stage 2b

In Stage 2b (*R*)-piperidone **6** was reacted with carbamoyl chloride **4** to give the piperidone-urea **3** (Scheme 6). The preparation of the carbamoyl chloride **4** is carried out in Stage 2e, the detailed discussion of which is reported in a previous paper.[4] It is worth noting that no QCPPs/QPPs have been identified for Stage 2e.

On the basis of the experimental conditions defined for the preparation of the carbamoyl chloride **4**, ethyl acetate and triethylamine were also selected as a starting point to perform Stage 2b. An excess of base was required to avoid the degradation of the piperazine-urea **3** to the unsaturated ketone **23**, occurring in strong acidic conditions as shown in Scheme 7. This excess of base also avoids epimerisation of the (*R*)-piperidone **6** as demonstrated by stability studies.

Scheme 6. **Piperidone-urea 3 formation**



Scheme 7. **Piperidone-urea 3 decomposition**

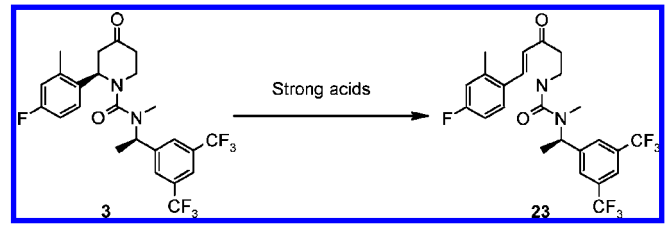


Table 6. **Potential QCPPs and ranges for Stage 2b**

parameter	range
concentration of **6** in ethyl acetate	from 4.5 to 5.5 vol
quantity of TEA	from 2.3 to 2.7 equiv[a]
quantity of carbamoyl chloride **4**	from 1.0 to 1.2 equiv[a]
temperature	from 75 to 85 °C (reflux temperature)

[a] The equivalents are calculated with respect to (*R*)-piperidone **6**.

An initial risk assessment was carried out, taking into account the available process knowledge and the reaction mechanism proposed. The following process parameters were identified as potential QCPPs, and some DOE studies were carried out to understand the impact of these potential QCPPs on drug substance-CQAs. Available knowledge allowed also the identification of the appropriate ranges for these studies. Table 6 summarises the potential QCPPs identified and the ranges used in the DOE studies.

The reactions were performed using an automated platform and gave yields between 82 and 99%. Analysis of the data coming from the DoE showed that the only factor affecting the yield was the quantity of carbamoyl chloride **4**, whereas the other factors did not affect this response. As can be seen in Figure 3, a higher quantity of chloride gave higher yields, and no curvature was observed; thus, 1.2 equiv of carbamoyl chloride **4** was selected. Regarding the other parameters, the centre point of the ranges studied was selected for the manufacturing process.

The Design Space knowledge derived from these studies, the additional knowledge gained in the production plant, knowledge gained from process models established in the laboratory, and performance of representative batches produced on scale were then used in a FMEA risk assessment, and the result of the assessment showed that these parameters had no impact on drug substance-CQA; thus, these parameters were

(4) Guercio, G.; Bacchi, S.; Perboni, A.; Leroi, C.; Bientinesi, I.; Hourdin, M.; Goodyear, M.; Curti, S.; Provera, S.; Cimarosti, Z. *Org. Process Res. Dev.* **2009**, *13*, 1100–1110.

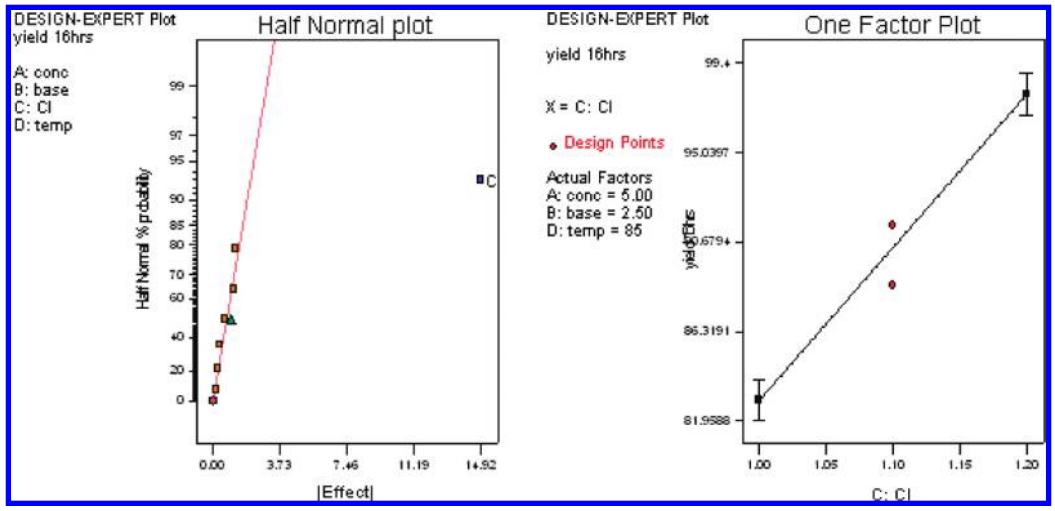


Figure 3. **Result of the DOE study for Stage 2b.**

neither QPPs nor QCPPs, and they were not considered in the definition of the control strategy.

7. Process Studies for Stage 2c

7.1. Initial Process Understanding Studies. Stage 2c is a reductive amination reaction where the piperidone-urea **3** reacts with 1-acetylpiperazine in the presence of a reducing system. The reductive amination reaction promoted by hydride reagents was selected over alternative approaches. Catalytic hydrogenation (Pt, Pd, Ni), catalytic transfer hydrogenation (with different hydrogen donor species), and attempts to form intermediates prone to reduction (formation of enamines and use of titanium derivatives) failed, giving low yields, high amounts of side products, or poor selectivity.

Having selected the reduction approach, the major hurdle to be overcome with this reaction was not only to achieve a good yield but also to have the highest selectivity, as the casopitant isomer **11** can also be formed as shown in Scheme 8, where a summary of the main side products is reported.

Many alternative reducing systems were tried in different solvents, and a summary of them is reported in Table 7.

Strong reducing systems (entries 1, 2, and 3) caused the formation of the alcohols **24** as the main product; this can be explained by considering that 1-acetylpiperazine is both poor nucleophile and weak base. This slows the initial nucleophilic attack on the carbonyl carbon and leads to slower overall reaction rates favoring the main side reaction which is the direct reduction of the carbonyl group to give the mixture of alcohols **24**. A solution to this problem was found by using less reactive hydrides that could minimise the extent of the carbonyl reduction (entry 4). Unfortunately, the use of $NaBH(OAc)_3$ did

Scheme 8. **Stage 2c: product and side products**

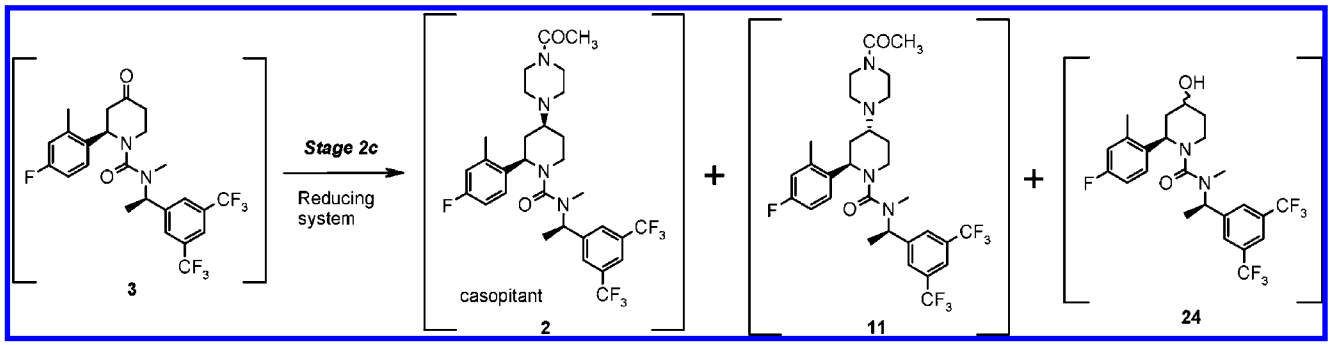


Table 7. **Reducing systems tried for Stage 2c**

entry	reducing system	solvent	**2** (% a/a)[a]	**2**/**11** ratio	alcohol **24** (% a/a)[b]	residual **3** (% a/a)[a]
1	$LiBH_4$	acetonitrile	–	–	100	–
2	$NaBH_4$	acetonitrile	–	–	80	20
3	L-Selectride	acetonitrile	–	–	50	50
4	$NaBH(OAc)_3$	acetonitrile	52	55/45	6.5	0.4
5	$NaBH_4$/HCOOH (1/3)	acetonitrile	58	71/29	18	0.3
6	$NaBH_4/CH_3COOH$ (1/1.75)	acetonitrile	46	77/23	37	4
7	$(CH_3)_4NBH(OAc)_3$	acetonitrile	24	52/48	–	53
8	$NaBH_4$/HCOOH/$Ti(O\text{-}iPr)_4$ (1/3/1)	ethyl acetate	43	73/27	25	15
9	$NaBH_4$/HCOOH/$Ti(O\text{-}iPr)_4$ (1/3/1)	IPA	63	68/32	4	4
10	$NaBH(OAc)_3$/HCOOH	acetonitrile	70	71/29	1	0.08

[a] HPLC walk-up method was used; the assumption that 100% area = area of (**2** + **11** + **24** + **3**) was made. [b] Alcohol **24** is a mixture of *syn*- and *anti*-isomers.

Table 8. **Potential QCPPs after initial risk assessment**

parameter	range[a]
amount of $NaBH(OAc)_3$	from 1.55 to 1.72 equiv
amount of HCOOH	from 5 to 6 equiv
temperature	from 5 to 25 °C
stirring time of the mixture $NaBH(OAc)_3$/formic acid	from 5 to 55 min
amount of 1-acetylpiperazine	from 2 to 2.54 equiv
addition time of the mixture **3**/1-acetylpiperazine	from 5 to 55 min

[a] The range of equivalents reported is related to piperidone-urea **3**. The amounts reported in the experimental procedure are calculated on the (*R*)-piperidone mandelate salt **7**, assuming a yield of 85% mol for Stage 2b.

not solve the selectivity problem (approx 1/1 diastereoisomeric ratio between **2** and **11** was observed).

Significant improvements were made when a modification of the boron substituent of the reducing system was introduced. During the studies to find the best reducing system, it was noted that the steric hindrance of the reducing system could have played a role in the definition of the stereoselectivity of this reaction. In particular, it was observed that the reduction by using $NaBH_4$ gave predominantly the *syn*-alcohol (80 to 20 with respect to the *anti*-alcohol) while the use of L-Selectride gave predominantly *anti*-alcohol (80 to 20 with respect to the *syn*-alcohol). On the basis of these observations, a series of trials was carried out by using systems with different steric hindrance; the results are reported in Table 7 (entries 4−10). The best results in terms of selectivity and yield were obtained with the systems $NaBH_4$/HCOOH (entry 5), $NaBH_4$/HCOOH/$Ti(OiPr)_4$ (entry 9), and $NaBH(OAc)_3$/HCOOH (entry 10). The latter was selected as the yield was higher (less alcohol formation), and the handling in view of plant scale-up was better (less hydrogen evolution during its preparation).

7.2. Initial Risk Assessment and DOE Studies. An initial risk assessment was carried out, keeping into account the available process knowledge and the reaction mechanism proposed. The following process parameters were identified as potential QCPPs, and some DOE studies were carried out to understand the impact of these potential QCPPs versus drug substance-CQAs. Available knowledge allowed the identification of the appropriate ranges for these parameters. Table 8 summarises the potential QCPPs identified and the ranges used in the DOE studies.

A 2 Level Factorial design (1/8 Fractional) with two centre points and 10 reactions was used to study the reaction; the responses collected were the yield and the **2**/**11** ratio.

Analysis of the obtained data showed that the centre point of the ranges selected (1.61 equiv of $NaBH(OAc)_3$, 5.5 equiv of formic acid, 2.27 equiv of 1-acetylpiperazine and 15 °C) gave the best yield and showed an acceptable robustness after reaction completion, as can be seen in Figure 4. These values were selected for the manufacturing process.

In this DOE study also the **2**/**11** ratio (see Scheme 8) was considered, and the variability seen in these experiments (from 70/30 to 75/25) was not considered significant. Process studies demonstrated that the performance of Stage 2d did not change even when a crude coming from the reduction with $NaBH(OAc)_3$ with ratio **2**/**11** = 55/45 (Table 7, entry 4) was used.

7.3. Final Risk Assessment. The Design Space knowledge derived from these studies, the additional knowledge gained in the production plant, knowledge gained from process models established in the laboratory and performance of representative batches produced on scale were then used in a FMEA risk assessment. The result of the assessment showed that these parameters had no impact on drug substance-CQA; thus, these parameters were neither QPPs nor QCPPs, and they were not considered in the definition of the control strategy.

8. Summary of the Control Strategy for Stages 2a, 2b, and 2c

A summary of the control strategy defined for the drug substance-CQAs discussed in this paper is reported in Table 9.

9. Conclusions

The QbD principles outlined in ICH and other guidances provide a structured approach to gaining process knowledge

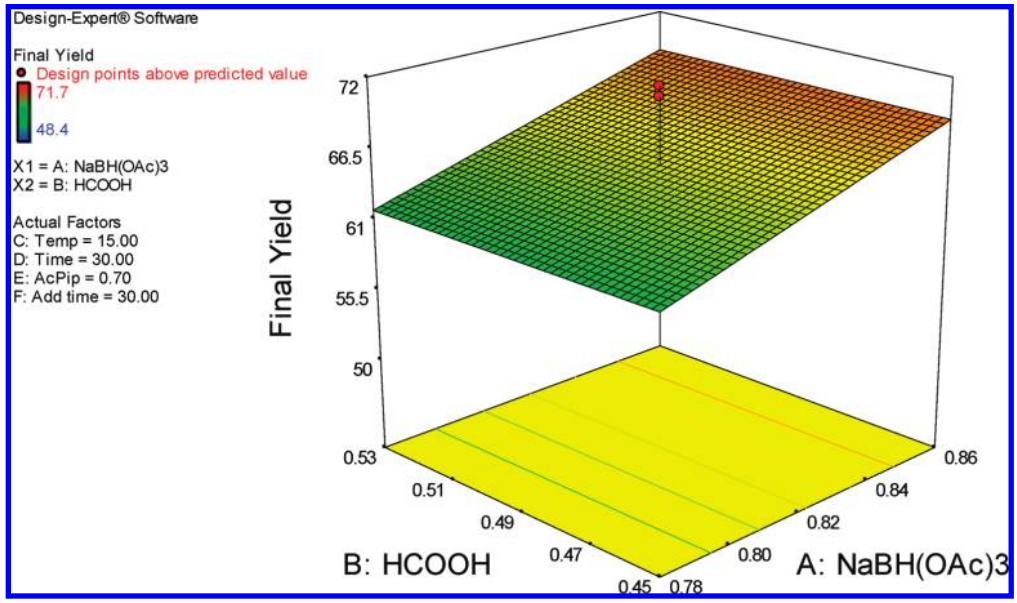


Figure 4. **Result of the DOE study for Stage 2c.**

Table 9. **Summary of the control strategy**

drug substance CQAs	elements of control: starting materials and intermediates specifications	elements of control: quality process parameters	drug substance specification
casopitant stereoisomers **11**[a], **14**, **15**, **16**, **17**, **18**, **19**	(*R*)-piperidone mandelate salt **7**	Stage 2a: **7** suspension temperature	yes
	(*R*)-amine **5**	Stage 2a: **6** distillation temperature Stage 2a: **6** distillation endpoint volume	
azine-related impurities **20**, **21** and **22**	1-acetylpiperazine	none	yes

[a] This stereoisomer is included as monitored with **15** (its enantiomer) in the achiral HPLC method, **11** is controlled in the final crystallisation step.

and developing robust manufacturing control strategies. This has been applied successfully to developing a control strategy for Stages 2a, 2b, and 2c of the casopitant mesylate **1** manufacturing process. On the basis of the process understanding provided, it has been demonstrated that the control of the drug substance-CQAs discussed can be robustly achieved by the elements of control defined above for Stages 2a and 2c.

The process understanding generated and the control strategy proposed could potentially lead to the removal of these drug substance-CQAs from the drug substance specification, undertaking a further step towards the full application of the QbD principles to manufacturing processes.

10. Experimental Section

(2*R*)-2-(4-Fluoro-2-methylphenyl)-4-piperidinone 6. (*R*)-Piridone mandelate salt **7** (1 kg, 2.78 mol) was added to a mixture of Na_2CO_3 [15% w/w solution (4 L)] and EtOAc (4 L). The mixture was stirred until dissolution was complete. The phases were separated, and the organic layer was washed with NaCl [20% w/w solution (4 L)]. EtOAc (4 L) was added, and the organic phase was concentrated to 2.5 L to give a solution of (*R*)-piperidone **6**.

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.51 (dd, 1H), 7.01 (m, 2H), 3.98 (m, 1H), 2.85 (m, 1H), 2.74 (br s, 1H), 2.49 (m, 1H), 2.42 (dd, 1H), 2.31 (s, 3H), 2.28 (m, 1H), 2.20 (m, 1H).

(2*R*)-*N*-{(1*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methyl-4-oxo-1-piperidinecarboxamide 3. Et_3N (0.98 L, 7.03 mol) was added over a solution of carbamoyl chloride **4** (2.5 L, 3.32 mol), and the resulting mixture was added to the solution of (*R*)-piperidone **6**; the line was washed with EtOAc (1 L), and then the mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature, and 1-acetylpiperazine neat (0.2 kg, 1.56 mol) was added, followed by a line wash with EtOAc (0.25 L). The reaction mixture was stirred for 30 min at room temperature; the organic solution was washed with malic acid 28% w/w (3 L), Na_2CO_3 [15% w/w solution (3 L)], and NaCl [20% w/w solution (4 L)]. CH_3CN (4 L) was added, and the solution was concentrated to 2.5 L; then CH_3CN (4 L) was added again, and the solution was concentrated to 3 L to give a solution of piperidone-urea **3** in CH_3CN.

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.98 (s, 1H), 7.78 (s, 2H), 7.25 (dd, 1H), 6.98 (dd, 1H), 6.89 (dt, 1H), 5.25 (dd, 1H), 5.16 (q, 1H), 3.63 (m, 1H), 3.56 (m, 1H), 2.75 (dd, 1H), 2.68 (dd, 1H), 2.57 (s, 3H), 2.53 (m, 1H), 2.46 (dt, 1H), 2.27 (s, 3H), 1.58 (d, 3H). MS: *m*/*z* 505 [MH]+.

(2*R*,4*S*)-4-(4-Acetyl-1-piperazinyl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methyl-1-piperidinecarboxamide (Casopitant 2). HCOOH (0.49 L, 13 mol) was added to a cooled suspension of $NaBH(OAc)_3$ (0.82 kg, 3.87 mol) in CH_3CN (4 L), keeping the internal temperature between 10−15 °C; then the lines were washed with more CH_3CN (1 L), and the mixture was stirred for 40 min.

1-Acetylpiperazine (0.7 kg, 5.46 mol) was added neat over the solution of piperidone-urea **3**, and the mixture was diluted with CH_3CN (3 L). The resulting mixture was added over the previous suspension; fresh CH_3CN (4 L) was used to wash the line. The reaction mixture was stirred at 15 °C for 12 h. The solvent was evaporated under reduced pressure to 4 L.

The resulting suspension was diluted with fresh EtOAc (4 L), and then washed with ammonia [21% w/w solution (4 L, ∼11.25 M in NH_3)], Na_2CO_3 [15% w/w solution (4 L)]. More EtOAc (4 L) was added, and the organic layer was washed with water (4 L). The organic phase was then concentrated to 2.5 L; again fresh EtOAc (4 L) was added, and the solution was concentrated to 2.5 L to give a solution of casopitant **2**.

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.68 (s, 2H), 7.18 (dd, 1H), 6.90 (dd, 1H), 6.76 (td, 1H), 5.33 (q, 1H), 4.14 (dd, 1H), 3.38 (m, 5H), 2.71 (s, 3H), 2.72 (m, 1H), 2.54 (m, 1H), 2.47 (m, 2H), 2.41 (m, 2H), 2.34 (s, 3H), 1.95 (s, 3H), 1.85 (m, 1H), 1.77 (m, 1H), 1.62 (dq, 1H), 1.47 (d, 3H), 1.40 (q, 1H).

(2*R*,4*S*)-4-(4-Acetyl-1-piperazinyl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methyl-1-piperidinecarboxamide Methanesulfonate Salt (Casopitant Mesylate 1). The solution of casopitant **2** was then diluted with EtOAc (overall solution of **2** in EtOAc was 4 L) and acetone (4.5 L) and was heated to the required temperature (from 39 °C). Then, neat methanesulfonic acid (0.12 L, 1.64 mol) was added, followed by a slurry of **2** (0.005 kg) in EtOAc (0.05 L) as seed. The obtained suspension was stirred for 1 h. Then, isooctane (3 L) was added in the required time (1 h), and the slurry was cooled to 20 °C in 2 h and aged 3 h.

The suspension was filtered, and the solid was washed with EtOAc (3 × 4 L). The white solid was dried overnight under vacuum at 40 °C to give the desired casopitant mesylate **1** (0.94 kg, yield 48% mol with respect to **7**).

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.57 (br s, 1H), 7.99 (br s, 1H), 7.68 (br s, 2H), 7.23 (m, 1H), 6.95 (dd, 1H), 6.82 (m, 1H), 5.31 (q, 1H), 4.45 (m, 1H), 4.20 (dd, 1H), 3.99 (m, 1H), 3.56 (m, 1H), 3.47 (m, 3H), 3.37 (m, 1H), 3.15 (m, 1H), 2.96 (m, 1H), 2.87 (m, 1H), 2.80 (t, 1H), 2.74 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H), 2.13 (m, 1H), 2.08 (m, 1H), 2.10 (s, 3H), 1.87 (m, 1H), 1.73 (m, 1H), 1.46 (d, 3H). MS: *m*/*z* 617 [MH]+, as free base.

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Glossary

Drug Product Critical Quality Attributes or Drug Substance Critical Quality Attributes measurable properties of drug product or API that are critical to ensuring patient safety and efficacy. The property must be within a predetermined range to ensure product quality. A property which is measured outside the range indicates a batch failure.

Critical Quality Attributes in the unit operation or stage inputs, stage outputs, device, etc. measurable properties of inputs and outputs that (as determined by Risk Assessment) present a **high risk** to the process falling outside the design space or proven acceptable ranges.

Quality Attribute in the unit operation or stage inputs, stage outputs, device, etc. measurable property of inputs and outputs that (as determined by Risk Assessment) present a low risk to the process falling outside the Design Space or proven acceptable ranges.

Quality Critical Process Parameter process parameter that influences a Critical Quality Attribute and (as determined by Risk Assessment) presents a high risk to the process falling outside the Design Space or proven acceptable ranges.

Quality Process Parameter process parameter that influences a Critical Quality Attribute but (following a Risk Assessment) presents a low risk of the process falling outside the Design Space or proven acceptable ranges.

Control Strategy a (planned) set of controls, derived from (current) product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10 definition: words in parentheses are felt unnecessary.)

Proven Acceptable Range (PAR): upper and/or lower limits for process parameter or attribute values between which the parameter or attribute is known to produce a process output (e.g. intermediate, API or DP) that meets the CQAs. The PAR may or may not represent the point of failure. The PAR for a given process parameter or attribute may be dependent upon the PAR values for one or more other process parameters or attributes (e.g. multivariate).

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