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RESEARCH ARTICLE

Dose Selection for Clinical Development in the Treatment of Hypertension: The Aprocitentan Case and Lessons from the Past

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ABSTRACT

Dose selection plays a critical role in the clinical development of a drug. This current review highlights the lessons learned from previous dose finding studies (DFSs) of antihypertensive drugs and from the recent example of aprocitentan, a novel endothelin receptor antagonist for the treatment of resistant hypertension. Based on these, the authors provide 10 key recommendations for an efficient DFS for a new antihypertensive medication. These recommendations respect critical comments repeatedly made by the U.S. Food and Drug Administration (FDA) Division of Cardiology and Nephrology over the last 5 decades and go beyond the more limited recommendations made in the 2016 Committee for Medicinal Products for Human Use (CHMP) guideline on the development of new antihypertensive medications. The added value of a dose-response modelling approach enriches prior regulatory advice on DFSs.

Introduction

The dose selection for a new chemical entity is a pivotal aspect of its clinical development, as highlighted by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E4 guidance and discussed in a large European Medicines Agency (EMA)/ European Federation of Pharmaceutical Industries and Associations (EFPIA) workshop.[1,2] It requires the characterisation of the shape and location of the dose-efficacy relationship, the identification of the smallest dose that provides a discernible benefit and the highest dose beyond which no significant further benefit is observed, as well as consideration for the safety dose response and the individual variability of the response.[3] Phase 2 dose-response studies are central in the dose selection process. However, historically, this critical part of drug development has often been abbreviated and flawed, and still today continues sometimes to be insufficiently robust. According to a retrospective review of FDA documents from 2000 to 2012, the most frequent reason for the delay or even rejection of a new drug approval was 'uncertainties related to the selected dose', in 16% of applications, ahead of 'study end points failing to adequately reflect a clinically meaningful effect', reported in 13% of cases.[4] Moreover, dosage change requested by regulatory authorities after initial approval is not infrequent.[5]

Deficiencies in dose selection apply to almost all therapeutic domains and/or indications. However, they are particularly damning in the field of hypertension, in which simple rules were derived from past clinical development experiences. Dose selection for an antihypertensive therapy seems a straightforward exercise as the main endpoint of phase 3 studies, i.e., change in blood pressure (BP), is an accepted surrogate in predicting morbidity and mortality outcomes.[6,7] BP is a continuous variable, easy to measure and reversible, which makes it also an effective endpoint in Phase 2 dose finding studies (DFSs). Yet, many deficiencies in DFSs have been reported since the 1960's during the development of antihypertensive compounds.

These deficiencies, which entailed delays in clinical development and detrimental impacts on the overall cost of development, were reviewed, discussed, and criticised at the 08 October 1991 FDA Cardio Renal Advisory Committee meeting prepared by the Cardio-Renal Division Director, Raymond Lipicky. Based on a collaborative data sharing effort between the FDA and 15-20 drug companies, the cost of DFSs for 13 antihypertensive drug therapies (9 angiotensin converting enzyme inhibitors [ACEIs] and 4 non ACEIs) was estimated at 1.8 billion US dollars, equivalent to 4.1 billion USD in 2023, whereas it could have been much lower with a more efficient dose finding approach.

More important than the financial aspect, these deficiencies led to inadequate dose selection; even if the subsequent Phase 3 studies were positive, the non-optimal dose selection resulted in detrimental medical consequences and often in a need to adjust the recommended dose.

The aim of this review is to take the reader through the evolution of DFSs in antihypertensive drugs while highlighting the availability of more recent analytical approaches such as the Multiple Comparison Procedure – Modelling (MCP-Mod). The authors also provide 10 recommendations based on their collective experiences, lessons learned from the past, and from the recent example of aprocitentan, a new dual endothelin receptor antagonist [ERA][8] on how to design an effective DFS for a new antihypertensive drug.

Lessons learned from the past

Thiazides and ACEIs, which remain two of the main antihypertensive classes today, provide landmark historical cases of an inadequate dose selection biased towards higher doses.

Higher doses used in clinical practice versus those observed in DFSs

Thiazide type diuretics such as chlorthalidone have been prescribed for two decades (1960-1982) at daily doses of up to 100 mg, exceeding the dose(s) identified in well-designed DFSs. In these studies, the effect of fixed doses of chlorthalidone (12.5 mg to 75 mg in one study and 25 mg to 200 mg in the other study) were investigated on BP [between patients][9] and on biochemical (e.g., potassium, chloride, uric acid) parameters [within patients].[10] The studies concluded that, balancing efficacy and safety, doses of 25 or 50 mg would be adequate. Subsequently, the Multiple Risk Factor Intervention Trial (MRFIT) performed in 12,866 men at high risk of death from coronary heart disease (CHD), followed for 7 years, compared patients receiving special intervention defined as stepped-care treatment for hypertension (including thiazides or thiazide-like diuretics), counselling for cigarette smoking, and dietary advice for lowering blood cholesterol to patients with usual care. Despite improvement of these well-known risk factors, only a statistically nonsignificant difference of 7.1% (90% confidence interval, -15% to 25%) on mortality from CHD was observed in the special intervention group. This surprising outcome suggested a possible unfavourable response to

antihypertensive drug therapy in certain but not all hypertensive patients.[11] It took an additional decade to confirm the relationship between high dose diuretic therapy (25-100 mg of thiazide) and primary cardiac arrest [12] due to hypokalaemia, a fact that had been overlooked. Labelling of chlorthalidone today recommends a low starting dose of 15 mg with a possible increase to a maximum daily dose of 50 mg.

This example illustrates the value of well-designed DFSs and the importance of aligning medical practice to the dose identified in these studies.

Inappropriate approach for dose selection

The captopril case in the 1980's is an example of an inappropriate DFS design. The doses were selected based on an up-titration scheme, i.e., incremental dose according to BP response. This approach is unsuitable for dose determination, because of i) subgroups of patient who are less responsive (thus pushing the dose to higher levels), ii) time effects triggering BP decrease during the trial, iii) carry over effect from one step to the next, and iv) lack of independence of the effect observed at each incremental dose. The up-titration scheme of captopril led to the selection of a daily dose of up to 1000 mg[13], triggering severe adverse events including granulopenia that did not occur at lower dosages.[14] This severe adverse event challenged the breakthrough of this new pharmacological class. Captopril was subsequently approved at lower daily doses of 75 mg in three divided doses (t.i.d.) with weekly increases to daily doses of 150, 300, and 450 mg without diuretics. When the synergism with diuretics was later observed, the highest doses of captopril (300 and 450 mg/day) were rarely used for adequate pressure control as a third-line therapy, with safety warnings.[14] Several years later, a new, well-designed, double-blind, placebo-controlled DFS with fixed-dose treatment for 14 weeks concluded that the optimal dose range of captopril was 12.5 to 50 mg t.i.d, a range which was then selected for the treatment of mild to moderate hypertension without the previously observed safety issues.[15]

Multiple studies needed to define the dose response relationship

Losartan, the first angiotensin receptor blocker (ARB), was identified in 1989 and its dose determination was based on 3 separate studies. The pivotal DFS, adequately designed with a placebo, an active control, and 5 losartan arms (10-150 mg), was preceded by 2 other studies, one over 5 treatment days covering a range of 10-150 mg and a second study lasting 4 weeks with different regimens (o.d. vs b.i.d.)[16] . The combined analysis of the two preliminary studies could not provide a clear dose selection as their initial goals were not truly dose determination. However, these two studies were useful enablers as they provided proof of concept and determination of frequency of dosing, respectively, and thereby informed the design of the definitive DFS.

For aliskiren, the last new antihypertensive drug approved worldwide in 2008, several placebo control studies were performed to investigate a wide dose range under monotherapy (i.e., 75, 150, 300 and 600 mg o.d.). However, none of these studies investigated the full dose range. In each study, a narrower dose range was investigated: two studies focused on lower doses (i.e., 75-300 mg) and two others on higher dosages (i.e., 150-600 mg). There was no linear trend from 75 to 600mg across any of these four studies. Taking collectivelly the results of the studies into account, only the doses of 150 and 300 mg were considered and selected for further development.[17] A well-designed study exploring the full dose range would have been a more cost- and time-efficient approach.

Recent example: the aprocitentan phase 2 study

Aprocitentan is a new, oral, dual endothelin receptor antagonist [ERA] that blocks both ETA and ETB receptors and is currently in development in hypertension[8]. Its preclinical pharmacological characterisation demonstrated its potential for once-a-day dosing and suitable activity in models mimicking resistant hypertension (e.g., low renin models, combination with other antihypertensive drugs).[18]

A) Preclinical stage: characterisation of aprocitentan's pharmacological profile

The pharmacology of aprocitentan was characterized in preclinical models of hypertension via telemetry. Use of telemetry in conscious animals allows researchers to comprehensively analyse the hemodynamic activity of BP lowering drugs in hypertensive animals, such as, investigation of acute vs chronic dosing, effect on heart rate, pharmacokinetic/ pharmacodynamic (PK/PD) relationship, and the phenomenon of desensitisation following repeated administration. The construction of dose-response curves is a key element to analyse the pharmacology of new drug candidates. The range of doses of aprocitentan that impacted BP was relatively wide, i.e., a factor of 1000. When comparing the profile of the dose-response curve of aprocitentan with that of other pharmacological classes, it was identified that aprocitentan behaved like ACEI or ARB, i.e., had a 'shallow' profile (Figure

1, left), in contrast to the steeper profile of calcium channel blockers (Figure 1, right). Such data suggest that, while calcium channel blockers present a narrow dose-response curve of efficacy, a broad range of doses needs to be tested to investigate the hemodynamic activity of an ERA like aprocitentan.

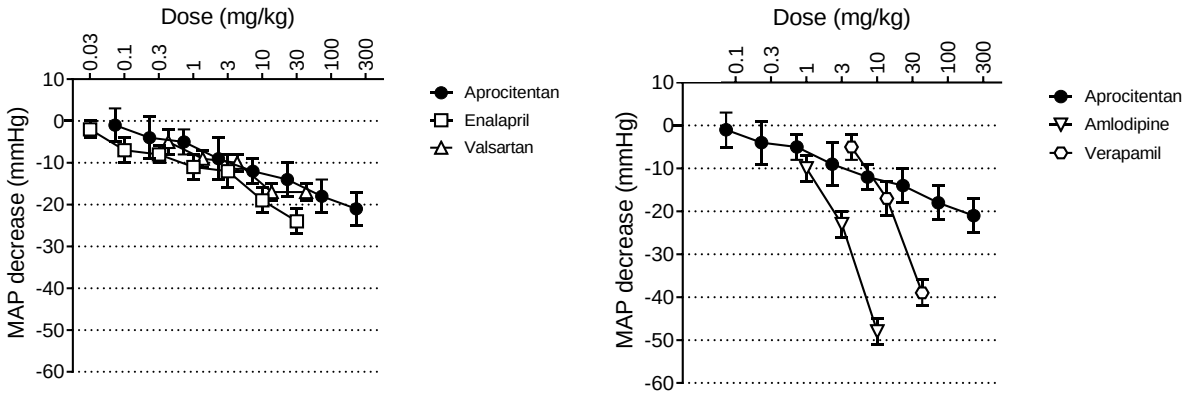

Figure 1. Dose-response relationship on maximal mean arterial blood pressure (MAP) decreases after single oral administration of antihypertensive drugs in conscious spontaneously hypertensive rats (SHR) equipped with telemetry. Data are presented as mean +/- S.E.M. (n=4-8/group). Unpublished data.

B) Clinical stage: aprocitentan dose finding study in hypertensive patients

Prior to initiating the DFS, some prerequisites must be obtained during the phase 1 in heathy subjects. For aprocitentan, a single ascending dose, placebo-controlled study investigated doses up to 600 mg. This initial study was followed by a multiple dose escalation study up to 100 mg daily for 10 days. A signal of body weight increase due to expected fluid retention was detected in elderly subjects. Based on these results, the 50 mg dose was selected as the highest dose for further investigation in hypertensive patients. In addition, these studies showed that aprocitentan has a long half-life of 46 hours a PK profile suitable for o.d. regimen and that it can be administered irrespectively of food intake.

DESIGN OF PHASE 2 STUDY

The DFS with aprocitentan was intended to estimate the minimum effective dose as well as the highest dose beyond which no further lowering of BP would be expected. The study explored the dose-response of aprocitentan as monotherapy across a wide range of doses in patients with hypertension and was conducted between December 2015 and December 2016. Results of this trial have been published previously.[19]

To investigate aprocitentan as monotherapy, patients with grade 1 or 2 essential hypertension, with or without antihypertensive treatment(s) were recruited; those treated with antihypertensive medication(s) entered a 4 to 6-week placebo run-in (RI) period to wash out their antihypertensive medication(s). Patients with a mean sitting diastolic BP (SiDBP) ≥90 and <110 mm Hg as recorded by an unattended automatic office BP device (uAOBP), under placebo run-in treatment condition, were randomized.

The multicentre, placebo-controlled, double-blind, double-dummy study of 8 weeks included placebo, 4 fixed doses of aprocitentan (5, 10, 25 and 50 mg once daily) and an active reference group treated with lisinopril. The latter group was used as an 'internal control' but was not included in the dose-response analysis of aprocitentan (Figure 2).

Figure 2. Phase 2 study design in essential hypertension

The primary endpoint was the change from baseline to week 8 in mean trough SiDBP measured by uAOBP, and the secondary endpoint was similarly based on SiSBP. Additionaly, 24-h ambulatory (out-office) BP measurments were collected.

The primary and secondary endpoints were first analysed using an Analysis of Covariance with a factor for treatment group and a covariate for baseline SiDBP (or SiSBP). The Least Squares Mean (LSMean) changes for each dose group were then analysed using an MCP-Mod approach,[20] which consists of two steps:

1. MCP-step: test for the presence of a dose-response signal using multiple candidate models, to be specified before having seen the data. In the aprocitentan DFS, six models were prespecified: linear, linear in log dose, Emax, sigmoidal Emax, logistic, and quadratic. The first five models assume a monotone dose-response relationship, whereas the quadratic model captures non-monotonicity. The models also differed in complexity, the linear and linear in log models simply having an intercept and slope (2 parameters), whereas the Emax and quadratic (3 parameters) and sigmoidal Emax and logistic (4 parameters) are more complex.
2. Mod-step: if a dose-response is detected in the MCP-step, then each of the prespecified models is fitted to the data. The best fitting model (based on the AIC, Akaike's Information Criterion) will be the main model for determining the dose, with the other models providing supportive information.

An early application of MCP-Mod (although not yet by that name) in dose-finding in hypertension was given by Calhoun and colleagues.[21] The MCP-Mod approach has since been recognized as an efficient statistical methodology for DFSs by regulatory agencies[22,23] and has been implemented in the R-package DoseFinding.[24]

In the aprocitentan DFS, the main analysis was performed on the per protocol set which included patients who completed the 8 weeks of treatment and, therefore, had no missing data. A supportive analysis was performed on all randomized patients, imputing missing data using Last Observation Carried Forward. A more modern mixed model for repeated measurements (also including changes from baseline to weeks 2 and 4) was used as a sensitivity analysis.

Assuming a maximum difference versus placebo of 5 mm Hg and an SD of 9 mm Hg for the change from baseline in SiDBP, 70 patients per group would provide 90% power to detect a dose-response with MCP-Mod in the per-protocol set (for a total of 420 patients).

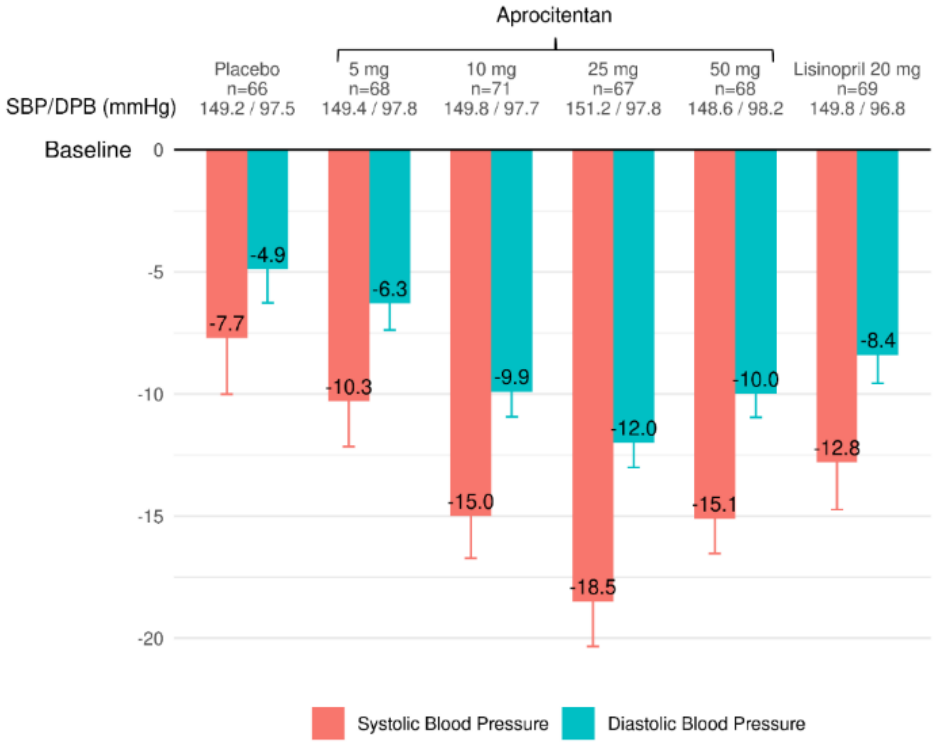

Figure 3. Mean change from baseline to Week 8 in sitting SBP (red) and DBP (blue)

RESULTS

A clinically relevant decrease in trough SiDBP (and SiSBP) occurred within 2 weeks in the aprocitentan 10, 25, and 50 mg groups, and was maintained up to week 8, returning to placebo levels during the withdrawal period.

Mean changes in office SiDBP and SiSBP from baseline to week 8 are displayed by treatment group in Figure 3.

The dose-response relationship for the change in mean trough SiDBP from baseline to week 8 was statistically significant (P<0.001 for all 6 prespecified dose-response models). The results of these models are displayed in Figure 4a. A quadratic model fitted the data best. According to this model, the maximum BP effect (versus placebo) is predicted to occur at a dose of around 30 mg, with a substantial part of this effect predicted to be already achieved at a dose of approximately 10mg (Figure 4b).

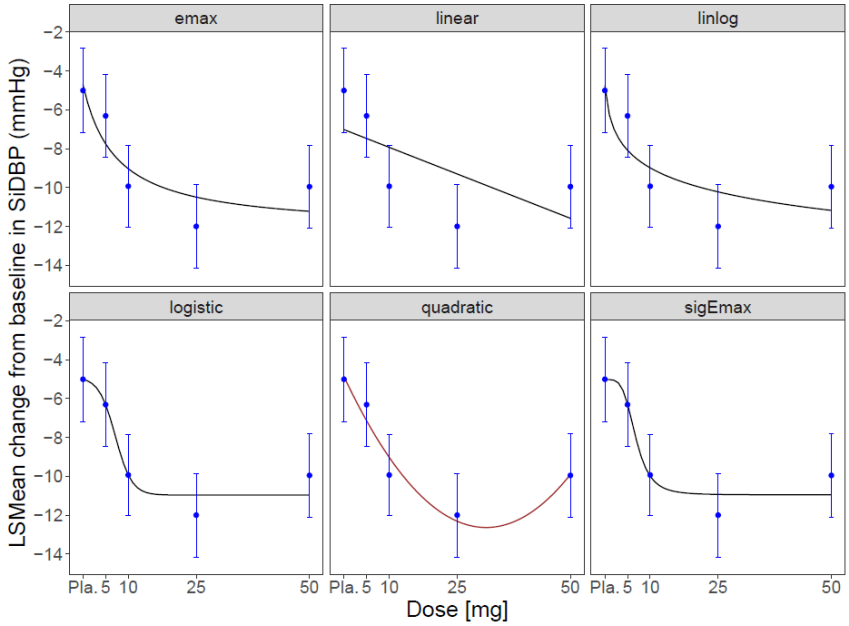

Figure 4a. MCP-Mod: six candidate models fit to the LSMean changes from baseline to week 8 in SiDBP

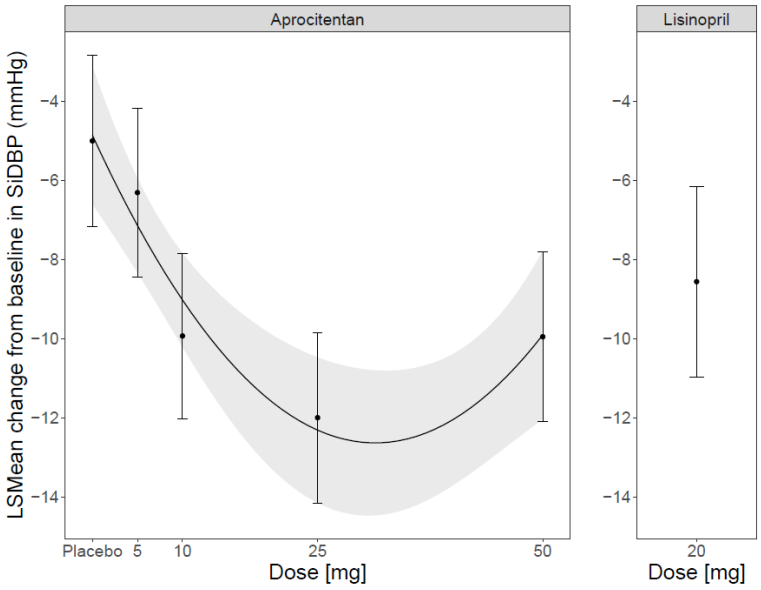

Figure 4b. MCP-Mod: best fitting quadratic model for LSMean changes from baseline to week 8 in SiDBP

The ambulatory BP measurement (ABPM) analyses were based on a subset of the per-protocol set with a valid ABPM at baseline and at week 8 (n=281; 69%). The mean changes from baseline to week 8 in 24h-mean SBP/DBP (Figure 5) showed the same pattern as the mean changes in SiSBP/SiDBP as measured by uAOBP (Figure 3), confirming the shape of the dose-response curve as well once-a-day regimen (trough to peak ratio >50%).

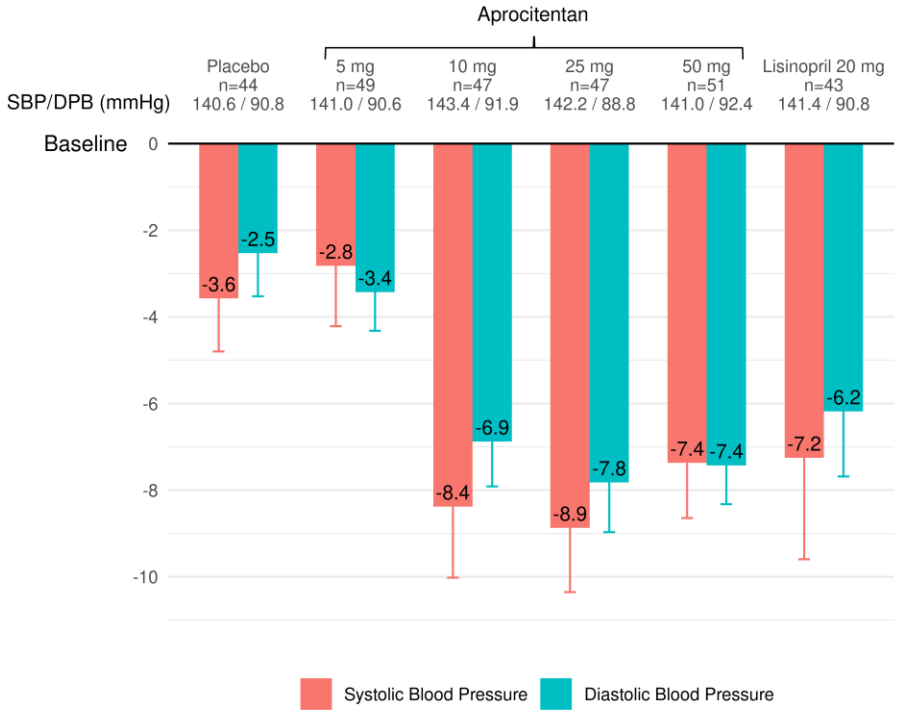

Figure 5. Mean change from baseline to Week 8 in 24-h mean SBP (red) and DBP (blue) in the aprocitentan DFS

In selecting doses for clinical development, efficacy data should be supplemented by relevant safety data. Due to the potential for fluid retention with endothelin antagonists, the relevant safety information was decreases in haemoglobin concentration and increases in estimated plasma volume (e-PV). All aprocitentan doses lowered haemoglobin, hematocrit, and albumin from baseline to week 8, and there was a dose dependent increase in e-PV from baseline, although with no substantial change in body weight[19] (Figure 6 and 7).

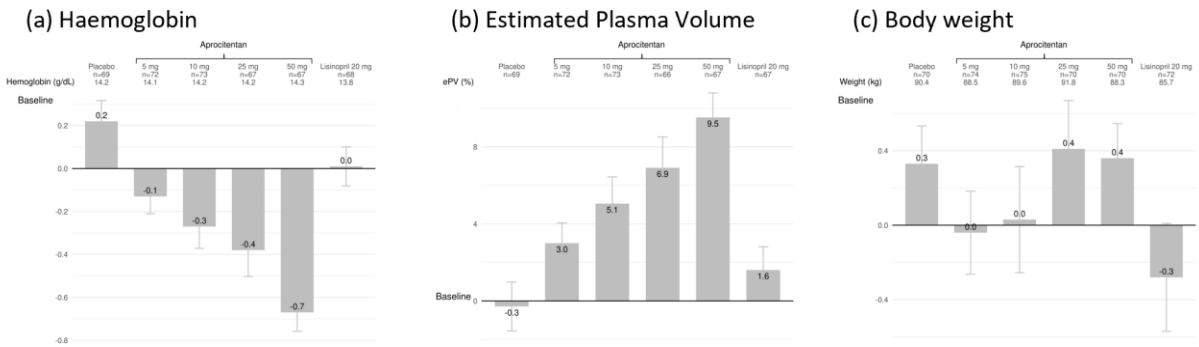

Figure 6. Mean Change from Baseline to Week 8 in Haemoglobin (a), Estimated Plasma Volume (b) and Body Weight (c)

These results showed that the 25 mg dose was associated with a mean haemoglobin decrease of 0.38 g/dL and a mean PV increase of 6.9% (versus +0.22 g/dL and –0.3% with placebo). Aprocitentan 50 mg did not decrease BP further but enhanced the effects on haemoglobin (to –0.67 g/dL) and e-PV (to +9.5%). The 10 mg dose (which provided 70 to 80% of the observed BP effect at 25 mg) was associated with a smaller mean haemoglobin decrease of 0.27 g/dL and an e-PV increase of 5.1%. These endpoints can also be modeled using MCP-Mod. As an example, we show six models (the same as prespecified for efficacy endpoints) fitted to the LSMean changes from baseline in haemoglobin. The dose-response analysis for haemoglobin differed from the analyses for BP in that a log-linear model fitted the data best, with every doubling of the aprocitentan dose resulting in an estimated decrease in haemoglobin of ~0.125 g/dL.[19]

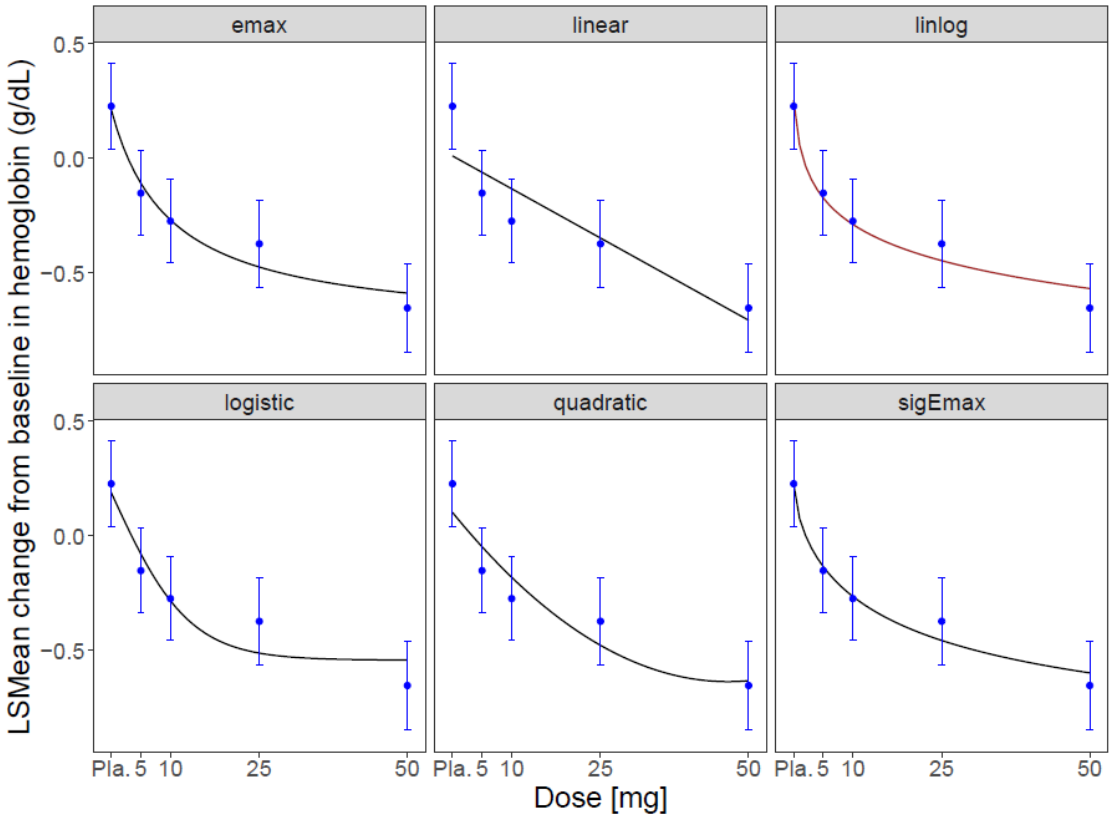

Figure 7. MCP-Mod: six candidate models fitted to the LSMean changes from baseline to week 8 in haemoglobin (g/dL)

INTERPRETATION

The dose-efficacy response curve suggests that the effect of aprocitentan 5 mg on BP was indistinguishable from that of placebo, while higher doses provided significant responses. The effect reached a maximum around approximately 25 mg, with fluctuations of the effect at lower and higher doses around the value observed at 25 mg. In contrast, the safety dose response curve did not reach a maximum effect, with a continuous decrease in haemoglobin and increase in e-PV as doses increased from 5 to 50 mg. The combination of the efficacy and safety results allowed the lowest and the highest doses to be discarded when moving to Phase 3.

However, even after a well-conducted DFS, uncertainty remained as to the relative benefit-risk balance of the two middle doses, with the 10 mg dose being slightly less effective in reducing BP but also having a slightly smaller fluid retention effect than the 25 mg dose. Consequently, doses of 12.5 mg (adjusted from 10 mg for simplicity) and 25 mg were both selected for Phase 3.

The Phase 3 study (PRECISION; NCT03541174) has now been completed and published,[25] allowing a critical review of the design of the Phase 2 study in the light of the pivotal study results. The Phase 2 and Phase 3 studies differed on important design elements. First, aprocitentan was studied as monotherapy in Phase 2, whereas in PRECISION it was studied on background of at least 3 antihypertensive therapies. Second, patients with grade 1 and 2 essential hypertension were included in Phase 2, while Phase 3 included patients with difficult-to-control, or resistant hypertension. Third, patients in PRECISION had considerably more co-morbidities, in particular diabetes, chronic kidney disease, obesity, and sleep apnea, and more geographical diversity than the Phase 2. On the other hand, the Phase 2 study included a larger proportion of African Americans (30%). Fourth, baseline systolic blood pressure was slightly higher, and diastolic blood pressure lower in PRECISION compared to the Phase 2 study, as a result of the inclusion criteria that differed between these two studies. Fifth, the primary endpoint in the Phase 2 was sitting DBP while SBP was the primary endpoint in PRECISION.

When designing DFS, with the anticipation of determining the dose(s) to be pursued in Phase 3, the question remains as to the acceptable differences in patient population and endpoints

between studies. The choice of the ultimate target population for aprocitentan was already made when designing the DFS. It appeared impractical to conduct the Phase 2 in resistant hypertension for multiple reasons. In particular, the recruitment of patients in this DFS study would have been considerably more challenging. More importantly, it seemed essential to study a new chemical entity, and especially a first-in-class compound in this indication, as monotherapy so that the absolute efficacy and safety responses could be adequately determined without the interference of co-morbidities or concurrent medications. It was also anticipated that the effect of medications of different mechanisms of action would be additive and therefore, the monotherapy setting was adequate for dose determination even if ultimately the drug would be given concurrently with other antihypertensive molecules.

The results of PRECISION, aligned to those of the Phase 2, suggest that the approach taken for aprocitentan was acceptable.

Discussion

To prevent late-stage disenchantment, the developers of any new antihypertensive drug should pay utmost attention to the dose selection process during the clinical development of the new chemical entity. This will lead to an optimal choice of doses for the Phase 3 program and further on, to acceptance from regulatory authorities during their review that the dose-benefit-risk profile is adequately described. The dose-selection process has been shown to rely on three pillars: 1) consideration of all existing preclinical data, from the mode of action to pharmacology, including a detailed dose response curve; 2) good phase 1 data, including mechanistic studies if needed (e.g., for aprocitentan, a dose-dependent fluid- and sodium-retention study was performed in healthy subjects[26]; and 3) design of a tailored, single DFS complying with specific recommendations.

Based on a review of previous cases of DFS for antihypertensive medications, and the example of aprocitentan, 10 recommendations for the design of DFSs can be made (Box 1).

Box 1. Ten recommendations for a single well-designed DFS for new antihypertensive drugs

1. Selection of a well-characterised population, in need of treatment, in whom a response can be measured
2. Randomized, double-blind, 4- to 8-week, fixed-dose design
3. Role of placebo
4. Role of other antihypertensive medications
5. Broad (at least 10-fold) therapeutic dose range
6. At least 3 doses of the product under investigation, each of them tested in arms of sufficient size
7. Appropriate endpoint such as office BP measurements at trough
8. Limited reliance on biomarkers
9. Integrated monitoring of adverse event(s)
10. Use of the totality of information in a dose-response model

The key aspects of these recommendations are as follows:

A- Study design features

1. Selection of a well-characterised population in whom a response can be measured.

The selection of the population can affect the shape and location of the dose response curve. For instance, African Americans are known to be less responsive to certain classes of molecules, such as ACE inhibitors, compared to white population[27]. The benazepril DFS conducted in the US enrolled 45% of African Americans; the results of this study differed from those of studies conducted in Europe, which contributed to different dose recommendations in the US label of benazepril (20 mg o.d) vs the EU SmPC (10 mg o.d). Although a homogeneous population with a high likelihood of responding to the new therapy with a BP drop facilitates the determination of the dose-response, ethnicity, or other relevant factors of heterogeneity of the population to be treated need to be considered in the design of the study, for example by including sufficient numbers of subjects to allow description of the dose-response relationship in subgroups of relevance. The lack of diversity in the DFS can be a major issue which will have to be addressed in Phase 3. This would entail a full clinical program on patient specific factors accounting for intrinsic factors such as age, race, genetics, and organ function, and extrinsic factors such as concomitant medication.[28] In the aprocitentan DFS, African Americans adequately represented approximately a third of the patient population.

2. Randomized, double-blind, 4- to 8-week, fixed-dose design.

In the past, several DFSs had an up titration scheme to a target BP.[29,30] Although closer to medical practice, this approach obscures the dose-response relationship as the subgroup of drug resistant patients will push the dose-response curve towards

higher dosages. Forced titration will result in similar biases due to time effects and progressive decreases in BP during the trial.[31] Consequently, a fixed dose should be used for the main observation period of the trial, although an initial short, blinded titration phase may be needed to reach the intended dose levels.[32] The duration of the DFS should not exceed 8 weeks, to help minimize missing data and avoid ethical concerns with the placebo group (see point 03).[33] In principle, 4 weeks should be sufficient (except for diuretics[34]) to attain the maximum effect on BP. A treatment for 8 weeks may be preferable if a specific adverse event which may require a few weeks to reach its full expression is intended to be monitored. In some cases, a single blind withdrawal period could be a useful addition. This was used, for instance, to characterize a potential rebound effect (characterised by BP higher than at baseline) linked for example, to counter-regulation phenomena (e.g., increase of endothelin levels[18]) and to reinforce the reversible pharmacological effect (i.e., BP fall).

3. Role of placebo

Placebo can be used during run in. After washout/screening, a placebo run-in period, though not used in medical practice, is recommended in a DFS. This period helps minimize regression towards the mean and the placebo response during the treatment phase, which can dilute the pharmacological effect of the therapy under investigation.[35]

The inclusion of a placebo group is mandatory to characterise the clinical effect.[36] The use of placebo is accepted from a safety and ethical standpoint in subjects with mild to moderate hypertension, for up to 8 weeks.[37]

4. Anti-hypertensive medications may have multiple roles in DFS.

First, the inclusion of an active control group allows validation of the study through assay sensitivity[32,38]; it is recommended to use a well-recognized and evaluated antihypertensive drug with expected similar onset, slope of BP curve, and dosing regimen. Lisinopril was selected in the aprocitentan DFS as it had been tested in well-designed DFSs.[39]

Second, antihypertensive medications have sometimes been considered as background therapy. However, even if the new compound is designed for use exclusively as a combination with existing treatment, the DFS should preferably be performed as monotherapy to obtain results unaffected by concurrent therapies, and avoid the very high placebo responses that have been reported in hypertension studies involving multiple background therapies.[40] If it is essential to explore the dose response on background therapy, a factorial design may be suitable, though more difficult to design, conduct, analyse, and interpret.

5. Broad (at least 10-fold) therapeutic dose range

The main preclinical learnings that influence the preparation of the DFS are the characterisation of the dose-response steepness of the compound in hypertensive animals and its comparison with other pharmacological classes. Data from aprocitentan demonstrated that the BP profile (shallow slope of BP decrease) was closer to that of ACEIs and ARBs than to that of calcium channel blockers, suggesting that a broad range of doses would have to be tested during the clinical program. We suggest that the range of tested doses from the lowest to the highest, should cover at least a 10-fold increase, unless the pre-clinical safety margin or the safety in healthy subjects (phase 1) or in early studies in patients (phase 2a) do not allow such a broad range.

6. At least 3 doses of the product under investigation, each of them tested in arms of sufficient size

A correct dose-response modelling requires at least 3 (preferably 4) active groups of increasing doses. The size of each group should be estimated according to the requirements of the model and prior evaluation of the expected variability, considering that a placebo corrected, DBP change from baseline of approximately 4 mmHg is usually considered clinically relevant (see point 3). Sample size may be inflated if additional information, in particular from subgroups of interest, is needed at this early stage of development.

Sample sizes for DFSs in hypertension vary from 30[41] to 70 evaluable participants[21,42] per group, like in the aprocitentan DFS. Most studies used a primary endpoint based on office BP, even though these measurements have substantial variability: in the aprocitentan DFS standard deviation of changes from baseline within the group was 14.1/9.0 mmHg for SiSBP/SiDBP. From a statistical perspective it would be more beneficial to use ABPM which is less variable: in the aprocitentan DFS the within group standard deviation was 8.7/5.9 mmHg for 24-hour mean SBP/DBP. From a patient perspective, however, ABPM presents a burden as described below (point 7).

B- Efficacy measures in DFS

7. Appropriate office BP measurements at trough

The technique and timing of BP measurements are critical. Trough measures are mandatory to estimate the BP therapeutic coverage up to the next drug intake (i.e., inter-dosing interval). ABPM, despite its lower placebo effect[43], lower variability, and high clinical relevance, and thus high attractiveness, does not seem appropriate for a DFS due to potential

erratic data (recorded in the aliskiren clinical development)[44] and the need to repeat the ABPM when it is used in the primary endpoint[45], both posing challenges to the method's validity. However, ABPM is of interest to confirm the dose-response by uAOBP and to characterize the time course of BP over 24 hours and the trough to peak ratio (>50%) to justify an o.d. regiment.

UAOBP measurement, which can evaluate the primary endpoint, is an efficient solution to reduce variability and ensure stable data during the trial. It can be repeated at each visit and decreases white coat effect[46] (due to decrease of sympathetic activation).[47] Furthermore, office BP measurements have been used[48] as validated BP fall surrogacy in therapeutic morbidity/mortality clinical trials with positive outcomes to the contrary of ABPM.[49] The choice between SBP and DBP as the primary endpoint is debatable. DBP seems to be less variable than SBP and has been previously used in positive controls with lisinopril (see point 4). However, several experts recommend using SBP due to better responsiveness to BP lowering compounds secondary to the Wilder principle.[50] Practically, both measures will be collected to determine the endpoint to be used in Phase 3.

8. Limited reliance on biomarkers

The idea of improving the DFS by incorporating efficacy biomarkers beyond BP is tempting. However, it should be acknowledged that even for a well understood mechanism of action like RAAS inhibition, these biomarkers, such as angiotensin converting enzyme inhibition, only provide ancillary information (e.g., perhaps on duration of action) vis a vis its therapeutic effect but are poorly informative for dose selection.[51]

C- Safety measures in DFS

9. Integrated monitoring of adverse event incidence

One aspect that may too often be disregarded in DFSs for hypertension is the need to complement the efficacy measures by valid safety measures to provide dose-dependent benefit/risk assessment. Hypertension is more an indicator of a disease, than a disease and the safety aspects of any new hypertensive therapy are paramount. This aspect is relatively easy to incorporate when AEs have been characterized in prior healthy subject studies or are suspected based on class effects. Examples are central-acting agents such as alpha-2 agonists (dizziness, drowsiness, dry mouth), dihydropyridines (flush, leg edema), and betablockers (bradycardia). Safety consideration is more complex when AE are rare, the new chemical entity is well tolerated as is the case with ARBs or if individual tolerability is unpredictable such as hyperkalaemia with spironolactone or non-specific cough with ACEIs. In the development of aprocitentan, we took advantage of one well-known ERA class effect, a decrease of Hb blood concentration due to haemodilution, which can be easily monitored in every study participant and contributed to the dose selection of aprocitentan.

D- Dose-response modelling

10. Use of a dose-response model (avoiding inter-dose comparisons).

The analysis of the aprocitentan dose-response study was based on modelling instead of the traditional pairwise comparisons vs. placebo within an ANCOVA. The MCP-Mod approach uses data more efficiently (i.e., requiring a smaller sample size than with the pairwise comparisons, hence exposing less patients to unproven treatment), while still controlling the type I error (i.e., the false positive rate) at a prespecified level (usually, 2.5% one-sided). In addition, the best fitting model can be used to support the determination of the minimal effective dose and optimal dose.

Even though MCP-Mod has been qualified by regulatory agencies[22,23], there are still DFSs using pairwise comparisons based on smaller[41] or larger[21] group sizes. However, a statistically qualified reader would be able to perform an approximate MCP-Mod analysis when summary statistics (including variability) are provided,[39] which, however, is not always the case.[21,42]

There is no consensus about whether a DFS should be analysed using a 'per protocol' or an 'intent-to-treat' approach. In the aprocitentan DFS a per protocol approach was chosen, but the 'intent-to-treat' approach gave similar results.[19] Of note, these approaches are now embedded in the estimand framework[52] as 'hypothetical' and 'treatment policy' strategy approaches, respectively. However, this framework was not available at the time of the aprocitentan dose-response study.

The above recommendations may seem overly prescriptive, but it is important to reassert them in a straightforward, 10-point message designed to avoid repeated mistakes and ensure well-designed, informative DFSs. Some of these recommendations are clearly expressed in the 2016 CHMP Guideline on clinical investigation of medicinal products in the treatment of hypertension.[53] For instance: "[DFSs] [following a run-in period of 2, preferably 4 weeks] should be randomized, placebo-controlled and double-blinded using at least 3 dosages". However, other recommendations are more softly expressed ("[DFSs] should preferably be designed as parallel group studies") and some are less clear: for instance, the parallel group design using fixed doses is only recommended to be applied in "some"

studies. In particular, the key recommendations 1, 4, 5, 8, 9 and 10 proposed in Box 1 are currently not expressed in the EU guidelines. The most important reason to stress the present recommendations is that methodological limitations continue to be reported in recent clinical developments of new anti-hypertensive agents.

Recent examples of DFSs for hypertension

In November 2022 at the American Heart Association break out session, a negative phase 3 double blind placebo-controlled study in resistant hypertension (RHT) with firibastat was reported. This study tested the first orally active brain aminopeptidase A inhibitor, a new class of centrally acting renin-angiotensin system blocker.[54] However, doses selected for the phase 3 were based on an uncontrolled, open-label, dose-titrating DFS performed in overweight hypertensive patients, at least 50% of whom self-identified as Black or Hispanic, and with the use of automated office BP monitoring to establish the primary endpoint. Although the authors consider the diversity of the included population as an asset and boldly conclude that *"our results demonstrate the efficacy of firibastat in lowering BP in a high-risk population"*, this conclusion is unduly optimistic in the context of a potentially inadequate open-labelled dose titration DFS .[55] Could a better design of the DFS have prevented the conduct of the failed Phase 3? This is an important question, as every study carries risk to patients and, if not scientifically legitimate, raises ethical concerns.

Another recent example derives from the results of Target-HTN, a randomized clinical trial with a new aldosterone synthase Inhibitor (ASI), lorundrostat, for uncontrolled hypertension [41]. According to all of the above defined rules for a well-designed DFS, Target-HTN trial is not sufficient for efficacy dose determination purpose. It is a preliminary investigation in patients that needs to be supplemented by a DFS, as reported with another ASI a decade ago.[21] In this setting, the study is nevertheless important for testing patient safety, in particular vis a vis cortisol levels under ACTH stimulation, and to ensure that BP decreases whatever the dosage (proof of concept). A titration trial design for safety purpose coupled with a placebo control group up to a maximum tolerated dose might have been more efficient.

CONCLUSION

Based on lessons learned from the past 5 decades[30,32,36,53] and from the recent example of aprocitentan, a novel endothelin receptor antagonist for the treatment of RHT,[19,25] we have provided 10 key recommendations for designing an efficient single DFS for a new antihypertensive medication. The recommendations will offer a high likelihood of success in selecting and defining the best dose-range to bring over to Phase 3. We also acknowledge that the full dose-finding exercise should start in the pre-clinical and Phase 1 segments, culminating with the DFS, and that additional considerations may be needed based on mode of action or other characteristics of a new treatment. Undoubtedly, dose selection is not finished with the results of the DFS, as the determination of the optimal dose(s) will need to incorporate the results of the Phase 3 studies, which will ideally include more than one dose. However, it would ensure that the dose-finding effort would have started on the right track.

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Conflicts of interest

Marc Bellet, Guy Braunstein, Pierre Verweij, Parisa Danaietash, Marc Iglarz, and Bruno Flamion are employees of Idorsia Pharmaceuticals Ltd.

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